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LÉKAŘSKÁ FAKULTA

HABILITAČNÍ PRÁCE

Brno 2025 MUDr. Martin Štork, Ph.D.

MASARYKOVA UNIVERZITA
LÉKAŘSKÁ FAKULTA
INTERNÍ HEMATOLOGICKÁ A ONKOLOGICKÁ KLINIKA

EXTRAOSEÁLNÍ MNOHOČETNÝ MYELOM

Komentovaný soubor publikovaných prací

Habilitační práce v oboru Onkologie

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ABSTRAKT

Úvod:

Mnohočetný myelom je maligní onemocnění krvetvorby charakterizované klonální proliferací plazmocytů. Má velmi heterogenní klinický průběh. Zvláštní podskupinu představuje extraoseální mnohočetný myelom charakterizovaný přítomností plazmocytomů mimo kostní dřeň. Tato forma onemocnění je většinou spojena s nepříznivou prognózou.

Metody:

Habilitační práci tvoří soubor komentovaných publikací. Týkají se možností diagnostiky a léčby extraoseálních forem mnohočetného myelomu.

Výsledky:

Data ukazují, že primární paraskeletární plazmocytomy (asociované s kostními ložisky) neovlivňují prognózu negativně, zatímco extramedulární plazmocytomy (rostoucí v měkkých tkáních) jsou spojeny s významně kratším přežitím. Molekulární analýzy potvrzují, že aberace chromozomu 1 (gain(1q21), del(1p32)) a mutace MAPK dráhy jsou klíčovými prediktory rozvoje extramedulárního myelomu. Sekundární extramedulárním myelom vykazuje rezistenci na standardní léčbu i moderní imunoterapii včetně bispecifických protilátek.

Závěr:

Extraoseální mnohočetný myelom je stále výzvou klinické i experimentální hematologie. Přestože byly identifikovány významné genetické faktory a popsány klíčové rozdíly mezi paraskeletárními a extramedulárními formami, terapeutické možnosti zůstávají omezené. Další pokroky lze očekávat od integrace molekulární diagnostiky, nových zobrazovacích metod a imunoterapie cílené na více antigenů.

KLÍČOVÁ SLOVA:

mnohočetný myelom, extramedulárním plazmocytom, paraskletární plazmocytom, molekulární prediktory

ENGLISH ABSTRACT

Introduction:
Multiple myeloma is a hematologic malignancy defined by the clonal proliferation of plasma cells. The clinical presentation is notably heterogeneous. Extramedullary multiple myeloma constitutes a distinct subset, marked by the occurrence of plasmacytomas outside the bone marrow, and is generally associated with a poorer prognosis.

Methods:
This habilitation thesis consists of a set of commented publications focused on the diagnostic and therapeutic aspects of extramedullary forms of multiple myeloma.

Results:
The data show that primary paraskeletal plasmacytomas (associated with bone lesions) do not negatively affect prognosis, whereas extramedullary plasmacytomas (growing in soft tissues) are associated with significantly shorter survival. Molecular analyses confirm that chromosome 1 aberrations (gain(1q21), del(1p32)) and mutations in the MAPK pathway are key predictors of extramedullary myeloma development. Secondary extramedullary myeloma demonstrates resistance to both standard therapies and modern immunotherapies, including bispecific antibodies.

Conclusion:
Extramedullary multiple myeloma remains a major challenge in both clinical and experimental hematology. Although significant genetic factors have been identified and essential differences between paraskeletal and extramedullary forms have been described, therapeutic options remain limited. Further progress can be expected from the integration of molecular diagnostics, novel imaging methods, and multi-targeted immunotherapy.

KEY WORDS: multiple myeloma, extramedullary plasmacytomas, para-skeletal plasmacytomas, molecular predictors

Prohlašuji, že jsem práci vypracoval samostatně s využitím zdrojů uvedených v soupisu literatury.

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podpis autora

Rád bych vyjádřil svou hlubokou vděčnost své ženě Tereze a dětem Martinovi, Jakubovi a Ester za jejich trpělivost, podporu a toleranci, bez nichž by tato práce nikdy nevznikla. Zvláštní poděkování patří také mému příteli Luďkovi a celému týmu kolegů, díky nimž je pro mě práce nejen profesí, ale i radostí a koníčkem.

Obsah:

1. Úvod:

Mnohočetný myelom je maligní monoklonální gamapatie. Nádorové klonální plazmatické buňky svou proliferací a sekreční aktivitou poškozují orgánové systémy nemocného (1). Onemocnění postihuje převážně starší populaci (medián věku 69 let, jen 1 % nemocných mladších 40 let), s incidencí 6,6/100 000 a prevalencí 31,9/100 000 (2,3). Typickými projevy jsou osteolytické léze, hyperkalcémie, anémie a renální insuficience.

Diagnostika zahrnuje detekci monoklonálního imunoglobulinu v séru nebo moči a průkaz orgánového poškození, což zahrnuje vyšetření krevního obrazu, základních biochemických parametrů (tj. iontogram, renální a jaterní funkce atd.) a zobrazovací vyšetření skeletu (4). Standardem mezi zobrazovacími metodami je low-dose CT nebo celotělová MR, případně doplněné o FDG-PET/CT (5; 6). Pro stanovení diagnózy je nezbytné provést i vyšetření kostní dřeně – jak klasickou morfologii, tak průtokovou cytometrii (7). Prognostická stratifikace vyžaduje genetické vyšetření nádorových buněk, přičemž za rizikové faktory jsou považovány translokace t(4;14), t(14;16), t(14;20), aberace chromozomu 1, delece 17p a mutace TP53 (8). Na našem pracovišti je standardně využívána kombinace I-FISH a panelového NGS vyšetření (9). Prognostický význam má také kvantifikace cirkulujících plazmocytů (10; 11).

Léčebné strategie se odvíjejí od věku a stavu nemocného. Pacienti mladší 70 let a v dobré kondici podstupují indukci moderními čtyřkombinacemi s anti-CD38 protilátkou, inhibitorem proteasomu, lenalidomidem a kortikosteroidem, následovanou vysokodávkovanou chemoterapií a autologní transplantací (12; 13). U vysoce rizikových pacientů je indikována tandemová transplantace (14). Následuje konsolidace a udržovací léčba, v ČR standardně lenalidomidem (15), nově se prosazuje kombinovaná udržovací terapie pomocí anti-CD38 protilátek (16). U části pacientů se standardním rizikem se diskutuje i možný kurativní potenciál léčby (1).

U starších pacientů bez transplantace je preferována troj- či čtyřkombinace s anti-CD38 protilátkou (17; 18). V klinických studiích se testují i bispecifické protilátky a CAR-T buňky (19,20,21). Léčba relapsu se řídí předléčeností, v pokročilých liniích jsou indikovány bispecifické protilátky či CAR-T (22; 23).

Za posledních 20 let se diagnostika i terapie myelomu zásadně proměnily. Z původně infaustního onemocnění se stalo u většiny pacientů chronické nádorové onemocnění a u vybrané skupiny lze očekávat i kurativní potenciál (24).

2. Extraoseální mnohočetným myelom

2.1. Historie výzkumu extraoseálního mnohočetného myelomu na LF MUNI

Pracovní skupina pro mnohočetný myelom má na IHOK FN Brno již dlouhou tradici a je její součástí již od počátku kliniky. Autor této práce se již jako student LF podílel na výzkumných aktivitách na poli monoklonálních gamapatií (25) a po absolutoriu LF a zaměstnání na IHOK je nedílnou součástí této skupiny. V prvních letech práce na klinice se autor věnoval v rámci doktorského studia optimalizaci léčby mnohočetného myelomu novými léky (26, 27, 28). Od dokončení doktorského studia je klíčovým tématem autora extraoseální mnohočetný myelom. Od roku 2024 je autor také školitelem studentky 3. ročníku LF (program pro nadané studenty P-Pool) jejímž tématem jsou „Klinické a molekulární aspekty pacientů s extraoseálním mnohočetným myelomem“.

Výzkum extraoseálního mnohočetného myelomu má v Pracovní skupině pro mnohočetný myelom rovněž dlouhou tradici. Zásadní mezinárodní význam mají práce *„Soft-tissue extramedullary multiple myeloma prognosis is significantly worse in comparison to bone-related extramedullary relapse“* Prof. MUDr. Luďka Poura, Ph.D., jako první popisující extrémně agresivní chování sekundárních extraoseálních plazmocytomů v měkkých tkáních (29), „*Cytogenetics in multiple myeloma patients progressing into extramedullary disease“* RNDr. Lenky Bešše, Ph.D. porovnávající párové vzorky extraoseálních plazmocytomů a kostní dřeně (30) či přehledový článek „*Extramedullary disease in multiple myeloma - controversies and future directions*“ (31) doc. RNDr. Sabiny Ševčíkové, Ph.D. Extraoseální myelom je taktéž důležitým tématem v rámci rozsáhlé celorepublikové spolupráce v dikci České Myelomové Skupiny (32,33).

2.2. Definice a typy extraoseálního mnohočetného myelomu

Nádorové plazmatické buňky mnohočetného myelomu jsou u většiny pacientů závislé na mikroprostředí kostní dřeně. Ložiska mnohočetného myelomu, nazývaná plazmocytomy, se však mohou nacházet i mimo mikroprostředí kostní dřeně. Takto tvoří mimo-kostní, tzn. extraoseální plazmocytomy (31).

Názvosloví extraoseálních plazmocytomů je bohužel mezinárodně nekonzistentní. V České Myelomové Skupině se od roku 2021 používá názvosloví navržené Laurou Rosignol v kooperaci se všemi významnými evropskými centry pro léčbu tohoto onemocnění. Ložiska mnohočetného myelomu mimo kostní dřeň nazýváme extraoseální plazmocytomy. Ty dále dělíme na paraskeletární plazmocytomy a extramedulární plazmocytomy (34).

Paraskeletární plazmocytomy jsou měkkotkáňová ložiska asociovaná s kostními osteolytickými ložisky, ze kterých přímo vyrůstají. Extramedulární plazmocytomy jsou měkkotkáňová ložiska rostoucí v různých typech tkání zcela bez závislosti na kostní dřeni. Mohou infiltrovat jakékoliv tkáně. Nejčastěji pojiva, parenchymatózní orgány, kůži a vzácněji také CNS. Za extramedulární projev mnohočetného myelomu se také považují maligní výpotky a nález maligních plazmocytů v likvoru. Ve vztahu k léčbě rozlišujeme primární extraoseální mnohočetný myelom. Jedná se o onemocnění, které je s extraoseálním plazmocytomem nově diagnostikováno a není zde žádný vztah k léčbě. Dále pak sekundární extraoseální mnohočetný myelom, který vzniká jako obraz rezistence onemocnění na léčbu. Sekundární extraoseální mnohočetný myelom je zpravidla agresivní onemocnění spjaté s časnou mortalitou (29, 35).

Pro vyloučení záměny je vhodné zmínit diagnózu solitárního plazmocytomu a solitárního plazmocytomu s minimální infiltrací kostní dřeně. Toto onemocnění nesplňuje diagnostická kritéria mnohočetného myelomu. Jedná se o výlučně solitární ložisko (kostní či měkkotkáňové), bez přítomnosti jiných známek orgánového poškození. V některých případech může být doprovázenou malou infiltrací kostní dřeně klonálními plazmocyty (do 10 % ze všech jaderných buněk kostní dřeně) (1). Dále v tomto textu je rozebírána jen problematika extraoseálních plazmocytomů u pacientů, kteří splnili diagnostická kritéria pro symptomatický mnohočetný myelom.

2.3.Molekulární patogeneze extraoseálního mnohočetného myelomu

Proces onkogeneze mnohočetného myelomu lze zjednodušeně popsat jako postupnou maligní transformaci B-lymfocytů v klonální plazmatickou buňku odpovídající fenotypu benigní monoklonální gamapatie nejistého významu. Další genetické a epigenetické změny určují proliferační potenciál buněk (36), jejich schopnost uniknout imunitnímu dohledu (37), uvolnit se z mikroprostředí kostní dřeně a cirkulovat v periferní krvi (38), indukovat

osteolýzu (39) nebo potlačit zdravou erytropoézu (40). Tyto fenotypové změny odpovídají symptomatickému mnohočetnému myelomu, který vyžaduje léčbu.

Extraoseální expanze maligních plazmocytů je komplexní vícestupňový proces, který je výsledkem klonální evoluce. Nádorové buňky původem z kostní dřeně získávají schopnost migrace, usazení a přežití buď v okolí osteolytických ložisek (paraskeletální plazmocytomy), nebo v měkkých tkáních či orgánech kdekoliv v těle (extramedulární plazmocytomy). I přes odlišnou anatomickou lokalizaci si tyto buňky zachovávají základní vlastnosti plazmocytů z kostní dřeně, ale získávají i nové charakteristiky (31).

Genetický podklad těchto změn není zcela objasněn. Autorem byla prokázána vyšší frekvence aberace gain(1q21) u nově diagnostikovaných pacientů s následným rozvojem extramedulárního postižení (41). Později se ukázalo, že riziko extramedulárního relapsu je vyšší u pacientů s mutacemi v MAPK dráze (mitogen-activated protein kinase) v kombinaci s gain(1q21) (33, 42). Autorem byla dále prokázána silná vazba delecí v oblasti 1p32 na výskyt extramedulárního onemocnění (43). Bialelické delece oblasti 1p32 nebo kombinace del(1p32) se zisky v oblastech 1q21 představují významné rizikové faktory (8, 44). Společný výskyt těchto aberací je spojen s nepříznivou prognózou. Pacienti bez těchto aberací překvapivě nejevili známky agresivního chování onemocnění ani v případě sekundárního extramedulárního myelomu. Analýza párových vzorků kostní dřeně a tkáně extramedulárních plazmocytomů ukázala, že delece 1p32 jsou téměř vždy sdílené, což naznačuje, že by se mohlo jednat o časnou a důležitou událost ve vývoji extramedulárního myelomu (43). Při genomické analýze (NGS panel LYNX, (9)) tkání paraskeletárních a extramedulárních plazmocytomů i párových plazmocytů kostní dřeně byla potvrzena vazba delecí chromozomu 1 na extramedulární plazmocytomy. Tyto delece často zahrnovaly tumor supresorové geny TENT5C v oblasti 1p12 a CDKN2C v oblasti 1p32. V tkáních plazmocytomů byly identifikovány nové aktivační mutace MAPK dráhy (KRAS, BRAF) nebo bialelické inaktivace tumor supresorových genů TP53, RB1 a SAMHD1 (45).

Nálezy autora odpovídají současnému poznání genetických změn extramedulárních plazmocytomů. Tyto vykazují vyšší mutační nálož než buňky kostní dřeně (46), časté jsou mutace MAPK dráhy a aberace chromozomu 1 (47, 46, 33) či ztráty tumor-supresorových genů vedoucí ke genomické instabilitě. U pacientů bez mutací MAPK dráhy se objevují translokace IGH::MAF/MAFB spojené s horší prognózou (47) a mutace epigenetických regulátorů (EP300, ARID1A, EZH2, KMT2A/B) (46, 33). Nádorové buňky ztrácejí adhezní

molekuly (CXCR4, CCR1, CCR2, NCAM) i povrchové molekulární terapeutické cíle (CD38, SLAMF7, BCMA, GPRC5D, FCRH5) (33). Mikroprostředí je chudé na CD8+ T a NK buňky, přítomné T-lymfocyty jsou vyčerpané a exprimují PD-1, LAG-3 a TIM-3. Typická je výrazná prostorová heterogenita exprese antigenů (BCMA, GPRC5D), zvýšená exprese BCL2 a EZH2 a snížená exprese CD38 (48).

Paraskeletární plazmocytomy jsou genomicky heterogenní – od indolentních po vysoce rizikové s profilem podobným extramedulárním lézím (43,45). Jejich mikroprostředí charakterizuje dominance nádorových plazmocytů, vyčerpané NK a T buňky a M2-like makrofágy (alternativně aktivované makrofágy podporující nádorový růst), se sníženou produkcí CXCL12, KITL a IL7 a zvýšenou expresí ANXA1, STC1 a VEGFC. Prostorová analýza ukazuje výraznou intralezionální heterogenitu s paralelní klonální evolucí a adaptivní imunitní odpovědí (49).

2.4.Extraoseální plazmocytomy u nově diagnostikovaného mnohočetného myelomu

Extraoseální plazmocytom u nově diagnostikovaného mnohočetného myelomu se někdy označuje jako tzv. primární. Opět se může manifestovat jak v oblasti přiléhající k osteolytickým ložiskům (primární paraskeletární plazmocytom) či vzácněji v měkkých tkáních, parenchymatózních orgánech či CNS (primární extramedulární plazmocytom). Pro velmi odlišné biologické chování a prognózu budou tyto jednotky diskutovány odděleně.

2.4.1. Primární paraskeletární plazmocytomy

Primární paraskeletární plazmocytomy jsou diagnostikovány přibližně u 20–25 % nově zjištěných případů mnohočetného myelomu. Incidence těchto nálezů v posledních letech narůstá, což je dáno širší dostupností vysoce senzitivních zobrazovacích metod (6, 50). Data španělských autorů udávají incidenci 20 % za období mezi lety 2000–2018 (51). Nejčastější lokalizací paraskeletárních plazmocytomů je oblast hrudníku (25–40 %) a axiálního skeletu (39–43 %). Méně často se vyskytují v oblasti lebky (4–13 %), pánve (11–15 %) a dlouhých kostí (1–6 %) (51, 52).

Současné výsledky ukazují, že prognóza pacientů s primárními paraskeletárními plazmocytomy je srovnatelná s prognózou pacientů s intraoseálním mnohočetným myelomem

(51, 52, 53). Autor analyzoval česká data z reálné klinické praxe za období 2004 – 2021. Více-rozměrná analýza upravená na R-ISS stadium neprokázala přítomnost primárního paraskeletárního plazmocytomu jako rizikový faktor pro PFS (HR 1,10; 95% CI: 0,90–1,36; p = 0,343) ani OS (HR 1,10; 95% CI: 0,87–1,39; p = 0,431). Klíčovým rizikovým faktorem pro dlouhé přežití byla malá nádorová nálož - pacienti s nízkou intramedulární nádorovou náloží (<5 % plazmocytů při splnění kritérií mnohočetného myelomu) vykazovali nejlepší prognózu – medián PFS činil 58,3 měsíce (95% CI: 33–NA) a medián OS nebyl dosažen. Tato skupina byla rovněž spojena s dalšími nízce rizikovými charakteristikami, jako ISS stadium 1, nižší podíl klonálních plazmocytů v kostní dřeni či absence translokací *IGH* genu (54).

2.4.2. Primární extramedulární plazmocytomy

Extramedulární plazmocytomy u nově diagnostikovaného myelomu jsou velmi vzácné. Týkají se zhruba 1-2,4 % nově diagnostikovaných pacientů. Nejčastější lokalizací jsou ledviny a uropoetický trakt (6-60%), kůže (20 - 30%), lymfatické uzliny (17%), CNS (4-10%), plíce a dýchací cesty (6-23%), gastrointestinální trakt a játra (5-21%) a maligní výpotky (3-5%) (55, 51, 53).

Oproti paraskeletárním plazmocytomům jsou primární extramedulárním plazmocytomy vesměs agresivní nádory, jejichž přítomnost vede ke zkrácení přežití pacientů s nově diagnostikovaným mnohočetným myelomem (51) Je však nutné říct, že negativní prognostický dopad primárních extramedulárních plazmocytomů není tak významný jako těch sekundárních, vzniklých rezistencí na léčbu (medián OS: 46,5 měsíce vs 11,4 měsíce; p=0,001) (56). Více-rozměrnou analýzou korigovanou na R-ISS autor potvrdil negativní dopad primárního extramedulárního myelomu i v české kohortě pacientů (PFS: HR 1.70 (95 % CI: 1,29-2,26); p<0,001 a OS: HR 1,38 (95 % CI: 1,01-1,90), p=0,046). V době publikace se jednalo o největší soubor pacientů s primárními extramedulárním myelomem. Autor dále hledal rizikové faktory, které určují agresivitu primárních extramedulárních plazmocytomů vzhledem k jejich anatomické podobnosti, ale rozdílné prognóze oproti sekundárním extramedulárním plazmocytomům. V kohortě pacientů s ≥3 extramedulárními plazmocytomy byla prognóza signifikantně horší než u pacientů s méně plazmocytomy (medián PFS: 11.1 měsíce (95% CI 7,0-16,3) a medián OS 16,9 měsíce (95% CI: 9,1 – NA)). Zajímavým faktem je, že větší extramedulární nádorová nálož nebyla asociována s vyššími ISS či R-ISS stádiem,

infiltrací kostní dřeně, četnějšími osteolytickými ložisky či nepříznivými cytogenetickými aberacemi (54).

2.5.Sekundární extraoseální mnohočetný myelom

Sekundární extraoseální plazmocytomy vznikají u léčených pacientů nejčastěji v důsledku lékové rezistence. Bez ohledu na vztah ke kostním ložiskům se jedná o vysoce agresivní nádory, které se nejzávažněji projevují v měkkotkáňových (extramedulárních) lokalizacích (29). Jejich incidence v čase narůstá – od 60. let do první dekády nového milénia vzrostla téměř osmkrát (57). Tento trend je dán jednak dostupností vysoce citlivých zobrazovacích metod, ale také celkově delším přežíváním pacientů s mnohočetným myelomem. Intenzivně diskutovaná je otázka, zda léčba může indukovat tuto agresivní formu onemocnění procesem klonální selekce (31). Dosud však nebylo prokázáno, že inhibitory proteasomu nebo IMiDy zvyšují incidenci extramedulárního onemocnění (58,59). V současnosti se extramedulární plazmocytom popisuje až u 40 % pacientů s refrakterním nebo relabovaným myelomem (23).

Analýza dat z české reálné klinické praxe ukazuje, že přítomnost sekundárního extraoseálního plazmocytomu představuje nezávislý negativní prognostický faktor (PFS: HR 1,39; 95% CI 1,06–1,81; p = 0,016; OS: HR 1,61; 95% CI 1,20–2,15; p = 0,001) (42). Vývoj výsledků léčby v čase je málo povzbudivý. V kohortě léčené v letech 2005–2008, kdy 60 % pacientů dostávalo bortezomib nebo thalidomid, činil po vzniku sekundárního extraoseálního plazmocytomu medián OS 12 měsíců u paraskelárních plazmocytomů a pouze 5 měsíců u extramedulárních lézí (29). Ani novější autorova analýza z období 2005–2017, zahrnující 30 % pacientů s extramedulárními plazmocytomy a 85 % pacientů předléčených inhibitory proteasomu a/nebo IMiDy, neukázala zásadně odlišné výsledky: medián PFS po vzniku léze dosáhl 4,7 měsíce (95% CI 3,5–5,8) a medián OS 8,6 měsíce (95% CI 6,3–11,0) (41).

Nepříliš pozitivních výsledků bylo dosaženo také při léčbě anti-CD38 protilátkou daratumumabem. U pacientů se sekundárním extraoseálním plazmocytomem byl medián PFS 9,9 měsíce (95% CI 3,9–16,5) (60). Rezistence těchto lézí na anti-CD38 monoklonální protilátky souvisí se sníženou expresí CD38 na povrchu maligních plazmocytů (32). Podobně nepříznivá jsou i dosavadní data pro léčbu bispecifickou protilátkou teclistamabem – u pacientů se sekundárním extramedulárním plazmocytomem byl medián PFS jen 3,9 měsíce (95% CI 1,4–NA) a medián OS 11,0 měsíce (95% CI 5,0–NA). U pacientů s paraskelárními ložisky činil medián PFS 10,1 měsíce (95% CI 6,4–NA), zatímco medián OS nebyl dosažen

(61). V tomto případě je rezistence dána anergními či senescentními T-lymfocyty v plazmocytomech (33, 49).

2.6.Nové perspektivy v diagnostice a léčbě extraoseálního myelomu.

Diagnostika extraoseálního mnohočetného myelomu se v posledních letech významně posunula díky moderním zobrazovacím metodám. Kromě standardního FDG-PET/CT a celotělové MR se zkoumají nové trasery jako 11C-methionin nebo CXCR4, které umožňují detekci ložisek s nízkou glykolytickou aktivitou (62). Umělá inteligence a radiomika se jeví jako slibné nástroje schopné identifikovat časné obrazové znaky agresivních forem myelomu, včetně extramedulárního postižení, z FDG-PET/CT a MR vyšetření. Tyto výsledky jsou však zatím omezeny na exploratorní studie a vyžadují validaci na rozsáhlejších kohortách (63).

Hmotnostní spektrometrie představuje novou metodu pro sledování minimální reziduální choroby. Umožňuje detekovat stopová množství monoklonálních imunoglobulinů v periferní krvi s vyšší citlivostí než klasická elektroforéza nebo imunofixace a může tak poskytnout méně invazivní alternativu k opakovaným vyšetřením kostní dřeně (64). Tento postup by mohl též najít využití u extramedulárního postižení, kde až 50 % pacientů může mít oligo-sekreční onemocnění či dynamiku onemocnění neodpovídající dynamice paraproteinu (65)

Analýza cirkulující nádorové DNA (ctDNA) představuje další slibný neinvazivní přístup k hodnocení aktivity extramedulárního mnohočetného myelomu. Studie ukazuje, že ctDNA dokáže lépe odrážet velikost nádorové masy a dynamiku onemocnění u extraoseálního myelomu citlivěji než standardní metody (66). Na našem centru tuto slibnou technologii nyní intenzivně studujeme s cílem zpřesnění sledování pacientů s extramedulárním onemocněním.

Efektivita bispeficických anti-BCMA protilátek teclistamabu a elranatamabu je u extramedulárního myelomu nízká. Jedno z možných vysvětlení je T-buněčná anergie a snížená exprese BCMA antigenu na nádorových buňkách (23). CAR-T buňky cílené proti BCMA (preparát cilta-cel) v současnosti vykazuje u těchto nemocných nejvyšší efektivitu. Aktivitu ještě zvyšuje snížení nádorové masy před podáním CAR-T buněk (67). Perspektivní jsou také kombinace bispecifických protilátekvči CAR-T buněk s duálním cílením (např. BCMA+GPRC5D), které vykazují vyšší účinnost u nemocných s extramedulárními ložisky (68, 23)

2.7.Přílohy ke kapitole Extraoseální mnohočetný myelom

2.7.1. Stork M, Sevcikova S, Minarik J, Krhovska P, Radocha J, Pospisilova L, Brozova L, Jarkovsky J, Spicka I, Straub J, Pavlicek P, Jungova A, Jelinek T, Sandecka V, Maisnar V, Hajek R, Pour L. **Identification of patients at high risk of secondary extramedullary myeloma.** Br J Haematol. 2022;196(4):954–962.

bjh research paper

Identification of patients at high risk of secondary extramedullary multiple myeloma development

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Summary

Multiple myeloma (MM) is characterized by malignant plasma cell infiltration of the bone marrow. In extramedullary multiple myeloma (EMD), a subclone of these cells migrates out of the bone marrow. Out of 4 985 MM patients diagnosed between 2005 and 2017 in the Czech Republic, we analyzed 234 secondary EMD patients to clarify risk factors of secondary EMD development. We found younger age [<65 years; odds ratio (OR) 4·38, 95% confidence interval (CI): 2·46–7·80, $P < 0·0001$], high lactate dehydrogenase (LDH) levels (>5 μkat/l; OR 2·07, 95% CI: 1·51–2·84, $P < 0·0001$), extensive osteolytic activity (OR 2·21, 95% CI: 1·54–3·15, $P < 0·001$), and immunoglobulin A (IgA; OR 1·53, 95% CI: 1·11–2·11, $P = 0·009$) or the non-secretory type of MM (OR 2·83; 95% CI: 1·32–6·04, $P = 0·007$) at the time of MM diagnosis to be the main risk factors for secondary EMD development. Newly diagnosed MM (NDMM) patients with subsequent EMD had inferior median progression-free (PFS) and overall (OS) survival when compared to NDMM patients without future EMD [mPFS: 13·8 months (95% CI: 11·4–16·3) vs 18·8 months (95% CI: 17·7–19·9), $P = 0·006$; mOS: 26·7 months (95% CI: 18·1–35·4) vs 58·7 months (95% CI: 54·8–62·6), $P < 0·001$]. We found that NDMM patients with specific risk factors associated with secondary EMD development have a more aggressive disease course before secondary EMD develops.

Keywords: multiple myeloma, extramedullary disease, prognostic factors.

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Introduction

Multiple myeloma (MM) is the second most common haematological malignancy. It accounts for 1·7% of all cancers and 10% of all haematological malignancies.[1] Average incidence in Europe is 5/100 000.[2,3] In the last 20 years, novel drugs [proteasome inhibitors (PIs), immunomodulatory drugs (IMIDs), monoclonal antibodies, etc.] have significantly prolonged survival of newly diagnosed MM (NDMM) as well as relapsed/refractory MM (RRMM) patients.[1,4]

Better imaging techniques [computed tomography (CT), positron emission tomography (PET), PET-CT or magnetic resonance imaging (MRI)] show higher detection rates of so-called extramedullary myeloma (EMD).[5–9] In EMD, a subclone of plasma cells (PCs) migrates out of the bone marrow (BM) infiltrating soft tissues.[10] Changes in adhesion as well as secondary genetic changes in this subdone have been described, including *TP53* mutations, translocation t(4;14), deletion del(13), etc.[6,11,12] However, causes of EMD have not been clarified.

EMD is classified as primary EMD (found at the time of MM diagnosis) and secondary EMD (at the time of MM relapse); clinical behaviour of primary and secondary EMD is markedly different.[7,11] While prognosis of primary EMD *versus* NDMM without EMD is similar,[13,14] secondary EMD is associated with a poor prognosis.[6] We previously showed that in secondary EMD patients, the worst prognosis was observed in soft-tissue EMD (EMD-S), when PCs completely lose their dependence on the BM microenvironment, infiltrating soft tissues. On the other hand, extramedullary lesions arising from bone (EMD-B) have relatively better prognosis.[7]

According to unsatisfactory treatment outcomes, there is a clinical need to diagnose patients with high risk of secondary EMD development as early as possible. Unfortunately, there is a lack of evidence about clinical features of the patients before secondary EMD develops. Therefore, we analyzed disease course before EMD appearance in a real-life group of secondary EMD patients.

Methods

Clinical characteristics of patients

This real-life retrospective study was carried out at haematological centres in the Czech Republic between 2005 and 2017. All MM patients' data were recorded in the Registry of Monoclonal Gammopathies (RMG) of the Czech Myeloma Group. All participants provided written informed consent approved by institutional Ethics boards in accordance with the latest Helsinki declaration.

In total, 4 985 MM patients were evaluated; 543 EMD patients (10·9%) were found. Out of this number, 309 primary EMD and 234 secondary EMD patients were identified. As reference, 2 092 MM patients with no EMD involvement during the entire follow-up period were included — we excluded living patients with shorter follow-up than five years.

Secondary EMD was found in 111 patients at first relapse, in 61 at second and 62 at third or higher relapse. Median follow-up of secondary EMD patients from the time of MM diagnosis was 3·8 years. In secondary EMD patients, 61·1% (143/234) of patients had EMD-B, 30·3% (71/234) had EMD-S, and 8·6% (20/234) of patients were missing data. Only first occurrences of EMD were evaluated.

Before secondary EMD diagnosis, 19·2% of patients were treated with PIs, 22·6% with IMIDs, and 41·5% of patients with both PIs and IMIDs; 16·7% of patients were treated with conventional chemotherapy without novel drugs, and 54·2% of patients underwent autologous stem cell transplant (ASCT). No obligatory diagnostic protocol was used in this study. Diagnostic methods and clinical evaluations at the time of secondary EMD diagnosis were used in a real-life setting corresponding to patients' symptoms and actual clinical availability of diagnostics.

Diagnostics of secondary EMD lesions

In secondary EMD patients, EMD lesions were detected in 119 patients by skeletal survey, in 41 patients by MRI, in 21 patients by CT and in 12 by PET/CT. EMD involvement was also diagnosed by other methods, i.e. scintigraphy, ultrasonography, endoscopy or clinical evaluation. Findings of EMD lesions were confirmed by surgical sampling and histology evaluation, when clinically needed and safe for the patient.

Cytogenetics

Interphase fluorescent *in situ* hybridization (I-FISH) analysis was performed on separated PCs as previously described[12] at the time of MM diagnosis.

