KEY DRIVERS FOR TREATMENT CHOICE IN LENALIDOMIDE-EXPOSED AND REFRACTORY MULTIPLE MYELOMA PATIENTS IN THE REAL WORLD. ANALYSIS CONDUCTED IN THE EU5 COUNTRIES AND IN THE US

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INTRODUCTION

Progress in multiple myeloma (MM) treatment includes improved risk stratification, recognition of clonal heterogeneity, personalized therapies (1-2). MM remains complex with significant impact of therapies on long-term outcomes due to mutational burden, immune exhaustion, infections, myelosuppression, organ damage, extramedullary escape (3).

Definition of relapsed/refractory MM (RRMM) is clarified with progressive disease based on IMWG criteria (4) after at least a minimal response or disease progression less than 60 days of the last treatment (5-6), and primary refractory disease defined by lack of at least minimal response on a given treatment (7).

Lenalidomide is a cornerstone in first (1L) and second (2L) line treatments, but many patients become refractory to lenalidomide by 2L+.

Guidelines recommend treatment selection at relapse based on timing of relapse, response to prior therapy, disease aggressiveness, patient's performance status (8). Treatment selection principles include using triplets considering at least two new drugs, considering transplant, enrolling in clinical trials.

Despite these guidelines and availability of efficient new combinations at relapse, treatment for lenalidomide refractory MM varies significantly among institutions and countries.

AIM

The study aimed to identify in the real world setting the main regimens used in lenalidomide refractory 2L+ MM patients and analyze key drivers for drug selection across France, Germany, Italy, Spain, UK (EU5) and the US.

METHOD

Anonymous patient charts from hematologists in EU5 and the US were analyzed.
The study included 2645 patient charts in 2L, 1997 in 3L, 1600 in 4L, 971 in 5L+ from Q4 2022 to Q4 2023.
Among these, 432 patients in 2L, 682 in 3L, 739 in 4L, 511 in 5L+ were lenalidomide exposed and refractory.
The analysis focused on regimens used indifferent lines and key drivers for drug selection comparing EU5 and the US.

RESULTS

Among lenalidomide exposed/refractory 2L patients (n= 432), common regimens were DVd (17%), DKd (12%), Kd (7%), Isa-Kd (7%), DPd (7%), PVd (5%), KPd (5%). Higher carfilzomib-based combinations in the US: DKd (17% vs 11% in EU5). (Fig 2.)

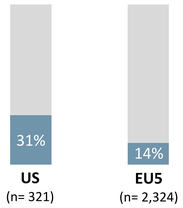

Fig 1. Percentage of 2L patients lenalidomide exposed/refractory

2L	US (n= 432)	EU5 (n= 333)
DVd	9%	19%
DKd	17%	11%
Kd	7%	7%
IsaKd	0%	9%
DPd	7%	6%
D±d	1%	8%
PVd	1%	6%
KPd	5%	4%
Vd	5%	3%
Other regimens	47%	28%

Fig 2. Regimens shares in lenalidomide exposed/refractory patients in 2L

DVd was preferred for older patients (mean age 73 vs 67 for DKd, 70,9 for DPd, 71,7 for PVd) and those with at least 1 comorbidity (92%) vs DKd (74%) DPd (94%). High-risk cytogenetics were more common in DKd and PVd (36% and 20% vs 14% and 13% for DVd and DPd). No difference regarding carfilzomib-based DKd was associated with better ECOG status (77%) ECOG 0-1 vs PVd (73%), DVd (64%). (Fig 3.)

2L US and EU5	ECOG STATUS ECOG 0-1 (n= 298)	ECOG 2+ (n= 132)	CYTOGENETIC RISK HIGH-RISK (n= 103)	STANDARD-LOW RISK (n= 124)
DVd	15%	19%	10%	18%
DKd	14%	9%	20%	7%
Kd	8%	4%	4%	9%
IsaKd	8%	5%	10%	7%
DPd	8%	5%	4%	9%
D±d	5%	9%	5%	3%
PVd	5%	4%	4%	6%
KPd	5%	4%	7%	6%
Vd	2%	6%	3%	5%
Other regimens	31%	35%	32%	30%

Fig 3. Regimens shares in lenalidomide exposed/refractory patients in 2L: focus on ECOG status and cytogenetic risk

3L (n= 682): Common regimens were Isa-Pd (11%), Kd (10%), Pd (8%), EPd (7%), DPd (7%). Isa-Pd was more frequent in EU5 (12%) vs the US (1%). (Fig 5.)

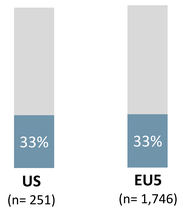

Fig 4. Percentage of 3L patients lenalidomide exposed/refractory

3L	US (n= 682)	EU5 (n= 82)	EU5 (n= 600)
IsaPd	1%		12%
D±d	5%		12%
Kd	7%		10%
Pd	5%		9%
EPd	6%		8%
DPd	17%		5%
DVd	-		7%
KPd	5%		5%
cilta-cel	7%		0%
Other regimens	46%		31%

Fig 5. Regimens shares in lenalidomide exposed/refractory patients in 3L

Subgroup analysis didn't show differences except Del17p slightly more frequent in the Kd subgroup (10%) and at least one comorbidity in Isa-Pd (91%), Kd (89%), Pd (96%), EPd (96%).

