International Myeloma Society

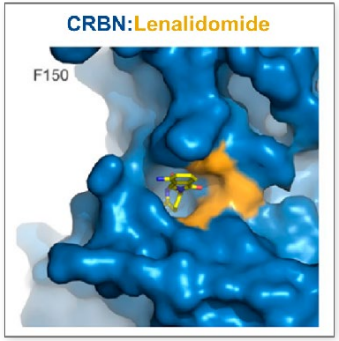
All-oral triplet iberdomide ixazomib and dexamethasone in elderly patients with multiple myeloma at first relapse : results of the IFM phase 2 study I2D

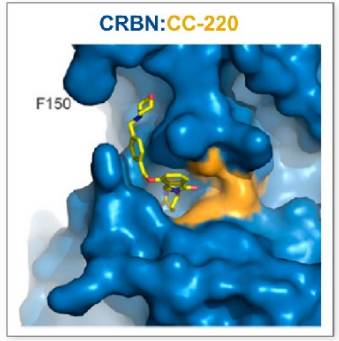
Cyrille Touzeau[1], Xavier Leleu[2], Mourad Tiab[3], Margaret Macro[4], Aurore Perrot[5], Julie Gay[6], Carine Chateleix[7], Murielle Roussel[8], Lionel Karlin[9], Caroline Jacquet[10], Salomon Manier[11], Cyrille Hulin[12], Olivier Decaux[13], Valentine Richez[14], Thomas Chalopin[15], Mohamad Mohty[16], Frédérique Orsini-Piocelle[17], Denis Caillot[18], Cécile Sonntag[19], Hervé Avet-Loiseau[5], Alexandra Jobert[20], Lucie Planche[20], Jill Corre[5], Philippe Moreau[1]

[1] Service d'hématologie, CHU Hotel Dieu, Université de Nantes, France.[2] Service d'hématologie, CHU de Poitiers, Université de Poitiers, France.[3] Service d'hématologie, Centre Hospitalier Départemental Vendée, La Roche sur Yon, France.[4] Service d'hématologie, CHU Caen, France.[5] CHU de Toulouse, IUCT-O, Université de Toulouse, UPS, Service d'hématologie, Toulouse, France.[6] Service d'hématologie, Centre Hospitalier Bayonne, France.[7] Service d'hématologie, CHU de Clermont-Ferrand, France.[8] Service d'hématologie, CHU de Limoges, France.[9] Hôpital Lyon Sud, Pierre-Bénite, France. [10] Service d'hématologie, CHU Nancy, Vandoeuvre-lès-Nancy, France.[11] Maladies du Sang, CHRU de Lille, France.[12] Service d'hématologie, Hôpital Haut-Lévêque, CHU de Bordeaux, Pessac, France.[13] Service d'hématologie, CHU de Rennes, France.[14] Service d'hématologie, CHU de Nice, France.[15] Service d'hématologie, CHU de Tours, France.[16] Service d'hématologie, Hôpital Saint Antoine, Paris, France.[17] Service d'hématologie, CHR Annecy, France.[18] Hématologie Clinique, CHU Dijon Bourgogne, France.[19] Hématologie Clinique, Institut de Cancérologie de Strasbourg Europe, Strasbourg, France.[20] Département de recherche clinique, CHU Hotel Dieu, Nantes, France.

Background

- Triplet (DRd, VRd) or quadruplet (IsaVRd, DVRd) combinations are considered standard of care in transplant ineligible NDMM[1,2,3]
- At first relapse, elderly, less fit patients refractory to LEN±CD38 are in need for effective and tolerable options
- Iberdomide is a novel cereblon E3 ligase modulator (CELMoD) that demonstrated promising efficacy with a favorable safety profile in multi-class refractory patients[4]
  - IBER binds cereblon with higher affinity, inducing the closed conformation required for more rapid degradation and greater potency compared with IMiDs
- Ixazomib is an oral proteasome inhibitor, approved for the treatment of relapsed MM





Compound	CRBN Binding Affinity (IC_{50})[5]	Active CRBN Confirmation[6]
Lenalidomide	~1.5uM	20-25%
Pomalidomide	~1.2uM	20-25%
Iberdomide	~0.06uM	50%