Statistics

Data were described by absolute and relative frequencies of categorical variables. Logistic regression analysis was used to assess the association of baseline characteristics at MM diagnosis with EMD occurrence in relapse. Differences in overall (OS) and progression-free (PFS) survival between patients with future EMD and RRMM group not evolving EMD according to line of therapy was computed by the Kaplan–Meier method and statistical significance of differences in survival among subgroups was assessed using the log-rank test. The same methodology was used for identification of secondary EMD as prognostic factor of survival in RRMM patients. Treatment response was assessed according to the current International Myeloma Working Group (IMWG) criteria.[15] Independence of secondary EMD as a prognostic survival factor was verified in a multivariable Cox proportional hazard model in context of other well-known prognostic

factors. All statistical tests were performed at a significance level of $\alpha = 0{\cdot}05$ (all tests two-sided). Analysis was performed in the SPSS software (release 2017: IBM SPSS Statistics for Windows, Version 25·0·0·1; IBM Corp. Armonk, NY, USA) and R version 4·0·1. (www.r-project.org).

Results

Clinical features associated with secondary EMD development

Clinical characteristics at the time of MM diagnosis of both secondary EMD patients as well as reference MM patients are summarized in Table I. We compared these groups and identified associations between clinical, laboratory and cytogenetic features at MM diagnosis and risk for subsequent development of EMD (Fig 1).

In younger NDMM patients (<65 years), there was a significantly higher risk of secondary EMD development [odds ratio (OR) 4·38; 95% confidence interval (CI): 2·46–7·80, $P < 0{\cdot}0001$). Moreover, NDMM patients who developed secondary EMD had significantly higher LDH levels (>5 μkat/l; OR 2·07, 95% CI: 1·51–2·84, $P < 0{\cdot}0001$), more than two osteolytic lesions diagnosed by skeletal survey (OR 2·21, 95% CI: 1·54–3·15, $P < 0{\cdot}001$), hypercalcaemia (>2·65 mmol/l; OR 1·71, 95% CI: 1·21–2·42, $P = 0{\cdot}002$) and IgA M-protein type (OR 1·53, 95% CI: 1·11–2·11, $P = 0{\cdot}009$) or the non-secretory type of MM (OR 2·83, 95% CI: 1·32–6·04, $P = 0{\cdot}007$).

In NDMM patients who subsequently developed secondary EMD, there were significant differences in the presence of del(13)(q14) (48·3% vs 78·2%, $P < 0{\cdot}001$) and gain (1q21) (44·2% vs 71·4%, $P < 0{\cdot}001$). While other aberrations were analyzed, they were not statistically significant. Detailed results of I-FISH analysis are shown in Table SI.

Survival of MM patients before secondary EMD development

We compared survival intervals of MM patients with secondary EMD involvement in the next relapse/progression with patients without any EMD involvement in the future. We analyzed survival from the start of the first line of treatment according to the state of EMD in the second line based on a condition that both groups had to initiate the second line of treatment. Patients who developed EMD in the third or higher lines were not included in this calculation. We proceeded analogously for survival from the second and third lines of therapy (Fig 2).

NDMM patients. NDMM patients who subsequently developed EMD had significantly shorter median PFS, when compared to NDMM patients without future EMD involvement (13·8 months, 95% CI: 11·4–16·3 vs 18·8 months, 95% CI: 17·7–19·9; $P = 0{\cdot}006$). Median OS was significantly shorter in NDMM patients who subsequently developed secondary EMD when compared to NDMM patients without any future EMD involvement (26·7 months, 95% CI: 18·1–35·4 vs 58·7 months, 95% CI: 54·8–62·6; $P < 0{\cdot}001$).

RRMM patients after one previous treatment line. RRMM patients who developed EMD in the next disease progression and RRMM patients without future EMD involvement had comparable median PFS (10·1 months, 95% CI: 8·1–12·0 vs 12·1 months, 95% CI: 11·3–12·8; $P = 0{\cdot}558$). Median OS was significantly shorter in RRMM patients who developed EMD when compared to RRMM without any future EMD involvement (28·6 months, 95% CI: 21·1–36·0 vs 41·0 months, 95% CI: 38·0–43·9; $P = 0{\cdot}006$).

RRMM patients after two previous treatment lines. RRMM patients after two previous treatment lines who developed EMD in the next disease progression and RMMM patients without future EMD involvement had comparable median PFS (9·4 months, 95% CI: 6·1–12·8 vs 9·7 months, 95% CI: 8·8–10·5; $P = 0{\cdot}510$). While there was trend toward worse OS between RRMM patients who developed EMD and RRMM patients who did not (17·8 months, 95% CI: 9·3–26·3 vs 31·1 months, 95% CI: 27·8–34·5; $P = 0{\cdot}158$), these results were not statistically significant.

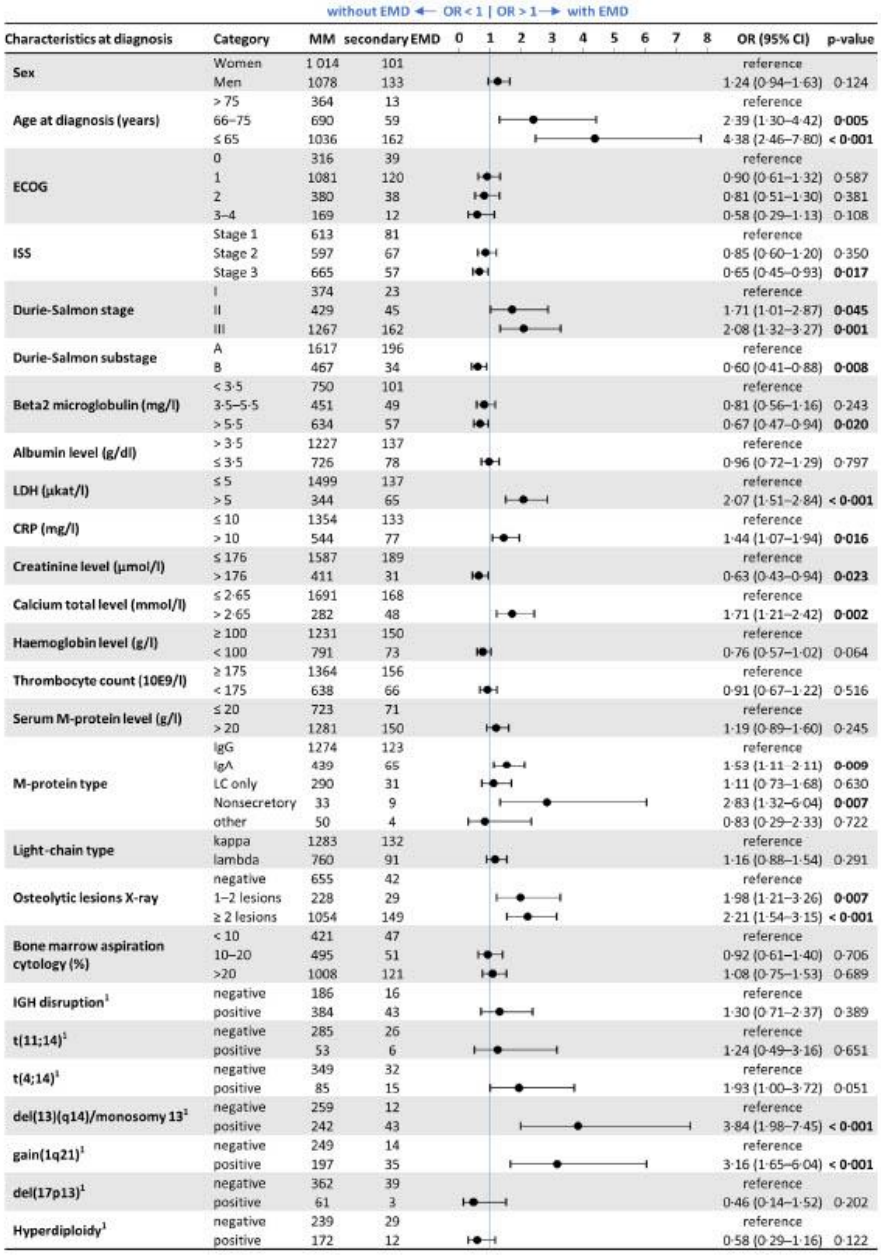
Survival after the secondary EMD development

Multivariate analysis showed secondary EMD as an independent risk factor for PFS [hazard ratio (HR) 1·39, 95% CI: 1·06–1·81, $P = 0{\cdot}016$] and OS (HR 1·61, 95% CI: 1·20–2·15, $P = 0{\cdot}001$) of RRMM patients. From the time of secondary EMD diagnosis, median PFS was 4·7 months (95% CI: 3·5-5·8) and median OS was 8·6 months (95% CI: 6·3-11·0).

Discussion

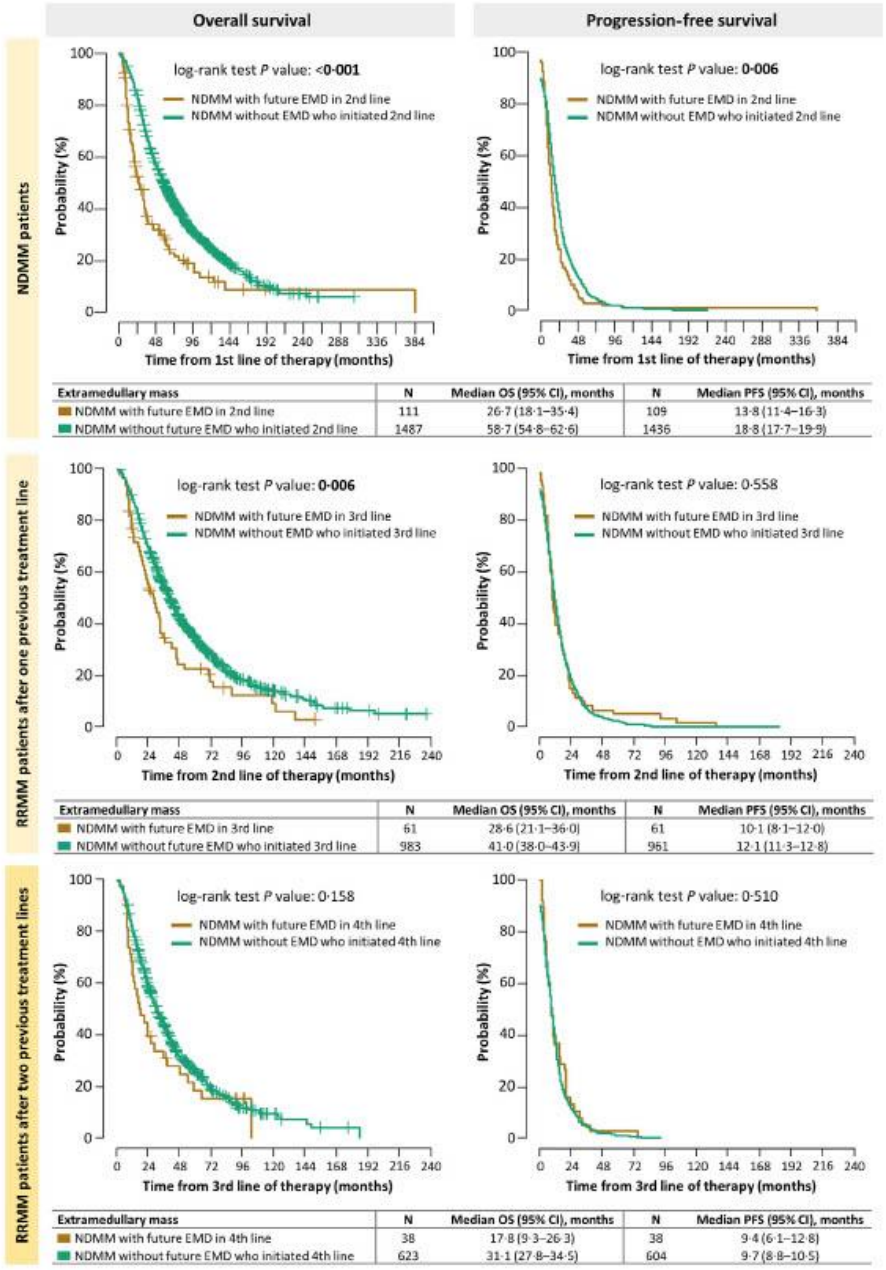
As a result of remarkable progress in the treatment of MM, it is slowly turning into a chronic disease. Due to the widespread use of new drugs, better treatment results are achieved even at MM relapse. In case of relapsed or even refractory MM patients, the disease may become stabilized several times.[1,4,16–19]

At the same time, extramedullary myeloma is still a challenge even in the era of new drugs. Especially, secondary EMD is a hard-to-treat entity associated with poor prognosis.[7,13] Standard widespread treatment protocols for RRMM patients based on bortezomib, lenalidomide or pomalidomide do not significantly improve prognosis of secondary EMD.[20–24] There are only limited data for the second-generation PI carfilzomib in this patient population. Case reports and analyses of small cohorts showed unsatisfactory results, far worse than in non-EMD patients.[25–28] Similarly, ixazomib did not show significant improvement of secondary EMD prognosis in real-life analysis.[29] Anti-CD38 antibodies (daratumumab, isatuximab) have not overcome poor prognosis of secondary EMD, possibly due to low expression of the CD38 surface antigen in EMD PCs.[30,31] A much lower



Characteristics at diagnosis	Category	MM	secondary EMD	OR (95% CI)	p-value
Sex	Women	1 014	101	reference	
	Men	1078	133	1·24 (0·94–1·63)	0·124
Age at diagnosis (years)	> 75	364	13	reference	
	66–75	690	59	2·39 (1·30–4·42)	**0·005**
	≤ 65	1036	162	4·38 (2·46–7·80)	**< 0·001**
ECOG	0	316	39	reference	
	1	1081	120	0·90 (0·61–1·32)	0·587
	2	380	38	0·81 (0·51–1·30)	0·381
	3–4	169	12	0·58 (0·29–1·13)	0·108
ISS	Stage 1	613	81	reference	
	Stage 2	597	67	0·85 (0·60–1·20)	0·350
	Stage 3	665	57	0·65 (0·45–0·93)	**0·017**
Durie-Salmon stage	I	374	23	reference	
	II	429	45	1·71 (1·01–2·87)	**0·045**
	III	1267	162	2·08 (1·32–3·27)	**0·001**
Durie-Salmon substage	A	1617	196	reference	
	B	467	34	0·60 (0·41–0·88)	**0·008**
Beta2 microglobulin (mg/l)	< 3·5	750	101	reference	
	3·5–5·5	451	49	0·81 (0·56–1·16)	0·243
	> 5·5	634	57	0·67 (0·47–0·94)	**0·020**
Albumin level (g/dl)	> 3·5	1227	137	reference	
	≤ 3·5	726	78	0·96 (0·72–1·29)	0·797
LDH (µkat/l)	≤ 5	1499	137	reference	
	> 5	344	65	2·07 (1·51–2·84)	**< 0·001**
CRP (mg/l)	≤ 10	1354	133	reference	
	> 10	544	77	1·44 (1·07–1·94)	**0·016**
Creatinine level (µmol/l)	≤ 176	1587	189	reference	
	> 176	411	31	0·63 (0·43–0·94)	**0·023**
Calcium total level (mmol/l)	≤ 2·65	1691	168	reference	
	> 2·65	282	48	1·71 (1·21–2·42)	**0·002**
Haemoglobin level (g/l)	≥ 100	1231	150	reference	
	< 100	791	73	0·76 (0·57–1·02)	0·064
Thrombocyte count (10E9/l)	≥ 175	1364	156	reference	
	< 175	638	66	0·91 (0·67–1·22)	0·516
Serum M-protein level (g/l)	≤ 20	723	71	reference	
	> 20	1281	150	1·19 (0·89–1·60)	0·245
M-protein type	IgG	1274	123	reference	
	IgA	439	65	1·53 (1·11–2·11)	**0·009**
	LC only	290	31	1·11 (0·73–1·68)	0·630
	Nonsecretory	33	9	2·83 (1·32–6·04)	**0·007**
	other	50	4	0·83 (0·29–2·33)	0·722
Light-chain type	kappa	1283	132	reference	
	lambda	760	91	1·16 (0·88–1·54)	0·291
Osteolytic lesions X-ray	negative	655	42	reference	
	1–2 lesions	228	29	1·98 (1·21–3·26)	**0·007**
	≥ 2 lesions	1054	149	2·21 (1·54–3·15)	**< 0·001**
Bone marrow aspiration cytology (%)	< 10	421	47	reference	
	10–20	495	51	0·92 (0·61–1·40)	0·706
	>20	1008	121	1·08 (0·75–1·53)	0·689
IGH disruption[1]	negative	186	16	reference	
	positive	384	43	1·30 (0·71–2·37)	0·389
t(11;14)[1]	negative	285	26	reference	
	positive	53	6	1·24 (0·49–3·16)	0·651
t(4;14)[1]	negative	349	32	reference	
	positive	85	15	1·93 (1·00–3·72)	0·051
del(13)(q14)/monosomy 13[1]	negative	259	12	reference	
	positive	242	43	3·84 (1·98–7·45)	**< 0·001**
gain(1q21)[1]	negative	249	14	reference	
	positive	197	35	3·16 (1·65–6·04)	**< 0·001**
del(17p13)[1]	negative	362	39	reference	
	positive	61	3	0·46 (0·14–1·52)	0·202
Hyperdiploidy[1]	negative	239	29	reference	
	positive	172	12	0·58 (0·29–1·16)	0·122

Fig 1. Clinical features measured at diagnosis in multiple myeloma (MM) and secondary extramedullary multiple myeloma (EMD) patients. CI, confidence interval; CRP, C-reactive protein; ECOG, Eastern Cooperative Oncology Group; IGH, immunoglobulin heavy chain; ISS, International Staging System; LDH, lactate dehydrogenase; OR, overall response. [Colour figure can be viewed at wileyonlinelibrary.com]



Extramedullary mass	N	Median OS (95% CI), months	N	Median PFS (95% CI), months
NDMM with future EMD in 2nd line	111	26·7 (18·1–35·4)	109	13·8 (11·4–16·3)
NDMM without future EMD who initiated 2nd line	1487	58·7 (54·8–62·6)	1436	18·8 (17·7–19·9)
NDMM with future EMD in 3rd line	61	28·6 (21·1–36·0)	61	10·1 (8·1–12·0)
NDMM without future EMD who initiated 3rd line	983	41·0 (38·0–43·9)	961	12·1 (11·3–12·8)
NDMM with future EMD in 4th line	38	17·8 (9·3–26·3)	38	9·4 (6·1–12·8)
NDMM without future EMD who initiated 4th line	623	31·1 (27·8–34·5)	604	9·7 (8·8–10·5)

Fig 2. Effect of future secondary extramedullary multiple myeloma (EMD) development on progression-free (PFS) and overall (OS) survival in separate treatment lines. CI, confidence interval; NDMM, newly diagnosed multiple myeloma; RRMM, as relapsed/refractory multiple myeloma. [Colour figure can be viewed at wileyonlinelibrary.com]

response rate was also shown in a subset of EMD patients treated with the anti-BCMA (B cell maturation antigen) drug conjugate belantamab.[32] Preliminary results of the peptide–drug conjugate melphalan flufenamide (melflufen) in a heavily pretreated cohort of secondary EMD patients seem promising, but longer follow-up is necessary.[33] In the current era of immunotherapy, promising results were achieved in several trials of BCMA-targeted CAR-T cells. The CAR-T cells had impressive results even in secondary EMD-S patients, resulting in longer remissions in some trials.[34–36]

Unfortunately, there are no current protocols for secondary EMD treatment.

For better understanding of development of secondary EMD, we identified 234 secondary EMD among almost 5 000 MM patients diagnosed in Czech haematologic centres from 2005 to 2017. To the best of our knowledge, this dataset is the largest in the world so far. With respect to our retrospective cohort and relatively low number of patients pretreated by both IMIDs and PIs, as a recently most frequent induction treatment regimen,[32,37–40] we found similar numbers of EMD patients as in recently published large clinical trials focusing on (PI + IMIDs)-exposed patients.[41,42] These results show PI and IMIDs do not induce EMD; we indirectly confirmed that fact in a much larger cohort of patients.[22] Moreover, similar numbers of EMD patients were found in previous analyses of heavily pretreated patients[21,22] when compared to recent clinical trials, focusing on triple or penta-refractory patients.[43–46] From those findings, we suppose that modern treatment regimens including a new generation of IMIDs, PI and monoclonal antibodies do not induce more EMD. Comparing length of previous treatment in different analyses and incidence of EMD, time of disease duration seems to play an important role in EMD development.[21] Thus, we focused on patient- and disease-related factors as the most important aspects in EMD development.

In our analysis, younger age, extensive bone disease (numerous osteolytic lesions and hypercalcaemia), higher LDH and IgA or a non-secretory type of MM at the time of MM diagnosis were significantly associated with further development of secondary EMD. In similar studies, comparable results for younger age, type of monoclonal immunoglobulin and extensive bone disease were found.[21] In another analysis, hypercalcaemia was also confirmed as a risk factor for secondary EMD development.[22]

We found an increased presence of del(13)/monosomy13 and gain (1q21) at the time of MM diagnosis in patients with future secondary EMD. These results are in concordance with our previous results that showed increased presence of both aberrations at the time of EMD diagnosis both in primary and secondary EMD patients.[47] In other analyses, del (17p) was found to be the most frequent cytogenetic aberration in EMD patients, both in BM and in the extramedullary tumour site.[48–50] We did not observe a higher incidence of del (17p) or other tested aberrations in patients with future EMD development. Possibly, subsequent acquisition of del (17p) in the disease course, influencing secondary EMD development, occurs.[51,52] However, with respect to the low number of analyzed EMD samples in our study, more robust cytogenetic analyses need to be performed.

In our study, NDMM patients before EMD development had significantly inferior median PFS when compared to NDMM patients who never developed EMD. We presume that NDMM patients who progress to EMD early have a specific and more aggressive disease from the onset of MM. A similar situation was described in NDMM patients with high-risk cytogenetics when the disease course was impaired from the beginning.[53,54] While EMD pathogenesis has not been clarified yet, there may be a hidden molecular mechanism affecting disease course before EMD is revealed. Thus, these patients subsequently manifest with extramedullary involvement, leading to further disease escalation and early death.

Surprisingly, more advanced RRMM patients who developed EMD in the further disease course had comparable treatment outcomes as reference RRMM patients who never developed EMD. However, like in NDMM patients with EMD progression, their prognosis dramatically changed with EMD development.[6]

These clinical observations may be explained by more sudden changes in the MM clone leading to EMD involvement in advanced MM patients.[55] As previously described, treatment-related factors do not seem to be involved in EMD development.[21] Another explanation may be a sudden loss of balance between different subclones leading to expansion of an aggressive clone, independent of the BM environment.[56] Unfortunately, mechanisms leading to these changes in secondary EMD patients remain unknown. Regardless of the time of the secondary EMD development, patients' outcomes remain poor.[6]

A clear limitation of our analysis was the low number of highly sensitivity diagnostic methods such as PET/CT or whole-body MRI. These limitations arise from the retrospective character of this study and time of our data collection during which access to these diagnostic methods dramatically changed.[9,57–59] In our study, the most frequent diagnostic method was X-ray, what clearly could lead to bias from undetected small EMD-B or asymptomatic EMD-S lesions.[9] On the other hand, incidence of secondary EMD in our cohort was comparable to that in the longitudinal real-life study (1971–2007) published by Varettoni *et al.*[6] In a newer study, only 3% of secondary EMD were found threenyears after MM diagnosis.[23] A similar incidence of secondary EMD (3–7%) within five years from the diagnosis was found by the Arkansas group while using PET/CT in diagnostic work-up.[11] Taken together, according to recent recommendations, PET/CT or whole-body MRI clearly reveals more EMD patients due to their well-defined sensitivity.[9,57] In our study, the approach based on combining basic diagnostic methods according to patient's symptoms had acceptable results.

Despite the absence of clearly defined data from dinical trials, an aggressive treatment approach to EMD patients is

generally accepted.[60,61] Using high-sensitive diagnostic methods, describing clinical features of MM patients at high risk of EMD development may lead to closer follow-up. We believe that a future focus on the pre-EMD period may lead to improvement of the poor prognosis of these patients. More clinical and molecular analyses should be performed to identify the optimal treatment approach.

Conclusion

We found that MM patients with future EMD development show specific features (younger age, extensive bone disease, IgA, or non-secretory type of MM) which are present already at the time of MM diagnosis. In NDMM patients, secondary EMD developed shortly after MM diagnosis, showing the aggressive disease pattern from the beginning. In more pretreated MM patients, disease course before secondary EMD development was similar to that in other MM patients. After a yet unknown event, EMD occurs probably as a terminal event in MM evolution. Regardless of time, when PCs lose their dependence on the BM microenvironment, there is an absolute turnover of the disease course, leading to early death. We confirmed secondary EMD development as a strong independent negative prognostic factor in MM.

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Authors contribution

MS, SS and LP designed the study. PK, JR, IS, JS, PP, AJ, TJ, VS, VM and RH performed research. MS, SS, LP and JM cowrote the paper. LP, LB and JJ analyzed data. All authors critically reviewed and approved the manuscript.

Institutional review board statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Ethics Committee of the University Hospital Brno, Czech Republic (2016).

Informed consent statement

Informed consent was obtained from all subjects involved in the study.

Conflicts of interest

The authors declare to have no conflicts of interest. The funders had no role in the design of the investigation, in the collection, analyses or interpretation of data, in the writing of the manuscript or in the decision to publish the results".

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table SI. Cytogenetic aberrations at the time of MM diagnosis (MM *versus* secondary EMD patients).

References

1. Kumar SK, Rajkumar V, Kyle RA, van Duin M, Sonneveld P, Mateos M-V, et al. Multiple myeloma. *Nat Rev Dis Primers*. 2017;3:nrdp201746.
2. Malúšková D, Svobodová I, Kučerová M, Brožová L, Mužík J, Jarkovský J, et al. Epidemiology of multiple myeloma in the Czech Republic. *Klin Onkol*. 2017;30(Suppl 2):35–42.
3. Sant M, Allemani C, Tereanu C, De Angelis R, Capocaccia R, Visser O, et al. Incidence of hematologic malignancies in Europe by morphologic subtype: results of the HAEMACARE project. *Blood*. 2010;116(19):3724–34.
4. Morgan GJ, Rasche L. Haematological cancer: where are we now with the treatment of multiple myeloma? *Nat Rev Clin Oncol*. 2017;14(8):461–2.
5. Sevcikova S, Minarik J, Stork M, Jelinek T, Pour L, Hajek R. Extramedullary disease in multiple myeloma - controversies and future directions. *Blood Rev*. 2019;36:32–9.
6. Varettoni M, Corso A, Pica G, Mangiacavalli S, Pascutto C, Lazzarino M. Incidence, presenting features and outcome of extramedullary disease in multiple myeloma: a longitudinal study on 1003 consecutive patients. *Ann Oncol*. 2010;21(2):325–30.
7. Pour L, Sevcikova S, Greslikova H, Kupska R, Majkova P, Zahradova L, et al. Soft-tissue extramedullary multiple myeloma prognosis is significantly worse in comparison to bone-related extramedullary relapse. *Haematologica*. 2014;99(2):360–4.
8. Zamagni E, Patriarca F, Nanni C, Zannetti B, Englaro E, Pezzi A, et al. Prognostic relevance of 18-F FDG PET/CT in newly diagnosed multiple myeloma patients treated with up-front autologous transplantation. *Blood*. 2011;118(23):5989–95.
9. Minarik J, Hrbek J, Pika T, Novak M, Bacovsky J, Heman M, et al. X-ray in multiple myeloma - not a golden standard any more: case series. *J Bone Marrow Res*. 2014;02.
10. Menu E, Asosingh K, Indraccolo S, Raeve HD, Riet IV, Valckenborgh EV, et al. The involvement of stromal derived factor 1alpha in homing and progression of multiple myeloma in the 5TMM model. *Haematologica*. 2006;91(5):605–12.
11. Usmani SZ, Heuck C, Mitchell A, Szymonifka J, Nair B, Hoering A, et al. Extramedullary disease portends poor prognosis in multiple myeloma and is over-represented in high-risk disease even in the era of novel agents. *Haematologica*. 2012;97(11):1761–7.
12. Besse L, Sedlarikova L, Greslikova H, Kupska R, Almasi M, Penka M, et al. Cytogenetics in multiple myeloma patients progressing into extramedullary disease. *Eur J Haematol*. 2016;97(1):93–100.
13. Beksac M, Seval GC, Kanellias N, Coriu D, Rosiñol L, Ozet G, et al. A real world multicenter retrospective study on extramedullary disease from Balkan Myeloma Study Group and Barcelona University: analysis of parameters that improve outcome. *Haematologica*. 2020;105(1):201–8.
14. Montefusco V, Gay F, Spada S, De Paoli L, Di Raimondo F, Ribolla R, et al. Outcome of paraosseous extra-medullary disease in newly diagnosed multiple myeloma patients treated with new drugs. *Haematologica*. 2020;105(1):193–200.
15. Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos M-V, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol*. 2014;15(12):e538–48.