However, no difference could be identified between the different subgroups regarding ISS score, frailty status and level of comorbidities. (Fig 6.)

3L US and EU5	ECOG STATUS ECOG 0-1 (n= 411)	ECOG 2+ (n= 267)	CYTOGENETIC RISK HIGH-RISK (n= 145)	STANDARD-LOW RISK (n= 253)
IsaPd	11%	10%	10%	13%
D±d	11%	12%	8%	10%
Kd	10%	9%	10%	11%
Pd	5%	13%	7%	7%
EPd	7%	8%	8%	8%
DPd	5%	9%	7%	10%
DVd	7%	5%	5%	7%
KPd	6%	4%	7%	6%
Other regimens	37%	30%	39%	27%

Fig 6. Regimens shares in lenalidomide exposed/refractory patients in 3L: focus on ECOG status and cytogenetic risk

4L (n= 739): Common regimens were Isa-Pd (14%), teclistamab (10%), Darzalex monotherapy (mono) (9%), belantamab mafodotin mono (8%), Pd (6%), Kd (5%), ide-cel (5%), Dd (5%). (Fig 8.)
Mean age was similar; Isa-Pd and teclistamab (70,1), belantamab mafodotin mono (68,7), Pd (70,9).
Subgroup analysis didn't show differences except higher proportion of high-risk cytogenetic profile and del17p mutation in the ide-cel group. ISS score and frailty status were equivalent between all subgroups and countries.

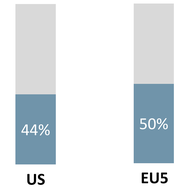

Fig 7. Percentage of 4L+ patients lenalidomide exposed/refractory

4L+	US (n= 1,250)	EU5 (n= 162)	EU5 (n= 1,088)
teclistamab	12%		12%
belantamab mafodotin mono	1%		13%
IsaPd	2%		11%
D±d	2%		11%
Pd	1%		9%
ide-cel	13%		4%
Kd	2%		5%
cilta-cel	11%		3%
X±d	11%		2%
Other regimens	43%		30%

Fig 8. Regimens shares in lenalidomide exposed/refractory patients in 4L+

5L+ (n= 511): Regimens included belantamab mafodotin mono (16%), teclistamab (15%), Pd (9%), ide-cel (6%), cilta-cel (5%). CAR-T subgroups had younger patients; ide-cel (mean age: 66.1), cilta-cel (63.5) vs belantamab mafodotin (70,8), teclistamab (69,8). High-risk cytogenetics were more frequent in cilta-cel (15% del17p, 58% ISS III) vs ide-cel (6% del17p, 75% ISS III) teclistamab (10% del17p, 56% ISS III). (Fig 9.)

Cardiac disease or high blood pressure reduced the likelihood of carfilzomib-based regimen use, peripheral neuropathy or cardiac dysfunction reduced bortezomib use across all countries and lines of therapy.

Patients in 4L+		US CAR-T (n= 77) 21%	US BISPECIFIC (n= 40) 11%	EU5 CAR-T (n= 70) 6%	EU5 BISPECIFIC (n= 148) 13%
Mean age		61yrs	64yrs	64yrs	70yrs
Frailty status	Fit	51%	13%	50%	37%
	Frail	8%	10%	1%	11%
ECOG score > 2		15%	30%	19%	31%
One comorbidity or more		66%	83%	81%	83%

Fig 9. Profile of CAR-T patients vs. Bispecific patients in 4L+

CONCLUSIONS

This real-world study reveals heterogeneous treatment choices in 2L+ lenalidomide refractory patients among EU5 and the US.
Carfilzomib-based treatments are preferred for younger patients without cardiovascular comorbidities and with high-risk cytogenetics.
Pomalidomide-based treatments are common in 3L and 4L regardless of age and comorbidities.
Anti-BCMA bispecific are standard from the 4L and anti-BCMA CAR-T cells in 5L, especially for younger fit patients with high-risk disease.
Treatment differences between regions are mainly due to access and prescriber experience.

REFERENCES

1. **Morgan**. Nat Rev Cancer. 2012;12:335
2. **Manier**. Nat Rev Clin Oncol.2017;14:100
3. **Richardson**. Blood Cancer J. 2018;8:109
4. **Kumar**. Lancet Oncol. 2016;17:e328
5. **Nooka**. Blood. 2015;125:3085
6. **Rajkumar**. Blood. 2011;117:4691
7. **Richardson**. Cancer. 2006;106:1316
8. **Moreau et al**. Lancet Oncol. 2021;22(3):e105-e118

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