Here, we report efficacy and safety results of the all-oral triplet iberdomide, ixazomib, and dexamethasone in elderly patients with MM at first relapse

1 Dimopoulos et al. Ann Oncol 2021 ; 2 Facon et al. NEJM 2024 ; 3 Usmani et al. IMS 2024 ; 4 Lonial et al. Lancet Haematol 2022 ; 5 Matyskiela ME, et al. J Med Chem 2018; 6 Watson ER, et al. Science 20222;

I2D study design

Key inclusion criteria:

- **Age ≥ 70**
- **Relapsed myeloma ; 1 prior line of therapy**
- ECOG 0-2
- Creatine Cl ≥ 30 mL/min
- ANC >1000 G/L ; Plt > 75 G/L

Objectives:

- Primary Objective :
Very good partial response (VGPR) rate

- Secondary Objectives:
Safety, ORR, DOR, PFS, OS

Cycle 1 and 2	Cycle 3 to 6	Cycle 7 +
Iberdomide 1.6 mg D1-D21 **Ixazomib** 3 mg D1,8,15 **Dexamethasone** 20mg D1,8,15,22	**Iberdomide** 1.6 mg D1-D21 **Ixazomib** 3 mg D1,8,15 **Dexamethasone** 10mg D1,8,15,22	**Iberdomide** 1.6 mg D1-D21 **Ixazomib** 3 mg D1,8,15

28-day cycle; treatment given until disease progression or unacceptable toxicity

Patient characteristics

	N=70
Median age (range), years	76 (70-87)
Age >80 (%)	20 (29)
ECOG PS (n,%)	
0-1	65 (94%)
2	4 (6%)
IMWG frailty score (n,%)	
0-1(fit/intermediate fit)	35 (50%)
≥2 (frail)	35 (50%)
High-risk cytogenetics (n=54)	
t(4;14)	8 (15%)
del(17p)*	10 (18.5%)

	N=70
Median time from MM diagnosis to study enrolment (range), months	28 (5-130)
Prior proteasome inhibitor	31 (44%)
Prior lenalidomide	61 (87%)
Len refractory	52 (74%)
Prior anti CD38	28 (40%)
Anti CD38 refractory	26 (37%)
Anti CD38 + Len refractory	26 (37%)

** positivity cut-off : 30%*

Treatment disposition

Patient disposition	70 (100%)
Ongoing	**31 (44%)**
Discontinued	**39 (56%)**
progressive disease	33 (47%)
adverse event	4 (6%)
death	2 (3%)

Data cut-off: March 2024

I2D Safety

Hematologic treatment related AE:

	Any grade n(%)	Grade 3/4 n(%)
Neutropenia	34 (54%)	29 (46%)
Anemia	7 (11%)	1 (2%)
Thrombocytopenia	7 (11%)	6 (9%)

AE leading to treatment discontinuation (n=4):
Skin rash (n=1), cytopenia (n=2), peripheral neuropathy (n=1)

Grade 3-4 infection (n=5)
COVID-19 (n=2) ; pneumonia (n=2) , septicemia (n=1)

Death due to AE (n=2)
Septic shock (n=2)