16. Dimopoulos MA, Oriol A, Nahi H, San-Miguel J, Bahlis NJ, Usmani SZ, et al. Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma. *N Engl J Med*. 2016;375(14):1319–31.
17. Dimopoulos MA, Dytfeld D, Grosicki S, Moreau P, Takezako N, Hori M, et al. Elotuzumab plus Pomalidomide and Dexamethasone for Multiple Myeloma. *N Engl J Med*. 2018;379(19):1811–22.
18. Richardson PG, Attal M, Rajkumar SV, San Miguel J, Beksac M, Spicka I, et al. A phase III randomized, open label, multicenter study comparing isatuximab, pomalidomide, and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed/refractory multiple myeloma (RRMM). *J Clin Oncol*. 2019;37(Suppl 15):8004.
19. Chari A, Martinez-Lopez J, Mateos M-V, Bladé J, Benboubker L, Oriol A, et al. Daratumumab plus carfilzomib and dexamethasone in patients with relapsed or refractory multiple myeloma. *Blood*. 2019;134(5):421–31.
20. Laura R, Cibeira MT, Uriburu C, Yantorno S, Salamero O, Blade J, et al. Bortezomib: an effective agent in extramedullary disease in multiple myeloma. *Eur J Haematol*. 2006;76(5):405–8.
21. Mangiacavalli S, Pompa A, Ferretti V, Klersy C, Cocito F, Varettoni M, et al. The possible role of burden of therapy on the risk of myeloma extramedullary spread. *Ann Hematol*. 2017;96(1):73–80.
22. Varga C, Xie W, Laubach J, Ghobrial IM, O'Donnell EK, Weinstock M, et al. Development of extramedullary myeloma in the era of novel agents: no evidence of increased risk with lenalidomide–bortezomib combinations. *Br J Haematol*. 2015;169(6):843–50. Available from: http://www.readcube.com/articles/ https://doi.org/10.1111/bjh.13382
23. Short KD, Rajkumar SV, Larson D, Buadi F, Hayman S, Dispenzieri A, et al. Incidence of extramedullary disease in patients with multiple myeloma in the era of novel therapy, and the activity of pomalidomide on extramedullary myeloma. *Leukemia*. 2011;25(6):906–8.
24. Jiménez-Segura R, Granell M, Gironella M, Abella E, García-Guiñón A, Oriol A, et al. Pomalidomide-dexamethasone for treatment of soft-tissue plasmacytomas in patients with relapsed/refractory multiple myeloma. *Eur J Haematol*. 2019;102(5):389–94.
25. Zhou X, Flüchter P, Nickel K, Meckel K, Messerschmidt J, Böckle D, et al. Carfilzomib based treatment strategies in the management of relapsed/refractory multiple myeloma with extramedullary disease. *Cancers*. 2020;12(4):1035.
26. Español I, Romera M, Gutiérrez-Meca MD, García MDC, Tejedor A, Martínez A, et al. Carfilzomib and dexamethasone for extramedullary myeloma with pleuropericardial involvement. *Clin Case Rep*. 2017;5(8):1258–60.
27. Atalay F. The use of carfilzomib to treat extramedullary plasmacytoma and review of the literature [Internet]. 2020 [cited 2021 Sep 27]. Available from: https://www.jahjournal.org/article.asp?issn=1658-5127;year=2020;volume=11;issue=2;spage=74;epage=76;aulast=Atalay
28. Siegel DS, Dimopoulos MA, Ludwig H, Facon T, Goldschmidt H, Jakubowiak A, et al. Improvement in overall survival with carfilzomib, lenalidomide, and dexamethasone in patients with relapsed or refractory multiple myeloma. *J Clin Oncol*. 2018;36(8):728–34.
29. Minarik J, Pika T, Radocha J, Jungova A, Straub J, Jelinek T, et al. Survival benefit of ixazomib, lenalidomide and dexamethasone (IRD) over lenalidomide and dexamethasone (Rd) in relapsed and refractory multiple myeloma patients in routine clinical practice. *BMC Cancer*. 2021;21(1):73.
30. Jelinek T, Sevcikova T, Zihala D, Popkova T, Kapustova V, Broskevicova L, et al. Limited efficacy of daratumumab in multiple myeloma with extramedullary disease. *Leukemia*. 2021;1–4. Online ahead of print. https://doi.org/10.1038/s41375-021-01343-w
31. Beksac M, Richardson PG, Unal A, Corradini P, DeLimpasi S, Gulbas Z, et al. Isatuximab Plus Pomalidomide and Dexamethasone in Patients with Relapsed/Refractory Multiple Myeloma and Soft-Tissue Plasmacytomas: Icaria-MM Subgroup Analysis. In ASH; 2020 [cited 2021 Sep 27]. Available from: https://ash.confex.com/ash/2020/webprogram/Paper134727.html
32. Lonial S, Lee HC, Badros A, Trudel S, Nooka AK, Chari A, et al. Longer term outcomes with single-agent belantamab mafodotin in patients with relapsed or refractory multiple myeloma: 13-month follow-up from the pivotal DREAMM-2 study. *Cancer* [Internet]. 2021 [cited 2021 Sep 27];n/a(n/a). Available from: https://onlinelibrary.wiley.com/doi/abs/ https://doi.org/10.1002/cncr.33809
33. Richardson PG, Mateos M-V, Oriol A, Larocca A, Cavo M, Rodríguez-Otero P, et al. MM-186: HORIZON (OP-106): Melflufen Plus Dexamethasone in 55 Patients with Relapsed/Refractory Multiple Myeloma (RRMM) with Extramedullary Disease (EMD): subgroup analysis. *Clin Lymphoma Myeloma Leuk*. 2021;21:S427.
34. Wang DI, Wang J, Hu G, Wang W, Xiao YI, Cai H, et al. A phase 1 study of a novel fully human BCMA-targeting CAR (CT103A) in patients with relapsed/refractory multiple myeloma. *Blood*. 2021;137(21):2890–901.
35. Raje NS, Siegel DS, Jagannath S, Lonial S, Munshi NC, Moreau P, et al. Idecabtagene Vicleucel (ide-cel, bb2121) in relapsed and refractory multiple myeloma: analyses of high-risk subgroups in the KarMMa study. *Blood*. 2020;136(Suppl 1):37–8.
36. Deng H, Liu M, Yuan T, Zhang H, Cui R, Li J, et al. Efficacy of humanized anti-BCMA CAR T cell therapy in relapsed/refractory multiple myeloma patients with and without extramedullary disease. *Front Immunol*. 2021;12:3050.
37. Gay F, Cerrato C, Petrucci MT, Zambello R, Gamberi B, Ballanti S, et al. Efficacy of carfilzomib lenalidomide dexamethasone (KRd) with or without transplantation in newly diagnosed myeloma according to risk status: results from the FORTE trial. *J Clin Oncol*. 2019;37(Suppl 15):8002.
38. Cavo M, Pantani L, Pezzi A, Petrucci MT, Patriarca F, Di Raimondo F, et al. Bortezomib-thalidomide-dexamethasone (VTD) is superior to bortezomib-cyclophosphamide-dexamethasone (VCD) as induction therapy prior to autologous stem cell transplantation in multiple myeloma. *Leukemia*. 2015;29(12):2429–31.
39. Moreau P, Hulin C, Macro M, Caillot D, Chaleteix C, Roussel M, et al. VTD is superior to VCD prior to intensive therapy in multiple myeloma: results of the prospective IFM2013-04 trial. *Blood*. 2016;127(21):2569–74.
40. Durie BGM, Hoering A, Abidi MH, Rajkumar SV, Epstein J, Kaharic SP, et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. *Lancet*. 2017;389(10068):519–27.
41. Richardson PG, Oriol A, Beksac M, Liberati AM, Galli M, Schjesvold F, et al. Pomalidomide, bortezomib, and dexamethasone for patients with relapsed or refractory multiple myeloma previously treated with lenalidomide (OPTIMISMM): a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2019;20(6):781–94.
42. Attal M, Richardson PG, Rajkumar SV, San-Miguel J, Beksac M, Spicka I, et al. Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): a randomised, multicentre, open-label, phase 3 study. *Lancet*. 2019;394(10214):2096–107.
43. Lonial S, Lee HC, Badros A, Trudel S, Nooka AK, Chari A, et al. Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2): a two-arm, randomised, open-label, phase 2 study. *Lancet Oncol*. 2020;21(2):207–21.
44. Richardson PG, Bringhen S, Voorhees P, Plesner T, Mellqvist U-H, Reeves B, et al. Melflufen plus dexamethasone in relapsed and refractory multiple myeloma (O-12-M1): a multicentre, international, open-label, phase 1–2 study. *Lancet Haematol*. 2020;7(5):e395–407.
45. Cohen AD, Garfall AL, Stadtmauer EA, Melenhorst JJ, Lacey SF, Lancaster E, et al. B cell maturation antigen–specific CAR T cells are clinically active in multiple myeloma. *J Clin Invest*. 2019;129(6):2210–21.
46. Berdeja JG, Madduri D, Usmani SZ, Jakubowiak A, Agha M, Cohen AD, et al. Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study. *Lancet*. 2021;398(10297):314–24.
47. Besse L, Sedlarikova L, Kryukov F, Nekvindova J, Radova L, Slaby O, et al. Circulating serum microRNA-130a as a novel putative marker of extramedullary myeloma. *PLoS One*. 2015;10(9):e0137294.

48. Billecke L, Murga Penas EM, May AM, Engelhardt M, Nagler A, Leiba M, et al. Cytogenetics of extramedullary manifestations in multiple myeloma. *Br J Haematol*. 2013;161(1):87–94.
49. Gozzetti A, Cerase A, Lotti F, Rossi D, Palumbo A, Petrucci MT, et al. Extramedullary intracranial localization of multiple myeloma and treatment with novel agents: a retrospective survey of 50 patients. *Cancer*. 2012;118(6):1574–84.
50. Deng S, Xu Y, An G, Sui W, Zou D, Zhao Y, et al. Features of extramedullary disease of multiple myeloma: high frequency of P53 deletion and poor survival: a retrospective single-center study of 834 cases. *Clin Lymphoma Myeloma Leuk*. 2015;15(5):286–91.
51. López-Anglada L, Gutiérrez NC, García JL, Mateos MV, Flores T, San Miguel JF. P53 deletion may drive the clinical evolution and treatment response in multiple myeloma. *Eur J Haematol*. 2010;84(4):359–61.
52. Hebraud B, Magrangeas F, Cleynen A, Lauwers-Cances V, Chretien M-L, Hulin C, et al. Role of additional chromosomal changes in the prognostic value of t(4;14) and del(17p) in multiple myeloma: the IFM experience. *Blood*. 2015;125(13):2095–100.
53. Rajkumar SV. Updated diagnostic criteria and staging system for multiple myeloma. *Am Soc Clin Oncol Educ Book*. 2016;36:e418–23.
54. Sonneveld P, Avet-Loiseau H, Lonial S, Usmani S, Siegel D, Anderson KC, et al. Treatment of multiple myeloma with high-risk cytogenetics: a consensus of the International Myeloma Working Group. *Blood*. 2016;127(24):2955–62.
55. Neuse CJ, Lomas OC, Schliemann C, Shen YJ, Manier S, Bustoros M, et al. Genome instability in multiple myeloma. *Leukemia*. 2020;34(11):2887–97.
56. Keats JJ, Chesi M, Egan JB, Garbitt VM, Palmer SE, Braggio E, et al. Clonal competition with alternating dominance in multiple myeloma. *Blood*. 2012;120(5):1067–76.
57. Zamagni E, Tacchetti P, Cavo M. Imaging in multiple myeloma: How? When? *Blood*. 2019;133(7):644–51.
58. Dimopoulos M, Terpos E, Comenzo RL, Tosi P, Beksac M, Sezer O, et al. International myeloma working group consensus statement and guidelines regarding the current role of imaging techniques in the diagnosis and monitoring of multiple Myeloma. *Leukemia*. 2009;23(9):1545–56.
59. Zamagni E, Nanni C, Dozza L, Carlier T, Bailly C, Tacchetti P, et al. Standardization of 18F-FDG–PET/CT according to deauville criteria for metabolic complete response definition in newly diagnosed multiple myeloma. *J Clin Oncol*. 2021;39(2):116–25.
60. Touzeau C, Moreau P. How I treat extramedullary myeloma. *Blood*. 2016;127(8):971–6.
61. Gagelmann N, Eikema D-J, Koster L, Caillot D, Picitelli P, Lleonart JB, et al. Tandem autologous stem cell transplantation improves outcomes in newly diagnosed multiple myeloma with extramedullary disease and high-risk cytogenetics: a study from the chronic malignancies working party of the European society for blood and marrow transplantation. *Biol Blood Marrow Transplant*. 2019;25(11):2134–42.

2.7.2. Stork M, Ondrouskova E, Bohunova M, Boichuk I, Fric D, Adam Z, Krejci M, Sandecka V, Knechtova Z, Radova L, Jelinkova Z, Adlerova T, Krticka M, Nekuda V, Borsky M, Sevcikova S, Jarosova M, Pour L. **Del(1p32) is an early and high-risk event in multiple myeloma patients with extraosseous disease.** Blood Cancer J. 2024;14(1):146.

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Del(1p32) is an early and high-risk event in multiple myeloma patients with extraosseous disease

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Dear Editor,

Considerable discussion surrounds the prognostic relevance of chromosome 1 aberrations in multiple myeloma (MM), from which most important are gains of 1q21 region and deletions of 1p32 locus [1]. Approximately 10–40% of MM patients develop extraosseous disease (EMM), where plasma cells outside of the bone marrow form tumors called plasmacytomas. Patients with EMM found at disease onset (primary EMM) represent a challenge due to a high risk of relapse and shorter survival. Patients developing plasmacytomas during therapy (secondary EMM) often experience an aggressive disease course, characterized by treatment resistance and early mortality. The exact mechanism of EMM development is not well known, but acquiring genetic alterations is one of the important hallmarks in clonal evolution, leading to EMM spread [2, 3]. Thus, we conducted a detailed evaluation of the distribution and clonal heterogeneity of chromosome 1 aberrations using paired samples from bone marrow and plasmacytoma tissue plasma cells. To assess the broader applicability of our findings, we performed a population-based cytogenetic analysis encompassing both EMM patients and a control cohort of MM patients without a history of EMM.

In twenty-two MM patients, who were diagnosed with EMM between 2022 and 2024 at the University Hospital Brno, a paired sampling of sorted bone marrow plasma cells (BMPCs) and plasmacytoma tissue plasma cells (TPCs) was performed. The interphase fluorescent in situ hybridization (I-FISH) analyses of commonly found aberrations were performed on sorted BMPCs or imprints of plasmacytoma tissue plasma cells (TPCs). Population cytogenetic data of EMM patients treated at the same site between 2015 and 2024 were retrospectively analyzed. During this period, a total of 1020 newly diagnosed multiple myeloma (NDMM) patients were identified at our institution. Among them, 16.3% (167/1020) of patients had a clear presence of EMM (primary EMM in 66.5% (111/167) and secondary EMM was identified in 33.5% of them (56/167)). For comparison, 243 NDMM patients without a history of EMM and with available cytogenetic data were used. Cytogenetics, clinical, and survival data of all primary EMM and control NDMM patients were evaluated from the time of diagnosis. For secondary EMM patients, data were evaluated from the onset of extraosseous plasmacytoma development. To present the cytogenetic findings, we organized them into two main categories reflecting key events in MM pathogenesis: primary events, which include hyperdiploidy (characterized by two or more trisomies of odd chromosomes) and translocations involving the IGH gene, and secondary events, which involve aberrations in chromosomes 1, 13, and 17 [4].

Description of patients' selection, methods, and statistical analysis is provided in a Supplementary data file.

In total, we assessed paired BMPCs and TPCs samples from 10 primary EMM and 12 secondary EMM cases. In all patients, as expected, the primary events were always shared between BMPCs and TPCs. Del(13q14)/monosomy of 13 was found in 72.7% (16/22) of patients and shared in 87.5% (14/16) of cases. Del(17p)/monosomy of 17 was found in 40.9% (9/22) of patients and it was shared in 44.4% (4/9) of cases. We found chromosome 1 aberrations in 90.9% (20/22) of EMM patients, more often in TPCs than BMPCs (86.4% (19/22) vs 68.2% (15/22)). Only 35.0% (7/20) of patients shared the same 1q21 aberrations between BMPCs and TPCs. The 1q21 aberrations present only in TPCs were found in 30.0% (6/20) of patients. The del(1p32) was in 31.8% (7/22) of patients, in 85.7% (6/7) cases shared between BMPCs and TPCs. We found del(1p32) exclusively in samples from secondary EMM patients. In 71.4% (5/7) of cases, del(1p32) was associated with 1q21 gains. All chromosomal aberrations in patients' BMPCs and TPCs are shown in Fig. 1. Plasmacytoma sites, survival, and other clinical characteristic of those patients are presented in Supplementary Fig. 1 and Supplementary Table 1. Fluorescence microscopy images of BMPC and TPC sub-clones are presented in Supplementary Fig. 2.

Evaluating the population cytogenetic data among patients with primary EMM, secondary EMM, and a control group of NDMM patients without EMM, we found a significant difference in the distribution of del(1p32). A higher proportion of del(1p32) was found in EMM patients, particularly among those with secondary EMM (20.7% (23/111) vs. 28.6% (16/56) vs. 11.1% (27/243); $p = 0.002$). Interestingly, in EMM patients, del(1p32) was significantly associated with 1q21 gains (12.6% (14/111) vs. 25.0% (14/56) vs. 6.2% (15/243); $p < 0.001$). The difference in the proportion of del(1p32) or del(1p32) with 1q21 gains was higher in secondary EMM but did not reach statistical significance (del(1p32) (28.6% (16/56) vs. 20.7% (23/111); $p = 0.33$) and del(1p32) + 1q21 gains (87.5% (14/16) vs. 60.9% (14/23); $p = 0.086$)). Furthermore, in secondary EMM patients, del(1p32) was more frequently observed in those with plasmacytoma found in soft tissues (extramedullary type, EMD) compared to those with plasmacytomas arising from the bone lesions (paraskeletal type, PS) (50.0% (8/16) vs. 20.0% (8/40); $p = 0.046$). Cytogenetics aberrations in all patients' groups are summarized in Table 1.

Thus, we evaluated the survival of EMM patients in the context of del(1p32) and 1q21 gains. For primary EMM patients with both del(1p32) and 1q21 gains, the median PFS was significantly reduced to 7.9 months (95% CI: 3.4–NA), compared to 16.6 months (95% CI: 10.8–NA) in patients with only del(1p32), and 40.2 months (95% CI: 21.9–NA) in patients without either aberration ($p = 0.003$). The median OS for patients with both del(1p32) and 1q21 gains was also significantly reduced, to 10.6 months (95% CI: 8.3–NA), compared to 28.0 months (95% CI: 22.7–NA) and 69.4 months (95% CI: 45.5–NA), respectively ($p = 0.03$). In secondary EMM patients with both del(1p32) and 1q21 gains, the median PFS was significantly shorter at 2.0 months (95% CI: 1.5–5.3), compared to 0.5 months (95% CI: 0.4–NA) in patients with only del(1p32) and 6.6 months (95% CI: 4.8–17.2) in patients without either aberration ($p < 0.001$). Similarly, a significant reduction in median OS was observed in secondary EMM patients with both del(1p32) and 1q21 gains, namely 2.7 months

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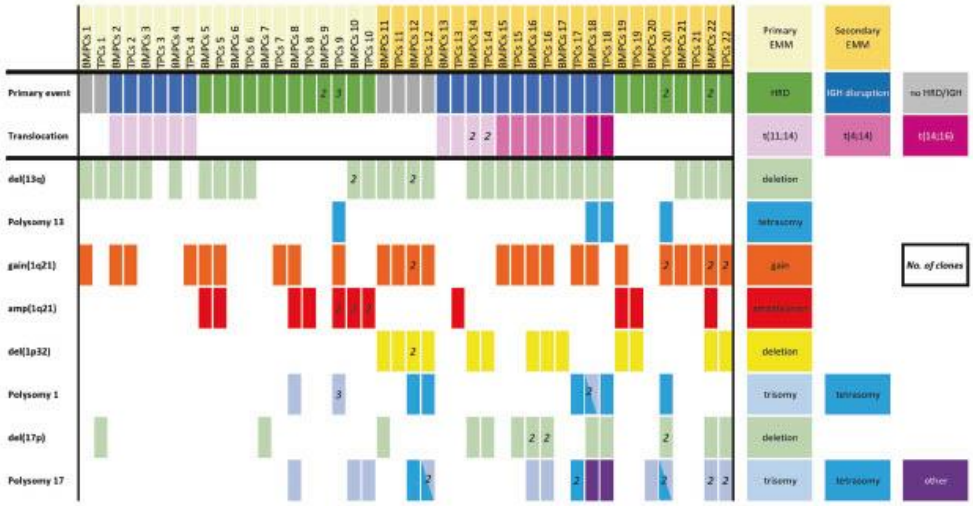

Fig. 1 Chromosomal aberrations visualized in individual patient's paired samples. BMPCs—bone marrow plasma cells. TPCs—plasmacytoma tissue plasma cells. HRD—hyperdiploidy. Numbers in boxes indicate the number of clones found for individual aberration.

Table 1. Cytogenetic data of patients' groups.

Category	NDMM without plasmacytoma ($N = 243$)	Primary EMM ($N = 111$)	Secondary EMM ($N = 56$)	p-value *
t (4;14)	9.1% (22/243)	9.9% (11/111)	14.3% (8/56)	0.499
t (14;16)	2.9% (7/243)	3.6% (4/111)	1.8% (1/56)	0.916
Del(13q14)/monosomy 13	54.7% (133/243)	56.8% (63/111)	69.6% (39/56)	0.124
Gain (1q21)	35.6% (84/243)	36.0% (40/111)	44.6% (25/56)	0.477
Amp (1q21)	12.3% (30/243)	12.6% (14/111)	16.1% (9/56)	0.477
Del (1p32)	11.1% (27/243)	20.7% (23/111)	28.6% (16/56)	**0.002**
Del (1p32) + 1q21	6.2% (15/243)	12.6% (14/111)	25.0% (14/56)	**<0.001**
Chromosome 1 polysomy	6.6% (16/243)	7.2% (8/111)	3.6% (2/56)	0.640
Del (17p)/monosomy 17	13.6% (33/243)	18.9% (21/111)	32.1% (18/56)	**0.004**
Chromosome 17 polysomy	15.6% (38/243)	18.9% (21/111)	14.3% (8/56)	0.653

*Fisher exact test. Bold values indicate statistically significant results

(95% CI: 1.9–8.9), compared to 1.7 months (95% CI: 0.6–NA) and 22.2 months (95% CI: 10.6–NA), respectively ($p < 0.001$).

Baseline clinical characteristics and survival data of primary and secondary EMM patients in the context of chromosome 1 aberrations are shown in Supplementary Tables 2, 3A, 3B and Supplementary Figs. 3 and 4.

In conclusion, we found chromosome 1 aberrations in nearly all our paired samples with a slightly higher incidence in plasmacytoma tissue rather than bone marrow compartment. Moreover, we encountered very high intra-patient heterogeneity in the 1q21 region between BMPCs and TPCs samples. Our findings were in accord with other studies investigating plasmacytoma tissue samples, reporting the comparable prevalence and variability of these aberrations, with respect to the different detection limits of FISH analyses [5–8]. According to these findings, 1q21 gains appear to be a rather later event or aberration undergoing significant evolutionary changes within cancer cell lines [9]. Our findings regarding del(17p) revealed a shared pattern between BMPCs and TPCs in less than half of the samples bearing this aberration. Similar to 1q21 gains, del(17p) may represent a later event in EMM development [6–8].

The strong negative prognostic impact of del(1p32) in MM patients has been repeatedly confirmed [10, 11], and it is more pronounced in biallelic deletions or in combination with other high-risk aberrations, such as t(4;14), 1q21 gains or del(17p) [11]. Our results are consistent with these findings, highlighting the surprising association of this aberration with EMM patients. The highest incidence of del(1p32) along with 1q21 gains was observed in patients with secondary EMM, known for their poor prognosis [12]. The prognostic impact of these two aberrations combined was more severe across EMM patients than that of del(1p32) or 1q21 gains alone. Unfortunately, we were unable to detect biallelic deletions of 1p32 using I-FISH. These ultra-high-risk aberrations are rare, occurring in approximately 2% of cases. Other methods, such as single-nucleotide polymorphism arrays or next-generation sequencing, may be more effective in detecting them [11].

In the analysis of paired samples, deletions of 1p32 were found exclusively in secondary EMM patients, consistent with the population data mentioned above. Moreover, we observed this aberration more frequently in patients with EMD plasmacytomas. This coincidence may indicate a relation between del(1p32) and this aggressive entity [12]. The deletions of 1p32 were shared between bone marrow and plasmacytoma tissue in almost all cases. Shared deletions of 1p32 were also shown in the work of Liu Y et al. [7]. Compared to aberrations in the 1q21 region or TP53

deletions, our observation suggests that del(1p32) is likely a more conservative high-risk event in the clonal evolution and may play an important role in the initial stages of extraosseous disease development. Based on our results, we strongly recommend including the detection of del(1p32) alongside 1q21 gains in the standard prognostic assessment for MM patients.

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DATA AVAILABILITY

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

REFERENCES

1. Neupane K, Fortuna GG, Dahal R, Schmidt TM, Fonseca R, Chakraborty R, et al. Alterations in chromosome 1q in multiple myeloma randomized clinical trials: a systematic review. Blood Cancer J. 2024;14:20–30. https://doi.org/10.1038/s41408-024-00985-0
2. Jiménez-Segura R, Rosiñol L, Cibeira MT, Fernández de Larrea C, Tovar N, Rodríguez-Lobato LG, et al. Paraskeletal and extramedullary plasmacytomas in multiple myeloma at diagnosis and at first relapse: 50-years of experience from an academic institution. Blood Cancer J. 2022;12:135.
3. Sevcikova S, Minarik J, Stork M, Jelinek T, Pour L, Hajek R. Extramedullary disease in multiple myeloma - controversies and future directions. Blood Rev. 2019;36:32–9. https://doi.org/10.1016/j.blre.2019.04.002
4. Campo E, Jaffe ES, Cook JR, Quintanilla-Martinez L, Swerdlow SH, Anderson KC, et al. The International Consensus Classification of Mature Lymphoid Neoplasms: A Report from the Clinical Advisory Committee. Blood. 2022;140:1229–53. https://doi.org/10.1182/blood.2022015851
5. Besse L, Sedlarikova L, Greslikova H, Kupska R, Almasi M, Penka M, et al. Cytogenetics in multiple myeloma patients progressing into extramedullary disease. Eur J Haematol 2016;97:93–100.
6. Xia Y, Shi Y, Chen Z, Zhang J, Zhu Y, Guo R, et al. Characteristics and prognostic value of extramedullary chromosomal abnormalities in extramedullary myeloma. Chin Med J. 2022;135:2500–2. https://doi.org/10.1097/CM9.0000000000002351
7. Liu Y, Jelloul F, Zhang Y, Bhavsar T, Ho C, Rao M, et al. Genetic basis of extramedullary plasmablastic transformation of multiple myeloma. Am J Surg Pathol 2020;44:838–48. https://doi.org/10.1097/PAS.0000000000001459
8. Jelinek T, Zihala D, Sevcikova T, Anilkumar SA, Kapustova V, Sahinbegovic H, et al. Beyond the marrow: insights from comprehensive next-generation sequencing of extramedullary multiple myeloma tumors. Leukemia. 2024;38:1323–33. https://doi.org/10.1038/s41375-024-02206-w
9. Locher M, Steurer M, Jukic E, Keller MA, Fresser F, Ruepp C, et al. The prognostic value of additional copies of 1q21 in multiple myeloma depends on the primary genetic event. Am J Hematol 2020;95:1562–71. https://doi.org/10.1002/ajh.25994
10. Hebraud B, Leleu X, Lauwers-Cances V, Roussel M, Caillot D, Marit G, et al. Deletion of the 1p32 region is a major independent prognostic factor in young patients with myeloma: the IFM experience on 1195 patients. Leukemia. 2014;28:675–9. https://doi.org/10.1038/leu.2013.225
11. Schavgoulidze A, Talbot A, Perrot A, Cazaubiel T, Leleu X, Manier S, et al. Biallelic deletion of 1p32 defines ultra-high-risk myeloma, but monoallelic del(1p32) remains a strong prognostic factor. Blood. 2023;141:1308–15. https://doi.org/10.1182/blood.2022017863
12. Pour L, Sevcikova S, Greslikova H, Kupska R, Majkova P, Zahradova L, et al. Soft-tissue extramedullary multiple myeloma prognosis is significantly worse in comparison to bone-related extramedullary relapse. Haematologica. 2014;99:360–4. https://doi.org/10.3324/haematol.2013.094409

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AUTHOR CONTRIBUTIONS

SM, OE, and PL designed the study. OE and BohM performed the FISH analysis, JM analyzed and evaluated the FISH data. SM, OE, BI, FD, AZ, KM, SV, KM, BorM, SS, JM, and PL co-wrote the paper. JZ, AT, KM, NV selected patients for tissue sampling and provided surgical biopsies. KZ and RL analyzed data. All authors critically reviewed and approved the manuscript.

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COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Ethics Committee of the University Hospital Brno, Czech Republic (2016). Informed consent was obtained from all subjects involved in the study.

ADDITIONAL INFORMATION

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2.7.3. Stork M, Sevcikova S, Jelinek T, Minarik J, Radocha J, Pika T, Pospisilova L, Spicka I, Straub J, Pavlicek P, Jungova A, Knechtova Z, Sandecka V, Maisnar V, Hajek R, Pour L. **Unexpected heterogeneity of newly diagnosed multiple myeloma patients with plasmacytomas.** Biomedicines. 2022;10(10):2535.

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Unexpected Heterogeneity of Newly Diagnosed Multiple Myeloma Patients with Plasmacytomas

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Abstract: In multiple myeloma (MM), malignant plasma cells infiltrate the bone marrow. In some cases, plasma cells migrate out of the bone marrow creating either para-skeletal plasmacytomas (PS) or infiltrating soft tissues as extramedullary plasmacytomas (EMD). The aim of this study was to define risk groups in newly diagnosed MM (NDMM) patients with PS and EMD plasmacytomas. In total, 523 NDMM patients with PS plasmacytomas and 196 NDMM patients with EMD plasmacytomas were diagnosed in the Czech Republic between 2004 and 2021 using modern imaging methods. Patients' data were analyzed from the Registry of Monoclonal Gammopathies of the Czech Myeloma Group. In NDMM patients with PS plasmacytomas, we found a subgroup with <5% of bone-marrow plasma cells to have the best prognosis (mPFS: 58.3 months (95% CI: 33.0–NA); mOS: not reached). The subgroup with >5% of bone-marrow plasma cells and ≥3 plasmacytomas had the worst prognosis (mPFS: 19.3 months (95% CI: 13.4–28.8), $p < 0.001$; mOS: 27.9 months (95% CI: 19.3–67.8), $p < 0.001$). Our results show association between tumor burden and prognosis of NDMM patients with plasmacytomas. In the case of PS plasmacytomas, NDMM patients with low BM PC infiltration have an excellent prognosis.

Keywords: multiple myeloma; risk factors; survival; plasmacytomas

1. Introduction

Multiple myeloma (MM) is the second-most-common hematologic malignancy; in Europe, the average incidence is 5/100,000 [1,2]. In the last decade, MM has slowly become a chronic disease due to novel agents such as proteasome inhibitors (PI), immunomodulatory drugs (IMIDs), and monoclonal antibodies [3–6].

MM is characterized by infiltration of the bone marrow (BM) by malignant plasma cells (PCs). In some cases, these PCs migrate out of the BM creating two types of plasmacytomas: paraskeletal lesions (tumors arising directly from the bone lesion; PS plasmacytomas) or

extramedullary lesions (tumors infiltrating soft tissues; EMD plasmacytomas) possibly due to changes in adhesion molecules as well as rising independence of the BM [7–9]. Historically, plasmacytomas in MM were considered a high-risk feature [10]. In later analyses, EMD subsets of patients were shown to have the worst prognosis, while PS plasmacytomas had somehow better prognosis [11–13].

These plasmacytomas can be found in both newly diagnosed MM (NDMM) patients (2.4–11.5% of cases) [14–16] and in relapsed/refractory MM (RRMM) patients (3.4–27.4% of cases) [12,16–18]. The range of plasmacytoma incidence is predominantly caused by the different sensitivities of the imaging methods used [12–18], while historical methods, such as skeletal survey, have only a limited sensitivity for detection of PS or EMD plasmacytomas [7–9].

Although the appearance of plasmacytomas is generally associated with impaired prognosis, there are some treatment results of NDMM with plasmacytomas that are comparable to those of NDMM patients with strictly intra-medullar disease [14,19,20]. However, as we have previously described, development of plasmacytomas in RRMM patients is associated with extremely poor prognosis [12,18]. We believe that aggressivity of plasmacytomas in RRMM patients is likely due to disease-related factors. Molecular mechanisms of plasmacytoma development and expansion are still unclear, but especially in plasmacytomas of RRMM patients, mutations associated with poor prognosis (*TP53*, *K-RAS*, *N-RAS*, *RB1*, etc.), were often found. Similarly, the lack of adhesion molecules was found on PCs in plasmacytomas [7–9]. We have previously described NDMM patients with early progression with plasmacytomas. These patients had an aggressive disease course from the disease onset, together with gain (1q21) [18].

In this study, we evaluated clinical and laboratory data of one of the largest cohorts of NDMM patients with plasmacytomas to analyze their outcomes in real-life clinical practice conditions and to identify possible risk-groups.

2. Materials and Methods

2.1. Patient' Selection

This multicentric real-life retrospective study was carried out in major hematologic centers in the Czech Republic between 2004 and 2021. For the data search of NDMM with plasmacytomas, the Registry of Monoclonal Gammopathies (RMG) of the Czech Myeloma Group was used. In total, 7123 NDMM patients fulfilling International Myeloma Working Group (IMWG) diagnostic criteria for MM were evaluated. We excluded all patients treated only with conventional chemotherapy or diagnosed only by skeletal survey; 523 NDMM patients with PS plasmacytomas, 196 NDMM patients with EMD plasmacytomas, and 2440 reference NDMM patients with clear absence of plasmacytoma (proven by high-sensitivity imaging methods) were identified. Of the enrolled patients with BM PCs <10% fulfilled MM diagnostic criteria with plasmacytoma/bone lesion tissue histology together with CRAB (i.e., osteolytic lesions, hypercalcemia etc.), or myeloma-defining events according to IMWG criteria. Patients with other plasma-cell dyscrasias (i.e., solitary plasmacytoma or solitary plasmacytoma with minimal marrow involvement) were not enrolled into the study. All participants provided written informed consent approved by institutional ethics boards in accordance with the latest Helsinki declaration.

2.2. Imaging Methods

The entire study cohort was evaluated for the presence of plasmacytomas by modern imaging methods—computed tomography (CT), focused/whole body magnetic resonance imaging (MRI/WB-MRI), or positron-emission tomography/computed tomography (PET/CT) [21]. Multiple diagnostic methods were performed on patients when clinically needed. If there was a clinical need and when safe for the patient, plasmacytomas were confirmed by surgical sampling.

2.3. Bone-Marrow Assessment

Bone-marrow samples were evaluated at the time of NDMM diagnosis. The number of BM PCs was evaluated by cytology, the clonality of BM PCs was evaluated by flow-cytometry, and interphase fluorescent in-situ hybridization (I-FISH) analyses of commonly found aberrations was performed on separated PCs as previously described [22].

2.4. Response Assessment and Survival Intervals

Treatment response was assessed according to the current International Myeloma Working Group (IMWG) criteria [23]. Survival intervals (progression-free survival, PFS and overall survival, OS) were assessed from the NDMM diagnosis.

