# SABATI EMATOLOGICI DELLA ROMAGNA

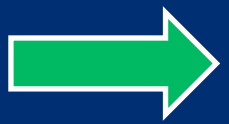

**Meldola, 24 Settembre 2016**

## L'utilizzo del Ixazomib nel trattamento dei pazienti Con Mieloma Multiplo ricaduti e refrattari

*Dott.ssa Michela Ceccolini*

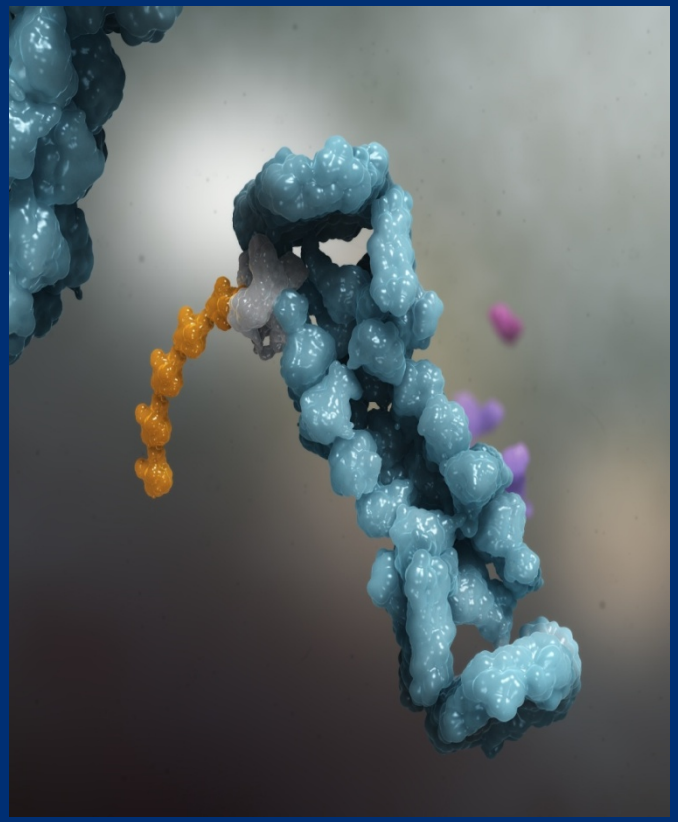
ISTITUTO SCIENTIFICO ROMAGNOLO PER LO STUDIO E LA CURA DEI TUMORI

# CARATTERISTICHE DEGLI INIBITORI DEL PROTEASOMA

| | Inhibitor of proteasome | Active moiety | Proteasome target | Key celullar effects | Binding |
|---|---|---|---|---|---|
| I generazione | **Bortezomib** | **Boronate** | Preferentially CT-L/ LMP7, C-L/LMP2 subunit, less T-L/ MECL-1 subunit | NF-κB, caspase-8, 9, p21, p27, p53, Bid and Bax, caveolin-1, p-H3, EZH2, miR-29b, miR-15a | Reversible |
| II generazione | **Carfilzomib** | **Epoxyketone** | Preferentially CT-L/ LMP7 subunit | Caspases-3, 7, 8 and 9, JNK, eIF2, NOXA | Irreversible |
| | **Marizomib** | **β-lactone** | Preferentially CT-L/ LMP7 subunit, T-L/ MECL-1 subunit, less C-L/LMP2 subunit | Caspase-8, NF-κB | Irreversible |
|  | **Ixazomib** | **Boronate** | Preferentially CT-L/ LMP7 subunit, less C-L/LMP2 and T-L/ MECL-1 subunit | Caspase-8, 9 and 3, p53, p21, NOXA, PUMA, E2F, cyclin D1 and CDK6, Bip, CHOP, miR-33b | **Reversible** |
| | **Oprozomib** | **Epoxyketone** | CT-L/LMP7 subunit | Caspases-8, -9, -3, PARP, JNK, NF-κB | Irreversible |
| | **Delanzomib** | **Boronate** | CT-L/LMP7 subunit | NF-κB | Reversible |


**Chauhan D, Cancer Cell 2005**
**Kuhn DJ, Blood 2007**
**Piva R, Blood 2008**

# IXAZOMIB (MLN9708, MLN2238)



INIBITORE REVERSIBILE DEL PROTEASOMA

VIA ORALE

IL PRIMO PI ORALE INSERITO IN STUDI DI FASE III

INIBISCE SUBUNITA' CTL β5 DEL PROTEASOMA

EMIVITA 18 MINUTI (vs 118 DI BORTEZOMIB)

apoptosi caspasi dipendente (caspasi 8,9,3) e inibisce il ciclo cellulare. p53, p21, noxa
↓ livelli di ciclina D1 e CDK6
↑ espressione di HSP90 e TF connessi con ER
Inibisce angiogenesi
Azione su miR-33b (oncosoppressore)

# Ixazomib: Overview Farmacologica

- Rapido assorbimento con T max mediano di 0.5-2.0 ore[1,2,3,5]
- Emivita 4-9 giorni; possibilità di assunzione settimanale o bisettimanale[1,2,3,5]
- Alta biodisponibilità con formulazione orale rispetto alla formulazione EV (F=67%)
- Caratteristiche farmacocinetiche simili nelle diverse popolazioni di pazienti studiate (tumori solidi, linfoma, MM) [5]
- In una analisi di 7 trials di fase I o I/II con ixazomib utilizzato come single-agent o in combinazione con lenalidomide e desametasone (len/dex), non sono state osservate interazioni PK nella combinazione con len/dex[5]
- Sesso, razza, età (range 23-86 aa), creatinina clearance (range 22-213.7 mL/min) non hanno modificato significativamente la PK
- Studio clinico in corso in pz con IR (NCT01830816)
- BSA (range 1.3-2.6 $m^2$) non richiede aggiustamento di dosaggio
- Non prolungamento dell'intervallo QTc


1. Gupta N, et al. ASH 2010; Orlando, USA (Abstract 1813)
2. Richardson P, et al. Blood 2014; 124(7): 1038-46
3. Kumar S, et al. Blood 2014; 124(7): 1047-55
4. Gupta N, et al. ASH 2011; San Diego, USA (Abstract 1433)
5. Gupta N et al. ASCPT 2013; Indianapolis, USA (Abstract PI-51)
6. Gupta N et al. EHA 2014; Milan, Italy (Abstract P981)