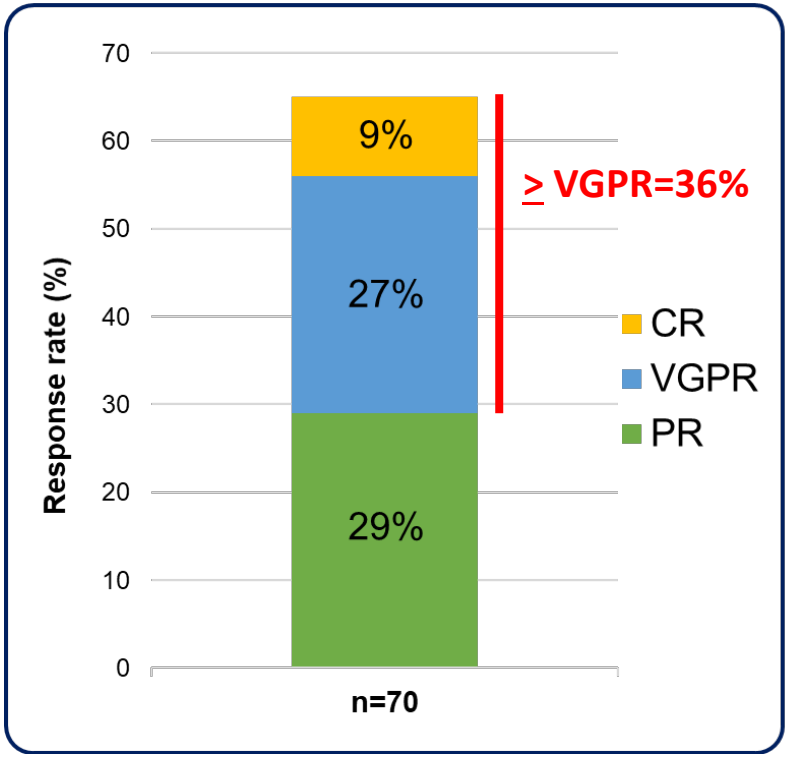
Most common (>5%) non hematologic treatment related AE:

	Any grade n(%)	Grade 3/4 n(%)
GI disorders	23 (36%)	3 (5%)
Infection	19 (30%)	5 (8%)
Fatigue	14 (22%)	2 (4%)
Insomnia/sleep disorders	14 (22%)	0
Peripheral neuropathy	14 (22%)	0
Muscle spasms	7 (11%)	1 (2%)
Skin rash	6 (9%)	3 (5%)

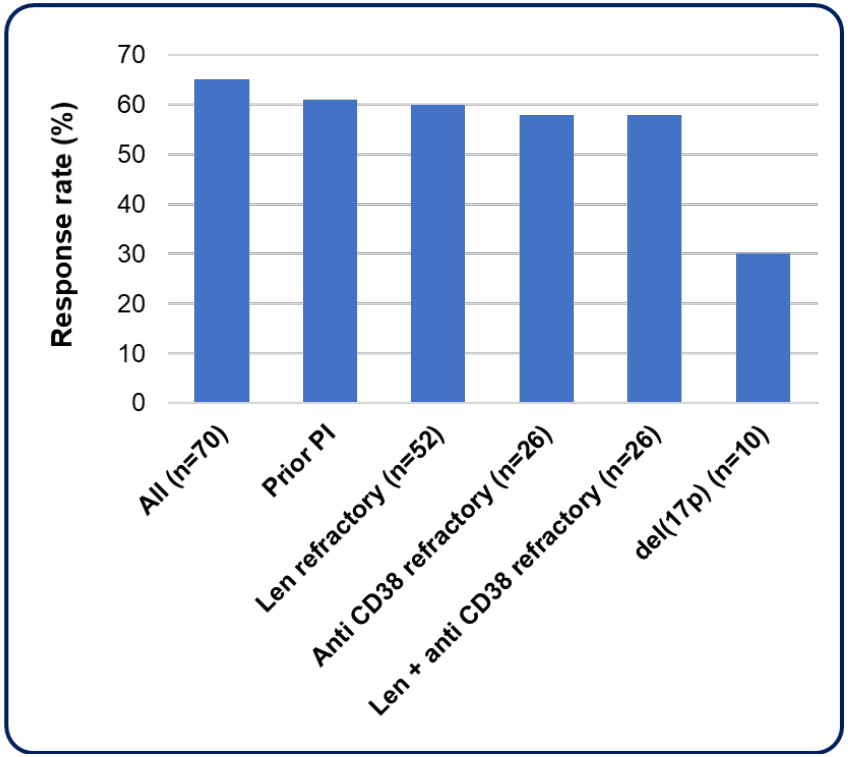
AE, adverse event ; GI, gastro intestinal