2.5. Statistics

Data were described by absolute and relative frequencies of categorical variables and median with 5th–95th percentile range for quantitative variables. Fisher's exact test was used to evaluate the association of selected features. The differences in survival (OS and PFS) among individual patient groups were assessed by the Kaplan–Meier method, and the statistical significance of differences in survival was evaluated using the log-rank test. The univariable Cox proportional-hazards model was used to quantify the effect of individual clinical features on the survival measures. The independence of selected features as prognostic survival factors was tested in the multivariable Cox proportional-hazards model in the context of R-ISS (Revised International Staging System). Statistical significance of hazard ratios (HR) was assessed by means of the Wald test. The cut-off for BM PCs was defined as the value where multivariable Cox regression adjusted to ISS showed highest HR and significance for OS and PFS, and the numbers of patients in the resulting groups was still sufficient. All statistical tests were performed at a significance level of $\alpha = 0.05$ (all tests two-sided). Analysis was performed in the SPSS software (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0.0.1 Armonk, NY, USA: IBM Corp.) and software R version 4.0.1. (www.r-project.org) [24].

3. Results

3.1. Clinical Characteristics of Patients

Altogether, 523 NDMM patients with PS plasmacytomas, 196 NDMM patients with EMD plasmacytomas, and 2440 reference NDMM patients were included into this study.

Median follow-up from diagnosis was 25.5 months (range 0.8–115.3 months) in the PS subgroup, 20.8 months (range 1.1–95.0 months) in the EMD subgroup, and 31.2 months (range 1.2–108.1 months) in reference patients. Clinical characteristics are summarized in Supplementary Table S1.

NDMM patients with PS and EMD plasmacytomas more frequently had lower BM PC infiltration (<10%) than reference patients (43.8% vs. 47.6% vs. 22.2%; $p < 0.001$). Correspondingly, these patients more frequently had a lower ratio of clonal BM PCs (<95% from all BM PCs) when compared to reference patients (32.2% vs. 38.7% vs 19.3%; $p < 0.001$).

In the PS subgroup, plasmacytomas were found by CT in 72.2% (380/523) of patients, by WB-MRI in 7.8% (41/523) of patients, by focused MRI in 38.4% (201/523) of patients, and by PET/CT in 31.0% (162/523) of patients. In 65.6% (343/523) of cases, only one plasmacytoma was found; in 9.8% (51/523) of patients two plasmacytomas were found, and in 12.6% (66/523), three and more plasmacytomas were found. In 12.0% (63/523) of patients, plasmacytoma count was missing.

In the EMD subgroup, plasmacytomas were found by CT in 64.3% (126/196) of patients, by WB-MRI in 12.7% (25/196) of patients, by focused MRI in 16.8% (33/196) of patients, and by PET/CT in 32.1% (63/196) of patients. In 68.8% (135/196) of cases, only one plasmacytoma was found; in 11.7% (23/196) of patients two plasmacytomas were found, and in 18.4% (36/196), three and more plasmacytomas were found. In 0.1% (2/196) of patients, plasmacytoma count was missing.

We also analyzed i-FISH data of all three subgroups of patients. Statistically significant differences between these groups of patients were not found.

3.2. Treatment of PS and EMD Subgroups of Patients after NDMM Diagnosis

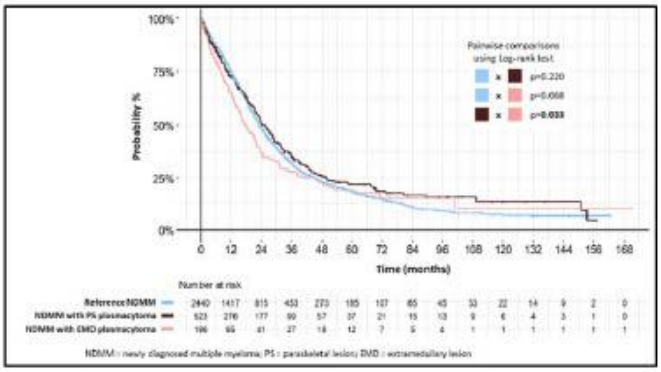
In the PS subgroup, 82.6% (432/523) of patients were treated with PI, 57.2% (299/523) with IMIDs, 2.7% (14/523) with anti-CD38 monoclonal antibodies (daratumumab or isatuximab), and 35.6% (186/523) underwent high-dose chemotherapy followed by ASCT. Radiotherapy of plasmacytomas was administered in 31.7% (166/523) of these patients.

Similarly, in the EMD subgroup, 84.7% (166/196) of patients were treated with PI, 55.1% (108/196) with IMIDs, 2.0% (4/196) with anti-CD38 monoclonal antibodies (daratumumab or isatuximab), and 33.7% (66/196) underwent high-dose chemotherapy followed by ASCT. Radiotherapy of plasmacytomas was administered in 35.2% (69/196) of these patients.

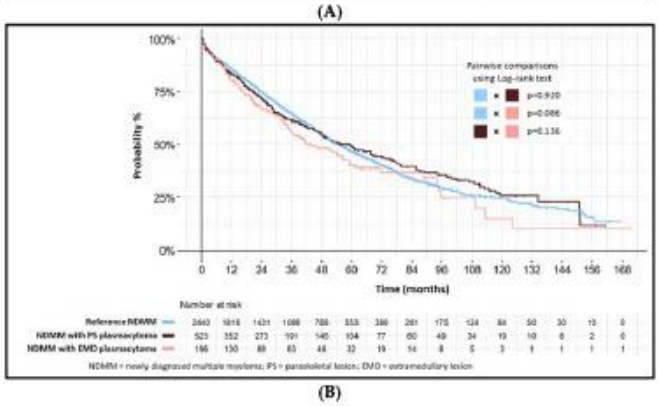
Median PFS in the PS subgroup of patients was 25.8 months (95% CI: 22.7–28.6) which was significantly longer than in the EMD subgroup (17.9 months (95% CI: 15.0–22.3), $p = 0.033$), and longer than for the reference patients; however, statistical significance was not reached (23.3 months (95% CI: 22.5–24.8), $p = 0.220$).

Median OS in the PS subgroup was longer than for the EMD subgroup or reference patients but did not reach statistical significance (59.4 months (95% CI: 48.1–73.3) vs. 43.8 months (95% CI: 34.9–61.5) vs. 55.0 months (95% CI: 51.6–58.9), $p = 0.229$).

Treatment modalities and results including survival intervals are summarized in Figure 1 and Supplementary Table S2.



(A)



(B)

Figure 1. (**A**) PFS from 1st line—NDMM with plasmacytomas by type versus reference NDMM. (**B**) OS from 1st line—NDMM with plasmacytomas by type versus reference NDMM.

3.3. High-Risk Features in PS Subgroup of Patients

By univariable analysis, we found high R-ISS stage (R-ISS III) (HR 2.13 (95% CI: 1.24–3.66), $p = 0.006$), BM PC infiltration >5% (HR 2.38 (95 % CI: 1.67–3.39), $p < 0.001$), a higher ratio of clonal BM PCs (≥95% from all BM PCs) (HR 1.59 (95% CI: 1.08–2.32), $p = 0.018$), and higher LDH levels (>300 IU/L) (HR 2.50 (95 % CI: 1.76–3.56), $p < 0.001$) as statistically significant risk factors for inferior PFS in these patients. All these prognostic factors were also associated with inferior OS. Negative prognostic impact of BM PC infiltration >5% was more pronounced, when combined with higher PS plasmacytoma count (>5% BM PCs and ≥3 plasmacytomas) (PFS: HR 3.17 (95% CI: 1.93–5.20), $p < 0.001$; OS: HR 4.86 (95% CI: 2.69–8.80), $p < 0.001$).

According to i-FISH analysis, gain(1q21) was found to be a risk factor for inferior PFS (HR 1.67 (95 % CI: 1.20–2.33), $p = 0.003$). Moreover, t(4;14) (HR 1.87 (95 % CI: 1.14–3.05), $p = 0.013$), and del(17p13) (HR 1.74 (95 % CI: 1.09–2.78), $p = 0.020$) were found as risk factors for inferior PFS. Del(17p13) and t(4;14) were also associated with inferior OS. Other cytogenetic aberrations were not associated with adverse prognosis. Results of univariable analysis of risk factors in these patients are shown in Table 1.

Table 1. Association of clinical features with OS and PFS in NDMM patients with PS plasmacytomas.

	Univariable Analysis			
	Overall Survival (OS)		Progression-Free Survival (PFS)	
	HR (95% CI) [1]	*p*	HR (95% CI) [1]	*p*
ISS				
Stage I	–	–	–	–
Stage II	2.01 (1.46–2.75)	<0.001	1.87 (1.41–2.48)	<0.001
Stage III	2.24 (1.60–3.13)	<0.001	2.30 (1.71–3.10)	<0.001
R-ISS				
Stage I	–	–	–	–
Stage II	3.00 (1.40–6.42)	0.005	1.73 (1.04–2.88)	0.035
Stage III	4.78 (2.20–10.38)	<0.001	2.13 (1.24–3.66)	0.006
Serum M-protein level (g/dL)				
≤2	–	–	–	–
>2	1.20 (0.92–1.55)	0.180	1.25 (0.98–1.58)	0.068
BM PCs %				
<5%	–	–	–	–
≥5%	3.12 (1.95–5.00)	<0.001	2.38 (1.67–3.39)	<0.001
Plasmacytoma count				
1–2 plasmacytomas	–	–	–	–
≥3 plasmacytomas	1.75 (1.20–2.55)	0.003	1.39 (0.97–1.99)	0.073
Tumor burden				
BM PCs < 5% and 1 and more plasmacytoma	–	–	–	–
BM PCs ≥ 5% and 1–2 plasmacytomas	3.01 (1.82–4.97)	<0.001	2.47 (1.68–3.62)	<0.001
BM PC ≥ 5% and 3 and more plasmacytomas	4.86 (2.69–8.80)	<0.001	3.17 (1.93–5.20)	<0.001
Clonal PCs from all BM PC (%)				
<95%	–	–	–	–
≥95%	2.01 (1.20–3.36)	0.008	1.59 (1.08–2.32)	0.018
Osteolytic lesions				
negative	–	–	–	–
1 lesion	1.10 (0.15–8.21)	0.925	0.52 (0.12–2.21)	0.375
2 lesions	1.33 (0.18–9.98)	0.779	0.90 (0.21–3.80)	0.882
≥3 lesions	1.36 (0.19–9.73)	0.758	0.89 (0.22–3.57)	0.866
Accelerated osteoporosis	0.54 (0.03–8.62)	0.662	0.57 (0.08–4.02)	0.569
LDH (IU/L)				
>300	2.52 (1.74–3.67)	<0.001	2.50 (1.76–3.56)	<0.001
IGH disruption				
Positive	1.18 (0.81–1.71)	0.385	1.16 (0.84–1.61)	0.378

Table 1. *Cont.*

	Univariable Analysis			
	Overall Survival (OS)		Progression-Free Survival (PFS)	
	HR (95% CI) [1]	*p*	HR (95% CI) [1]	*p*
t(11;14)				
Positive	1.39 (0.79–2.45)	0.258	1.03 (0.59–1.81)	0.913
t(4;14)				
Positive	2.37 (1.41–3.98)	0.001	1.87 (1.14–3.05)	0.013
Del(13)(q14)/monosomy 13				
Positive	1.44 (0.99–2.10)	0.059	1.12 (0.80–1.55)	0.516
Gain(1q21)				
Positive	1.32 (0.90–1.93)	0.157	1.67 (1.20–2.33)	0.003
Del(17p13)				
Positive	2.17 (1.32–3.56)	0.002	1.74 (1.09–2.78)	0.020
Hyperdiploidy				
Positive	0.64 (0.41–0.99)	0.045	0.79 (0.54–1.16)	0.227

[1] Hazard ratio (HR) from univariable Cox's proportional hazard model. Abbreviations: ISS, International Staging System; R-ISS, Revised-ISS; BM PCs, bone-marrow plasma cells; LDH, lactate dehydrogenase; IGH, immunoglobulin heavy chain.

By multivariable analysis adjusted for R-ISS stage, presence of PS plasmacytomas was not found as a risk factor for inferior PFS (HR 1.10 (95 % CI: 0.90–1.36), $p = 0.343$) and OS (HR 1.10 (95 % CI: 0.87–1.39), $p = 0.431$).

3.4. High-Risk Features in EMD Subgroup of Patients

By univariable analysis, we found high R-ISS stage (R-ISS III) (HR 5.03 (95% CI: 2.21–11.48), $p < 0.001$), ≥3 EMD plasmacytomas (HR 1.88 (95 % CI: 1.18–2.98), $p = 0.008$), and higher LDH levels (>300 IU/L) (HR 1.88 (95 % CI: 1.03–3.43), $p = 0.041$) as statistically significant risk factors for inferior PFS in these patients. All these prognostic factors were also associated with inferior OS. Interestingly, BM PC infiltration (>5%) or ratio of clonal BM PCs (>95%) had no prognostic impact.

According to i-FISH analysis, gain(1q21) (HR 1.82 (95 % CI: 1.11–2.99), $p = 0.019$) and del(17p13) (HR 2.96 (95 % CI: 1.46–6.00), $p = 0.003$) were found to be risk factors for inferior PFS as well as inferior OS. Results of univariable analysis of risk factors in these patients are summarized in Table 2.

Table 2. Association of clinical features with OS and PFS in NDMM patients with EMD plasmacytomas.

	Univariable Analysis			
	Overall Survival (OS)		Progression-Free Survival (PFS)	
	HR (95% CI) [1]	*p*	HR (95% CI) [1]	*p*
ISS				
Stage I	–	–	–	–
Stage II	1.49 (0.87–2.56)	0.151	1.48 (0.93–2.37)	0.102
Stage III	3.21 (1.94–5.31)	<0.001	2.49 (1.60–3.89)	<0.001
R-ISS				
Stage I	–	–	–	–
Stage II	1.77 (0.63–4.93)	0.276	2.07 (0.93–4.63)	0.075
Stage III	5.64 (2.08–15.26)	0.001	5.03 (2.21–11.48)	<0.001
Serum M-protein level (g/dL)				
>2	1.13 (0.75–1.71)	0.565	1.34 (0.93–1.94)	0.122
BM PCs %				
<5%	–	–	–	–
≥5%	1.30 (0.76–2.20)	0.338	1.56 (0.97–2.52)	0.066

Table 2. *Cont.*

	Univariable Analysis			
	Overall Survival (OS)		Progression-Free Survival (PFS)	
	HR (95% CI) [1]	*p*	HR (95% CI) [1]	*p*
Plasmacytoma count				
1–2 lesions	–	–	–	–
≥3 lesions	2.00 (1.21–3.30)	0.007	1.88 (1.18–2.98)	0.008
Clonal PCs from all BM PC (%)				
≥95%	1.36 (0.72–2.59)	0.346	1.41 (0.83–2.39)	0.210
Osteolytic lesions				
Negative	–	–	–	–
1 lesion	0.33 (0.11–1.03)	0.055	0.56 (0.16–2.04)	0.382
2 lesions	0.26 (0.07–0.90)	0.033	0.45 (0.12–1.70)	0.236
≥3 lesions	0.49 (0.20–1.21)	0.122	0.65 (0.20–2.06)	0.461
Accelerated osteoporosis	0.39 (0.09–1.62)	0.194	0.52 (0.12–2.19)	0.372
LDH (IU/L)				
> 300	2.29 (1.20–4.38)	0.012	1.88 (1.03–3.43)	0.041
IGH disruption				
Positive	1.19 (0.67–2.12)	0.557	1.14 (0.69–1.89)	0.612
t(11;14)				
Positive	1.01 (0.31–3.33)	0.988	0.57 (0.14–2.37)	0.441
t(4;14)				
Positive	0.77 (0.33–1.78)	0.542	1.55 (0.80–2.99)	0.191
Del(13)(q14)/monosomy 13				
Positive	1.06 (0.59–1.90)	0.851	1.53 (0.94–2.49)	0.087
Gain(1q21)				
Positive	1.86 (1.06–3.27)	0.031	1.82 (1.11–2.99)	0.019
Del(17p13)				
Positive	2.62 (1.21–5.67)	0.014	2.96 (1.46–6.00)	0.003
Hyperdiploidy				
Positive	1.06 (0.55–2.02)	0.867	1.18 (0.65–2.15)	0.593

[1] Hazard ratio (HR) from univariable Cox's proportional hazard model. Abbreviations: ISS, International Staging System; R-ISS, Revised-ISS; BM PCs, bone marrow plasma cells; LDH, lactate dehydrogenase; IGH, immunoglobulin heavy chain.

By multivariable analysis adjusted for R-ISS, presence of EMD plasmacytomas was found as a risk factor for inferior PFS (HR 1.70 (95 % CI: 1.29–2.26), $p < 0.001$) and OS (HR 1.38 (95 % CI: 1.01–1.90), $p = 0.046$).

3.5. Heterogeneity in PS and EMD Subgroups of Patients

In addition to generally accepted prognostic markers, such as the ISS and R-ISS stage, we found intra- and/or extramedullary tumor burden to be an important prognostic indicator of both subgroups of plasmacytomas.

In the PS subgroup, we found <5% of BM PCs (regardless of plasmacytoma count) to have the best prognosis (mPFS: 58.3 months (95% CI: 33.0–NA), $p < 0.001$; mOS: not reached). These patients had more frequent low ISS stage (ISS I), low monoclonal immunoglobulin secretory activity, lower ratio of clonal BM PCs (<95% from all BM PCs), intact IgH gene, and relatively low plasmacytoma count.

On the other hand, >5% of BM PCs together with 1–2 plasmacytomas had inferior prognosis (mPFS: 23.7 months, (95% CI: 20.1–27.2) $p < 0.001$; mOS: 49.1 months (95% CI: 39.8–68.0), $p < 0.001$); >5% of BM PCs together with ≥3 plasmacytomas had the worst prognosis (mPFS: 19.3 months (95% CI: 13.4–28.8), $p < 0.001$; mOS: 27.9 months (95% CI: 19.3–67.8), $p < 0.001$). In these patients, high ISS (ISS III), high monoclonal immunoglobulin secretory activity, higher ratio of clonal BM PCs (≥95% from all BM PCs), higher count of bone osteolytic lesion (≥3 lesions), and higher frequency of IgH translocations were present. Characteristics and survival intervals of these three cohorts of PS subgroup are shown in Figure 2 and Table 3.

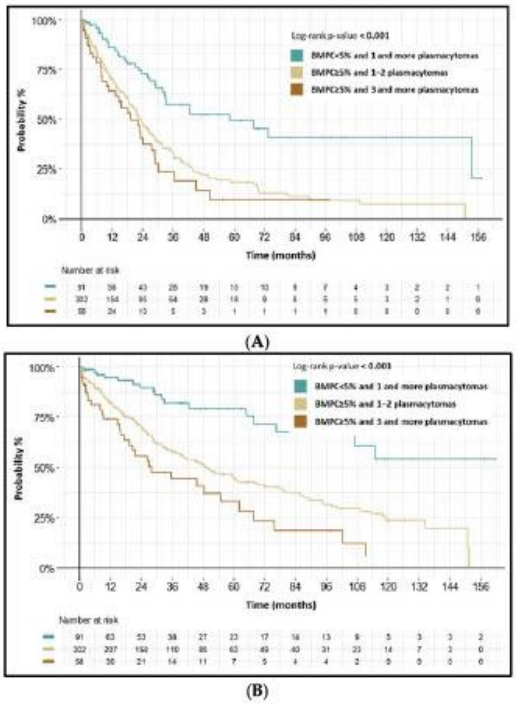


Figure 2. (**A**) PFS from 1st line—by tumor burden in NDMM patients with PS plasmacytomas. (**B**) OS from 1st line—by tumor burden in NDMM patients with PS plasmacytomas.

Table 3. Descriptive characteristics according to tumor burden in NDMM patients with PS plasmacytomas.

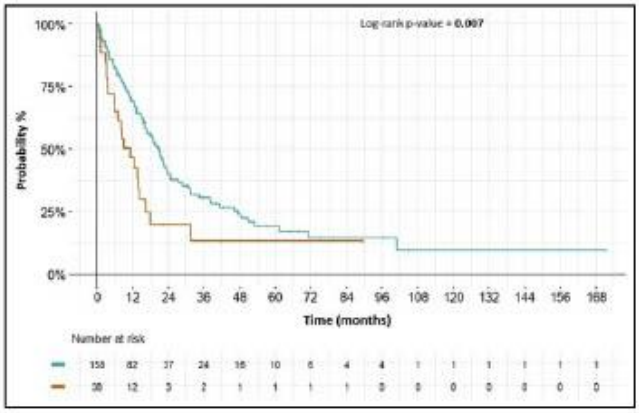
Characteristics [1]	BM PCs < 5% and 1 or More Plasmacytomas (n = 91)	BM PCs ≥ 5% and 1–2 Plasmacytomas (n = 302)	BM PCs ≥ 5% and ≥3 Plasmacytomas (n = 58)	p-Value [2]
ISS	n = 91	n = 298	n = 58	
Stage I	63 (69.2%)	113 (37.9%)	17 (29.3%)	
Stage II	16 (17.6%)	103 (34.6%)	17 (29.3%)	<0.001
Stage III	12 (13.2%)	82 (27.5%)	24 (41.4%)	
R-ISS	n = 18	n = 120	n = 38	
Stage I	7 (38.9%)	25 (20.8%)	4 (10.5%)	
Stage II	7 (38.9%)	63 (52.5%)	21 (55.3%)	0.195
Stage III	4 (22.2%)	32 (26.7%)	13 (34.2%)	
Serum M-protein level (g/dL)	n = 91	n = 302	n = 58	
≤2	66 (72.5%)	145 (48.0%)	26 (44.8%)	<0.001
>2	25 (27.5%)	157 (52.0%)	32 (55.2%)	
Plasmacytoma count	n = 91	n = 302	n = 58	
1 plasmacytoma	73 (80.2%)	263 (87.1%)	-	
2 plasmacytomas	12 (13.2%)	39 (12.9%)	-	<0.001
3 plasmacytomas	1 (1.1%)	-	16 (27.6%)	
>3 plasmacytomas	5 (5.5%)	-	42 (72.4%)	

Table 3. *Cont.*

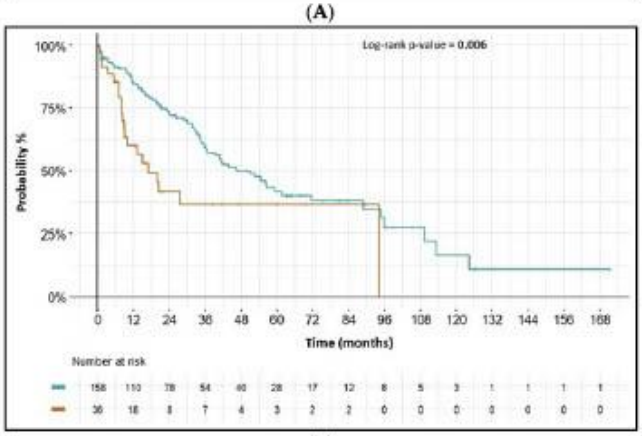
Characteristics [1]	BM PCs < 5% and 1 or More Plasmacytomas (*n* = 91)	BM PCs ≥ 5% and 1–2 Plasmacytomas (*n* = 302)	BM PCs ≥ 5% and ≥3 Plasmacytomas (*n* = 58)	*p*-Value [2]
Clonal PCs from all BM PC (%)	*n* = 57	*n* = 159	*n* = 25	
<95%	38 (66.7%)	37 (23.3%)	1 (4.0%)	<0.001
≥95%	19 (33.3%)	122 (76.7%)	24 (96.0%)	
Osteolytic lesions	*n* = 91	*n* = 302	*n* = 58	
Negative	0 (0.0%)	2 (0.7%)	0 (0.0%)	
1 lesion	17 (18.7%)	32 (10.6%)	0 (0.0%)	
2 lesions	3 (3.3%)	28 (9.3%)	0 (0.0%)	<0.001
≥3 lesions	70 (76.9%)	238 (78.8%)	58 (100.0%)	
Accelerated osteoporosis	1 (1.1%)	2 (0.7%)	0 (0.0%)	
LDH (IU/L)	*n* = 91	*n* = 296	*n* = 58	
≤300	84 (92.3%)	271 (91.6%)	53 (91.4%)	1.000
>300	7 (7.7%)	25 (8.4%)	5 (8.6%)	
IGH disruption	*n* = 24	*n* = 183	*n* = 37	
Negative	22 (91.7%)	106 (57.9%)	18 (48.6%)	0.001
Positive	2 (8.3%)	77 (42.1%)	19 (51.4%)	
t(11;14)	*n* = 23	*n* = 156	*n* = 32	
Negative	22 (95.7%)	135 (86.5%)	25 (78.1%)	0.195
Positive	1 (4.3%)	21 (13.5%)	7 (21.9%)	
t(4;14)	*n* = 25	*n* = 161	*n* = 34	
Negative	25 (100.0%)	145 (90.1%)	29 (85.3%)	0.119
Positive	0 (0.0%)	16 (9.9%)	5 (14.7%)	
Del(13)(q14)/monosomy 13	*n* = 24	*n* = 183	*n* = 36	
Negative	14 (58.3%)	100 (54.6%)	20 (55.6%)	0.975
Positive	10 (41.7%)	83 (45.4%)	16 (44.4%)	
Gain(1q21)	*n* = 24	*n* = 176	*n* = 38	
Negative	17 (70.8%)	111 (63.1%)	19 (50.0%)	0.203
Positive	7 (29.2%)	65 (36.9%)	19 (50.0%)	
Del(17p13)	*n* = 24	*n* = 165	*n* = 35	
Negative	24 (100.0%)	146 (88.5%)	30 (85.7%)	0.141
Positive	0 (0.0%)	19 (11.5%)	5 (14.3%)	
Hyperdiploidy	*n* = 20	*n* = 129	*n* = 36	
Negative	12 (60.0%)	75 (58.1%)	20 (55.6%)	0.945
Positive	8 (40.0%)	54 (41.9%)	16 (44.4%)	

[1] Described by absolute and relative frequencies for categorical variables and median (5th–95th percentile) for continuous variables. [2] *p*-value of Fisher's exact test for categorical variables or Kruskal–Wallis test for continuous variables. Abbreviations: ISS, International Staging System; R-ISS, Revised-ISS; BM PCs, bone marrow plasma cells; LDH, lactate dehydrogenase; IGH, immunoglobulin heavy chain.

In the EMD subgroup with 1–2 EMD plasmacytomas, median PFS was 20.9 months (95% CI: 16.2–24.6) and median OS was 50.9 months (95% CI: 36.3–89.0). If ≥3 plasmacytomas were present, prognosis was significantly worse (median PFS 11.1 months (95% CI: 7.0–16.3), and median OS 16.9 months (95% CI: 9.1–NA)). Interestingly, there was no significant differences in ISS or R-ISS stage, BM PCs count, osteolytic lesions, cytogenetics, etc., between these cohorts of patients. Characteristics and survival intervals in the EMD subgroups of patients are shown in Figure 3 and Table 4.



(A)



(B)

Figure 3. (**A**) PFS from 1st line—by plasmacytoma count in NDMM patients with EMD plasmacytomas. (**B**) OS from 1st line—by plasmacytoma count in NDMM patients with EMD plasmacytomas.

Table 4. Descriptive characteristics according to plasmacytoma count in NDMM patients with EMD plasmacytomas.

Characteristics [1]	1–2 EMD Plasmacytomas (n = 158)	≥3 EMD Plasmacytomas (n = 36)	p-Value [2]
ISS	n = 156	n = 36	
Stage I	68 (43.6%)	11 (30.6%)	
Stage II	43 (27.6%)	9 (25.0%)	0.189
Stage III	45 (28.8%)	16 (44.4%)	
R-ISS	n = 65	n = 21	
Stage I	17 (26.2%)	3 (14.3%)	
Stage II	26 (40.0%)	6 (28.6%)	0.173
Stage III	22 (33.8%)	12 (57.1%)	
Serum M-protein level (g/dL)	n = 158	n = 36	
≤ 2	81 (51.3%)	18 (50.0%)	1.000
> 2	77 (48.7%)	18 (50.0%)	
Clonal PCs from all BM PCs (%)	n = 95	n = 15	
<95%	37 (38.9%)	6 (40.0%)	1.000
≥95%	58 (61.1%)	9 (60.0%)	

Table 4. *Cont.*

Characteristics [1]	1–2 EMD Plasmacytomas (n = 158)	≥3 EMD Plasmacytomas (n = 36)	p-Value [2]
BM PCs %	n = 152	n = 33	
<5%	38 (25.0%)	9 (27.3%)	0.826
≥5%	114 (75.0%)	24 (72.7%)	
Osteolytic lesions	n = 156	n = 36	
Negative	6 (3.8%)	0 (0.0%)	
1 lesion	18 (11.5%)	2 (5.6%)	
2 lesions	15 (9.6%)	0 (0.0%)	0.115
≥3 lesions	110 (70.5%)	32 (88.9%)	
Accelerated osteoporosis	7 (4.5%)	2 (5.6%)	
LDH (IU/L)	n = 158	n = 36	
≤ 300	146 (92.4%)	31 (86.1%)	0.322
> 300	12 (7.6%)	5 (13.9%)	
IGH disruption	n = 88	n = 17	
Negative	58 (65.9%)	9 (52.9%)	0.409
Positive	30 (34.1%)	8 (47.1%)	
t(11;14)	n = 72	n = 14	
Negative	67 (93.1%)	12 (85.7%)	0.319
Positive	5 (6.9%)	2 (14.3%)	
t(4;14)	n = 86	n = 17	
Negative	76 (88.4%)	16 (94.1%)	0.686
Positive	10 (11.6%)	1 (5.9%)	
Del(13)(q14)/monosomy 13	n = 89	n = 17	
Negative	53 (59.6%)	11 (64.7%)	0.791
Positive	36 (40.4%)	6 (35.3%)	
Gain(1q21)	n = 88	n = 17	
Negative	51 (58.0%)	7 (41.2%)	0.287
Positive	37 (42.0%)	10 (58.8%)	
del(17p13)	n = 86	n = 15	
Negative	72 (83.7%)	11 (73.3%)	0.462
Positive	14 (16.3%)	4 (26.7%)	
Hyperdiploidy	n = 61	n = 14	
Negative	30 (49.2%)	5 (35.7%)	0.393
Positive	31 (50.8%)	9 (64.3%)	

[1] Described by absolute and relative frequencies for categorical variables and median (5th–95th percentile) for continuous variables. [2] p-value of Fisher's exact test for categorical variables or Kruskal–Wallis test for continuous variables. Abbreviations: ISS (International Staging System), R-ISS (Revised-ISS) BM PCs (bone marrow plasma cells), LDH (lactate dehydrogenase), IGH (immunoglobulin heavy chain).

4. Discussion

In the last decade, MM has gradually become a more manageable disease. Modern induction-treatment protocols lead to deeper responses and longer remissions in most NDMM patients [25–28]. Moreover, even treatment results of NDMM patients with plasmacytomas have improved when compared to historical data [13,14,19,20,29].

In this work, we analyzed NDMM patients with both paraskeletal and extramedullary plasmacytomas. As treatment regimens based on conventional chemotherapy are more than two decades obsolete in NDMM treatment [30], we censored historical patients treated with this approach from our analysis, with the aim of understanding the prognostic impact of plasmacytomas found in NDMM patients in real-life treatment scenarios. Similarly, as discussed above, we censored NDMM patients evaluated without high-sensitive imaging methods, such as CT, MRI, WB-MRI, or PET/CT.

In light of modern real-life treatment, we found NDMM patients with PS and EMD plasmacytomas to have comparable initial treatment results to those of NDMM patients without plasmacytomas (median PFS: 25.8 and 17.9 vs. 23.3 months; p = NS). Similarly to our analysis, in a study of NDMM with mostly PS plasmacytomas, predominantly IMID-based regimens lead to treatment results comparable to NDMM patients without plasmacytomas

(median PFS: 25.3 months vs. 25.2 months; $p = 0.46$) [14]. In another analysis of NDMM patients treated with bortezomib-based induction, patients with single PS plasmacytoma had comparable treatment results to NDMM patients without any plasmacytomas (median PFS: 34.6 months vs. 38.1 months; $p = 0.662$). These results were improved with ASCT (median PFS: 46.0 months vs. 15.3 months; $p = 0.073$), but only 16% of patients with plasmacytomas in this study underwent ASCT [20]. Tandem ASCT did not show significant benefit in NDMM patients with plasmacytomas when compared to single ASCT [19] but may somehow have improved the inferior outcome of NDMM patients with plasmacytomas with high-risk cytogenetic aberrations [31]. Taken together, real-life induction protocols containing PIs, IMIDs and, in eligible patients, high-dose chemotherapy followed by ASCT, could change the outcome of NDMM patients with PS plasmacytomas.

Unfortunately, even our real-life dataset did not have many patients treated with anti-CD38 antibodies. While there is a lack of data about activity of anti-CD38 antibodies in the NDMM patients with plasmacytomas, data from RRMM patients with plasmacytomas are not promising [19,32].

