A INIBIÇÃO FARMACOLÓGICA DO EIXO IGF1R/IRS INDUZ EFEITOS ANTINEOPLÁSICOS EM MIELOMA MÚLTIPLO

GN Queiroz [a], KC Lima [b], LBL Miranda [a], EM Rego [b], F Traina [c], JA Machado-Neto [a]

[a] *Departamento de Farmacologia, Instituto de Ciências Biomédicas, Universidade de São Paulo (USP), São Paulo, SP, Brasil*
[b] *Laboratório de Investigação Médica em Patogênese e Terapia Dirigida em Onco-Imuno-Hematologia (LIM-31), Departamento de Clínica Médica, Divisão de Hematologia, Faculdade de Medicina, Universidade de São Paulo (HCFMUSP), São Paulo, SP, Brasil*
[c] *Departamento de Imagem Médica, Hematologia e Oncologia, Faculdade de Medicina de Ribeirão Preto (FMRP), Universidade de São Paulo (USP), Ribeirão Preto, SP, Brasil*

Objetivo: O mieloma múltiplo (MM) é uma neoplasia hematológica caracterizada pela proliferação clonal de plasmócitos malignos que causam hipercalcemia, anemia, lesões osteolíticas, insuficiência renal, imunossupressão e apresenta altas taxas de recaída. O IGF1 induz proliferação e efeitos antiapoptóticos através da via PI3K/AKT e MAPK, mesmo em modelos de MM independentes de IL6, indicando que o eixo IGF1R/IRS1 desempenha um papel importante no desenvolvimento e progressão da doença. NT157 é um composto sintético que leva à inibição a longo prazo da sinalização IGF1R-IRS1/2. No presente estudo, nós avaliamos os níveis de expressão dos genes envolvidos no eixo IGF1/IGF1R/IRS1-2 em uma coorte de MM, assim como caracterizamos os efeitos da inibição farmacológica desta via, com NT157, em modelos celulares da doença. **Material e métodos:** Os dados de expressão de *IGF1, IGF1R, IRS1 e IRS2* foram derivados de banco de dados AmaZonia! 2008. Análise do escore de dependência gênica foram gerados para 20 linhagens celulares distintas de MM pelo DepMap e obtidos do banco de dados MyeloDB. As linhagens celulares de MM, MM1.S, MM1.R, U266 e RPMI 8226, foram utilizadas. A viabilidade celular foi avaliada por ensaio de MTT, a clonogenicidade pelo ensaio de formação de colônias, a apoptose por citometria de fluxo e anexina V/PI e as vias de sinalização por Western blotting. Os testes de Spearman, Mann-Whitney ou ANOVA foram utilizados conforme apropriado. Valores de $p < 0.05$ foram considerados significativos. **Resultados:** Os níveis de RNAm de *IGF1* e *IRS1* foram aumentados nos pacientes com MM, enquanto os níveis de *IGF1R* e *IRS2* foram reduzidos ($p < 0.05$). Foi observada uma correlação positiva entre os níveis de *IGF1R* e *IRS2* ($r = 0.38$, $p = 0.03$). A fosforilação de IGF1R foi observada nas células MM1.S e MM1.R, sendo a expressão do receptor observada também nas células RPMI 8226. A expressão de IRS1 foi observada em todas as linhagens celulares. A expressão de IRS2 foi observada nas células MM1.S, MM1.R e RPMI 8226. O escore de dependência foi 0.032 para *IGF1*, -0.519 para o *IGF1R*, -0.503 para o *IRS1* e -0.455 para o *IRS2*. O tratamento com NT157 reduziu de forma dependente de tempo e de concentração a viabilidade celular de todos os modelos avaliados. Foram observadas também redução dependente de concentração da formação de colônias e indução de apoptose nas células de MM ($p < 0.05$). No cenário molecular, o NT157 induziu marcadores de apoptose (clivagem de PARP1), dano em DNA (γH2AX) e estresse celular (p-ERK1/2) e reduziu proteínas associas à síntese proteína (p-RPS6) em células MM1.S e U266. Em células MM1.S foi observada uma redução da fosforilação de IGF1R, STAT3 e STAT5. Os níveis de IRS1 foram reduzidos em células U266. **Discussão e conclusão:** A eixo de sinalização IGF1/IGF1R/IRS é diferencialmente ativado em células de MM, sendo que a análise de dependência gênica sugere que a presença do receptor e das proteínas adaptadoras intracelulares são mais importantes que o IGF1 autócrino, provavelmente que esse pode ser obtidos de fontes parácrina. A inibição farmacológica do IGF1R/IRS1 apresentou efeitos antineoplásicos marcantes em modelos celulares de MM. A análise molecular, sugere uma maior complexidade da ação do NT157 frente ao repertório de alvos expressos em cada modelo celular e merece futuras investigações. **Apoio:** FAPESP, CNPq e CAPES.