# Ixazomib: Studi Clinici

| Study | Disease | Phase | Regimen | Route |
|---|---|---|---|---|
| C16003 [1] | Relapsed/Refractory MM | 1 | Ixazomib (twice-weekly) | Oral |
| C16004 [2] | Relapsed and Refractory MM | 1 | Ixazomib (weekly) | Oral |
| MC1181 [3] | Relapsed and Refractory MM | 2 | Ixazomib (weekly) ± dexamethasone | Oral |
| C16005 [4-7] | Previously Untreated MM | 1 / 2 | Ixazomib (weekly) lenalidomide, dexamethasone | Oral |
| C16008 [8-9] | Previously Untreated MM | 1 / 2 | Ixazomib (twice-weekly) lenalidomide, dexamethasone | Oral |
| C16006 [10] | Previously Untreated MM | 1 | Ixazomib (weekly or twice-weekly), melphalan, prednisone | Oral |
| 2012-0277 [11] | Previously Untreated MM | 2 | Ixazomib plus lenalidomide maintenance post-ASCT | Oral |
| C16007 [12] | Relapsed/Refractory Light Chain Amyloidosis | 1 | Ixazomib (weekly dosing) | Oral |
| C16002 [13] | Relapsed/Refractory Lymphoma | 1 | Ixazomib (weekly dosing) | IV |
| C16001 [14] | Advanced Non-Hematologic Malignancies | 1 | Ixazomib (twice-weekly) | IV |

1. Richardson P, et al. Blood 2014; 124(7): 1038-46; 2. Kumar S, et al. Blood 2014; 124(7): 1047-55; 3. Shah JJ, et al. ASH 2013 (Abstract 1983); 4. Kumar S, et al. ASH 2012 (Abstract 332); 5. Kumar et al. IMW 2013 (Abstract P-230); 6. Richardson PG, et al. EHA 2013 (Abstract p236); 7. Kumar S, et al. Lancet Oncol 2014; 15(13): 1503-1502; 8. Richardson PG, et al. ASH 2013 (Abstract 535); 9. Richardson PG, et al. EHA 2014 (Abstract P355); 10. San Miguel J, et al. EHA 2012 (Abstract 0293); 11. Kumar SK, et al. ASH 2013 (Abstract 1944); 12. Sanchorawala V, et al. IMW 2013 (Abstract P-229); 13. Assouline SE, et al. Blood Cancer J 2014; 4:e251; 14. Smith DC, et al. Invest New Drugs 2015; 33(3): 652-63

# Ixazomib

## Clinical data in relapsed and refractory Multiple Myeloma

# C16003: Phase 1 Study of Oral Ixazomib in Relapsed/Refractory MM (Twice-Weekly Dosing): Study Design

**Dose-escalation cohorts**

**Dose-escalation: 3+3 schema, based on Cycle 1 DLTs**

0.24→0.48→0.8→1.2→1.68→2.23→2.0 mg/m²

**MTD established at 2.0 mg/m²**

**Expansion cohorts†**

**Relapsed and refractory cohort**
**(n = 20)**

Refractory to most recent therapy (PD while on therapy or within 60 days after last dose of therapy)

**Bortezomib-relapsed cohort**
**(n = 12)**

Relapsed after previous bortezomib therapy but not refractory

**Proteasome inhibitor-naïve cohort**
**(n =6)**

Relapsed after ≥1 therapy, must include an IMiD and corticosteroids, no proteasome inhibitor

**Prior carfilzomib cohort**
**(n = 2)**

Received prior carfilzomib and with relapsed or refractory disease

IMiD=immunomodulatory drug PD=progressive disease
*Patients could receive prolonged treatment if benefitting from therapy including 6 patients from the 2.0 mg/m² MTD dose escalation cohort

† Richardson P, et al. Blood 2014; 124(7): 1038-46.

## Twice-Weekly Dosing: Objectives and Patient Characteristics

- **Objectives:** *Primary*: Safety profile, tolerability, MTD; *Secondary:* ORR ; CR+PR, PK
- **Select Inclusion/Exclusion Criteria:** Relapsed or refractory MM, measurable disease, no peripheral neuropathy ≥ grade 2; no grade > 1 diarrhea; in dose-escalation cohort, must have relapsed following ≥2 prior lines of therapy that included bortezomib, thalidomide or lenalidomide, and corticosteroids, in any combination

| Patient Characteristics | Total (N=60) |
|---|---|
| Median age, years (range) | 65 (50-86) |
| Median time since MM diagnosis, years (range) | 4.8 (1.0-24.3) |
| Median no. prior lines of therapy (range) | 4 (1-28) |
| Bortezomib, % | 88 |
| Lenalidomide, % | 88 |
| Thalidomide, % | 62 |
| Carfilzomib / marizomib, % | 5 |
| Stem cell transplant, % | 60 |
| Refractory to last therapy, % | 60 |
| Bortezomib-refractory, % | 27 |



Richardson P, et al. Blood 2014; 124(7): 1038-46

# C16003: Phase 1 Study of Oral Ixazomib in Relapsed/Refractory MM (Twice-Weekly Dosing): AEs

| AE | Dose-escalation cohorts (n=26) | Expansion cohorts (n=40)* | Total (N=60) |
|---|---|---|---|
| Any drug-related AE, % | 81 | 95 | 88 |
| Any drug-related grade ≥3 AE, % | 50 | 68 | 62 |
| Any drug-related grade 4 AE, % | 19 | 33 | 27 |
| Any dose reduction due to AEs, % | 27 | 53 | 45 |
| Any serious AE (SAE), % | 42 | 60 | 52 |

* Includes 6 patients from MTD dose-escalation cohort

† Common drug-related SAEs included 8% thrombocytopenia, 7% pyrexia, 5% abdominal pain, and 3% each dehydration and orthostatic hypotension; all other drug-related SAEs were reported in only 1 patient each

Richardson P, et al. Blood 2014; 124(7): 1038-46.