In recently published papers, heterogeneity of MM patients with plasmacytomas is evident [7,8]. Moreover, this heterogeneity is strongly reflected in patients' prognosis. It is obvious that the clinical course of NDMM patients with plasmacytomas and RRMM patients with plasmacytomas is dramatically different [12,14,18,19].

Further, there is a difference in clinical characteristics and prognosis between patients with EMD and PS plasmacytomas [7,8]. In accord with recent papers [7,8,33], our clinical and research groups have long considered PS and EMD plasmacytomas as very different entities in both NDMM and RRMM patients. Thus, we have studied them separately [9,12,18,34]. However, other groups describe all plasmacytomas outside of BM environment as one unit often making comparisons impossible [13,28,35].

The robust size of our dataset provides deeper insight, surprisingly revealing a significant heterogeneity even within subgroups of patients with PS or EMD plasmacytomas. This heterogeneity was reflected in far different prognoses.

In our study, the subgroup with PS plasmacytomas with very low BM PC (<5%) infiltration had surprisingly good prognosis; we found significantly more patients with clinical features associated with better prognosis, such as low ISS stage and lower proportion of clonal PCs in BM, called MGUS-like phenotype. MGUS-like phenotype is associated with an indolent clinical course and long survival [36]. in addition to low intramedullary tumor burden, plasmacytoma count was also low.

On the other hand, patients with higher BM PC infiltration together with increasing plasmacytoma count had worse prognosis. More patients with unfavorable characteristics were present, together with a higher frequency of numerous osteolytic lesions and higher paraprotein secretory activity. Our findings are supported by recent analyses, showing the negative prognostic impact of BM infiltration (cut-off >30% BM PCs) together with multiple plasmacytomas [20]. Similarly to other analyses, multiple PS plasmacytomas were also connected with inferior prognosis [11,14].

The most important result of our analysis was the prognostic impact of EMD plasmacytomas in NDMM patients. Generally, the presence of EMD plasmacytoma is a strong negative prognostic factor in MM patients, more pronounced in RRMM patients [11–13,16,18,19,35]. Interestingly, beside long-known prognostic indicators, such as ISS and R-ISS stage, we found EMD plasmacytoma count to be a strong biomarker of worse prognosis. The subgroup of our patients with numerous EMD plasmacytomas had dismal prognosis, with median overall survival near 17 months. On the other hand, we showed that in NDMM patients with a low number (1–2) of EMD plasmacytomas, treatment results were somehow comparable with NDMM patient without plasmacytoma presence (median PFS: 20.9 months vs. 23.3 months, median OS: 50.9 months vs. 55.0 months). Our results highlight the importance of high-sensitive imaging methods especially in patients with EMD plasmacytomas. According to the high prognostic impact of EMD plasmacytoma count, we recommend whole-body

methods, such as PET/CT or WB-MRI in the standard diagnostic workup of NDMM patients with plasmacytomas [21].

These findings are in strict contrast with the dismal effect of EMD presence in RRMM patients [12,18,19] but, to the best of our knowledge, we have described the largest so-far published cohort of NDMM patients with EMD plasmacytomas detected by modern diagnostic methods and treated in real-life scenarios. Our findings are supported by another analysis of transplant-eligible NDMM patients where EMD patients with localized plasmacytoma involvement had a comparable 3-year PFS to that of NDMM patients without plasmacytomas (HR 1.03 (95% CI: 0.66-1.62; $p = 0.88$)), but patients with disseminated EMD plasmacytomas had worse prognosis (3-year PSF: HR 3.40 (95% CI: 1.74-6.61; $p < 0.001$) [11].

We found well-known high-risk cytogenetic aberrations del(17p) a t(4;14) retaining their negative prognostic impact predominantly in NDMM patients with PS plasmacytomas, as described in other studies [37,38]. Moreover, we found a negative prognostic impact of gain(1q21) in NDMM patients with EMD plasmacytomas. This finding is interesting, as we have previously published the higher risk of future plasmacytoma development in NDMM patients with gain(1q21) [18]. Similarly, analyses of a small groups of patients described higher incidence of gain(1q21) in NDMM patients with numerous EMD plasmacytomas [39,40]. Unfortunately, our results are based on a low number of evaluated samples. Another limitation was the absence of plasmacytoma tissue cytogenetics analysis in our work. Routine evaluation of plasmacytoma tissue can be complicated, mostly due to possible risk for patients from surgical sampling (i.e., paraspinal plasmacytomas and EMD in parenchymatous organs or the CNS).

5. Conclusions

Taken together, there is emerging evidence of the importance of the distinction between EMD and PS plasmacytomas in NDMM patients. Moreover, within these two entities, we found significant clinical heterogeneity, based on intra- and extramedullary tumor burden. These easy-to-assess biomarkers might reflect far different disease biology. Patients with PS plasmacytomas and low BM PC infiltration predominantly harbor low-risk features and have surprisingly good prognosis. In contrast, patients with higher BM PC infiltration and numerous PS plasmacytomas have poor prognosis. Prognosis of NDMM patients with EMD plasmacytomas is highly dependent on extramedullary burden. Patients with 1–2 EMD plasmacytomas had surprisingly comparable outcomes to NDMM patients without plasmacytoma. On the other hand, those with numerous EMD plasmacytomas had a dismal prognosis, resembling aggressivity of EMD plasmacytomas in RRMM patients.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/biomedicines10102535/s1, Table S1. Descriptive characteristics of patients' groups at NDMM diagnosis. Table S2. Treatment in first line of therapy.

Author Contributions: M.S., S.S. and L.P. (Ludek Pour) designed the study; M.S., T.J., J.M., J.R., T.P., I.S., J.S., P.P., A.J., Z.K., V.S., V.M., R.H. and L.P. (Ludek Pour) performed the research; M.S., S.S., L.P. (Lenka Pospisilova), L.P. (Ludek Pour) and J.M. wrote the paper; L.P. (Lenka Pospisilova) analyzed the data. All authors have read and agreed to the published version of the manuscript.

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References

1. Sant, M.; Allemani, C.; Tereanu, C.; De Angelis, R.; Capocaccia, R.; Visser, O.; Marcos-Gragera, R.; Maynadié, M.; Simonetti, A.; Lutz, J.-M.; et al. Incidence of Hematologic Malignancies in Europe by Morphologic Subtype: Results of the HAEMACARE Project. *Blood* **2010**, *116*, 3724–3734. [CrossRef] [PubMed]
2. Maluskova, D.; Svobodová, I.; Kucerova, M.; Brozova, L.; Muzik, J.; Jarkovský, J.; Hájek, R.; Maisnar, V.; Dusek, L. Epidemiology of Multiple Myeloma in the Czech Republic. *Klin. Onkol. Cas. Ceske Slov. Onkol. Spol.* **2017**, *30*, 35–42. [CrossRef]
3. Cavo, M.; San-Miguel, J.; Usmani, S.Z.; Weisel, K.; Dimopoulos, M.A.; Avet-Loiseau, H.; Paiva, B.; Bahlis, N.J.; Plesner, T.; Hungria, V.; et al. Prognostic Value of Minimal Residual Disease Negativity in Myeloma: Combined Analysis of POLLUX, CASTOR, ALCYONE, and MAIA. *Blood* **2022**, *139*, 835–844. [CrossRef]
4. Rodriguez-Otero, P.; Paiva, B.; San-Miguel, J.F. Roadmap to Cure Multiple Myeloma. *Cancer Treat. Rev.* **2021**, *100*, 102284. [CrossRef]
5. Kumar, S.K.; Rajkumar, V.; Kyle, R.A.; van Duin, M.; Sonneveld, P.; Mateos, M.-V.; Gay, F.; Anderson, K.C. Multiple Myeloma. *Nat. Rev. Dis. Primer* **2017**, *3*, 1–20. [CrossRef] [PubMed]
6. Morgan, G.J.; Rasche, L. Haematological Cancer: Where Are We Now with the Treatment of Multiple Myeloma? *Nat. Rev. Clin. Oncol.* **2017**, *14*, 461–462. [CrossRef] [PubMed]
7. Bladé, J.; Beksac, M.; Caers, J.; Jurczyszyn, A.; von Lilienfeld-Toal, M.; Moreau, P.; Rasche, L.; Rosiñol, L.; Usmani, S.Z.; Zamagni, E.; et al. Extramedullary Disease in Multiple Myeloma: A Systematic Literature Review. *Blood Cancer J.* **2022**, *12*, 45. [CrossRef] [PubMed]
8. Rosiñol, L.; Beksac, M.; Zamagni, E.; Van de Donk, N.W.C.J.; Anderson, K.C.; Badros, A.; Caers, J.; Cavo, M.; Dimopoulos, M.-A.; Dispenzieri, A.; et al. Expert Review on Soft-Tissue Plasmacytomas in Multiple Myeloma: Definition, Disease Assessment and Treatment Considerations. *Br. J. Haematol.* **2021**, *194*, 496–507. [CrossRef]
9. Sevcikova, S.; Minarik, J.; Stork, M.; Jelinek, T.; Pour, L.; Hajek, R. Extramedullary Disease in Multiple Myeloma–Controversies and Future Directions. *Blood Rev.* **2019**, *36*, 32–39. [CrossRef] [PubMed]
10. Durie, B.G.M. The Role of Anatomic and Functional Staging in Myeloma: Description of Durie/Salmon plus Staging System. *Eur. J. Cancer Oxf. Engl. 1990* **2006**, *42*, 1539–1543. [CrossRef]
11. Gagelmann, N.; Eikema, D.-J.; Iacobelli, S.; Koster, L.; Nahi, H.; Stoppa, A.-M.; Masszi, T.; Caillot, D.; Lenhoff, S.; Udvardy, M.; et al. Impact of Extramedullary Disease in Patients with Newly Diagnosed Multiple Myeloma Undergoing Autologous Stem Cell Transplantation: A Study from the Chronic Malignancies Working Party of the EBMT. *Haematologica* **2018**, *103*, 890–897. [CrossRef]
12. Pour, L.; Sevcikova, S.; Greslikova, H.; Kupska, R.; Majkova, P.; Zahradova, L.; Sandecka, V.; Adam, Z.; Krejci, M.; Kuglik, P.; et al. Soft-Tissue Extramedullary Multiple Myeloma Prognosis Is Significantly Worse in Comparison to Bone-Related Extramedullary Relapse. *Haematologica* **2014**, *99*, 360–364. [CrossRef]
13. Varettoni, M.; Corso, A.; Pica, G.; Mangiacavalli, S.; Pascutto, C.; Lazzarino, M. Incidence, Presenting Features and Outcome of Extramedullary Disease in Multiple Myeloma: A Longitudinal Study on 1003 Consecutive Patients. *Ann. Oncol. Off. J. Eur. Soc. Med. Oncol.* **2010**, *21*, 325–330. [CrossRef] [PubMed]
14. Montefusco, V.; Gay, F.; Spada, S.; Paoli, L.D.; Raimondo, F.D.; Ribolla, R.; Musolino, C.; Patriarca, F.; Musto, P.; Galieni, P.; et al. Outcome of Paraosseous Extra-Medullary Disease in Newly Diagnosed Multiple Myeloma Patients Treated with New Drugs. *Haematologica* **2020**, *105*, 193–200. [CrossRef]
15. Short, K.D.; Rajkumar, S.V.; Larson, D.; Buadi, F.; Hayman, S.; Dispenzieri, A.; Gertz, M.; Kumar, S.; Mikhael, J.; Roy, V.; et al. Incidence of Extramedullary Disease in Patients with Multiple Myeloma in the Era of Novel Therapy, and the Activity of Pomalidomide on Extramedullary Myeloma. *Leukemia* **2011**, *25*, 906–908. [CrossRef]
16. Usmani, S.Z.; Heuck, C.; Mitchell, A.; Szymonifka, J.; Nair, B.; Hoering, A.; Alsayed, Y.; Waheed, S.; Haider, S.; Restrepo, A.; et al. Extramedullary Disease Portends Poor Prognosis in Multiple Myeloma and Is Over-Represented in High-Risk Disease Even in the Era of Novel Agents. *Haematologica* **2012**, *97*, 1761–1767. [CrossRef] [PubMed]
17. Varga, C.; Xie, W.; Laubach, J.; Ghobrial, I.M.; O'Donnell, E.K.; Weinstock, M.; Paba-Prada, C.; Warren, D.; Maglio, M.E.; Schlossman, R.; et al. Development of Extramedullary Myeloma in the Era of Novel Agents: No Evidence of Increased Risk with Lenalidomide-Bortezomib Combinations. *Br. J. Haematol.* **2015**, *169*, 843–850. [CrossRef]
18. Stork, M.; Sevcikova, S.; Minarik, J.; Krhovska, P.; Radocha, J.; Pospisilova, L.; Brozova, L.; Jarkovsky, J.; Spicka, I.; Straub, J.; et al. Identification of Patients at High Risk of Secondary Extramedullary Multiple Myeloma Development. *Br. J. Haematol.* **2022**, *196*, 954–962. [CrossRef]
19. Beksac, M.; Seval, G.C.; Kanellias, N.; Coriu, D.; Rosiñol, L.; Ozet, G.; Goranova-Marinova, V.; Unal, A.; Bila, J.; Ozsan, H.; et al. A Real World Multicenter Retrospective Study on Extramedullary Disease from Balkan Myeloma Study Group and Barcelona University: Analysis of Parameters That Improve Outcome. *Haematologica* **2020**, *105*, 201–208. [CrossRef] [PubMed]
20. He, J.; Yue, X.; He, D.; Zhao, Y.; Yang, Y.; Zheng, G.; Zhang, E.; Han, X.; Wu, W.; Yang, L.; et al. Multiple Extramedullary-Bone Related and/or Extramedullary Extraosseous Are Independent Poor Prognostic Factors in Patients With Newly Diagnosed Multiple Myeloma. *Front. Oncol.* **2021**, *11*, 668099. [CrossRef]

21. Zamagni, E.; Nanni, C.; Dozza, L.; Carlier, T.; Bailly, C.; Tacchetti, P.; Versari, A.; Chauvie, S.; Gallamini, A.; Gamberi, B.; et al. Standardization of 18F-FDG-PET/CT According to Deauville Criteria for Metabolic Complete Response Definition in Newly Diagnosed Multiple Myeloma. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* **2021**, *39*, 116–125. [CrossRef]
22. Besse, L.; Sedlarikova, L.; Greslikova, H.; Kupska, R.; Almasi, M.; Penka, M.; Jelinek, T.; Pour, L.; Adam, Z.; Kuglik, P.; et al. Cytogenetics in Multiple Myeloma Patients Progressing into Extramedullary Disease. *Eur. J. Haematol.* **2016**, *97*, 93–100. [CrossRef]
23. Rajkumar, S.V.; Dimopoulos, M.A.; Palumbo, A.; Blade, J.; Merlini, G.; Mateos, M.-V.; Kumar, S.; Hillengass, J.; Kastritis, E.; Richardson, P.; et al. International Myeloma Working Group Updated Criteria for the Diagnosis of Multiple Myeloma. *Lancet Oncol.* **2014**, *15*, e538–e548. [CrossRef]
24. R Core Team. *R: A Language and Environment for Statistical Computing*; R Foundation for Statistical Computing: Vienna, Austria, 2015; Available online: https://www.R-project.org/ (accessed on 20 October 2020).
25. Mateos, M.-V.; Cavo, M.; Blade, J.; Dimopoulos, M.A.; Suzuki, K.; Jakubowiak, A.; Knop, S.; Doyen, C.; Lucio, P.; Nagy, Z.; et al. Overall Survival with Daratumumab, Bortezomib, Melphalan, and Prednisone in Newly Diagnosed Multiple Myeloma (ALCYONE): A Randomised, Open-Label, Phase 3 Trial. *Lancet Lond. Engl.* **2020**, *395*, 132–141. [CrossRef]
26. Facon, T.; Kumar, S.; Plesner, T.; Orlowski, R.Z.; Moreau, P.; Bahlis, N.; Basu, S.; Nahi, H.; Hulin, C.; Quach, H.; et al. Daratumumab plus Lenalidomide and Dexamethasone for Untreated Myeloma. *N. Engl. J. Med.* **2019**, *380*, 2104–2115. [CrossRef]
27. Yimer, H.; Melear, J.; Faber, E.; Bensinger, W.I.; Burke, J.M.; Narang, M.; Stevens, D.; Gunawardena, S.; Lutska, Y.; Qi, K.; et al. Daratumumab, Bortezomib, Cyclophosphamide and Dexamethasone in Newly Diagnosed and Relapsed Multiple Myeloma: LYRA Study. *Br. J. Haematol.* **2019**, *185*, 492–502. [CrossRef]
28. Landgren, O.; Sonneveld, P.; Jakubowiak, A.; Mohty, M.; Iskander, K.S.; Mezzi, K.; Siegel, D.S. Carfilzomib with Immunomodulatory Drugs for the Treatment of Newly Diagnosed Multiple Myeloma. *Leukemia* **2019**, *33*, 2127–2143. [CrossRef]
29. Wu, P.; Davies, F.E.; Boyd, K.; Thomas, K.; Dines, S.; Saso, R.M.; Potter, M.N.; Ethell, M.E.; Shaw, B.E.; Morgan, G.J. The Impact of Extramedullary Disease at Presentation on the Outcome of Myeloma. *Leuk. Lymphoma* **2009**, *50*, 230–235. [CrossRef]
30. Attal, M.; Harousseau, J.L.; Stoppa, A.M.; Sotto, J.J.; Fuzibet, J.G.; Rossi, J.F.; Casassus, P.; Maisonneuve, H.; Facon, T.; Ifrah, N.; et al. A Prospective, Randomized Trial of Autologous Bone Marrow Transplantation and Chemotherapy in Multiple Myeloma. Intergroupe Français Du Myélome. *N. Engl. J. Med.* **1996**, *335*, 91–97. [CrossRef]
31. Gagelmann, N.; Eikema, D.-J.; Koster, L.; Caillot, D.; Pioltelli, P.; Lleonart, J.B.; Reményi, P.; Blaise, D.; Schaap, N.; Trneny, M.; et al. Tandem Autologous Stem Cell Transplantation Improves Outcomes in Newly Diagnosed Multiple Myeloma with Extramedullary Disease and High-Risk Cytogenetics: A Study from the Chronic Malignancies Working Party of the European Society for Blood and Marrow Transplantation. *Biol. Blood Marrow Transplant. J. Am. Soc. Blood Marrow Transplant.* **2019**, *25*, 2134–2142. [CrossRef]
32. Jelinek, T.; Sevcikova, T.; Zihala, D.; Popkova, T.; Kapustova, V.; Broskevicova, L.; Capkova, L.; Rihova, L.; Bezdekova, R.; Sevcikova, S.; et al. Limited Efficacy of Daratumumab in Multiple Myeloma with Extramedullary Disease. *Leukemia* **2022**, *36*, 288–291. [CrossRef] [PubMed]
33. Bansal, R.; Rakshit, S.; Kumar, S. Extramedullary Disease in Multiple Myeloma. *Blood Cancer J.* **2021**, *11*, 161. [CrossRef] [PubMed]
34. Gregorova, J.; Vychytilova-Faltejskova, P.; Kramarova, T.; Knechtova, Z.; Almasi, M.; Stork, M.; Pour, L.; Kohoutek, J.; Sevcikova, S. Proteomic Analysis of the Bone Marrow Microenvironment in Extramedullary Multiple Myeloma Patients. *Neoplasma* **2022**, *69*, 412–424. [CrossRef] [PubMed]
35. Weinstock, M.; Aljawai, Y.; Morgan, E.A.; Laubach, J.; Gannon, M.; Roccaro, A.M.; Varga, C.; Mitsiades, C.S.; Paba-Prada, C.; Schlossman, R.; et al. Incidence and Clinical Features of Extramedullary Multiple Myeloma in Patients Who Underwent Stem Cell Transplantation. *Br. J. Haematol.* **2015**, *169*, 851–858. [CrossRef]
36. Paiva, B.; Vídriales, M.-B.; Rosiñol, L.; Martínez-López, J.; Mateos, M.-V.; Ocio, E.M.; Montalbán, M.-Á.; Cordón, L.; Gutiérrez, N.C.; Corchete, L.; et al. A Multiparameter Flow Cytometry Immunophenotypic Algorithm for the Identification of Newly Diagnosed Symptomatic Myeloma with an MGUS-like Signature and Long-Term Disease Control. *Leukemia* **2013**, *27*, 2056–2061. [CrossRef]
37. Abdallah, N.; Rajkumar, S.V.; Greipp, P.; Kapoor, P.; Gertz, M.A.; Dispenzieri, A.; Baughn, L.B.; Lacy, M.Q.; Hayman, S.R.; Buadi, F.K.; et al. Cytogenetic Abnormalities in Multiple Myeloma: Association with Disease Characteristics and Treatment Response. *Blood Cancer J.* **2020**, *10*, 82. [CrossRef]
38. Sonneveld, P.; Avet-Loiseau, H.; Lonial, S.; Usmani, S.; Siegel, D.; Anderson, K.C.; Chng, W.-J.; Moreau, P.; Attal, M.; Kyle, R.A.; et al. Treatment of Multiple Myeloma with High-Risk Cytogenetics: A Consensus of the International Myeloma Working Group. *Blood* **2016**, *127*, 2955–2962. [CrossRef]
39. Qu, X.; Chen, L.; Qiu, H.; Lu, H.; Wu, H.; Qiu, H.; Liu, P.; Guo, R.; Li, J. Extramedullary Manifestation in Multiple Myeloma Bears High Incidence of Poor Cytogenetic Aberration and Novel Agents Resistance. *BioMed Res. Int.* **2015**, *2015*, 787809. [CrossRef]
40. Biran, N.; Malhotra, J.; Bagiella, E.; Cho, H.J.; Jagannath, S.; Chari, A. Patients with Newly Diagnosed Multiple Myeloma and Chromosome 1 Amplification Have Poor Outcomes despite the Use of Novel Triplet Regimens. *Am. J. Hematol.* **2014**, *89*, 616–620. [CrossRef]

2.7.4. Stork M, Spicka I, Radocha J, Minarik J, Jelinek T, Jungova A, Pavlicek P, Pospisilova L, Sedlak F, Straub J, Pika T, Knechtova Z, Fidrichova A, Boichuk I, Sevcikova S, Maisnar V, Hajek R, Pour L. **Daratumumab with lenalidomide and dexamethasone in relapsed/refractory multiple myeloma – real world evidence.** Ann Hematol. 2023;102(6):1501–1511.

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ORIGINAL ARTICLE

Daratumumab with lenalidomide and dexamethasone in relapsed or refractory multiple myeloma patients – real world evidence analysis

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Abstract
We performed real world evidence (RWE) analysis of daratumumab, lenalidomide and dexamethasone (Dara-Rd) versus lenalidomide and dexamethasone (Rd) treatment in relapsed/refractory multiple myeloma patients (RRMM). In total, 240 RRMM patients were treated with Dara-Rd from 2016 to 2022 outside of clinical trials in all major Czech hematology centers. As a reference, 531 RRMM patients treated with Rd were evaluated. Patients' data were recorded in the Czech Registry of Monoclonal Gammopathies (RMG). Partial response (PR) or better response (ORR) was achieved in significantly more patients in Dara-Rd than in Rd group (91.2% vs. 69.9%; $p<0.001$). The median progression free survival (PFS) was 26.9 months in the Dara-Rd and 12.8 months in the Rd group ($p<0.001$). Median overall survival (OS) was not reached in the Dara-Rd compared to 27.2 months in the Rd group ($p=0.023$). In patients with 1–3 previous treatment lines, there was significant PFS benefit of Dara-Rd compared to Rd (median PFS not reached vs. 13.2 months; $p<0.001$). In patients with > 3 previous treatment lines, there was no significant PFS benefit of Dara-Rd treatment (7.8 months vs. 9.9 months; $p=0.874$), similarly in patients refractory to PI + IMIDs (11.5 months vs. 9.2 months; $p=0.376$). In RWE conditions, the median PFS in RRMM patients treated with Dara-Rd is shorter when compared to clinical trials. In heavily pretreated RRMM patients, efficacy of Dara-Rd treatment is limited; best possible outcomes of Dara-Rd are achieved in minimally pretreated patients.

Keywords Multiple myeloma · Treatment · Response rate · Relapse

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Introduction

In the last two decades, multiple myeloma (MM) treatment underwent significant progress [1]. The use of anti-CD38 monoclonal antibodies (mAbs) together with proteasome inhibitors (PI) and immunomodulatory drugs (IMIDs) became an emerging treatment modality with remarkable results. In clinical trials, anti-CD38 mAbs demonstrated high efficacy both in relapsed and newly diagnosed MM patients [2–6].

Daratumumab is the first widely used anti-CD38 mAb [7]. By binding to CD38 antigen on MM cells surface, daratumumab promotes apoptosis of MM cells and activates immune mechanisms (antibody-dependent cellular cytotoxicity (ADCC), antibody dependent cellular phagocytosis (ADCP) and complement dependent cytotoxicity (CDC)) leading to MM cell death [8, 9]. Immunomodulatory effect of daratumumab was also described to effect T-cells [10, 11]. In the first-in-human use, daratumumab monotherapy achieved response in 38% of heavily pretreated patients [12]. In preclinical tests, synergy of daratumumab and IMIDs was demonstrated [13]. Based on these results, in the phase III clinical trial POLLUX, daratumumab in combination with lenalidomide and dexamethasone (Dara-Rd) was compared to lenalidomide and dexamethasone (Rd). Dara-Rd regimen achieved deep responses (30.4% patients with negative minimal residual disease (MRD)) even in relapsed or refractory MM (RRMM) patients, and significantly prolonged median progression free survival (mPFS) to 45.5 months when compared to Rd alone (mPFS 17.5 months, $p < 0.001$) [2, 14]. Thus, Dara-Rd became a new standard-of-care for RRMM in many European countries [1, 15, 16].

However, randomized clinical trials (RCT) describe data different from real world evidence (RWE) conditions. In the RCT for MM, important subgroups of patients are often neglected. These subgroups are characterized with an aggressive disease course (extramedullary plasmacytoma, disease refractory to specific drugs, hyperviscosity with necessity of plasmapheresis, myeloma induced kidney failure, etc.) or significant comorbidities [17, 18].

With respect to these differences, we analyzed the outcomes of Dara-Rd regimen in real-world clinical conditions to define which patients benefit from Dara-Rd treatment the most.

Patients and methods

Our study is a multicentric real-life retrospective study carried out in major hematologic centers in the Czech Republic between 2016 and 2022. Patients represent real world RRMM population treated with best available treatment at the time.

Data from patients treated in Dara-Rd and Rd groups were collected from the Registry of Monoclonal Gammopathies (RMG) of the Czech Myeloma Group. In total, 240 RRMM patients treated with Dara-Rd and 531 RRMM patients treated with Rd were enrolled. Only one patient from the Dara-Rd group was enrolled in 2016, the rest of the cohort was enrolled from 2019 to 2022. Patients in the Rd group were enrolled from 2016 to 2019, when Rd was the golden standard for RRMM patients' treatment. Patients treated with Rd before 2016 were excluded for historical lenalidomide reimbursement rules in the Czech Republic (after cumulative dose of 4200 mg, lenalidomide treatment had to be stopped). Patients treated with Rd after 2019 were also censored, as modern lenalidomide-based triplets (with daratumumab, ixazomib or carfilzomib) were used in the Czech Republic as a new golden standard. Thus, after 2019, patients treated in the Czech Republic only with Rd were mostly palliative. Enrolling them could seriously bias our results, favoring Dara-Rd group. All enrolled patients were treated outside of clinical trials. All patients provided informed consent for participation in the study according to the declaration of Helsinki.

Patients in Dara-Rd group received standard dosing of Daratumumab 16 mg/kg intravenous or 1800 mg subcutaneous equivalent [19] on day 1, 8, 15, 22 in cycle 1–2, day 1, 15 in cycles 3–6, and day 1 at cycles 7 and more; lenalidomide 25 mg on days 1 through 21, and dexamethasone 20–40 mg on days 1, 8, 15 and 22 in 28-day cycles. Patients in Rd group received lenalidomide 25 mg on days 1 through 21 and dexamethasone 20–40 mg on days 1, 8, 15 and 22 in 28-day cycles. Reduction of lenalidomide or dexamethasone was allowed according to physicians' decision. Patients in Dara-Rd arm had corticosteroid-based premedication according to institutional guidelines before daratumumab administration.

All patients were required to use thromboprophylaxis and herpes zoster prophylaxis per institutional guidelines. Cytogenetic aberrations were evaluated at the time of newly diagnosed multiple myeloma (NDMM).

Assessments

All the data were recorded in the RMG. The endpoints were assessed based on the International Myeloma Working Group (IMWG) response criteria, incorporating an additional category of minimal response. Survival intervals progression free survival (PFS), duration of response (DOR) and overall survival (OS) were assessed from Dara Rd/Rd treatment beginning.

Statistical analysis

Depending on the nature of the data, suitable methods for description and statistical testing were selected. Categorical variables were described using absolute and relative

frequencies and continuous variables by median complemented with 5th and 95th percentile. In accordance with data continuity (categorical x continuous), Pearson Chi-Square (resp. Fisher's exact test in case of non-meeting criteria) or Mann–Whitney U test was used to examine the association between selected variables and treatment regimen. Event-free survival (PFS, DOR and OS) was assessed using the Kaplan–Meier methodology, and statistical significance of differences in survival between subgroups was assessed using the log-rank test. All statistical tests were performed at a significance level of $\alpha=0.05$ (all tests two-sided). The analysis was performed in SPSS software (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 25Armonk, NY: IBM Corp.) and software R version 3.4.2 (www.r-project.org).

Table 1 Characteristics of Dara-Rd vs. Rd patients

	Rd		Dara-Rd		p-value
	N	%	N	%	
Sex	531	100%	240	100%	
Woman	267	50.3%	108	45.0%	0.186
Man	264	49.7%	132	55.0%	
Age at treatment initiation [years]	531	100%	240	100%	
<65	127	23.9%	106	44.2%	<0.001
65–75	263	49.5%	113	47.1%	
>75	141	26.6%	21	8.8%	
median (5th–95th perc.)	71.1	54.1–82.6	66.0	45.9–77.7	<0.001
ECOG PS at treatment initiation	506	100%	238	100%	
PS 0	85	16.8%	58	24.4%	<0.001
PS 1	250	49.4%	143	60.1%	
PS 2	139	27.5%	34	14.3%	
PS 3–4	32	6.3%	3	1.3%	
ISS at treatment initiation	426	100%	200	100%	
Stage 1	154	36.2%	92	46.0%	0.037
Stage 2	150	35.2%	53	26.5%	
Stage 3	122	28.6%	55	27.5%	
Cytogenetic risk at diagnosis	204	100%	132	100%	
standard	144	70.6%	95	72.0%	0.806
high	60	29.4%	37	28.0%	
Number of previous lines of therapy	531	100%	240	100%	
1 previous line	341	64.2%	173	72.1%	0.045
2–3 previous lines	161	30.3%	52	21.7%	
>3 previous lines	29	5.5%	15	6.3%	
median (5th–95th perc.)	1	1.0–4.0	1	1.0–4.0	0.090
Previous treatment by:	531	100%	240	100%	
Proteasome inhibitors (PI)	497	93.6%	234	97.5%	0.034
Immunomodulatory drugs (IMiD)	271	51.0%	159	66.3%	<0.001
PI + IMiD	243	45.8%	154	64.2%	<0.001
Transplantation	178	33.5%	161	67.1%	<0.001
Refractory in previous treatment to:	531	100%	240	100%	
Proteasome inhibitors (PI)	155	29.2%	64	26.7%	0.491
Immunomodulatory drugs (IMiD)	69	13.0%	45	18.8%	0.038
Lenalidomide	11	2.1%	24	10.0%	<0.001
PI + IMiD	171	32.2%	71	29.6%	0.503
Plasmacytoma	531	100%	240	100%	
no	406	76.5%	166	69.2%	0.022
Found in NDMM	66	12.4%	48	20.0%	
Developed in RRMM	59	11.1%	26	10.8%	
Length of therapy [months]	466	100%	100	100%	
median (5th–95th perc.)	7.4	1.2–33.9	7.5	0.7–23.7	0.254

Results

Patients and treatment

Altogether, 240 patients were treated with Dara-Rd regimen and 531 patients with Rd regimen. Median age was 66.0 years (5^{th}–95^{th} percentile 45.9–77.7) in the Dara-Rd group and 71.1 years (5^{th}–95^{th} percentile 54.1–82.6) in the Rd group ($p<0.001$). There was a comparable number of patients with high-risk cytogenetic aberrations (HR-CA; t(4;14), t(14;16), del(17p)) in both groups (28.0% (37/132) vs. 29.4% (60/204), $p=0.806$).