https://doi.org/10.1016/j.htct.2023.09.752

TECLISTAMAB IN RELAPSED OR REFRACTORY MULTIPLE MYELOMA (RRMM): MAJESTEC-1 SUBGROUP ANALYSIS BY LINES OF THERAPIES

NWCJV Donk [a], R Popat [b], L Rosiol [c], B Besemer [d], JM Lopez [e], D Trancucci [f], R Verona [g], T Stephenson [g], K Chastain [f], N Bahlis [h]

[a] *Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Amsterdam, Netherlands*
[b] *University College London Hospitals, NHS Foundation Trust, London, United Kingdom*
[c] *Hospital Clínic de Barcelona (IDIBAPS), Barcelona, Spain*
[d] *University of Tuebingen, Tuebingen, Germany*
[e] *Hematología Hospital 12 de Octubre, Madrid, Spain*
[f] *Janssen Research & Development, Raritan, United States*
[g] *Janssen Research & Development, Spring House, United States*
[h] *Arnie Charbonneau Cancer Institute, University of Calgary, Calgary, Canada*

Background: Teclistamab is the first approved off-the-shelf BCMA×CD3 bispecific antibody, with personalized weight based dosing, for the treatment of patients (pts) with RRMM based on data from the pivotal phase 1/2 MajesTEC-1 study (NCT03145181/NCT04557098). Moreau et al (*NEJM* 2022) reported rapid, deep, and durable responses: overall response rate (ORR) was 63% (39% ≥ complete response [CR] rate), with a median duration of response (mDOR) of 18.4 mo, and median progression-free survival (mPFS) of 11.3 mo after a median follow-up (mFU) of 14.1 mo. This subgroup analysis of MajesTEC-1 reports the overall safety and efficacy of RRMM patients who received 2-3 prior lines of therapy vs. patients with 4 or more prior lines of therapies, with extended follow-

up of 23 months. **Methods:** Eligible pts were aged ≥18 y, had documented MM (per IMWG 2016 criteria), and had received ≥3 prior lines of therapy (LOT), including a proteasome inhibitor, an immunomodulatory drug, and an anti-CD38 antibody. Prior BCMA-targeted therapy was not allowed in this cohort. The primary endpoint was ORR (assessed per IMWG 2016 criteria by independent review committee). AEs were graded per CTCAE v4.03. Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) were graded per ASTCT guidelines. Safety was reported in the overall population and efficacy was evaluated in patients who received 2-3 prior lines of therapy (≤3 LoT) vs. patients who received more than 3 prior lines of therapies (>3 LoT). **Results:** As of Jan 4, 2023, 165 pts had received teclistamab at the RP2D (median age, 64 y; 58% male; 26% high-risk cytogenetics; 12% International Staging System stage III). Pts had a median of 5 prior LOT (range, 2–14). 43 patients received ≤3 prior LoT and 122 patients received >3 prior LoT. In patients with ≤3 and >3 prior LOT; 58.1% vs. 84.4% pts were TCR and 46.5% vs. 78.7% pts were penta-drug exposed respectively. At 23 mo mFU, patients with ≤3 and >3 prior LOT achieved an ORR of 74.4% with 58.1% of patients achieving ≥CR vs. 59% with 41% of pts achieving ≥CR; the mPFS was 18.1 mo (95% CI, 13.8–26.9) vs. 9.7 mo (95% CI, 6.4–13.1), and the mOS was 25.9mo (95% CI, 18.3–NE) vs. 17.7 mo (95% CI, 12.2–NE), respectively. In the overall population, Hematologic AEs (any grade [gr]/gr 3/4) included neutropenia (72%/65%), anemia (55%/38%), thrombocytopenia (42%/22%), and lymphopenia (36%/35%). Infections occurred in 80% of pts (55% gr 3/4); key infections included respiratory (58%), COVID-19 (29%), other key viral (12%), GI (9%), fungal (6%), PJP (4%), and hepatitis B (0.6%). CRS occurred in 72% of pts (0.6% gr 3; no gr 4/5); 5 (3%) pts reported 9 ICANS events (all gr 1/2; all resolved). 1 pt in phase 1 required a teclistamab dose reduction due to neutropenia. 7 treatment-related deaths have occurred (4 due to COVID-19). Of the 47 pts who remain on study, ~90% have received Q2W dosing. **Conclusions:** With a 23 mFU, these data support teclistamab as a safe and effective therapeutic option for RRMM patients. The subgroup of less heavily treated patients (≤3 prior LoT) demonstrates even better PFS and complete response rate results than those patients in later lines of treatment (>3 prior LOT). **Funding:** The development of this study was funded by Janssen Research & Development.