# C16003: Phase 1 Study of Oral Ixazomib in Relapsed/Refractory MM (Twice-Weekly Dosing): AEs

## Drug-related ≥3 AEs in ≥3% of patients overall, and deaths on study

| AE | | Dose-escalation cohorts (n=26) | Expansion cohorts (n=40)* | Total (N=60) |
|---|---|---|---|---|
| Most common drug-related grade ≥3 AEs, % | Thrombocytopenia | 27 | 45 | 37 |
| | Neutropenia | 15 | 18 | 17 |
| | Skin & SC tissue disorders† | 4 | 10 | 8 |
| | Fatigue | 0 | 10 | 7 |
| | Lymphopenia | 0 | 8 | 5 |
| | Abdominal pain | 4 | 3 | 3 |
| | Hypophosphatemia | 8 | 0 | 3 |
| | Leukopenia | 0 | 5 | 3 |
| | Orthostatic hypotension | 4 | 3 | 3 |
| | Decreased WBC count | 4 | 3 | 3 |
| Deaths on study, n | | 1‡ | 1** | 2 |

* Includes 6 patients from MTD dose-escalation cohort

† MedDRA System Organ Class, includes rash macular (n=11, 18%), rash (n=6, 10%), erythema, rash maculo-papular, rash papular (each n=4, 7%), pruritis (n=3, 5%), dry skin, rash pruritic, skin exfoliation (each n=2, 3%), erythema multiforme, hyperhidrosis, petechiae, photodermatosis, rash erythematous, skin discoloration, skin hyperpigmentation, skin lesion, swelling face, urticaria, and vasculitic rash (each n=1, 2%). Patients could have reported >1 AE.

‡ undiagnosed cardiac disorder (unrelated to ixazomib)

** Progressive disease (unrelated to ixazomib)

Richardson P, et al. Blood 2014; 124(7): 1038-46.

# MM (Twice-Weekly Dosing): MTD, Responses, and PK

- **MTD: 2.0 mg/m² on twice-weekly schedule**
- **DLT:** 1 grade 3 rash and 1 grade 4 thrombocytopenia at 2.23 mg/m²
- **Duration of Therapy:** Median 4 cycles (range 1-39); 18% received ≥12 cycles
- **Response**: 55 patients were evaluable for efficacy
  - **8 patients (15%) achieved ≥PR**
    - 1 CR (proteasome inhibitor-naive expansion cohort)
    - 1 VGPR (bortezomib-relapsed cohort)
    - 6 PR
      - 2 in the dose escalation cohort
      - 2 in the relapsed/refractory cohort
      - 1 in the bortezomib-relapsed cohort
      - 1 in the proteasome inhibitor-naive cohort
    - Duration of disease control was 3.8 to 28.3+ months
  - 1 (2%) patient achieved MR (bortezomib-relapsed cohort)
  - **33 (60%) patients achieved SD**

Richardson P, et al. Blood 2014; 124(7): 1038-46

# C16004: Phase 1 Study of Oral Ixazomib in Relapsed and Refractory MM (Weekly Dosing): Study Design

**Dose-escalation cohorts**

**Dose-escalation: 3+3 schema, based on Cycle 1 DLTs**

0.24→0.48→0.8→1.2→1.68→2.23→2.97 →3.95 mg/m²

**MTD established at 2.97** mg/m²

**Expansion cohorts**

**Relapsed and refractory cohort**
**(n = 11)**

Refractory to most recent therapy (PD while on therapy or within 60 days after last dose of therapy)

**Bortezomib-relapsed cohort**
**(n = 10)**

Relapsed after previous bortezomib therapy but not refractory

**Proteasome inhibitor-naïve cohort**
**(n =6)**

Relapsed or refractory after ≥1 therapy, must include an IMiD and corticosteroids, no proteasome inhibitor

**Prior carfilzomib cohort**
**(n = 4)**

Received prior carfilzomib and with relapsed or refractory disease

IMiD=immunomodulatory drug PD=progressive disease
*Patients could receive prolonged treatment if benefitting from therapy



Kumar S, et al. Blood 2014; 124(7): 1047-55

# C16004: Phase 1 Study of Oral Ixazomib in Relapsed and Refractory MM (Weekly Dosing)

- **Objectives:** *Primary*: Safety profile, tolerability, MTD; *Secondary*: PK, ORR, ≥MR
- **Select Inclusion/Exclusion Criteria:** Relapsed or refractory MM, measurable disease, no peripheral neuropathy ≥ grade 2; no grade > 1 diarrhea; in dose-escalation cohort, must have relapsed following ≥2 prior lines of therapy that included bortezomib, thalidomide or lenalidomide, and corticosteroids, in any combination

| Patient Characteristics | Total (N=60) |
|---|---|
| Median age, years (range) | 64.0 (40-79) |
| Median time since MM diagnosis, years (range) | 4.9 (1.5-18.8) |
| Median no. prior lines of therapy (range) | 4 (1-13) |
| Bortezomib, % | 85 |
| Lenalidomide, % | 97 |
| Thalidomide, % | 53 |
| Carfilzomib, % | 15 |
| Stem cell transplant, % | 77 |
| Refractory to last therapy, % | 72 |
| Bortezomib-refractory, % | 18 |
| Lenalidomide/thalidomide refractory, % | 38 |

Kumar S, et al. Blood 2014; 124(7): 1047-55

# C16004: Phase 1 Study of Oral Ixazomib in Relapsed and Refractory MM (Weekly Dosing): Safety profile

| AE, n (%) | Dose-escalation cohorts (n=32) | Expansion cohorts (n=31)* | Total (n=60) |
|---|---|---|---|
| Treatment-emergent AE | | | 59 (98) |
| Treatment-emergent grade ≥3 AE | | | 39 (65) |
| Drug-related AE | | | 51 (85) |
| Drug-related grade ≥3 AE | | | 32 (53) |
| Drug-related grade 4 AE | 3 (9) | 9 (29) | 11 (18) |
| Thrombocytopenia, | | | 9 (15) |
| Congestive cardiac failure | | | 1 (2) |
| Hyperuricemia | | | 1 (2) |
| Neutropenia | | | 1 (2) |
| Lymphopenia | | | 1 (2) |
| Drug-related serious AE | 3 (9) | 9 (29) | 11 (18) |
| AE leading to dose reductions | 6 (19) | 14 (45) | 19 (32) |
| On-study deaths† | 0 | 1 (3) | 1 (2) |

* Includes 3 patients from MTD dose-escalation cohort
† Due to complications related to disease progression