The median of previous treatment lines was comparable between both groups (1 [95% CI: 1–4] vs. 1 [95% CI: 1–4], $p=0.090$). There were significantly more patients exposed to PI + IMIDs (64.2% (154/240) vs. 45.8% (243/531), $p<0.001$) in the Dara-Rd group. Number of PI + IMIDs refractory patients were comparable in both groups (29.6% (71/240) vs. 32.2% (171/531), $p=0.503$. The median follow-up from Dara-Rd vs. Rd treatment initiation was 13.5 months [95% CI: 1.3–26.6] in the Dara-Rd group and 23.7 months [95% CI: 1.5–59.7] in the Rd group. Baseline characteristics of patients are summarized in Table 1.

Response to treatment

According to IMWG criteria, treatment response was evaluable in 181 patients in the Dara-Rd group and 429 patients in the Rd group. Complete response (CR) or stringent CR (sCR) was achieved in 4.4% (8/181) of patients in Dara-Rd group, compared to 3.3% (14/429) of patients in Rd group. Very good partial response (VGPR) or better response was achieved in 66.8% (121/181) of patients in Dara-Rd group, compared to 27.5% (118/429) of patients in Rd group. Partial response (PR) or better response (ORR) was achieved in significantly more patients in Dara-Rd group than in Rd group (91.2% vs. 69.9%). Differences in treatment responses were statistically significant ($p<0.001$), favoring Dara-Rd regimen (Table 2).

Survival intervals

Median PFS was 26.9 months [95% CI: 20.6-NA] in the Dara-Rd group and 12.8 months [95% CI: 11.2–14.6] in the Rd group (HR: 1.81; [95% CI: 1.43–2.29]; $p<0.001$) (Fig. 1A). Median OS was not reached in the Dara-Rd group compared to 27.2 months [95% CI: 24.0–31.3] in the Rd group (HR: 1.38; [95% CI: 1.05–1.83]; $p=0.023$) (Fig. 1B).

Progression free survival—subgroup analysis

In the subgroup of patients with 1–3 previous treatment lines, Dara-Rd treatment significantly prolonged PFS, when compared to Rd (Not reached vs. 13.2 months [95% CI: 11.4–14.7], HR: 1.94; [95% CI: 1.51–2.48]; $p<0.001$). In patients with > 3 previous treatment lines, there was no significant PFS benefit of Dara-Rd treatment (7.8 months [95% CI: 2.4–NA] vs. 9.9 months [95% CI: 7.6–22.1], HR: 0.94; [95% CI: 0.44–2.00]; $p=0.874$) (Fig. 2).

In subgroup of patients who were refractory to PI + IMIDs, there was no significant PFS benefit of Dara-Rd treatment over Rd treatment (11.5 months [95% CI: 8.1–NA] vs. 9.2 months [95% CI: 6.4–12.7], HR: 1.18; [95% CI: 0.82–1.70]; $p=0.376$) (Fig. 3).

In subgroup of patients who were refractory to lenalidomide, there was no significant PFS benefit of Dara-Rd treatment over Rd treatment (10.1 months [95% CI: 4.0–NA] vs. 12.7 months [95% CI: 4.9–NA], HR: 0.98; [95% CI: 0.39–2.45]; $p=0.961$) (Supplementary Fig. 1).

In the subgroup of patients with HR-CA (t(4;14), t(14;16), del(17p)), there was no significant PFS benefit of Dara-Rd treatment (9.7 months [95% CI: 5.8–13.7] vs. 10.2 months [95% CI: 6.4–13.5], HR: 0.82; [95% CI: 0.51–1.33]; $p=0.428$) (Supplementary Fig. 2), similarly to patients with gain(1q21) (13.8 months [95% CI: 9.9–20.7] vs. 10.2 months [95% CI: 6.9–12.8], HR: 1.33; [95% CI: 0.92–1.91); $p=0.129$) (Supplementary Fig. 3). In the subgroup of RRMM patients with plasmacytoma found at the time of NDMM, Dara-Rd treatment prolonged PFS, when compared to Rd, but did not reach the level of statistical significance (23.6 months [95% CI: 10.8–NA] vs. 10.0 months [95% CI: 7.0–16.1], HR: 1.60; [95% CI: 0.95–2.69]; $p=0.080$). In RRMM patients with plasmacytoma newly developed at disease relapse/progression, there was no significant PFS benefit of Dara-Rd treatment (9.9 months [95% CI: 3.9–16.5] vs. 6.4 months [95% CI: 4.4–12.8], HR: 0.85; [95% CI: 0.49–1.46]; $p=0.554$) (Supplementary Fig. 4).

Dara-Rd treatment effect on PFS in different patients' subgroups is summarized in Table 3.

Table 2 Treatment results of Dara Rd vs. Rd

	Rd		Dara-Rd		p-value
	N	%	N	%	
Maximal response to treatment	429*	100,0%	181*	100,0%	
sCR, CR	14	3,3%	8	4,4%	<0.001
VGPR	104	24,2%	113	62,4%	
PR	182	42,4%	44	24,3%	
MR	54	12,6%	9	5,0%	
SD	32	7,5%	6	3,3%	
PD	43	10,0%	1	0,6%	
Overal response rate (ORR)	429	100,0%	181	100,0%	
PR +	300	69,9%	165	91,2%	<0.001
worse than PR	129	30,1%	16	8,8%	

*Only evaluable patients according to IMWG criteria

Overall survival – subgroup analysis

In subgroup of patients who were refractory to PI + IMIDs, there was no significant OS benefit of Dara-Rd treatment over Rd treatment (19.6 months [95% CI: 13.7–NA] vs. 19.9 months [95% CI:14.6–24.4], HR: 1.07; [95% CI: 0.70–1.63]; p = 0.749). In the subgroup of patients with HR-CA, there was OS benefit of Dara-Rd treatment, but did not reach the level of statistical significance (13.7 months [95% CI: 10.1–NA] vs. 23.9 months [95% CI:15.3–29.6], HR: 0.72; [95% CI: 0.41–1.26]; p = 0.247). There was no significant OS benefit of Dara-Rd treatment over Rd in the subgroup of patients with gain(1q21) (not reached vs.24.6 months [95% CI: 17.8–31.4], HR: 1.10; [95% CI: 0.70–1.72); p = 0.690).

Dara-Rd treatment effect on OS in different patients' subgroups is summarized in Table 4.

Adverse events

Infusion related reactions (IRRs) gr. 2–3 after daratumumab administration were present in 13.3% (32/240) of patients. Higher grades of IRRs were not observed. Serious (gr. 3–4) adverse events (AEs) of Dara-Rd regimen were dominantly hematologic—neutropenia (50.9%

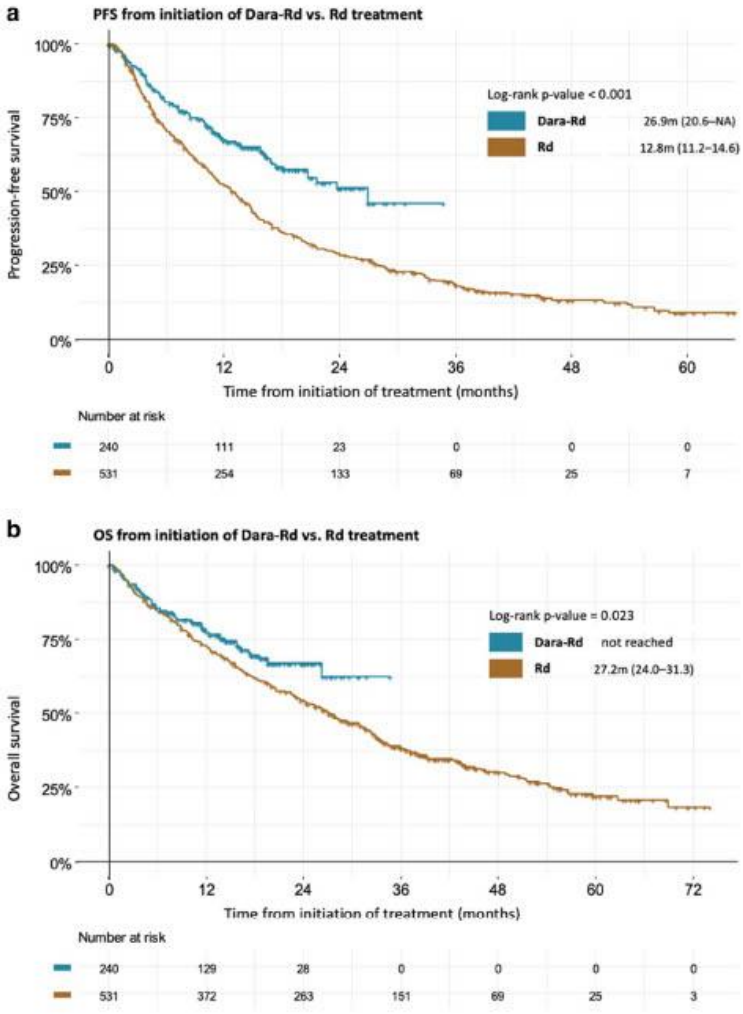

Fig. 1 **A** Progression-free survival of Dara-Rd vs. Rd group. **B** Overall survival of Dara-Rd vs. Rd group

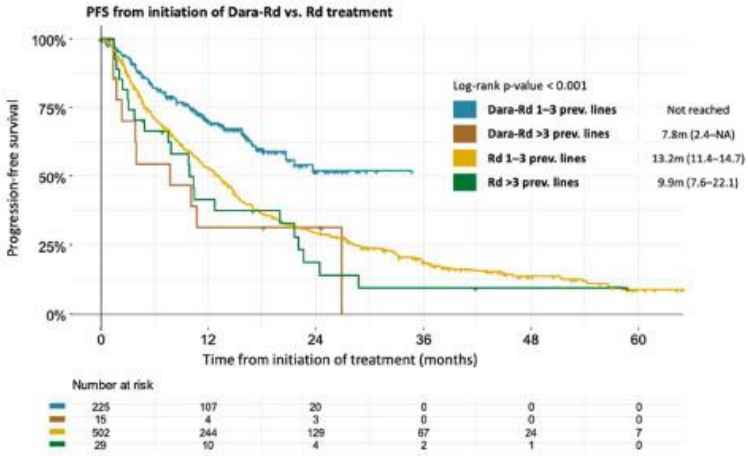

Fig. 2 Progression-free survival of Dara Rd vs Rd patients with 1–3 previous treatment lines

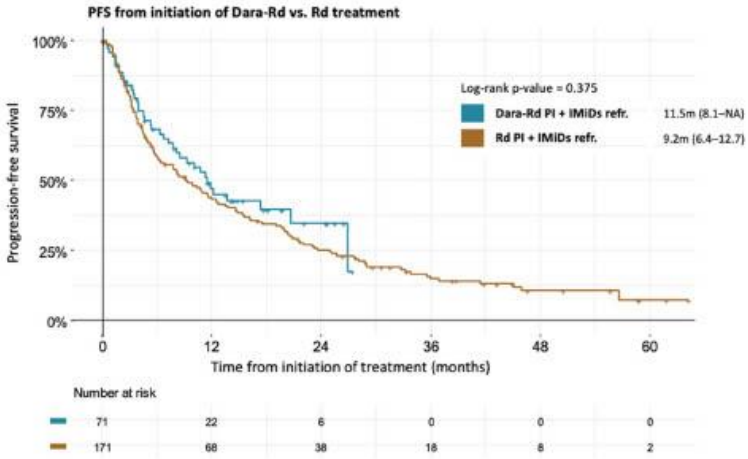

Fig. 3 No significantly different PFS in PI/IMIDs refractory patients

(80/157)), anemia (14.9% (23/154)) and thrombopenia (16.3% (25/153)). Other serious (gr.3–4) non-hematologic AEs was infections 16.2% (29/179), thromboembolic disease (4.5% (7/154)), diarrhea (2.9% (5/171)), fatigue (1.8% (3/169)), polyneuropathy (1.3% (2/157), nausea (1.3% (2/156), decompensation of diabetes mellitus (1.0% (1/101)), rash (0.6% (1/158)) and anorexia (0.6% (1/157)). In the Dara-Rd group, there were 5 deaths related to infection complications. Mild (gr.1–2) AEs and comparison with Rd group is summarized in supplementary Table 1.

Discussion

Novel drugs, such as daratumumab, isatuximab, carfilzomib and ixazomib, were carefully evaluated in RRMM patients in large multicentric RCT [2, 20]. Unluckily, population of MM patients eligible for RCT enrollment is significantly different from general MM patients' population [17]. Therefore, there is a rapidly emerging importance of RWE analyses. Following a general trend of personalized medicine [21], in real-life conditions, it is necessary to differentiate which patients would benefit

Table 3 Association of Dara-Rd and Rd with survival in selected subgroups

Variable	Category	Rd	Dara-Rd	PFS – Univariable Cox model		
				HR*	95% CI	p-value
Total	Total	531	240	1.81	(1.43–2.29)	<0.001
Age	≤75	390	219	1.75	(1.36–2.25)	<0.001
	>75	141	21	2.08	(0.97–4.49)	0.062
ISS	Stage 1	154	92	1.29	(0.85–1.96)	0.240
	Stage 2	150	53	2.23	(1.37–3.63)	0.001
	Stage 3	122	55	1.73	(1.11–2.71)	0.015
Creatinine level (µmol/l)	≤ 176	441	210	1.88	(1.45–2.43)	<0.001
	> 176	77	30	1.44	(0.81–2.55)	0.219
ECOG	PS 0–1	335	201	1.76	(1.34–2.31)	<0.001
	PS 2	139	34	1.35	(0.80–2.29)	0.267
	PS 3–4	32	3	0.52	(0.15–1.76)	0.293
Number of previous lines of therapy	1–3 previous lines	502	225	1.94	(1.51–2.48)	<0.001
	> 3 previous lines	29	15	0.94	(0.44–2.00)	0.874
Plasmacytoma	no	406	166	2.31	(1.69–3.14)	<0.001
	Found in NDMM	66	48	1.60	(0.95–2.69)	0.080
	Developed in RRMM	59	26	0.85	(0.49–1.46)	0.554
Cytogenetic risk at diagnosis	standard	144	95	1.88	(1.25–2.81)	0.002
	high	60	37	0.82	(0.51–1.33)	0.428
Gain(1q21)	no	158	89	1.96	(1.26–3.05)	0.003
	yes	111	84	1.33	(0.92–1.91)	0.129
Refractory to previous proteasome inhibitors (PI)	no	376	176	2.16	(1.60–2.91)	<0.001
	yes	155	64	1.24	(0.84–1.82)	0.281
Refractory to immunomodulatory drugs (IMiD)	no	462	195	2.22	(1.68–2.93)	<0.001
	yes	69	45	1.06	(0.67–1.70)	0.799
Refractory to lenalidomide	no	520	216	2.01	(1.56–2.58)	<0.001
	yes	11	24	0.98	(0.39–2.45)	0.961
Refractory to PI + IMiD	no	360	169	2.28	(1.68–3.10)	<0.001
	yes	171	71	1.18	(0.82–1.70)	0.376

*HR > 1 – Dara-Rd better; HR < 1 – Rd better

from specific treatment modality. Moreover, with various treatment options, proper timing of each treatment modality plays an important role [1]. Dealing with this issue, we performed a national RWE analysis of Dara-Rd treatment regimen.

Despite having an unselected patient population and not-evaluable treatment response in all patients, overall response to Dara-Rd treatment in our analysis was comparable to the POLLUX trial (91.2% vs. 92.9%) [14]. Low CR rate in our analysis is due to absence of routine BM evaluation in our RRMM patients, as the results would have had no practical impact on patients' treatment course, and the treatment was until progression. On the other hand, survival intervals of Dara-Rd treatment were nearly half-time, when compared to the POLLUX trial. Main explanation is in the differences between the patients' cohorts [14]. In our cohort, there was a higher proportion of patients with high-risk cytogenetic aberrations (28.0% vs. 15.0%), double refractory (PI+IMID) patients (29.6% vs 2.4%) and high proportion of patients with plasmacytomas (30.5%). In contrast with the POLLUX trial, we included 10% of lenalidomide refractory patients [14].

In our analysis, we found uncertain clinical benefit of Dara-Rd treatment in patients with more than 3 previous treatment lines. It is important to mention that our results may be influenced by low number of patients in this cohort. However, this finding was also shown in the POLLUX trial, when benefit from Dara-Rd was less pronounced in the more pretreated patients and vice versa (PFS: > 3 lines HR: 0.74 [CI 95% (0.24–2.26)] vs. HR: 0.42 [95% (0.30–0.58)]) [2]. Similarly, we found

Table 4 Association of Dara-Rd and Rd with survival in selected subgroups

Variable	Category	Rd	Dara-Rd	OS – Univariable Cox model		
				HR*	95% CI	p-value
Total	Total	531	240	1.38	(1.05–1.83)	0.023
Age	≤75	390	219	1.28	(0.95–1.73)	0.104
	>75	141	21	2.23	(0.81–6.12)	0.120
ISS	Stage 1	154	92	0.98	(0.58–1.66)	0.928
	Stage 2	150	53	1.53	(0.84–2.77)	0.164
	Stage 3	122	55	1.22	(0.74–1.99)	0.434
Creatinine level (µmol/l)	≤176	441	210	1.38	(1.01–1.89)	0.043
	> 176	77	30	1.38	(0.73–2.62)	0.321
ECOG	PS 0–1	335	201	1.20	(0.85–1.70)	0.289
	PS 2	139	34	1.09	(0.62–1.93)	0.769
	PS 3–4	32	3	0.56	(0.17–1.88)	0.349
Number of previous lines of therapy	1–3 previous lines	502	225	1.55	(1.14–2.09)	0.005
	> 3 previous lines	29	15	0.57	(0.26–1.25)	0.158
Plasmacytoma	no	406	166	1.72	(1.18–2.50)	0.004
	Found in NDMM	66	48	1.35	(0.73–2.47)	0.338
	Developed in RRMM	59	26	0.73	(0.39–1.39)	0.340
Cytogenetic risk at diagnosis	standard	144	95	1.56	(0.95–2.57)	0.081
	high	60	37	0.72	(0.41–1.26)	0.247
Gain(1q21)	no	158	89	1.34	(0.80–2.24)	0.272
	yes	111	84	1.10	(0.70–1.72)	0.690
Refractory to previous proteasome inhibitors (PI)	no	376	176	1.48	(1.03–2.12)	0.033
	yes	155	64	1.18	(0.76–1.85)	0.463
Refractory to immunomodulatory drugs (IMiD)	no	462	195	1.78	(1.26–2.50)	0.001
	yes	69	45	0.80	(0.47–1.36)	0.404
Refractory to lenalidomide	no	520	216	1.57	(1.16–2.14)	0.004
	yes	11	24	0.85	(0.31–2.32)	0.747
Refractory to PI + IMiD	no	360	169	1.60	(1.10–2.34)	0.015
	yes	171	71	1.07	(0.70–1.63)	0.749

*HR > 1 – Dara-Rd better; HR < 1 – Rd better

non-significant benefit of Dara-Rd treatment in patients refractory to PI, IMIDs or both. Our results are also unique for presence of lenalidomide refractory patients, while the POLLUX trial did not enroll them. These results show patients refractory to lenalidomide to have inferior outcome from the Dara-Rd treatment.

Overall, our analysis in accord with the POLLUX trial shows crucial role of Dara-Rd treatment timing, as the best effect is achieved in less pretreated patients [2]. These results are consistent with other RWE analysis, where the best results of daratumumab treatment were achieved in the first relapse (time to next treatment—25.9 months [22]). Similar results of Dara-Rd treatment in minimally pretreated patients were published by Italian [23, 24] or Spanish authors [25]. Results favoring the less pretreated patients were also shown in other triplet regimens, combining IMIDs and PI, like a pomalidomide-bortezomib-dexamethasone [26], or carfilzomib-lenalidomide-dexamethasone [27, 28]. These findings point to an actual unmet need for novel treatment strategies and molecular targets for multiple refractory MM patients instead of repeating of previously used drug classes [29–31].

In our analysis, we used HR-CA (del(17p), t(4;14) and t(14;16) based on the older classification from 2009 for better comparison with the POLLUX trial [32]. The benefit of Dara-Rd treatment in patients with HR-CA in our analysis was not significant, likewise in the patients with gain(1q21), nowadays recognized as a HR-CA [33]. This finding contrasts with the outcomes of the POLLUX trial where patients with HR-CA maintain PFS benefit by daratumumab treatment (HR: 0.43 [95% CI, 0.32–0.57]) [2]. Similarly, there was PFS benefit in daratumumab with dexamethasone over bortezomib with dexamethasone (HR: 0.41 [95% CI, 0.21–0.83]) [34] and in combination of daratumumab—carfilzomib—dexamethasone over carfilzomib—dexamethasone alone (HR: 0.56 [95% CI, 0.34–0.93]) [35]. Interestingly, RCTs dealing

with daratumumab in the front-line setting do not confirm clear benefit of daratumumab treatment in HR-CA patients [36–38]. This controversy only highlights necessity to consider HR-CA in a wider context of other high-risk factors, such as high LDH levels [39], extramedullary plasmacytomas [40] or circulating plasma cells [41]. Moreover, methods, such as FISH, may not reveal more complex aberrations (e.g., chromotrypsis or specific gene mutations), which have negative prognostic impact as well.

Daratumumab has limited efficiency in MM patients with plasmacytoma [42–44]. In our analysis, patients with plasmacytoma found at the time of NDMM had somehow better Dara-Rd treatment results than patients, who developed plasmacytoma in disease relapse or progression (RRMM). This interesting finding demonstrates different clinical course of these two entities, even in relapsed setting [45–47]. Our results were, however, influenced by relatively low number of patients with this form of MM.

Clear limitation of our study was a short follow-up of Dara-Rd cohort (median 13.5 months). Based on this limitation, we can more clearly point to patients with limited profit from Dara-Rd treatment than to patients who had the best outcomes. Another important limitation arises from the retrospective and non-randomized character of the analysis and limited cohorts size. For that reason, similarly to other non-randomized RWE studies, especially results in the subgroups should be assessed critically. Other limitation of our study was the absence of valid information of patients' MRD status while BM evaluations was not routinely done in all patients, as previously described. According to POLLUX results, best treatment results of Dara-Rd regimen were shown in patients achieving CR (42-month PFS rates of 73.6%) [2]. Other study dealing with daratumumab treatment showed achievement of MRD negative status as a most important predictor of treatment success [48].

Taken together, our RWE results emphasize the importance of timing of modern treatment protocols. Dara-Rd treatment in relapsed/refractory setting should be used as soon as possible to maintain best possible effect. Use of this regimen in heavily pretreated or high-risk patients should be individually considered with respect to other treatment options.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00277-023-05188-4.

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Data availability Data are available upon request from corresponding author.

Declarations

Conflict of interests Authors declare no conflict of interest.

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References

1. Rajkumar SV (2022) Multiple myeloma: 2022 update on diagnosis, risk stratification, and management. Am J Hematol 97:1086–1107. https://doi.org/10.1002/ajh.26590
2. Bahlis NJ, Dimopoulos MA, White DJ et al (2020) Daratumumab plus lenalidomide and dexamethasone in relapsed/refractory multiple myeloma: extended follow-up of POLLUX, a randomized, open-label, phase 3 study. Leukemia 34:1875–1884. https://doi.org/10.1038/s41375-020-0711-6
3. Avet-Loiseau H, San-Miguel J, Casneuf T et al (2021) Evaluation of Sustained Minimal Residual Disease Negativity With Daratumumab-Combination Regimens in Relapsed and/or Refractory Multiple Myeloma: Analysis of POLLUX and CASTOR. J Clin Oncol 39:1139–1149. https://doi.org/10.1200/JCO.20.01814
4. Voorhees PM, Rodriguez C, Reeves B et al (2021) Daratumumab plus RVd for newly diagnosed multiple myeloma: final analysis of the safety run-in cohort of GRIFFIN. Blood Adv 5:1092–1096. https://doi.org/10.1182/bloodadvances.2020003642
5. Facon T, Kumar S, Plesner T et al (2019) Daratumumab plus Lenalidomide and Dexamethasone for Untreated Myeloma. N Engl J Med 380:2104–2115. https://doi.org/10.1056/NEJMoa1817249
6. Attal M, Richardson PG, Rajkumar SV et al (2019) Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): a randomised, multicentre, open-label, phase 3 study. Lancet 394:2096–2107. https://doi.org/10.1016/S0140-6736(19)32556-5
7. Usmani SZ, Nahi H, Plesner T et al (2020) Daratumumab monotherapy in patients with heavily pretreated relapsed or refractory multiple myeloma: final results from the phase 2 GEN501 and SIRIUS trials. Lancet Haematol 7:e447–e455. https://doi.org/10.1016/S2352-3026(20)30081-8
8. Wang W, Erbe AK, Hank JA et al (2015) NK Cell-Mediated Antibody-Dependent Cellular Cytotoxicity in Cancer Immunotherapy. Front Immunol 6:368. https://doi.org/10.3389/fimmu.2015.00368
9. van de Donk NWCJ, Usmani SZ (2018) CD38 Antibodies in Multiple Myeloma: Mechanisms of Action and Modes of Resistance. Front Immunol 9:2134. https://doi.org/10.3389/fimmu.2018.02134

10. Krejcik J, Casneuf T, Nijhof IS et al (2016) Daratumumab depletes CD38+ immune regulatory cells, promotes T-cell expansion, and skews T-cell repertoire in multiple myeloma. Blood 128:384–394. https://doi.org/10.1182/blood-2015-12-687749
11. van de Donk NWCJ (2019) Reprint of "Immunomodulatory effects of CD38-targeting antibodies." Immunol Lett 205:71–77. https://doi.org/10.1016/j.imlet.2019.02.002
12. Lokhorst HM, Plesner T, Laubach JP et al (2015) Targeting CD38 with Daratumumab Monotherapy in Multiple Myeloma. N Engl J Med 373:1207–1219. https://doi.org/10.1056/NEJMoa1506348
13. van der Veer MS, de Weers M, van Kessel B et al (2011) Towards effective immunotherapy of myeloma: enhanced elimination of myeloma cells by combination of lenalidomide with the human CD38 monoclonal antibody daratumumab. Haematologica 96:284–290. https://doi.org/10.3324/haematol.2010.030759
14. Dimopoulos MA, Oriol A, Nahi H et al (2016) Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma. N Engl J Med 375:1319–1331. https://doi.org/10.1056/NEJMoa1607751
15. Mateos M-V, Ludwig H, Bazarbachi A et al. (2018) Insights on Multiple Myeloma Treatment Strategies. Hemasphere 3:e163 https://doi.org/10.1097/HS9.0000000000000163
16. Terpos E, Engelhardt M, Cook G et al (2020) Management of patients with multiple myeloma in the era of COVID-19 pandemic: a consensus paper from the European Myeloma Network (EMN). Leukemia 34:2000–2011. https://doi.org/10.1038/s41375-020-0876-z
17. Chari A, Romanus D, Palumbo A et al (2020) Randomized Clinical Trial Representativeness and Outcomes in Real-World Patients: Comparison of 6 Hallmark Randomized Clinical Trials of Relapsed/Refractory Multiple Myeloma. Clin Lymphoma Myeloma Leuk 20:8-17.e16. https://doi.org/10.1016/j.clml.2019.09.625
18. Richardson PG, San Miguel JF, Moreau P et al (2018) Interpreting clinical trial data in multiple myeloma: translating findings to the real-world setting. Blood Cancer J 8:109. https://doi.org/10.1038/s41408-018-0141-0
19. Mateos M-V, Nahi H, Legiec W et al (2020) Subcutaneous versus intravenous daratumumab in patients with relapsed or refractory multiple myeloma (COLUMBA): a multicentre, open-label, non-inferiority, randomised, phase 3 trial. Lancet Haematol 7:e370–e380. https://doi.org/10.1016/S2352-3026(20)30070-3
20. Moreau P, Masszi T, Grzasko N et al (2016) Oral Ixazomib, Lenalidomide, and Dexamethasone for Multiple Myeloma. N Engl J Med 374:1621–1634. https://doi.org/10.1056/NEJMoa1516282
21. Pawlyn C, Davies FE (2019) Toward personalized treatment in multiple myeloma based on molecular characteristics. Blood 133:660–675. https://doi.org/10.1182/blood-2018-09-825331
22. Szabo AG, Klausen TW, Levring MB et al. (2021) The real-world outcomes of multiple myeloma patients treated with daratumumab. PLoS One 16:e0258487. https://doi.org/10.1371/journal.pone.0258487
23. Fazio F, Franceschini L, Tomarchio V et al (2022) Daratumumab combined with dexamethasone and lenalidomide or bortezomib in relapsed/refractory multiple myeloma (RRMM) patients: Report from the multiple myeloma GIMEMA Lazio group. EJHaem 3:121–128. https://doi.org/10.1002/jha2.359
24. Antonioli E, Staderini M, Pilerci S et al (2020) Daratumumab, lenalidomide, and dexamethasone combination in relapsed/refractory myeloma patients: a real-life single-center experience. Leuk Lymphoma 61:3255–3258. https://doi.org/10.1080/10428194.2020.1802452
25. Fucci L, Gensini L, Coppetelli U et al. (2022) Daratumumab triplet therapies in patients with relapsed or refractory multiple myeloma: A "real world" experience. Leuk Res Rep 17:100330 https://doi.org/10.1016/j.lrr.2022.100330
26. Richardson PG, Oriol A, Beksac M et al (2019) Pomalidomide, bortezomib, and dexamethasone for patients with relapsed or refractory multiple myeloma previously treated with lenalidomide (OPTIMISMM): a randomised, open-label, phase 3 trial. Lancet Oncol 20:781–794. https://doi.org/10.1016/S1470-2045(19)30152-4
27. Stewart AK, Rajkumar SV, Dimopoulos MA et al (2015) Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. N Engl J Med 372:142–152. https://doi.org/10.1056/NEJMoa1411321
28. Rocchi S, Tacchetti P, Pantani L et al (2021) A real-world efficacy and safety analysis of combined carfilzomib, lenalidomide, and dexamethasone (KRd) in relapsed/refractory multiple myeloma. Hematol Oncol 39:41–50. https://doi.org/10.1002/hon.2820
29. van de Donk NWCJ, Usmani SZ, Yong K (2021) CAR T-cell therapy for multiple myeloma: state of the art and prospects. Lancet Haematol 8:e446–e461. https://doi.org/10.1016/S2352-3026(21)00057-0
30. Rodriguez-Otero P, Paiva B, San-Miguel JF (2021) Roadmap to cure multiple myeloma. Cancer Treat Rev 100:102284. https://doi.org/10.1016/j.ctrv.2021.102284
31. Lancman G, Sastow DL, Cho HJ et al (2021) Bispecific Antibodies in Multiple Myeloma: Present and Future. Blood Cancer Discov 2:423–433. https://doi.org/10.1158/2643-3230.BCD-21-0028
32. Fonseca R, Bergsagel P, Drach J et al (2009) International Myeloma Working Group molecular classification of multiple myeloma: spotlight review. Leukemia 23:2210–2221. https://doi.org/10.1038/leu.2009.174
33. Sonneveld P, Avet-Loiseau H, Lonial S et al (2016) Treatment of multiple myeloma with high-risk cytogenetics: a consensus of the International Myeloma Working Group. Blood 127:2955–2962. https://doi.org/10.1182/blood-2016-01-631200
34. Weisel K, Spencer A, Lentzsch S et al (2020) Daratumumab, bortezomib, and dexamethasone in relapsed or refractory multiple myeloma: subgroup analysis of CASTOR based on cytogenetic risk. J Hematol Oncol 13:115. https://doi.org/10.1186/s13045-020-00948-5
35. Landgren O, Weisel K, Rosinol L et al (2022) Subgroup analysis based on cytogenetic risk in patients with relapsed or refractory multiple myeloma in the CANDOR study. Br J Haematol 198:988–993. https://doi.org/10.1111/bjh.18233
36. Mateos M-V, Dimopoulos MA, Cavo M et al (2018) Daratumumab plus Bortezomib, Melphalan, and Prednisone for Untreated Myeloma. N Engl J Med 378:518–528. https://doi.org/10.1056/NEJMoa1714678
37. Bahlis N, Facon T, Usmani SZ et al (2019) Daratumumab Plus Lenalidomide and Dexamethasone (D-Rd) Versus Lenalidomide and Dexamethasone (Rd) in Patients with Newly Diagnosed Multiple Myeloma (NDMM) Ineligible for Transplant: Updated Analysis of Maia. Blood 134:1875. https://doi.org/10.1182/blood-2019-123426
38. Moreau P, Attal M, Hulin C et al (2019) Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): a randomised, open-label, phase 3 study. Lancet 394:29–38. https://doi.org/10.1016/S0140-6736(19)31240-1
39. Palumbo A, Avet-Loiseau H, Oliva S et al (2015) Revised International Staging System for Multiple Myeloma: A Report From International Myeloma Working Group. J Clin Oncol 33:2863–2869. https://doi.org/10.1200/JCO.2015.61.2267
40. Pour L, Sevcikova S, Greslikova H et al (2014) Soft-tissue extramedullary multiple myeloma prognosis is significantly worse in comparison to bone-related extramedullary relapse. Haematologica 99:360–364. https://doi.org/10.3324/haematol.2013.094409