https://doi.org/10.1016/j.htct.2023.09.753

REAL-WORLD TREATMENT PATTERNS AND OUTCOMES IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA WITH AT LEAST ONE PRIOR THERAPY IN BRAZIL

A Maiolino [a], M Capra [b], PL Lin [c], T Rajput [d], HS Friedman [e], C Tekle [c], P Bueno [f], E Carmo [f], A Freitas [f], F Magro [f]

[a] *Universidade Federal do Rio de Janeiro (UFRJ) and Instituto Americas, Rio de Janeiro, RJ, Brazil*
[b] *Centro Integrado de Hematologia e Oncologia, Hospital Mãe de Deus, Porto Alegre, Brazil*
[c] *Sanofi, Cambridge, United States*
[d] *Sanofi, Hyderabad, Telangana, India*
[e] *DataMed Solutions LLC, New York, United States*
[f] *Sanofi, São Paulo, Brazil*

Objectives: The treatment landscape for relapsed/refractory multiple myeloma (RRMM) has witnessed a paradigm shift over the last decade, and several therapeutic options are now available in Brazil. However, approval and access to new treatments may be delayed, potentially impacting patient (pt) outcomes. This study assessed real-world (RW) treatment patterns and outcomes of pts with RRMM to understand the current treatment landscape and unmet needs in Brazil. **Material and methods:** This retrospective, cross-sectional chart review included pts with RRMM who initiated a second-line (2L) or third-line (3L) MM-specific treatment regimen between 01-Jan-2015 and 31-Dec-2020. Physicians (*N* =50; mean practice duration: 11 months [m]; spent at least 60.0% of their time in pt care; practiced in the private sector: 56.0%; practiced in private and public sectors: 42.0%; practiced in the public sector: 2.0%) managing at least 10 MM pts for previous 12 m contributed data from pt charts via a structured data collection form. The International Centralized Institutional Review Board approved this study. Data on demographics, clinical characteristics, treatment patterns, and overall survival (OS) were collected and analyzed. **Results:** Of the included 133 pts (mean [SD] age at first RRMM diagnosis: 64.3 [10.1] years; male: 58.7%), most had moderate-to-good performance status based on Eastern Cooperative Oncology Group scores (Grade 1: 57.9%; Grade 2: 26.3%); reported Stage 2 (40.0%) and Stage 3 (45.9%) disease based on the International Staging System and low comorbidity burden (Charlson Comorbidity Index: mean [SD]: 2.8 [1.4]). Anemia (79.0%) and bone lesions (60.9%) were the most common reported symptoms, followed by hypercalcemia (42.9%) and renal failure (33.8%). Nearly one-third of pts (*n* /*N* =30/100; 30.0%) reported high-risk cytogenic status. Bortezomib (BOR) and lenalidomide (LEN)-based regimens were the most used first-line (1L) therapy in non-stem cell transplant (SCT) pts (BOR+cyclophosphamide+dexamethasone [VCd, 25.0%], LEN [R, 18.8%], V +thalidomide+d [VTd, 8.8%]) and as 1L induction therapy (VCd [32.1%], VRd [15.1%], VTd [9.4%]) in SCT pts. LEN and thalidomide-based regimens (37.7% each) were used as maintenance therapy in 1L. Daratumumab (DARA)- and carfilzomib (CARF)-based regimens were most utilized in 2L (DARA+R+d [DRd, 20.9%], CARF+R+d [KRd, 18.6%], DVd [13.2%]) and in 3L (DRd [19.7%], KRd [18.4%], Kd/LEN [7.9% each]). Among pts with private health insurance, 18.8% were LEN-refractory. Median (interquartile range [IQR]) duration of treatment for 1L (SCT induction), 2L, and 3L were 4.6 (3.2–5.8), 7.3 (5.0–16.0) and 8.0 (3.0–13.0) m, respectively. Nearly 60.0% of pts initiating 2L experienced disease progression. Majority of pts (65.1%) were alive at the time of study. Among pts who had died (35%; *n* =45), the median OS since 2L initiation was 20.5 m. **Discussion:** Treatment patterns observed were consistent with previous RW studies, with significant use of BOR- and LEN-based regimens noted in 1L and newer therapies in 2L and 3L. The generalizability of study findings may be limited due to the small sample size. **Conclusion:** A high proportion of patients with lenalidomide refractoriness and short duration of