Kumar S, et al. Blood 2014; 124(7): 1047-55

# MM (Weekly Dosing): Drug-Related Grade ≥3 AEs

## Drug-related grade ≥3 AEs in ≥2 patients

| AE, n (%) | Dose-escalation cohorts (n=32) | Expansion cohorts (n=31)* | Total (n=60) |
|---|---|---|---|
| Any drug-related grade ≥3 AE | 13 (41) | 22 (71) | 32 (53) |
| **Thrombocytopenia**† | 9 (28) | 12 (39) | 20 (33) |
| **Diarrhea** | 4 (13) | 7 (23) | 10 (17) |
| **Nausea** | 3 (9) | 1 (3) | 4 (7) |
| **Fatigue** | 2 (6) | 4 (13) | 5 (8) |
| Vomiting | 2 (6) | 1 (3) | 3 (5) |
| Decreased appetite | 0 | 4 (13) | 4 (7) |
| Neutropenia | 4 (13) | 8 (26) | 11 (18) |
| Skin/SC tissue disorders‡ | 1 (3) | 1 (3) | 2 (3) |
| PN not elsewhere classified** | 0 | 1 (3) | 1 (2) |
| Anemia | 2 (6) | 2 (6) | 4 (7) |
| Dehydration | 1 (3) | 1 (3) | 2 (3) |
| Lymphopenia | 3 (9) | 3 (10) | 5 (8) |
| Leukopenia | 1 (3) | 3 (10) | 3 (5) |

*Includes 3 patients from MTD dose-escalation cohort

† Thrombocytopenia appeared transient and cyclical, with recover of platelet count toward baseline in the rest period at the end of each cycle

‡ Skin/SC tissue disorders cover all AEs within this MedDRA system organ class; overall rate includes rash macular (n=3, 5%), hyperhidrosis, exfoliative rash (each n=2, 3%), acute febrile neutrophilic dermatosis, alopecia, erythema multiforme, night sweats, petechiae, rash, rash erythematous, rash papular, skin exfoliation, and an event coded as Stevens–Johnson syndrome with a clinical diagnosis of erythema multiforme (each n=1, 2%)

** PN NEC (high level MedDRA term, including the preferred terms of “neuropathy peripheral,” “peripheral sensory neuropathy,” and “peripheral motor neuropathy”)



Kumar S, et al. Blood 2014; 124(7): 1047-55

## MM (Weekly Dosing): MTD, DLT, Responses, and PK

- **MTD:** 2.97 mg/m² on weekly schedule
- **DLT:** 3 DLT were observed:
  - 2 at 3.95 mg/m² (grade 3 rash, and grade 3 nausea, vomiting, and diarrhea)
  - 1 at 2.97 mg/m² (grade 3 nausea, vomiting, and diarrhea)
- **Response**: 50 evaluable, with **18% achieving ≥PR and 20% ≥MR**
  - 1 patient with VGPR
  - 8 patients with PR
  - 1 patient with MR
  - 15 patients with SD
  - Among 30 response-evaluable patients treated at the MTD, the ORR (≥PR) was 27%
  - The median duration of ≥SD was 4.0 months (1.4+ to 9.8+)
- **PK:** data were similar across the expansion cohorts

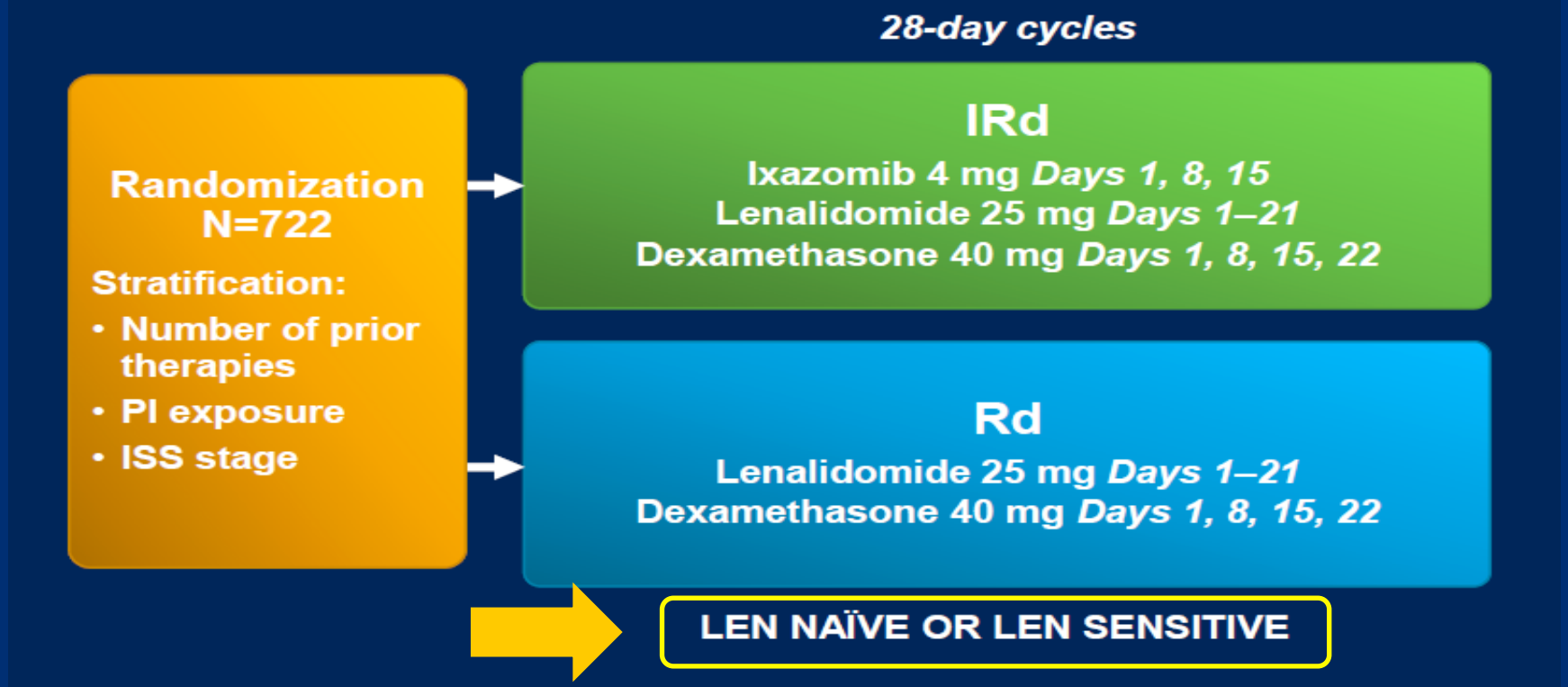
Kumar S, et al. Blood 2014; 124(7): 1047-55

# Ixazomib, an Oral Proteasome Inhibitor, in Combination with Lenalidomide and Dexamethasone (IRd), Significantly Extends Progression-Free Survival for Patients with Relapsed and/or Refractory Multiple Myeloma: The Phase 3 TOURMALINE-MM1 Study (NCT01564537)