41. Jelinek T, Bezdekova R, Zihala D et al. (2022) More Than 2% of Circulating Tumor Plasma Cells Defines Plasma Cell Leukemia-Like Multiple Myeloma. J Clin Oncol JCO2201226 https://doi.org/10.1200/JCO.22.01226
42. Jelinek T, Sevcikova T, Zihala D et al (2022) Limited efficacy of daratumumab in multiple myeloma with extramedullary disease. Leukemia 36:288–291. https://doi.org/10.1038/s41375-021-01343-w
43. Byun JM, Min C-K, Kim K et al (2022) Phase II trial of daratumumab with DCEP in relapsed/refractory multiple myeloma patients with extramedullary disease. J Hematol Oncol 15:150. https://doi.org/10.1186/s13045-022-01374-5
44. Beksac M, Spicka I, Hajek R et al. (2022) Evaluation of isatuximab in patients with soft-tissue plasmacytomas: An analysis from ICARIA-MM and IKEMA. Leuk Res 122:106948. https://doi.org/10.1016/j.leukres.2022.106948
45. Richardson PG, Perrot A, San-Miguel J, Beksac M, Spicka I, Leleu X, Schjesvold F, Moreau P, Dimopoulos MA, Shang-Yi Huang J, Minarik J, Cavo M, Prince HM, Malinge L, Dubin F, van de Velde H, Anderson KC (2022) Isatuximab plus pomalidomide and lowdose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refraktory multiple myeloma (ICARIA-MM): follow-up analysis of a randomised, phase 3 study. Lancet Oncol 23(3):416–427. https://doi.org/10.1016/S1470-2045(22)00019-5
46. Stork M, Sevcikova S, Jelinek T et al (2022) Unexpected Heterogeneity of Newly Diagnosed Multiple Myeloma Patients with Plasmacytomas. Biomedicines 10:2535. https://doi.org/10.3390/biomedicines10102535
47. Gagelmann N, Eikema D-J, Iacobelli S et al (2018) Impact of extramedullary disease in patients with newly diagnosed multiple myeloma undergoing autologous stem cell transplantation: a study from the Chronic Malignancies Working Party of the EBMT. Haematologica 103:890–897. https://doi.org/10.3324/haematol.2017.178434
48. Cavo M, San-Miguel J, Usmani SZ et al (2022) Prognostic value of minimal residual disease negativity in myeloma: combined analysis of POLLUX, CASTOR, ALCYONE, and MAIA. Blood 139:835–844. https://doi.org/10.1182/blood.2021011101

2.7.5. Stork M, Radocha J, Mihalyova J, Spicka I, Pika T, Jungova A, Boichuk I, Mensikova K, Straub J, Sedlak F, Minarik J, Krhovska P, Novakova D, Hornakova M, Knechtova Z, Sendlerova N, Dekojova T, Maisnar V, Jelinek T, Hajek R, Pour L. **De-escalated teclistamab dosing in relapsed/refractory multiple myeloma: Czech myeloma group real-world analysis.** Ann Hematol. 2025 Aug;104(8):4141-4147

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RESEARCH

De-escalated Teclistamab dosing in relapsed/refractory multiple myeloma: Czech myeloma group real-world evidence analysis

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Abstract
Teclistamab, a BCMA×CD3 bispecific antibody, demonstrates high efficacy in relapsed/refractory multiple myeloma (RRMM). However, optimal dosing strategies outside clinical trials remain undefined. Thus, we performed a retrospective, multicentre analysis of 73 RRMM patients treated with teclistamab monotherapy at Czech Myeloma Group centres between 2023 and 2025. The study compared efficacy and safety between patients receiving standard weekly dosing and those with reduced-frequency dosing. The whole cohort had a median age of 67 years; 68.5% were penta-refractory. Dosing was de-escalated in 24.7% of patients, typically within one month of treatment initiation. Median progression-free survival (PFS) was 9.41 months and was comparable between weekly and non-weekly groups (9.1 vs. 11.3 months; $p=0.141$), despite a significantly lower relative dose intensity in the latter (60.5% vs. 87.0%; $p<0.001$). Infection rates and severe adverse events were similar between groups. A lower incidence of neutropenia was observed with less frequent dosing, but this did not translate into reduced infection burden. In conclusion, in real-world practice, early de-escalation of teclistamab dosing appears to maintain clinical efficacy. These findings support ongoing efforts to individualize treatment schedules with the aim of balancing effectiveness, tolerability, and patient-specific factors in BCMA-targeted therapy.

Keywords Multiple myeloma · Teclistamab · Immunotherapy · Real-world-evidence

Introduction

Teclistamab is a bispecific antibody that targets multiple myeloma (MM) by binding to B-cell maturation antigen (BCMA) on MM cells and CD3 on T cells, triggering a T-cell-mediated anti-tumor response. In the MajesTEC-1 trial, it showed high efficacy in heavily pretreated patients with relapsed/refractory MM (RRMM) [1], supported by emerging real-world evidence [2–4]. However, teclistamab carries a high risk of infections due to B-cell depletion and

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immune dysregulation. Recurrent infections affect ~ 60–75% of patients, mostly related to teclistamab-induced hypogammaglobulinemia [5].

In the MajesTEC-1 trial, patients received an initial step-up dosing of teclistamab followed by a fixed weekly maintenance dose. For those who achieved a complete response after six months of treatment, the dosing frequency could be reduced to biweekly administration [1]. In real-world clinical practice, however, dosing schedules are often adapted for various reasons, potentially deviating from the standardized protocols used in controlled clinical trials.

Patients and methods

We conducted a retrospective analysis of teclistamab monotherapy in heavily pretreated RRMM patients across all major Czech haematology centres between 2023 and 2025. The primary objective of this study was to compare the efficacy and safety of standard dosing versus reduced-frequency dosing. All data were collected and analysed from the Czech Registry of Monoclonal Gammopathies (RMG) of Czech Myeloma Group (CMG). All participants provided written informed consents approved by institutional Ethics boards in accordance with the latest Helsinki declaration. Data collection cut-off date was 10th January 2025.

The study population consisted of 73 RRMM patients with a median age of 67.0 years (range, 41–83). The median number of prior lines of therapy was 5 (range, 3–13), with 68.5% (50/73) of patients being penta-refractory. Totally 24.7% (18/73) of patients had extramedullary plasmacytomas (EMD, not associated to bone lesions). Of the 59 patients with available cytogenetics, 45.8% (27/59) had two or more high-risk cytogenetic aberrations (HR-CA, defined as t(4;14), t(14;16), del(17p), del(1p32) and gain/amp(1q21)). The median follow-up was 4.9 months (range, 0.3–17.9).

Teclistamab was administered subcutaneously in all patients according to a step-up dosing protocol (0.06 mg/kg on Day 1 and 0.3 mg/kg on Day 4, followed by the first full dose of 1.5 mg/kg on Day 7). Subsequently, in the Weekly group, teclistamab is given at a maintenance dose of 1.5 mg/kg once weekly until disease progression or unacceptable toxicity occurs. In patients who achieved a complete response (CR) or better for at least six months, the dosing frequency of teclistamab was reduced to every other week. Patients who had earlier dosing frequency de-escalation for various reasons were categorized as the Non-weekly group.

Response was assessed according to International Myeloma Working Group criteria. Relative dose intensity (RDI) was counted as the ratio of real cumulative dose (RCD) to maximal ideal dose (MID). Event-free survival (progression free survival - PFS, and overall survival - OS) was defined as the time from treatment initiation to the event or patient's last follow-up. If the event didn't occur, the censoring was done at the time of a last follow-up. It was assessed using the Kaplan-Meier methodology and all point estimates include 95% confidence intervals (95% CI). The statistical significance of differences in survival between subgroups was assessed using the log-rank test. The statistical significance of differences in categorical or continuous variables between the subgroups was tested by Fisher Exact test or Mann-Whitney U test. All statistical tests were performed at a significance level of $\alpha = 0.05$ (all tests two-sided).

Results

Response and survival in all patients

The overall response rate (ORR) in evaluable patients was 58.8% (40 out of 68), with 52.9% (36 out of 68) achieving a very good partial response (VGPR) or better. The median PFS was 9.41 months (95% CI: 7.11–not applicable), and the median OS was 15.38 months (95% CI: 10.95–not applicable).

Prognostic subgroups

Achievement of a deeper response was strongly associated with improved survival outcomes. Patients who achieved a VGPR or better had significantly longer median PFS compared to those with a partial response (PR) or less: 15.38 months (95% CI: 11.18–not estimable) vs. 1.38 months (95% CI: 1.28–3.48), respectively ($p < 0.001$). This benefit was also reflected in estimated 12-month overall survival (OS) rates, which were 75.0% (95% CI: 57.2–98.4) for patients with VGPR or better, compared to 27.8% (95% CI: 12.5–61.8) for those with PR or worse ($p < 0.001$).

Additionally, patients with extramedullary disease (EMD) had shortest median PFS compared to those with para-skeletal plasmacytomas (growing outside of bone lesions) or those with the absence of plasmacytomas: 3.87 months (95% CI: 1.38–not estimable) vs. 10.1 months (95% CI: 6.4– not estimable) vs. not estimable; $p = 0.059$. Moreover, patients harbouring ≥ 2 high-risk HR-CA had shorter median PFS when compared to those with 1 or no HR-CA: 1.84 months (95% CI: 1.38–not estimable) vs. 9.4 months (95% CI: 7.97–not estimable); $p = 0.022$, respectively. A full overview of survival outcomes in whole cohort and subgroups is provided in Supplementary Figs. 1–8.

Dosing frequency and relative dose intensity

Dosing frequency was modified in 24.7% (18/73) of patients, with 72.2% (13/18) receiving teclistamab every two weeks and 27.8% (5/18) every four weeks. The median time to de-escalation was 1 month (range, 0–3). The most common reason for de-escalation was achievement of a favourable response (55.6%, 10/18), followed by adverse events (33.3%, 6/18) and patient frailty (11.1%, 2/18).

The median relative dose intensity (RDI), calculated as the ratio of actual cumulative dose (RCD) to the maximum ideal dose (MID), was 80.1% (range, 25.3–100.0%) across the entire cohort. Patients in the non-weekly dosing group had a significantly lower median RDI of 60.5% (range, 37.2–93.8%) compared to 87.0% (range, 25.3–100.0%) in the weekly group ($p<0.001$).

Baseline characteristics were generally balanced between groups. The median age was slightly higher in the non-weekly group (69 years [range, 49–83]) than in the weekly group (66 years [range, 41–85]; $p=0.065$). Median ECOG performance status was 1 in both groups (range, 0–3; $p=0.37$). Additional comparisons of baseline characteristics and supportive treatment are provided in Table 1.

Survival outcomes by dosing frequency

Progression-free survival (PFS) was comparable between patients receiving weekly and non-weekly teclistamab dosing. The median PFS was 9.1 months (95% CI: 2.7–not estimable) in the weekly group and 11.3 months (95% CI: 6.4–not estimable) in the non-weekly group ($p=0.141$).

Overall survival (OS) data were still immature at the time of analysis. However, estimated 12-month OS rates suggested a clinically meaningful trend in favour of weekly dosing: 62.3% (95% CI: 47.6–81.5) in the weekly group versus 36.6% (95% CI: 14.0–95.9) in the non-weekly group. This difference did not reach statistical significance ($p=0.667$). The survival according to dosing frequency is shown in Fig. 1a, b.

Adverse events by dosing frequency

Cytokine release syndrome (CRS) occurred in 49.3% (36/73) of patients, predominantly grade 1 (39.7%, 29/73), with an additional 9.6% (7/73) experiencing grade 2 events. Immune effector cell-associated neurotoxicity syndrome (ICANS) was reported in two patients (2.7%), both cases being grade 1. Tocilizumab was administered to 9.6% (7/73) of patients to manage CRS and/or ICANS.

Infection rates were comparable between dosing groups when analysed after de-escalation. Infections occurred in 80.0% (44/55) of patients in the weekly group and 66.7% (12/18) in the non-weekly group ($p=0.335$). Severe infections (grade 3–4) were reported in 29.1% (16/55) of weekly-dosed patients and 50.0% (9/18) of non-weekly patients ($p=0.152$). One patient in the weekly group died from severe sepsis linked to teclistamab treatment.

Among patients in the non-weekly group, infection incidence remained similar before and after dose de-escalation. A total of 55.6% (10/18) experienced infections prior to de-escalation, and 66.7% (12/18) thereafter ($p=0.733$). Severe infections occurred in 22.2% (4/18) before de-escalation and in 50.0% (9/18) afterward ($p=0.164$), indicating a numerical increase that did not reach statistical significance.

Table 1 Demographic characteristics and treatment in non-weekly and weekly dosing groups

	Non weekly dosing	Weekly dosing	*p* value‡
Number of pts (%, n/N)	24.7% (18/73)	75.3% (55/73)	-
Median age (y, range)	69.0 (49.0–83.0)	66.0 (41.0–85.0)	0.065
Gender (female, % n/N)	55.6% (10/18)	49.1% (27/55)	0.787
ISS stage (%, 1/2/3)	27.8%/38.9%/33.3%	30.9%/45.5%/23.6%	0.716
ECOG performance status (median, range)	1 (0–3)	1 (0–3)	0.370
No. of previous treatment lines (median, range)	4 (3–9)	5 (3–13)	0.459
Penta-refractory patients	55.6% (10/18)	88.9% (40/55)	0.242
Previous anti-BCMA therapy	5.6% (1/18	14.5% (8/55)	0.436
Extramedullary plasmacytomas	11.1% (2/18)	29.1% (16/55)	0.207
2 or more HR-CA^{+}	28.6% (4/14)	48.9% (22/45)	0.227
Without IVIG* administration	27.8% (5/18)	23.6% (13/55)	0.758
Median monthly IVIG* dose (grams/patient)	19.1 (4.0-22.7)	22.4 (4.0-100.0)	0.056
Median follow up (months, range)	5.9 (1.3–13.9)	4.7 (0.3–17.9)	0.327

HR-CA– high-risk cytogenetic aberrations^{+};* intravenous immunoglobulins

‡ Fisher Exact test or Chi-square test, Mann-Whitney U test

$^{+}$ t(4;14), t(14;16), del(17p), del(1p32) and gain/amp(1q21)

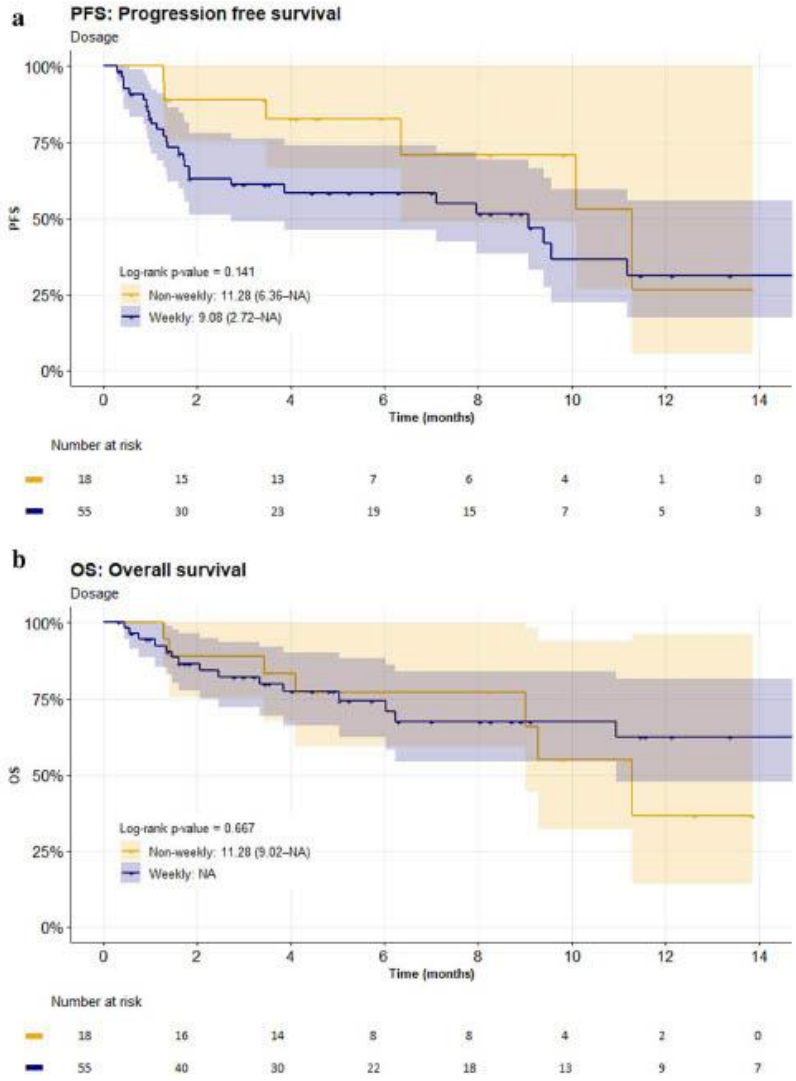

Fig. 1 a -Progression free survival (PFS) - Non-weekly vs. Weekly dosingb - Overall survival (OS) - Non-weekly vs. Weekly dosing

When assessing cumulative infection episodes irrespective of timing, the median number of all infection events was 2 (range, 0–12) in the weekly group and 1 (range, 0–11) in the non-weekly group ($p=0.730$). However, the median number of grade 3–4 infection episodes was significantly higher in the non-weekly group (median 1; range, 0–3) compared to the weekly group (median 0; range, 0–4; $p=0.033$).

Neutropenia occurred more frequently in patients receiving weekly dosing: 61.8% (34/55) versus 22.2% (4/18) in the non-weekly group ($p=0.006$). The incidence of severe neutropenia (grade 3–4) was similar between groups (23.6% vs. 16.7%; $p=0.745$). In the non-weekly group, severe neutropenia occurred in 5.5% (1/18) of patients prior to de-escalation and in 16.7% (3/18) after de-escalation ($p=0.603$). Rates of anemia and thrombocytopenia were comparable between the two groups. Detailed toxicity data are presented in Table 2. Severe toxicity before and after de-escalation is summarized in the Supplementary Table 1.

Table 2 Toxicity according to dosing scheme

Adverse event	Gr.	Non-weekly dosing	Weekly dosing	*p* value*
CRS	Gr.1–2	44.4% (8/18)	49.1% (27/55)	0.790
ICANS	Gr.1	11.1% (2/18)	0.0%	1.000
Infection^{+}	Total	66.7% (12/18)	80.0% (44/55)	0.335
	Gr.3–4	50.0% (9/18)	29.1% (16/55)	0.152
	Gr.5	0.0%	1.8% (1/55)	1.000
Anemia^{+}	Total	38.9% (7/18)	63.6% (35/55)	0.099
	Gr.3–4	5.6% (1/18)	7.3% (4/55)	1.000
Thrombopenia^{+}	Total	22.2% (4/18)	41.8% (23/55)	0.167
	Gr.3–4	16.7% (3/18)	10.9% (6/55)	0.680
Neutropenia^{+}	Total	22.2% (4/18)	61.8% (34/55)	**0.006**
	Gr.3–4	16.7% (3/18)	23.6% (13/55)	0.745

CRS – Cytokine Release Syndrome; ICANS – Immune effector Cell Associated Neurotoxicity Syndrome; * Fisher exact test; $^{+}$ - counted in the non-weekly group after the de-escalation;

Bold values are statistically significant

Discussion

This multicentre real-world study demonstrates that teclistamab dosing in routine clinical practice often diverges from the fixed weekly maintenance schedule employed in the MajesTEC-1 trial. Despite less frequent dosing, PFS remained comparable to weekly dosing, indicating sustained efficiency in responding patients.

Clinical data on dosing de-escalation of anti-BCMA bispecific antibodies remain limited. In a real-world study, 32% (25/77) of patients transitioned to every-other-week dosing of teclistamab after three months due to toxicity or achieving partial response. At six months, the progression-free survival rate was 94% among these patients, compared to 52% in the overall cohort, likely reflecting positive selection of responders [6]. For elranatamab, the MagnetisMM-3 trial showed that responders could reduce dosing from weekly to every-other-week after six months, then to every-four-week after another six months without losing efficacy [7]. Our data uniquely show the median time to dosing frequency de-escalation was just one month—much shorter than previous studies. Current clinical trials are designed to evaluate both the efficacy and safety of teclistamab at reduced dosing as a monotherapy [8], as well as in combination with other antimyeloma agents [9, 10].

Despite maintained efficacy in non-weekly dosing, no reduction of infection events was observed. This may be due to the prolonged impact of teclistamab on immunoglobulin production, extending beyond the 2- or 4-week off-therapy periods. Variability in intravenous immunoglobulin administration and supportive care across real-world settings also likely contributes to generally inconsistent toxicity outcomes [5, 11, 12]. In our country, immunoglobulin substitution practices vary between centers, with a significant shift from secondary to primary prophylaxis during the study duration. Based on these findings, primary prophylaxis with intravenous immunoglobulins may play an important role in infection management during anti-BCMA therapy, potentially more so than dose reductions. Moreover, response to treatment was the primary reason for dose de-escalation, but frailty and recurring infections also contributed, potentially biasing adverse event reports in the non-weekly group. Also, these patients were generally older. While bispecific antibodies' efficacy is unaffected by age [1, 6, 13], elderly patients are more susceptible to infections and hematologic toxicity. Both groups were balanced regarding EMD and high-risk cytogenetics, which negatively influenced prognosis both in our study and in so far published works [1, 3].

We noted a reduced incidence of neutropenia with the non-weekly dosing schedule. Since BCMA is not typically expressed on myeloid cells or neutrophils, this might result from less immune cell-mediated myelosuppression due to lower teclistamab plasma levels [13]. The impact of teclistamab dosing frequency on myeloid cells remains unclear and warrants further study.

The OS data, though still immature, seems to favor weekly dosing. Factors such as patient age or alternative treatments like GPRC5D or FCRH5 bispecific antibodies for teclistamab-refractory patients may influence results [14, 15]. More research is needed on how reduced anti-BCMA bispecific antibody dosing affects subsequent therapy efficacy, particularly regarding T-cell exhaustion [16, 17].

The retrospective nature of our study, small sample size and the variability in clinical decision-making processes are limitations that should be acknowledged. However, our findings offer valuable insights into the real-world application of teclistamab and may guide future research efforts aimed at optimizing dosing protocols to balance efficacy, safety, and treatment costs. Our approach may also assist clinicians with teclistamab dosing decisions in challenging cases.

Taken together, in a real-world setting, early de-escalation of teclistamab dosing did not compromise efficacy especially in responding patients. However, reduced dosing was not associated with a lower rate of infectious complications. These findings suggest that flexible, response-adapted dosing strategies may be appropriate in select patients, particularly those with frailty or tolerability concerns. Further prospective studies are needed to validate these observations and to better define the impact of dosing modifications on long-term outcomes, immune recovery, and subsequent therapy sequencing.

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Author contributions MS designed the study and wrote the manuscript. MS, JR, JM, IS, TP, AJ, IB, KM, JS, FS, JM, PK, DN, MH, TD, VM, TJ, RH and LP treated the patients and provided clinical data. ZK and NS provided and analyzed preclinical data. All authors interpreted and discussed the results. All authors approved the final version of the manuscript prior to submission. LP and RH are joined last authors.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests MS: Jonhson & Jonhnson: Consultancy, Other: Travel support, Honoraria for lectures JR: BMS: Consultancy, Honoraria; Sanofi: Consultancy, Honoraria; Johnson & Johnson: Consultancy, Honoraria; GSK: Consultancy; Pfizer: Consultancy, Honoraria. TJ: Janssen: Consultancy, Other: Honoraria for lectures, Research Funding; Sanofi: Other: Honoraria for lectures, Research Funding; Pfizer: Consultancy,Other: Honoraria for lectures; BristolMyers Squibb:Other:Honoraria for lectures; GlaxoSmithKline: Consultancy, Other: Honoraria for lectures; Amgen: Research Funding. IS: BMS: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Travel Support; Amgen: Consultancy, Honoraria; Janssen-Cilag: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Travel support; Takeda: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; Sanofi: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Travel Support; GSK: Consultancy, Membership on an entity's Board of Directors or advisory committees. JM: Amgen: Consultancy, Honoraria; BMS: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; GSK: Membership on an entity's Board of Directors or advisory committees; Janssen: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; Pfizer: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; Sanofi: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees. RH: Takeda: Consultancy, Honoraria, Research Funding; Janssen: Consultancy, Honoraria, Research Funding; Amgen: Consultancy, Honoraria, Research Funding; Celgene: Consultancy, Honoraria, Research Funding; AbbVie: Consultancy; BMS: Consultancy, Honoraria, Research Funding; PharmaMar: Consultancy, Honoraria; Novartis: Consultancy, Research Funding.

References

1. Moreau P, Garfall AL, van de Donk NWCJ, Nahi H, San-Miguel JF, Oriol A et al (2022) Teclistamab in relapsed or refractory multiple myeloma. N Engl J Med 387(6):495–505. https://doi.org/10.1056/NEJMoa2203478
2. Mohan M, Monge J, Shah N, Luan D, Forsberg M, Bhatlapenumarthi V et al (2024) Teclistamab in relapsed refractory multiple myeloma: multi-institutional real-world study. Blood Cancer J 14(1):35. https://doi.org/10.1038/s41408-024-01003-z
3. Riedhammer C, Bassermann F, Besemer B, Bewarder M, Brunner F, Carpinteiro A et al (2024) Real-world analysis of Teclistamab in 123 RRMM patients from Germany. Leukemia 38(2):365–371. https://doi.org/10.1038/s41375-024-02154-5
4. Tan CRC, Asoori S, Huang CY, Brunaldi L, Popat R, Kastritis E et al (2025) Real-world evaluation of Teclistamab for the treatment of relapsed/refractory multiple myeloma (RRMM): an international myeloma working group study. Blood Cancer J 15(1):53
5. Nooka AK, Rodriguez C, Mateos MV, Manier S, Chastain K, Banerjee A et al (2024) Incidence, timing, and management of infections in patients receiving Teclistamab for the treatment of relapsed/refractory multiple myeloma in the MajesTEC-1 study. Cancer 130(6):886–900. https://doi.org/10.1002/cncr.35107
6. Tan CRC, Derkach A, Maclachlan K, Hultcrant M, Hassoun V, Mailankody S et al (2024) Real-world schedule de-escalation of Teclistamab in patients with relapsed/refractory multiple myeloma. J Clin Oncol 42:7536–7536. https://doi.org/10.1200/JCO.2024.42.16_suppl.7536
7. Prince HM, Bahlis NJ, Rodriguez-Otero P, Karlin L, Akard Luke, Varshavsky-Yanovsky A et al (2024) MagnetisMM-3: Long-Term update of efficacy and safety of less frequent dosing of Elranatamab in patients with relapsed or refractory multiple myeloma. Blood 144(Supplement 1):4738. https://doi.org/10.1182/blood-2024-208192
8. ClinicalTrials.gov MMRC Horizon One Adaptive Platform Trial Evaluating Therapies in RRMM. NCT06171685. Available from: https://clinicaltrials.gov/study/NCT06171685 [Accessed 27 Jun 2025]
9. Touzeau C, Beksac M, Terpos E, Usmani SZ, Krishnan AY, Nijhof IS et al (2024) Safety results from the phase 3 MajesTEC-7 study in patients (pts) with transplant ineligible/not intended newly diagnosed multiple myeloma (NDMM). J Clin Oncol 42:7506
10. Raab MS, Weinhold N, Kortüm KM, Krönke J, Podola L, Bertsch U et al (2024) Phase 2 study of teclistamab-based induction regimens in patients with transplant-eligible (TE) newly diagnosed multiple myeloma (NDMM): results from the GMMG-HD10/DSMM-XX (MajesTEC-5) trial. Blood 144:493
11. Cortes-Selva D, Perova T, Skerget S, Vishwamitra D, Stein S, Boominathan R et al (2024) Correlation of immune fitness with response to Teclistamab in relapsed/refractory multiple myeloma in the MajesTEC-1 study. Blood 144(6):615–628. https://doi.org/10.1182/blood.2023022823
12. Lancman G, Parsa K, Kotlarz K, Avery L, Lurie A, Lieberman-Cribbin A et al (2023) IVIg use associated with ten-fold reduction of serious infections in multiple myeloma patients treated with anti-BCMA bispecific antibodies. Blood Cancer Discov 4(6):440–451. https://doi.org/10.1158/2643-3230.BCD-23-0049
13. Leclercq G, Servera LA, Danilin S, Challier J, Steinhoff N, Bossen C et al (2022) Dissecting the mechanism of cytokine release induced by T-cell engagers highlights the contribution of neutrophils. Oncoimmunology 11(1):2039432. https://doi.org/10.1080/2162402X.2022.2039432
14. Chari A, Minnema MC, Berdeja JG, Oriol A, van de Donk NWCJ, Rodriguez-Otero P et al (2022) Talquetamab, a T-cell-redirecting GPRC5D bispecific antibody for multiple myeloma. N Engl J Med 387(24):2232–2244. https://doi.org/10.1056/NEJMoa2204591

15. Richter J, Thomas SK, Krishnan AY, Laubach JP, Cohen AD, Trudel S et al (2024) Cevostamab in Patients with Heavily Pretreated Relapsed/Refractory Multiple Myeloma (RRMM): Updated Results from an Ongoing Phase I Study Demonstrate Clinically Meaningful Activity and Manageable Safety and Inform the Doses and Regimen for Combination Studies. Blood; 144 (Supplement 1): 1021. https://doi.org/10.1182/blood-2024-199542
16. Merz M, Dima D, Hashmi H, Ahmed N, Stölzel F, Holderried TAW et al (2024) Bispecific antibodies targeting BCMA or GPRC5D are highly effective in relapsed myeloma after CAR T-cell therapy. Blood Cancer J 14(1):214. https://doi.org/10.1038/s41408-024-01197-2
17. van de Donk NWCJ, Chari A, Mateos MV (2024) Mechanisms of resistance against T-cell engaging bispecific antibodies in multiple myeloma: implications for novel treatment strategies. Lancet Haematol 11(9):e693–e707. https://doi.org/10.1016/S2352-3026(24)00186-8

3. Závěr

Výzkumu extraoseálního mnohočetného myelomu se autor věnoval systematicky od dokončení doktorského studia. Podařilo se identifikovat významné genetické faktory, které předurčují vznik tohoto onemocnění, ukázat rozdílné chování paraskeletárních a extramedulárních plazmocytomů a popsat klinické i molekulární prognostické ukazatele u těchto jednotek. Přestože byly dosaženy dílčí úspěchy, stále mnoho otázek o biologii tohoto onemocnění zůstává nezodpovězeno. Rovněž není jasně popsána efektivní léčba či léčebná strategie pro vysoce rizikové pacienty. Téma extraoseálního myelomu tedy bude jistě patřit mezi živá témata klinické i experimentální hematologie řadu dalších let.