I2D response rates

Overall response rate : 65%

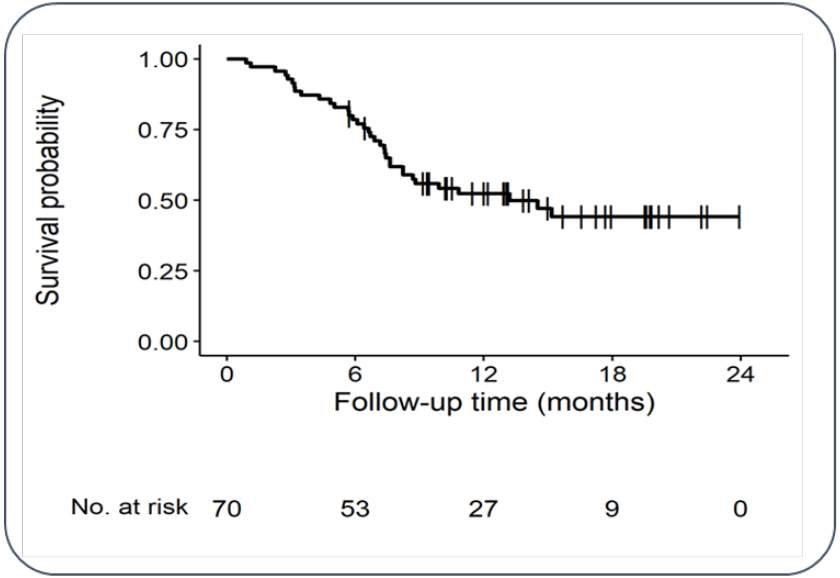


Subgroup analysis of ORR



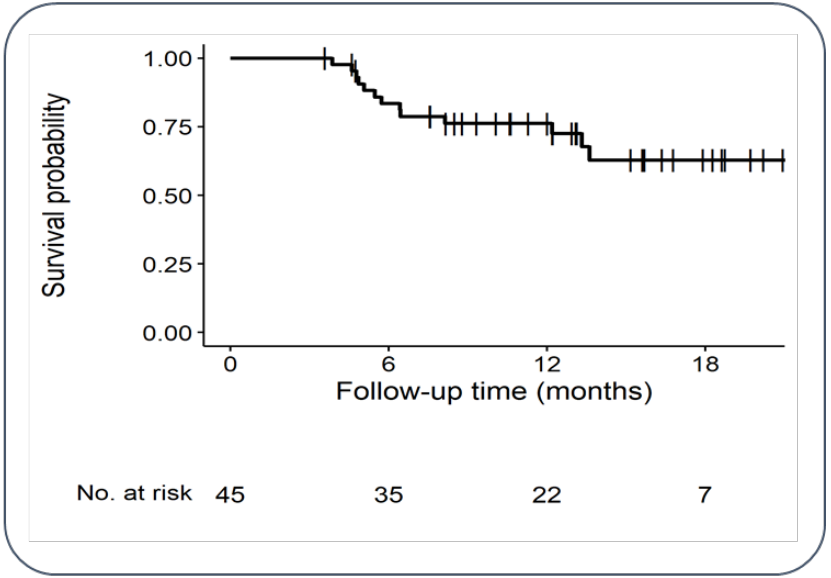
Progression-free Survival and Duration of response

Progression-free survival



12-month PFS : 52% (42% - 66%)

Duration of response



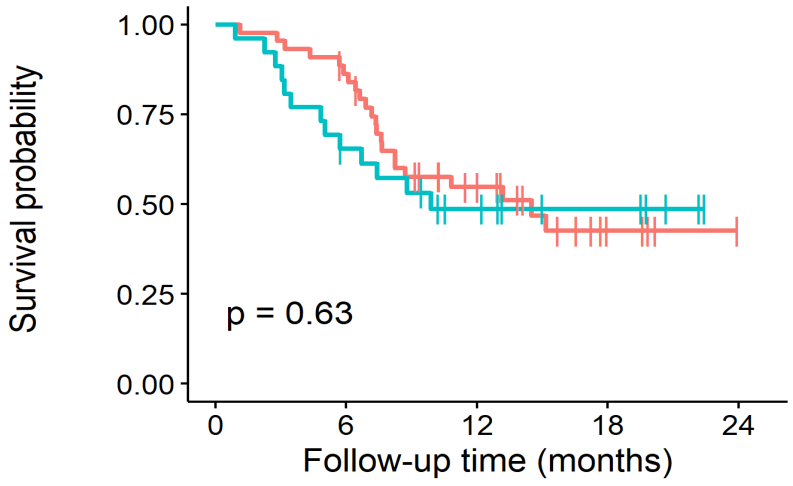
12-month DOR : 76% (64% - 90%)