Philippe Moreau,[1] Tamás Masszi,[2] Norbert Grzasko,[3] Nizar J. Bahlis,[4] Markus Hansson,[5] Ludek Pour,[6] Irwindeep Sandhu,[7] Peter Ganly,[8] Bartrum W. Baker,[9] Sharon Jackson,[10] Anne-Marie Stoppa,[11] David Simpson,[12] Peter Gimsing,[13] Antonio Palumbo,[14] Laurent Garderet,[15] Michele Cavo,[16] Shaji Kumar,[17] Cyrille Touzeau,[1] Francis K. Buadi,[17] Jacob P. Laubach,[18] Deborah Berg,[19] Jianchang Lin,[19] Alessandra Di Bacco,[19] Ai-Min Hui,[19] Paul G. Richardson[18]

[1]University Hospital Hôtel Dieu, Nantes, France; [2]St. István and St. László Hospital of Budapest, Budapest, Hungary; [3]Medical University of Lublin and St. John's Cancer Center, Lublin, Poland; [4]Southern Alberta Cancer Research Institute, University of Calgary, Alberta, Canada; [5]Skåne University Hospital, Lund University, Lund, Sweden; [6]University Hospital Brno, Brno, Czech Republic; [7]University of Alberta, Edmonton, Canada; [8]Christchurch Hospital, Christchurch, New Zealand; [9]Palmerston North Hospital, Palmerston North, New Zealand; [10]Middlemore Hospital, Auckland, New Zealand; [11]Institut Paoli-Calmettes, Marseille, France; [12]North Shore Hospital, Auckland, New Zealand; [13]University Hospital Rigshospitalet, Copenhagen, Denmark; [14]University of Torino, Torino, Italy; [15]Hôpital Saint Antoine, Paris, France; [16]Bologna University School of Medicine, Bologna, Italy; [17]Mayo Clinic, Rochester, MN; [18]Dana-Farber Cancer Institute, Boston, MA; [19]Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited

# TOURMALINE-MM1 Study Design




Moreau P et al. Presented at: 57th ASH Annual Meeting & Exhibition. Orlando, FL; December 2015. Abstract 727.

**Inclusion/Exclusion Criteria:**

- Relapsed and/ or refractory MM
- Measurable disease
- Received 1-3 prior therapies
- ECOG performance status 0-2
- Cannot be refractory to proteasome inhibition or lenalidomide
- Creatinine clearance > 0 = 30 ml/min

**Endpoints:**

Primary: PFS

Secondary: OS, ORR, CR + VGPR, DOR, TTP, adverse events, patient reported outcomes, PK

# Baseline Characteristics of Patients in the Intention-to-Treat Population.

**Table 1. Baseline Characteristics of Patients in the Intention-to-Treat Population.***

| Characteristic | Ixazomib Group (N = 360) | Placebo Group (N = 362) | Overall (N = 722) |
|---|---|---|---|
| Age | | | |
| Median (range) — yr | 66 (38–91) | 66 (30–89) | 66 (30–91) |
| >65 yr — no. (%) | 192 (53) | 186 (51) | 378 (52) |
| Male sex — no. (%) | 207 (58) | 202 (56) | 409 (57) |
| White race — no. (%)† | 310 (86) | 301 (83) | 611 (85) |
| ECOG performance status score — no./total no. (%)‡ | | | |
| 0 | 180/354 (51) | 170/358 (47) | 350/712 (49) |
| 1 | 156/354 (44) | 164/358 (46) | 320/712 (45) |
| 2 | 18/354 (5) | 24/358 (7) | 42/712 (6) |
| ISS disease stage at study entry — no. (%)§ | | | |
| I | 226 (63) | 233 (64) | 459 (64) |
| II | 89 (25) | 87 (24) | 176 (24) |
| III | 45 (12) | 42 (12) | 87 (12) |
| Median creatinine clearance (range) — ml/min per 1.73 $m^2$ | 78.4 (20–233) | 78.4 (27–233) | 78.4 (20–233) |
| Creatinine clearance — no. (%) | | | |
| <30 ml/min per 1.73 $m^2$ | 5 (1) | 5 (1) | 10 (1) |
| 30 to <60 ml/min per 1.73 $m^2$ | 74 (21) | 95 (26) | 169 (23) |
| 60 to <90 ml/min per 1.73 $m^2$ | 155 (43) | 129 (36) | 284 (39) |
| ≥90 ml/min per 1.73 $m^2$ | 126 (35) | 132 (36) | 258 (36) |
| Median time since initial diagnosis of multiple myeloma (range) — mo | 44.2 (3–281) | 42.2 (4–306) | 42.8 (3–306) |
| Cytogenetic features — no. of patients (%)¶ | | | |
| Standard-risk cytogenetic abnormalities | 199 (55) | 216 (60) | 415 (57) |
| High-risk cytogenetic abnormalities | 75 (21) | 62 (17) | 137 (19) |
| Data not available | 86 (24) | 84 (23) | 170 (24) |
| No. of prior therapies — no. of patients (%)‖ | | | |
| 1 | 224 (62) | 217 (60) | 441 (61) |
| 2 | 97 (27) | 111 (31) | 208 (29) |
| 3 | 39 (11) | 34 (9) | 73 (10) |
| Prior stem-cell transplantation | 212 (59) | 199 (55) | 411 (57) |
| Disease category — no./total no. (%) | | | |
| Relapsed | 276/359 (77) | 280/362 (77) | 556/721 (77) |
| Refractory | 42/359 (12) | 40/362 (11) | 82/721 (11) |
| Relapsed and refractory | 41/359 (11) | 42/362 (12) | 83/721 (12) |
| Primary refractory | 24/359 (7) | 22/362 (6) | 46/721 (6) |
| Prior proteasome inhibitor therapy — no. (%) | 249 (69) | 253 (70) | 502 (70) |
| Bortezomib | 248 (69) | 250 (69) | 498 (69) |
| Carfilzomib | 1 (<1) | 4 (1) | 5 (1) |
| Disease refractory to any prior proteasome inhibitor therapy — no. (%)** | 4 (1) | 8 (2) | 12 (2) |
| Prior immunomodulatory drug therapy — no./total no. (%) | 193/360 (54) | 204/362 (56) | 397/722 (55) |
| Lenalidomide | 44/360 (12) | 44/362 (12) | 88/722 (12) |
| Thalidomide | 157/360 (44) | 170/362 (47) | 327/722 (45) |
| Disease refractory to any prior immunomodulatory drug therapy†† | 41/193 (21) | 50/204 (25) | 91/397 (23) |