4. Literatura

1. Rajkumar SV. Multiple myeloma: 2024 update on diagnosis, risk-stratification, and management. Am J Hematol. 2024;99(9):1802–1824.
2. Národní onkologický registr [Internet]. Ústav zdravotnických informací a statistiky ČR; [cited 2025 Jul 29]. Available from: https://www.uzis.cz/index.php?pg=registry--nor
3. Maluskova D, Svobodova I, Kucerova M, Brozova L, Muzik J, Jarkovsky J, Hajek R, Dusek L. Epidemiology of multiple myeloma in the Czech Republic. Klin Onkol. 2017;30(Suppl 2):35–42.
4. Hájek R. Diagnostika a léčba mnohočetného myelomu 2023. Transfuze Hematol Dnes. 2023;29(Suppl 2).
5. Havel M, Jelínek T, Pour L, Štork M, Minařík J, Jungová A, Špička I, Pavlíček P, Radocha J, Maisnar V, Wróbel M, Sýkora M, Ulrychová J, Muroňová L, Krčálová E, Buriánková E, Henzlová L, Havlová G, Zogada D, Hájek R. Standardizace PET/CT u pacientů s mnohočetným myelomem. Transfuze Hematol Dnes. 2023;29(2).
6. Zamagni E, Nanni C, Dozza L, Carlier T, Bailly C, Tacchetti P, Versari A, Chauvie S, Gallamini A, Gamberi B, Caillot D, Patriarca F, Marco M, Boccadoro M, Garderet L, Barbato S, Fanti S, Perrot A, Gay F, Sonneveld P, Karlin L, Cavo M, Bodet-Milin C, Moreau P, Kraeber-Bodéré F. Standardization of 18F-FDG-PET/CT according to Deauville criteria for metabolic complete response definition in newly diagnosed multiple myeloma. J Clin Oncol. 2021;39(2):116–125.
7. Jelinek T, Bezdekova R, Zatopkova M, Burgos L, Simicek M, Sevcikova T, Paiva B Hajek R. Current applications of multiparameter flow cytometry in plasma cell disorders. Blood Cancer J. 2017;7(10):e617.
8. Avet-Loiseau H, Davies FE, Samur MK, Corre J, D'Agostino M, Kaiser MF, Raab MS, Weinhold N, Gutierrez NC, Paiva B, Neri P, Weisel K, Maura F, Walker BA, Bustoros M, Stewart AK, Usmani SZ, Hillengass J, Chng WJ, Keats JJ, Martinez-Lopez J, Sperling AS, Touzeau C, Zhan F, Raje NS, Cavo M, Bolli N, Ghobrial IM, Dhodapkar MV, Jagannath S, Spencer A, Parekh S, Bahlis NJ, Lonial S, Sonneveld P, Bergsagel L, Orlowski RZ, Morgan G, Mateos MV, Rajkumar SV, San Miguel JF, Anderson KC, Moreau P, Kumar S, Prósper F, Munshi NC. International Myeloma Society/International Myeloma Working Group consensus recommendations on the definition of high-risk multiple myeloma. J Clin Oncol. 2025;JCO2401893.

9. Navrkalova V, Plevova K, Hynst J, Pal K, Mareckova A, Reigl T, Jelinkova H, Vrzalova Z, Stranska K, Pavlova S, Panovska A, Janikova A, Doubek M, Kotaskova J, Pospisilova S. LYNX panel: a comprehensive capture-based sequencing tool for the analysis of prognostic and predictive markers in lymphoid malignancies. J Mol Diagn. 2021;23(8):959–974.
10. Bezdekova R, Jelinek T, Kralova R, Stork M, Polackova P, Vsianska P, Brozova L, Jarkovsky J, Almasi M, Boichuk I, Knechtova Z, Penka M, Pour L, Sevcikova S, Hajek R, Rihova L. Necessity of flow cytometry assessment of circulating plasma cells and its connection with clinical characteristics of primary and secondary plasma cell leukaemia. Br J Haematol. 2021;195(1):95–107.
11. Jelinek T, Bezdekova R, Zihala D, Sevcikova T, Anilkumar Sithara A, Pospisilova L, Sevcikova S, Polackova P, Stork M, Knechtova Z, Venglar O, Kapustova V, Popkova T, Muronova L, Chyra Z, Hrdinka M, Simicek M, Garcés JJ, Puig N, Cedena MT, Jurczyszyn A, Castillo JJ, Penka M, Radocha J, Mateos MV, San-Miguel JF, Paiva B, Pour L, Rihova L, Hajek R. More than 2% of circulating tumor plasma cells defines plasma cell leukemia-like multiple myeloma. J Clin Oncol. 2023;41(7):1383–1392.
12. Sonneveld P, Dimopoulos MA, Boccadoro M, Quach H, Ho PJ, Beksac M, Hulin C, Antonioli E, Leleu X, Mangiacavalli S, Perrot A, Cavo M, Belotti A, Broijl A, Gay F, Mina R, Nijhof IS, van de Donk NWCJ, Katodritou E, Schjesvold F, Sureda Balari A, Rosiñol L, Delforge M, Roeloffzen W, Silzle T, Vangsted A, Einsele H, Spencer A, Hajek R, Jurczyszyn A, Lonergan S, Ahmadi T, Liu Y, Wang J, Vieyra D, van Brummelen EMJ, Vanquickelberghe V, Sitthi-Amorn A, de Boer CJ, Carson R, Rodriguez-Otero P, Bladé J, Moreau P; PERSEUS Trial Investigators. Daratumumab, bortezomib, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med. 2024;390(4):301–313.
13. Mai EK, Bertsch U, Pozek E, Fenk R, Besemer B, Hanoun C, Schroers R, von Metzler I, Hänel M, Mann C, Leypoldt LB, Heilmeier B, Huhn S, Vogel SK, Hundemer M, Scheid C, Blau IW, Luntz S, Weinhold N, Tichy D, Holderried TAW, Trautmann-Grill K, Gezer D, Klaiber-Hakimi M, Müller M, Shumilov E, Knauf W, Michel CS, Geer T, Riesenberg H, Lutz C, Raab MS, Benner A, Hoffmann M, Weisel KC, Salwender HJ, Goldschmidt H; German-Speaking Myeloma Multicenter Group (GMMG) HD7 Investigators. Isatuximab, lenalidomide, bortezomib, and dexamethasone induction therapy for transplant-eligible newly diagnosed multiple myeloma: final Part 1 analysis of the GMMG-HD7 trial. J Clin Oncol. 2025;43(11):1279–1288.

14. Grieb N, Oeser A, Ferle M, Hanke F, Flossdorf S, Sauer S, Goldschmidt H, Müller-Tidow C, Salwender HJ, Fenk R, Engelhardt M, Zeiser R, Vucinic V, Franke GN, Blau IW, Teschner D, Einsele H, Kimmich C, Kull M, Besemer B, Gagelmann N, Kröger N, Neumuth T, Platzbecker U, Merz M. German Registry for Hematopoietic Stem Cell Transplantation and Cell Therapy (DRST). Single versus tandem autologous stem cell transplantation in newly diagnosed multiple myeloma. Bone Marrow Transplant. 2025;60(3):335–345.
15. Jackson GH, Davies FE, Pawlyn C, Cairns DA, Striha A, Collett C, Hockaday A, Jones JR, Kishore B, Garg M, Williams CD, Karunanithi K, Lindsay J, Jenner MW, Cook G, Russell NH, Kaiser MF, Drayson MT, Owen RG, Gregory WM, Morgan GJ. UK NCRI Haemato-oncology Clinical Studies Group. Lenalidomide maintenance versus observation for patients with newly diagnosed multiple myeloma (Myeloma XI). Lancet Oncol. 2019;20(1):57–73.
16. Badros A, Foster L, Anderson LD Jr, Chaulagain CP, Pettijohn E, Cowan AJ, Costello C, Larson S, Sborov DW, Shain KH, Silbermann R, Shah N, Chung A, Krevvata M, Pei H, Patel S, Khare V, Cortoos A, Carson R, Lin TS, Voorhees P. Daratumumab with lenalidomide as maintenance after transplant in newly diagnosed multiple myeloma: the AURIGA study. Blood. 2025;145(3):300–310.
17. Facon T, Kumar S, Plesner T, Orlowski RZ, Moreau P, Bahlis N, Basu S, Nahi H, Hulin C, Quach H, Goldschmidt H, O'Dwyer M, Perrot A, Venner CP, Weisel K, Mace JR, Raje N, Attal M, Tiab M, Macro M, Frenzel L, Leleu X, Ahmadi T, Chiu C, Wang J, Van Rampelbergh R, Uhlar CM, Kobos R, Qi M, Usmani SZ. MAIA Trial Investigators. Daratumumab plus lenalidomide and dexamethasone for untreated myeloma. N Engl J Med. 2019;380(22):2104–2115.
18. Usmani SZ, Facon T, Hungria V, Bahlis NJ, Venner CP, Braunstein M, Pour L, Martí JM, Basu S, Cohen YC, Matsumoto M, Suzuki K, Hulin C, Grosicki S, Legiec W, Beksac M, Maiolino A, Takamatsu H, Perrot A, Turgut M, Ahmadi T, Liu W, Wang J, Chastain K, Vermeulen J, Krevvata M, Lopez-Masi L, Carey J, Rowe M, Carson R, Zweegman S. Daratumumab plus bortezomib, lenalidomide and dexamethasone for transplant-ineligible newly diagnosed multiple myeloma: the randomized phase 3 CEPHEUS trial. Nat Med. 2025;31(4):1195–1202.
19. Raab MS, Weinhold N, Kortüm KM, Krönke J, Podola L, Bertsch U, Frenking JH, Mersi J, Huhn S, Hundemer M, Mechtersheimer G, Fenk R, Weisel KC, Schub N, Bassermann N, Engelhardt M, Teipel R, Hänel M, Salwender H, Koster BD, Ershova E, Sakabedoyan

C, Barrott I, Balogh A, Vara S, Kampfenkel T, Goldschmidt H, Einsele H, Rasche L. Phase 2 study of teclistamab-based induction regimens in transplant-eligible newly diagnosed multiple myeloma. Blood. 2024;144(Suppl 1):493.

20. Dytfeld D, Dhakal B, Agha M, Manier S, Delforge M, Kuppens S, Afifi S, Deraedt W, Taraseviciute-Morris A, Schecter JM, Gilbert J, Yalniz F, Florendo E, Pacaud L, Hungria V, Usmani SZ, MV Mateos Bortezomib, lenalidomide and dexamethasone followed by ciltacabtagene autoleucel versus lenalidomide and dexamethasone maintenance: CARTITUDE-5. Blood. 2021;138(Suppl 1):1835.
21. Hang Q, Pour L, Sebastian G, Sia H, Minarik J, Byun JM, Toreau C, Liberatore C, Sullivan ST, Leip E, Shaikh E, Viqueira A, Dimopulos MA. Elranatamab in combination with daratumumab and lenalidomide in newly diagnosed multiple myeloma not eligible for transplant: MagnetisMM-6. J Clin Oncol. 2025;43:7504–7504.
22. Moreau P, Garfall AL, van de Donk NWCJ, Nahi H, San-Miguel JF, Oriol A, Nooka AK, Martin T, Rosinol L, Chari A, Karlin L, Benboubker L, Mateos MV, Bahlis N, Popat R, Besemer B, Martínez-López J, Sidana S, Delforge M, Pei L, Trancucci D, Verona R, Girgis S, Lin SXW, Olyslager Y, Jaffe M, Uhlar C, Stephenson T, Van Rampelbergh R, Banerjee A, Goldberg JD, Kobos R, Krishnan A, Usmani SZ. Teclistamab in relapsed or refractory multiple myeloma. N Engl J Med. 2022;387(6):495–505.
23. Cohen YC, Magen H, Gatt M, Sebag M, Kim K, Min CK, Ocio EM, Yoon SS, Chu MP, Rodríguez-Otero P, Avivi I, Quijano Cardé NA, Kumar A, Krevvata M, Peterson MR, Di Scala L, Scott E, Hilder B, Vanak J, Banerjee A, Oriol A, Morillo D, Mateos MV. RedirecTT-1 Investigators. Talquetamab plus teclistamab in relapsed or refractory multiple myeloma. N Engl J Med. 2025;392(2):138–149.
24. Štork M, Horňák T, Čičátková P, Žáčková D. Sledování a péče po kurativní léčbě pro ostatní hematologické malignity. In: Svoboda M and Halámková J. Péče o pacienty po ukončení kurativní onkologické léčby. Praha: Grada Publishing, 2023, pp. 689-694. ISBN 978-80-271-5021-2.
25. Adam Z, Štork M, Pour L, Krejčí M, Zahradová L, Sandecká V, Hájek R, Čermáková Z, Pospíšilová Y, Navrátil M, Král Z, Mayer J. Výsledky léčby AL-amyloidózy léčebnými režimy obsahujícími bortezomib. Vnitr Lek. 2012;58(12):896–903.
26. Štork M, Krejčí M, Sandecká V, Král Z, Pour L. Využití nových léků v primoterapii mnohočetného myelomu. Vnitr Lek. 2016;62(5):413–422.

27. Stork M, Sevcikova S, Adam Z, Krejci M, Sandecka V, Kral Z, Brozova L, Velichova R, Pour L. Retreatment with lenalidomide is an effective option in heavily pretreated refractory multiple myeloma patients. Neoplasma. 2018;65(4):585–591.
28. Stork M, Sevcikova S, Brozova L, Spicka I, Maisnar V, Minarik J, Jungova A, Gregora E, Velichova R, Hajek R, Jelinek T, Pour L. Bortezomib retreatment is effective in relapsed multiple myeloma patients. Neoplasma. 2020;67(1):178–184.
29. Pour L, Sevcikova S, Greslikova H, Kupska R, Majkova P, Zahradova L, Sandecka V, Adam Z, Krejci M, Kuglik P, Hajek R. Soft-tissue extramedullary multiple myeloma prognosis vs bone-related relapse. Haematologica. 2014;99(2):360–364.
30. Besse L, Sedlarikova L, Greslikova H, Kupska R, Almasi M, Penka M, Jelinek T, Pour L, Adam Z, Kuglik P, Krejci M, Hajek R, Sevcikova S. Cytogenetics in multiple myeloma patients progressing into extramedullary disease. Eur J Haematol. 2016;97(1):93–100.
31. Sevcikova S, Minarik J, Stork M, Jelinek T, Pour L, Hajek R. Extramedullary disease in multiple myeloma – controversies and future directions. Blood Rev. 2019;36:32–39.
32. Jelinek T, Sevcikova T, Zihala D, Popkova T, Kapustova V, Broskevicova L, Capkova L, Rihova L, Bezdekova R, Sevcikova S, Zidlik V, Havel M, Plonkova H, Jungova A, Minarik J, Stork M, Pour L, Pavlicek P, Spicka I, Maisnar V, Radocha J, Simicek M, Hajek R. Limited efficacy of daratumumab in multiple myeloma with extramedullary disease. Leukemia. 2022;36(1):288–291.
33. Jelinek T, Zihala D, Sevcikova T, Anilkumar Sithara A, Kapustova V, Sahinbegovic H, Venglar O, Muronova L, Broskevicova L, Nenarokov S, Bilek D, Popkova T, Plonkova H, Vrana J, Zidlik V, Hurnik P, Havel M, Hrdinka M, Chyra Z, Stracquadanio G, Simicek M, Hajek R. Beyond the marrow: insights from next-generation sequencing of extramedullary multiple myeloma tumors. Leukemia. 2024;38(6):1323–1333.
34. Rosiñol L, Beksac M, Zamagni E, Van de Donk NWCJ, Anderson KC, Badros A, Caers J, Cavo M, Dimopoulos MA, Dispenzieri A, Einsele H, Engelhardt M, Fernández de Larrea C, Gahrton G, Gay F, Hájek R, Hungria V, Jurczyszyn A, Kröger N, Kyle RA, Leal da Costa F, Leleu X, Lentzsch S, Mateos MV, Merlini G, Mohty M, Moreau P, Rasche L, Reece D, Sezer O, Sonneveld P, Usmani SZ, Vanderkerken K, Vesole DH, Waage A, Zweegman S, Richardson PG, Bladé J. Expert review on soft-tissue plasmacytomas in multiple myeloma. Br J Haematol. 2021;194(3):496–507.
35. Moreau P, Mateos MV, Goldschmidt H, Garcia MEG, Besemer B, Perez MSG, Mohty M, Lindsey-Hill J, Kirkpatrick S, Delforge M, Angelucci E, Raimondo FD, Vij R, Doyle M, Gray K, Albrecht C, Strulev V, Haddad I, Koskinen S, Acciarri L, Buyze J, Weisel

K. Outcomes of patients with extramedullary disease in triple-class exposed myeloma. Clin Lymphoma Myeloma Leuk. 2025;S2152-2650(25)00106-5.

36. Hose D, Rème T, Hielscher T, Moreaux J, Messner T, Seckinger A, Benner A, Shaughnessy JD Jr, Barlogie B, Zhou Y, Hillengass J, Bertsch U, Neben K, Möhler T, Rossi JF, Jauch A, Klein B, Goldschmidt H. Proliferation is a central independent prognostic factor in multiple myeloma. Haematologica. 2011;96(1):87–95.
37. Larrayoz M, Garcia-Barchino MJ, Celay J, Etxebeste A, Jimenez M, Perez C, Ordoñez R, Cobaleda C, Botta C, Fresquet V, Roa S, Goicoechea I, Maia C, Lasaga M, Chesi M, Bergsagel PL, Larrayoz MJ, Calasanz MJ, Campos-Sanchez E, Martinez-Cano J, Panizo C, Rodriguez-Otero P, Vicent S, Roncador G, Gonzalez P, Takahashi S, Katz SG, Walensky LD, Ruppert SM, Lasater EA, Amann M, Lozano T, Llopiz D, Sarobe P, Lasarte JJ, Planell N, Gomez-Cabrero D, Kudryashova O, Kurilovich A, Revuelta MV, Cerchietti L, Agirre X, San Miguel J, Paiva B, Prosper F, Martinez-Climent JA. Preclinical models for prediction of immunotherapy outcomes in genetically heterogeneous myeloma. Nat Med. 2023;29(3):632–645.
38. Garcés JJ, Simicek M, Vicari M, Brozova L, Burgos L, Bezdekova R, Alignani D, Calasanz MJ, Growkova K, Goicoechea I, Agirre X, Pour L, Prosper F, Rios R, Martinez-Lopez J, Millacoy P, Palomera L, Del Orbe R, Perez-Montaña A, Garate S, Blanco L, Lasa M, Maiso P, Flores-Montero J, Sanoja-Flores L, Chyra Z, Vdovin A, Sevcikova T, Jelinek T, Botta C, El Omri H, Keats J, Orfao A, Hajek R, San-Miguel JF, Paiva B. Transcriptional profiling of circulating tumor cells in multiple myeloma. Leukemia. 2020;34(2):589–603.
39. Terpos E, Ntanasis-Stathopoulos I, Gavriatopoulou M, Dimopoulos MA. Pathogenesis of bone disease in multiple myeloma: from bench to bedside. Blood Cancer J. 2018;8(1):1–12.
40. VanderWall K, Daniels-Wells TR, Penichet M, Lichtenstein A. Iron in multiple myeloma. Crit Rev Oncog. 2013;18(5):449–461.
41. Stork M, Sevcikova S, Minarik J, Krhovska P, Radocha J, Pospisilova L, Brozova L, Jarkovsky J, Spicka I, Straub J, Pavlicek P, Jungova A, Jelinek T, Sandecka V, Maisnar V, Hajek R, Pour L. Identification of patients at high risk of secondary extramedullary myeloma. Br J Haematol. 2022;196(4):954–962.
42. Nakamoto-Matsubara R, Nardi V, Horick N, Fukushima T, Han RS, Shome R, Ochi K, Panaroni C, Fulzele K, Rexha F, Branagan AR, Cirstea D, Yee AJ, Scadden DT, Raje NS.

Integration of outcomes and molecular features in extramedullary disease in myeloma. Blood Cancer J. 2024;14(1):224.

43. Stork M, Ondrouskova E, Bohunova M, Boichuk I, Fric D, Adam Z, Krejci M, Sandecka V, Knechtova Z, Radova L, Jelinkova Z, Adlerova T, Krticka M, Nekuda V, Borsky M, Sevcikova S, Jarosova M, Pour L. Del(1p32) is an early and high-risk event in multiple myeloma patients with extraosseous disease. Blood Cancer J. 2024;14(1):146.
44. Schavgoulidze A, Talbot A, Perrot A, Cazaubiel T, Leleu X, Manier S, Buisson L, Mahéo S, Do Souto Ferreira L, Pavageau L, Hulin C, Marolleau JP, Voillat L, Belhadj K, Divoux M, Slama B, Brechignac S, Macro M, Stoppa AM, Sanhes L, Orsini-Piocelle F, Fontan J, Chretien ML, Demarquette H, Mohty M, Avet-Loiseau H, Corre J. Biallelic deletion of 1p32 defines ultra-high-risk myeloma. Blood. 2023;141(11):1308–1315.
45. Stork M, Kotaskova J, Ondrouskova E, Mareckova A, Mensikova K, Sendlerova N, Boichuk I, Bilcikova M, Mayerova J, Ruzickova T, Knechtova Z, Jelinkova Z, Krticka M, Nekuda V, Rohan T, Borsky M, Hrabcakova V, Sevcikova S, Jarosova M, Pour L. Genomic landscape of para-skeletal and extramedullary plasmacytomas in multiple myeloma patients. HemaSphere. 2025;9(Suppl 1):PS1697.
46. Zanwar S, Novak J, Gonsalves W, Howe M, Braggio E, Rajkumar SV, Binder M, Jevremovic D, Dasari S, Kumar S. Extramedullary myeloma is genomically complex and characterized by MAPK pathway alterations. Blood Adv. 2025;9(15):3979–3987.
47. Bingham N, Shah J, Wong D, Lim SL, Bergin K, Kalff A, Reale A, Khong T, Mithraprabhu S, Spencer A. Whole genome sequencing and the genetics of extramedullary disease in multiple myeloma. Blood Cancer J. 2025;15(1):5.
48. Desantis V, Andriano A, Düking T, Hartwig O, Ingravallo G, Biondo M, Botta C, Ria R, Vacca A, Solimando AG. Spatial imaging unlocks the potential of charting multiple myeloma and extramedullary disease. J Hematol Oncol. 2025;18(1):47.
49. Lutz R, Poos AM, Solé-Boldo L, John L, Wagner J, Prokoph N, Baertsch MA, Vonficht D, Palit S, Brobeil A, Mechtersheimer G, Hildenbrand N, Hemmer S, Steiger S, Horn S, Pepke W, Spranz DM, Rehnitz C, Sant P, Mallm JP, Friedrich MJ, Reichert P, Huhn S, Trumpp A, Rippe K, Haghverdi L, Fröhling S, Müller-Tidow C, Hübschmann D, Goldschmidt H, Willimsky G, Sauer S, Raab MS, Haas S, Weinhold N. Bone marrow breakout lesions act as key sites for tumor-immune diversification in multiple myeloma. Sci Immunol. 2025;10(104):eadp6667.
50. Cavo M, Terpos E, Nanni C, Moreau P, Lentzsch S, Zweegman S, Hillengass J, Engelhardt M, Usmani SZ, Vesole DH, San-Miguel J, Kumar SK, Richardson PG,

Mikhael JR, da Costa FL, Dimopoulos MA, Zingaretti C, Abildgaard N, Goldschmidt H, Orlowski RZ, Chng WJ, Einsele H, Lonial S, Barlogie B, Anderson KC, Rajkumar SV, Durie BGM, Zamagni E. Role of 18F-FDG PET/CT in the diagnosis and management of multiple myeloma. Lancet Oncol. 2017;18(4):e206–e217.

51. Jiménez-Segura R, Rosiñol L, Cibeira MT, Fernández de Larrea C, Tovar N, Rodríguez-Lobato LG, Bladé E, Moreno DF, Oliver-Caldés A, Bladé J. Paraskeletal and extramedullary plasmacytomas in multiple myeloma at diagnosis and first relapse. Blood Cancer J. 2022;12(9):135.
52. Montefusco V, Gay F, Spada S, De Paoli L, Di Raimondo F, Ribolla R, Musolino C, Patriarca F, Musto P, Galieni P, Ballanti S, Nozzoli C, Cascavilla N, Ben-Yehuda D, Nagler A, Hajek R, Offidani M, Liberati AM, Sonneveld P, Cavo M, Corradini P, Boccadoro M. Outcome of paraosseous extra-medullary disease in newly diagnosed myeloma patients. Haematologica. 2020;105(1):193–200.
53. Gagelmann N, Eikema DJ, Iacobelli S, Koster L, Nahi H, Stoppa AM, Masszi T, Caillot D, Lenhoff S, Udvardy M, Crawley C, Arcese W, Mariette C, Hunter A, Leleu X, Schipperus M, Delforge M, Pioltelli P, Snowden JA, Itälä-Remes M, Musso M, van Biezen A, Garderet L, Kröger N. Impact of extramedullary disease in patients with newly diagnosed multiple myeloma undergoing autologous stem cell transplantation: a study from the Chronic Malignancies Working Party of the EBMT. Haematologica. 2018;103(5):890–897.
54. Stork M, Sevcikova S, Jelinek T, Minarik J, Radocha J, Pika T, Pospisilova L, Spicka I, Straub J, Pavlicek P, Jungova A, Knechtova Z, Sandecka V, Maisnar V, Hajek R, Pour L. Unexpected heterogeneity of newly diagnosed multiple myeloma patients with plasmacytomas. Biomedicines. 2022;10(10):2535.
55. Usmani SZ, Heuck C, Mitchell A, Szymonifka J, Nair B, Hoering A, Alsayed Y, Waheed S, Haider S, Restrepo A, Van Rhee F, Crowley J, Barlogie B. Extramedullary disease portends poor prognosis in multiple myeloma. Haematologica. 2012;97(11):1761–1767.
56. Beksac M, Seval GC, Kanellias N, Coriu D, Rosiñol L, Ozet G, Goranova-Marinova V, Unal A, Bila J, Ozsan H, Ivanaj A, Balić LI, Kastritis E, Bladé J, Dimopoulos MA. Real world multicenter retrospective study on extramedullary disease from Balkan Myeloma Study Group. Haematologica. 2020;105(1):201–208.
57. Varettoni M, Corso A, Pica G, Mangiacavalli S, Pascutto C, Lazzarino M. Incidence, presenting features and outcome of extramedullary disease in multiple myeloma: a longitudinal study. Ann Oncol. 2010;21(2):325–330.

58. Mangiacavalli S, Pompa A, Ferretti V, Klersy C, Cocito F, Varettoni M, Cartia CS, Cazzola M, Corso A. The possible role of burden of therapy on the risk of myeloma extramedullary spread. Ann Hematol. 2017;96(1):73–80.
59. Varga C, Xie W, Laubach J, Ghobrial IM, O'Donnell EK, Weinstock M, Paba-Prada C, Warren D, Maglio ME, Schlossman R, Munshi NC, Raje N, Weller E, Anderson KC, Mitsiades CS, Richardson PG. Development of extramedullary myeloma in the era of novel agents. Br J Haematol. 2015;169(6):843–850.
60. Stork M, Spicka I, Radocha J, Minarik J, Jelinek T, Jungova A, Pavlicek P, Pospisilova L, Sedlak F, Straub J, Pika T, Knechtova Z, Fidrichova A, Boichuk I, Sevcikova S, Maisnar V, Hajek R, Pour L. Daratumumab with lenalidomide and dexamethasone in relapsed/refractory multiple myeloma – real world evidence. Ann Hematol. 2023;102(6):1501–1511.
61. Stork M, Radocha J, Mihalyova J, Spicka I, Pika T, Jungova A, Boichuk I, Mensikova K, Straub J, Sedlak F, Minarik J, Krhovska P, Novakova D, Hornakova M, Knechtova Z, Sendlerova N, Dekojova T, Maisnar V, Jelinek T, Hajek R, Pour L. De-escalated teclistamab dosing in relapsed/refractory multiple myeloma: Czech myeloma group real-world analysis. Ann Hematol. 2025 Aug;104(8):4141-4147
62. Morales-Lozano MI, Viering O, Samnick S, Rodriguez-Otero P, Buck AK, Marcos-Jubilar M, Rasche L, Prieto E, Kortüm KM, San-Miguel J, Garcia-Velloso MJ, Lapa C. 11C-Methionine PET/CT in assessment of multiple myeloma: comparison to 18F-FDG PET/CT. Int J Mol Sci. 2022;23(17):9895.
63. Yan W, Shi H, He T, Chen J, Wang C, Liao A, Yang W, Wang H. Artificial intelligence based on routine labs for early diagnosis of multiple myeloma. Front Oncol. 2021;11:608191.
64. Puig N, Contreras MT, Agulló C, Martínez-López J, Oriol A, Blanchard MJ, Ríos R, Martín J, Iñigo MB, Sureda A, Hernández MT, de la Rubia J, González-Calle V, Krsnik I, Cabañas V, Palomera L, Moraleda JM, Bargay J, Cedena MT, Paiva B, Rosiñol L, Bladé J, San Miguel J, Lahuerta JJ, Mateos MV. Mass spectrometry vs immunofixation for treatment monitoring in multiple myeloma. Blood Adv. 2022;6(11):3234–3239.
65. Zamir I, Shragai T, Trestman S, Baran TZ, Luttwak E, Levy S, Avivi I, Cohen YC. Multiple myeloma oligosecretory relapse: frequency, characteristics and outcomes. Blood. 2021;138(Suppl 1):3772.
66. Martello M, Solli V, Mazzocchetti G, Solimando AG, Bezzi D, Taurisano B, Kanapari A, Poletti A, Borsi E, Armuzzi S, Vigliotta I, Pistis I, Desantis V, Marzocchi G, Rizzello I,

Pantani L, Mancuso K, Tacchetti P, Testoni N, Nanni C, Zamagni E, Cavo M, Terragna C. High level of circulating cell-free tumor DNA at diagnosis correlates with disease spreading and poor prognosis. Blood Cancer J. 2024;14(1):208.

67. Steinhardt MJ, Schaefers C, Leypoldt LB, Blau IW, Harzer M, Zhou X, Riedhammer C, Kamili A, Kosch R, Topp LS, Molwitz I, Gross-Fengels NO, Melzer YF, Artzenroth J, Al-Bazaz M, Alsdorf W, Topp MS, Duell J, Mersi J, Waldschmidt J, Bokemeyer C, Einsele H, Kortüm KM, Weisel K, Rasche L. Activity of CAR-T cells and bispecific antibodies in multiple myeloma with extramedullary involvement. Blood Cancer J. 2025;15(1):126.
68. Yao H, Ren SH, Wang LH, Ren MQ, Cai J, Chen D, He Y, Lai SH, Dou BT, Li MJ, Li YL, Cen YL, Chang AH, Su Y, Qiu L, Fan FY. BCMA/GPRC5D bispecific CAR T-cell therapy for relapsed/refractory multiple myeloma with extramedullary disease. J Hematol Oncol. 2025;18(1):56.

5. Seznam použitých zkratek

ANXA1 – annexin A1
ARID1A – AT-rich interaction domain 1A
BCL2 – B-cell lymphoma 2
BCMA – B-cell maturation antigen
BRAF – B-Raf proto-oncogene
CAR-T – chimeric antigen receptor T cells
CCR1 – C-C motif chemokine receptor 1
CCR2 – C-C motif chemokine receptor 2
CD38 – cluster of differentiation 38 (plazmocyty)
CD8 – cluster of differentiation 8 (cytotoxické T-lymfocyty)
CDKN2C – cyclin-dependent kinase inhibitor 2C
CI – confidence interval, interval spolehlivosti
CNS – central nervous systém
CR – complete response
CT – computed tomography
ctDNA – cirkulující nádorová DNA
CXCL12 – C-X-C motif chemokine ligand 12
CXCR4 – C-X-C motif chemokine receptor 4
del(1p32) – delece lokusu p32 na chromozomu 1
EZH2 – enhancer of zeste homolog 2
FCRH5 – Fc receptor-like protein 5
FDG-PET/CT – fluorodeoxyglucose positron emission tomography / computed tomography
GPRC5D – G protein-coupled receptor class C group 5 member D
HR – hazard ratio
IGH – immunoglobulin heavy locus
IMiD – immunomodulatory drug
IL6 – interleukin 6
IL7 – interleukin 7
ISS – International Staging Systém
KITL – KIT ligand
KRAS – Kirsten rat sarcoma virus
KMT2A/B – lysine methyltransferase 2A/B
LAG-3 – lymphocyte activation gene 3
LF – lékařská fakulta
LYNX – LYmphoid NeXt generation sequencing panel, NGS panel
MAPK – mitogen-activated protein kinase
MGUS – monoclonal gammopathy of undetermined significance
MR – magnetic resonance
NA – not available / not achieved (nedosaženo)
NCAM – neural cell adhesion molecule
NGS – next-generation sequencing
NK – natural killer (buňky)
NOR – Národní onkologický registr
OS – overall survival, celkové prežití
PD-1 – programmed cell death protein 1

PFS – progression-free survival, přežití bez progrese
R-ISS – Revised International Staging Systém
RB1 – retinoblastoma protein
SAMHD1 – SAM domain and HD domain-containing protein 1
SLAMF7 – signaling lymphocytic activation molecule family member 7
STC1 – stanniocalcin 1
TENT5C – terminal nucleotidyltransferase 5C
TIM-3 – T-cell immunoglobulin and mucin-domain containing-3
TP53 – tumor protein p53
VEGFC – vascular endothelial growth factor C