Median follow-up: 14 months

Data cut-off: March 2024

Progression-free Survival and Duration of response

PFS in patients refractory to len+antiCD38



refractory to len + anti CD38 (n=26)
non refractory to len or antiCD38 (n=44)

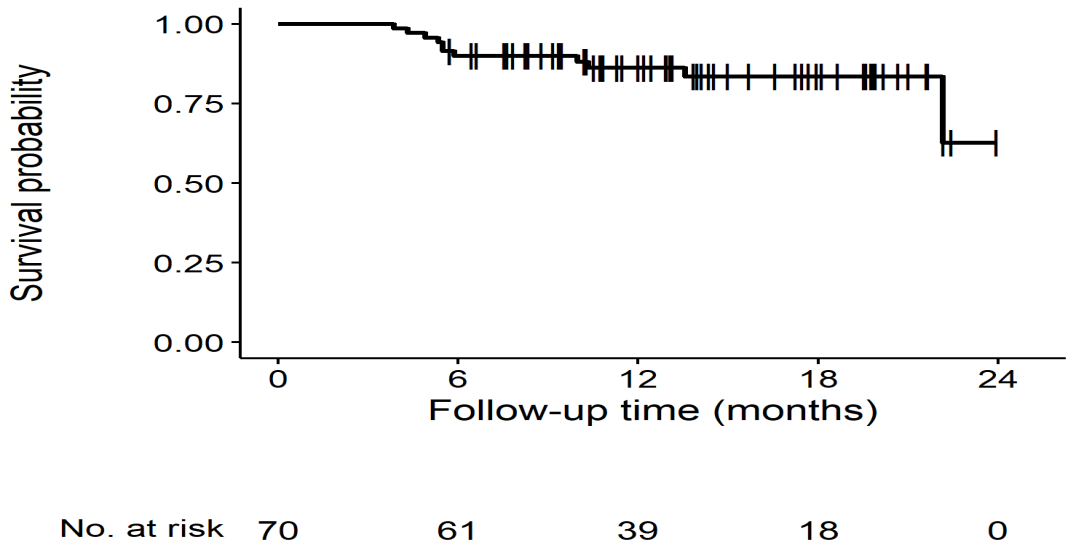
No significant difference in PFS based on :

- **age**
- **frailty score**

Median follow-up: 14 months

Data cut-off: March 2024

Overall Survival



12-month OS : 86% (78% - 95%)

Median follow-up: 14 months

Data cut-off: March 2024

Conclusion

- New options are needed for the treatment of patients with post MAIA/IMROZ/BENEFIT/CEPHEUS relapse : elderly population, potentially frail with LEN+CD38 refractory disease
- The I2D study enrolled a real-world patient population of elderly patients, many of whom are frail, had a short time since initial diagnosis (28 months), and may have limited options at relapse.
- The all-oral triplet IBER + Ixa + short-duration dex was well tolerated with low rates of non-hematologic grade 3-4 AEs, and few patients discontinued due to Aes.
- The overall response rate was 65%, including 36% VGPR/CR.
- With a median follow-up of 14 months, the 12-months PFS was 52% and the 12-months DOR was 76%
- Response rates and PFS were maintained in frail patients and those with LEN+CD38 refractory disease
- The 12-months overall survival was 86%

I2D is a safe, convenient and effective combination in older patients at first relapse including LEN+CD38 refractory disease

Acknowledgment

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- IFM clinical study teams

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  Takeda

Most frequent (>10%) first line regimen

L1 Regimen	n(%)
DRd	26 (37%)
VRd	22 (31.5%)
Rd	13 (18.5%)