* There were no significant differences at baseline between the two groups in the characteristics shown.
† Race was self-reported.
‡ Eastern Cooperative Oncology Group (ECOG) performance status is scored on a scale from 0 to 5, with 0 indicating no symptoms and higher scores indicating increasing disability related to tumor.
§ The International Staging System (ISS) consists of three stages: stage I, serum $\beta_2$-microglobulin level lower than 3.5 mg per liter (300 nmol per liter) and albumin level 3.5 g per deciliter or higher; stage II, neither stage I or III; and stage III, serum $\beta_2$-microglobulin 5.5 mg per liter or higher (470 nmol per liter). Higher stages indicate more severe disease.
¶ High-risk cytogenetic abnormalities were detected by fluorescence in situ hybridization (FISH) analysis and were defined as chromosome 17p deletion [del(17p)], translocation between chromosomes 4 and 14 [t(4;14)], and translocation between chromosomes 14 and 16 [t(14;16)]. A total of 36 patients in the ixazomib group and 33 patients in the placebo group had del(17p) alone or in combination with either t(4;14) or t(14;16) or both; 36 and 25 patients, respectively, had t(4;14) alone; and 3 and 4 patients, respectively, had t(14;16) alone. Standard-risk cytogenetic abnormalities were defined as the absence of high-risk abnormalities in the samples that were available for evaluation; samples from some patients were not available for testing because the sample was missing or clotted or for other reasons. In accordance with the protocol, the cutoff values for defining the presence of high-risk cytogenetic abnormalities were established by the central diagnostic laboratory on the basis of the false positive rates (or technical cutoff values) of the FISH probes that we used. These cutoff points were 5% positive cells for del(17p), 3% positive cells for t(4;14), and 3% positive cells for t(14;16).
‖ The number of prior therapies was determined by the sponsor in a blinded medical review of data on prior therapy.
** Refractoriness to any prior proteasome inhibitor therapy was determined by the sponsor in a blinded medical review.
†† All the patients had disease that had been refractory to prior therapy with thalidomide, except for one patient in the placebo group, who, on further blinded medical review by the sponsor, was determined to have disease that had been refractory to prior therapy with lenalidomide. Percentages are shown are those patients who received prior therapy with immunomodulatory drugs.

Moreau P et al. N Engl J Med 2016;374:1621-1634

The NEW ENGLAND JOURNAL of MEDICINE

# 722 patients enrolled at 147 study centers in 26 countries from 8/2012–5/2014

| | IRd (N=360) | Placebo-Rd (N=362) |
|---|---|---|
| **Demographics** | | |
| Median age, years (range) | 66 (38–91) | 66 (30–89) |
| Gender – male, % | 58 | 56 |
| Race – white / Black or African American / Other, % | 86 / 2 / 12 | 83 / 2 / 15 |
| ECOG performance status 0 / 1 / 2, %* | 50 / 43 / 5 | 47 / 45 / 7 |
| **Stratification factors** | | |
| ISS Stage at screening: I or II / III, % | 87 / 13 | 88 / 12 |
| Lines of prior therapy: 1 / 2 or 3, % | 59 / 41 | 59 / 41 |
| Proteasome inhibitor-exposed, % | 69 | 70 |

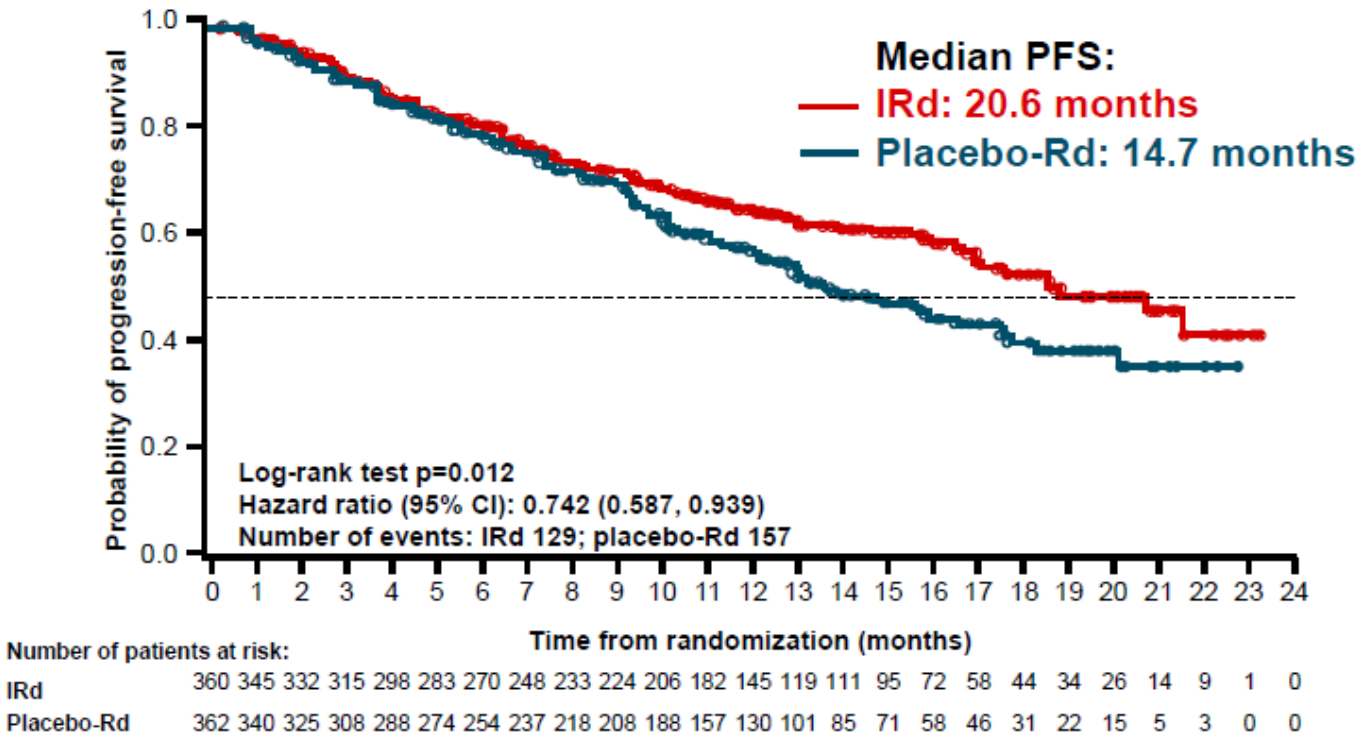
*Missing data for 2% and 1% in the IRd and placebo-Rd groups, respectively

# Prior therapy and baseline cytogenetics

| | IRd (N=360) | Placebo-Rd (N=362) |
|---|---|---|
| **Type of prior regimen** | | |
| Bortezomib-containing | 248 (69) | 250 (69) |
| Thalidomide-containing | 157 (44) | 170 (47) |
| Lenalidomide-containing | 44 (12) | 44 (12) |
| Carfilzomib-containing | 1 (<1) | 4 (1) |
| Melphalan-containing | 293 (81) | 291 (80) |
| Stem cell transplant | 212 (59) | 199 (55) |
| **Patient population categories[#]** | | |
| Relapsed | 276 (77) | 280 (77) |
| Refractory | 42 (12) | 40 (11) |
| Refractory and relapsed | 41 (11) | 42 (12) |
| Primary refractory (defined as no response to all prior lines of therapy) | 24 (7) | 22 (6) |
| **Cytogenetics** | | |
| Standard-risk[†] | 199 (55) | 216 (60) |
| High-risk (defined as del(17p), t(4;14), t(14;16)* | 75 (21) | 62 (17) |
| Not available[‡] | 86 (24) | 84 (23) |

[#]Data missing for 1 IRd patient
*97% of cytogenetics results were from a Clinical Laboratory Improvement Amendment (CLIA)-certified central laboratory, 3% from local laboratories.
[†]Defined as patients without high-risk abnormalities. [‡]Not able to test as sample was clotted, missing, etc.

# Final PFS analysis: A significant, 35% improvement in PFS with IRd vs placebo-Rd




Median follow-up: ~15 months

| At 23 mos of follow-up | IRd | Rd |
|---|---|---|
| mPFS (mos) | 20.6 | 14.7 |
| mOS (n) | 81 | 90 |

# Outcomes by cytogenetic risk group

| | ORR, % | | ≥VGPR, % | | ≥CR, % | | Median PFS, months | | |
|---|---|---|---|---|---|---|---|---|---|
| | IRd | Placebo-Rd | IRd | Placebo-Rd | IRd | Placebo-Rd | IRd | Placebo-Rd | HR |
| All patients | 78.3* | 71.5 | 48.1* | 39 | 11.7* | 6.6 | 20.6 | 14.7 | 0.742* |
| Standard-risk patients | 80 | 73 | 51 | 44 | 12 | 7 | 20.6 | 15.6 | 0.640* |
| All high-risk patients | 79* | 60 | 45* | 21 | 12* | 2 | 21.4 | 9.7 | 0.543 |
| Patients with del(17p)† | 72 | 48 | 39 | 15 | 11* | 0 | 21.4 | 9.7 | 0.596 |
| Patients with t(4;14) alone | 89 | 76 | 53 | 28 | 14 | 4 | 18.5 | 12.0 | 0.645 |

*p<0.05 for comparison between regimens. †Alone or in combination with t(4;14 or t(14;16).
Data not included on patients with t(14:16) alone due to small numbers (n=7).

- Median OS was not reached in either arm
- In the IRd arm, median PFS in high-risk patients was similar to that in the overall patient population and in patients with standard-risk cytogenetics

# Improved response rates, durable responses, and improved time to progression (TTP) with IRd

| Response rates | IRd (N=360) | Placebo-Rd (N=362) | p-value |
|---|---|---|---|
| Confirmed ORR (≥PR), % | 78.3 | 71.5 | p=0.035 |
| CR+VGPR, % | 48.1 | 39.0 | p=0.014 |
| **Response categories** | | | |
| CR, % | 11.7 | 6.6 | p=0.019 |
| PR, % | 66.7 | 64.9 | – |
| VGPR, % | 36.4 | 32.3 | – |
| Median time to response, mos | 1.1 | 1.9 | – |
| Median duration of response, mos | 20.5 | 15.0 | – |
| Median TTP, mos | 21.4 | 15.7 | HR 0.712<br>P=0.007 |

# OS interim analysis at a median follow-up of 23 months

- A subsequent pre-specified interim analysis for OS was conducted
  - Median follow-up was 23.3 and 22.9 months in the IRd and placebo-Rd groups, respectively
  - 171 deaths (only 35% of the required number of deaths for final OS analysis): 81 and 90 in the ixazomib and placebo regimens, respectively
  - The median OS was not reached in either arm

# Summary of treatment exposure and treatment-emergent adverse events

- Median follow-up: 23.3 months for IRd and 22.9 months for placebo-Rd
- Median number of treatment cycles: 17 (range 1–34) for IRd, and 15 (1–34) for placebo-Rd
  - 48% and 43% of patients had received ≥18 cycles, respectively
  - 20% and 19% of patients had received ≥25 cycles, respectively

| Adverse event (AE) | IRd (N=361), % | Placebo-Rd (N=359), % |
|---|---|---|
| Any AE | 98 | 99 |
| Any grade ≥3 AE | 74 | 69 |
| Any serious AE | 47 | 49 |
| AE resulting in discontinuation of study regimen | 17 | 14 |
| On-study death (death within 30 days of last dose) | 4 | 6 |

- Higher frequency of grade ≥3 AE, primarily due to thrombocytopenia
- Rates of AEs resulting in discontinuation or on-study death were similar between the two arms

# AEs after median follow-up of 23 months: increased rates with IRd driven by low-grade events

| | IRd (N=361), % | | | Placebo-Rd (N=359), % | | |
|---|---|---|---|---|---|---|
| **Preferred terms** | **All-grade** | **Grade 3** | **Grade 4** | **All-grade** | **Grade 3** | **Grade 4** |
| **AEs overlapping with lenalidomide** | | | | | | |
| Diarrhea | 45 | 6 | 0 | 39 | 3 | 0 |
| Constipation | 35 | <1 | 0 | 26 | <1 | 0 |
| Nausea | 29 | 2 | 0 | 22 | 0 | 0 |
| Vomiting | 23 | 1 | 0 | 12 | <1 | 0 |
| Rash* | 36 | 5 | 0 | 23 | 2 | 0 |
| Back pain | 24 | <1 | 0 | 17 | 3 | 0 |
| Upper respiratory tract infection | 23 | <1 | 0 | 19 | 0 | 0 |
| Thrombocytopenia | 31 | 12 | 7 | 16 | 5 | 4 |
| **AEs with proteasome inhibitors** | | | | | | |
| Peripheral neuropathy* | 27 | 2 | 0 | 22 | 2 | 0 |
| Peripheral edema | 28 | 1 | 0 | 20 | 1 | 0 |
| **AEs with lenalidomide** | | | | | | |
| Thromboembolism* | 8 | 2 | <1 | 11 | 3 | <1 |
| Neutropenia* | 33 | 18 | 5 | 31 | 18 | 6 |

*Represents multiple MedDRA preferred terms.

# Other infrequent AEs (median follow-up of 23 months): no safety concerns identified

| AE | IRd (N=361), % | Placebo-Rd (N=359), % |
|---|---|---|
| Arrhythmias* | 16 | 15 |
| Hypertension | 6 | 5 |
| Hypertension crisis | <1 | 0 |
| Hypotension* | 6 | 6 |
| Heart failure* | 4 | 4 |
| Myocardial infarction* | 1 | 2 |
| Acute renal failure* | 9 | 11 |
| Liver impairment* | 8 | 6 |
| Interstitial lung disease* | 1 | 2 |
| Encephalopathy* | <1 | 1 |
| **Events of special interest** | | |
| New primary malignancy*,† | 5 | 4 |

*Represents multiple MedDRA preferred terms.
†Includes treatment-emergent AEs and new primary malignancies reported during follow-up period.

# Conclusions: ixazomib, the first oral proteasome inhibitor, significantly extends PFS in a phase 3 trial

- Ixazomib when combined with Rd for patients with relapsed and/or refractory MM was associated with:
  - a significant and clinically meaningful improvement in PFS
  - significantly improved TTP and response rates
  - improved PFS in high-risk patients, similar to that in the overall patient population and in standard-risk patients
- Ixazomib added limited additional toxicity to that seen with placebo-Rd
  - Low rates of PN and no cardiovascular or renal signals
  - Patient-reported quality of life was maintained
- The all-oral regimen of IRd may become a new standard of care for relapsed and/or refractory MM
- Ixazomib was approved by the US FDA on November 20 under the name NINLARO®

# Recent phase 3 studies in RRMM comparing triplet regimens vs Rd

| | Median PFS | Median PFS – Rd arm | Hazard ratio for progression or death | Study |
|---|---|---|---|---|
| Ixazomib-Rd vs placebo-Rd | 20.6 | 14.7 | 0.74 | TOURMALINE-MM1 (double-blind, placebo-controlled) |
| Elotuzumab-Rd vs Rd | 19.4 | 14.9 | 0.70 | ELOQUENT-2[1] (open-label) |
| Carfilzomib-Rd vs Rd | 26.3 | 17.6 | 0.69 | ASPIRE[2] (open-label) |

- HR for progression/death with IRd is consistent with results from recent studies

1. Lonial S, et al. N Engl J Med 2015;373:621-631.

# Ixazomib
# Maintenance Therapy in RRMM

- There are no drugs approved for maintenance therapy in MM

- A Phase 3, randomized, placebo-controlled, double blind study of oral Ixazomib maintenance therapy in MM pts who have achieved at least PR to induction therapy folloved by HDT whit ASCT was initiated in 2014 (NCT02181413). Primary goal: efficacy of Ixazomib single-agent in maintenance therapy

- To select the appropriate dose: data analysis from NCT00963820 (weekly Ixazomib in RRMM → MTD 2.97 mg/mq = fixed dose of 5.5 mg)

- Exposure-response analysis using safety, efficacy and PK data in order to determine an appropriate dose of Ixazomib vs placebo

- Results: Ixazomib maintenance th. Once-weekly dose of 3 mg → escalation to 4 mg after 4 cycles

Gupta N., Invest New Drugs (2016) 34:338-346

# Ixazomib
# Ongoing Clinical Trials

# Relapsed/ Refractory MM

| Agent | Sponsor | Trial | Phase | Condition | Status |
|---|---|---|---|---|---|
| **Ixazomib** + dexamethasone | Mayo Clinic | MC1181 NCT01415882 | 2 | Relapsed MM, not refractory to bortezomib | Active, not recruiting |
| **Ixazomib** | SCRI Development Innovations | NCT02168101 | 2 | Maintenance post-allo-SCT | Recruiting |
| **Ixazomib +** cyclophosphamide + dexamethasone | Univ. of Leeds | NCT02461888 | 2 | Relapsed or refractory MM | Not yet recruiting |
| **Ixazomib** | NHLBI | NCT02440464 | 2 | Ixazomib or placebo maintenance post-allo-SCT for high-risk MM | Not yet recruiting |

www.clinicaltrials.gov; accessed June 2015

# Ixazomib: Ongoing Clinical Trials: Relapsed/ Refractory MM

| Agent | Sponsor | Trial | Phase | Condition | Status |
|---|---|---|---|---|---|
| **Ixazomib +** thalidomide + dexamethasone | AGMT | NCT02410694 | 2 | Relapsed and/or refractory MM | Not yet recruiting |
| Pomalidomide + dexamethasone **± ixazomib** | Alliance for Clinical Trials in Oncology | NCT02004275 A061202 | 1/2 | Refractory MM | Recruiting |
| **Ixazomib +** pomalidomide + dexamethasone | City of Hope | NCT02119468 | 1/2 | Relapsed/refractory MM | Recruiting |
| **Ixazomib +** bendamustine + dexamethasone | Medical College of Wisconsin | NCT02477215 | 1/2 | Relapsed/refractory MM | Not yet recruiting |
| **Ixazomib** as a replacement for bortezomib or carfilzomib in combination regimens | Oncothera-peutics | NCT02206425 | 1/2 | Relapsed/refractory MM | Recruiting |

www.clinicaltrials.gov; accessed June 2015

# Ixazomib: Ongoing Clinical Trials: Relapsed/ Refractory MM

| Agent | Sponsor | Trial | Phase | Condition | Status |
|---|---|---|---|---|---|
| **Ixazomib** + dexamethasone | Millennium | C16015 NCT01830816 | 1 | PK study in relapsed/ refractory MM with or without renal impairment | Recruiting |
| **Ixazomib** + lenalidomide + dexamethasone | Millennium | C16013 NCT01645930 | 1 | PK study in Asian patients with relapsed/refractory MM | Active, not recruiting |
| **Ixazomib +** panobinostat + dexamethasone | Case Comp Cancer Ctr | NCT02057640 | 1 | Relapsed/refractory MM | Recruiting |

www.clinicaltrials.gov; accessed June 2015

# Grazie per l'attenzione!