Long-Term Ixazomib Maintenance Is Tolerable and Improves Depth of Response Following Ixazomib-Lenalidomide-Dexamethasone Induction in Patients With Previously Untreated Multiple Myeloma (MM): Phase II Study Results

Abstract #82

Kumar SK, Berdeja JG, Niesvizky R, Lonial S, Laubach JP, Hamadani M, Stewart AK, Hari PN, Roy V, Vescio R, Kaufman JL, Berg D, Liao E, Hui A-M, Rajkumar SV, Richardson PG

Ixazomib

- Ixazomib is an investigational, oral, reversible, and specific 20S proteasome inhibitor
  - The first oral proteasome inhibitor in clinical development
  - Physiochemical properties distinct from bortezomib[1]
- Ixazomib has been evaluated in single-agent and combination studies in MM
  - Clinical activity of single-agent ixazomib seen in heavily pretreated patients[2,3]
  - Data suggest a manageable toxicity profile with low rates of peripheral neuropathy (PN)[2,3]
  - Phase III trials underway

1. Kupperman E, et al. *Cancer Res*. 2010;70:1970-1980.
2. Richardson PG, et al. *Blood*. 2014;124:1038-1046.
3. Kumar SK, et al. *Blood*. 2014;124:1047-1055.

Kumar SK, et al. *Blood.* 2014;124: Abstract 82.

Rationale

- Triplet regimens combining a proteasome inhibitor, an immunomodulatory drug, and a steroid shown to be active and well tolerated in previously untreated MM patients[1–3]
  - High response rates seen with the bortezomib, lenalidomide, dexamethasone (VRD/RVD) regimen[1,2]
- Increasing evidence suggests that extended treatment may add benefits to conventional induction strategies
  - Long-term maintenance therapy improves survival outcomes, including PFS and sometimes OS, in both the transplant and non-transplant settings
  - However, agents for continuous therapy need to be convenient and well tolerated
  - Oral weekly ixazomib may be an ideal maintenance drug in terms of tolerability/safety and convenience

1. Kumar S, et al. *Blood.* 2012;119:4375-4382.
2. Richardson PG, et al. *Blood.* 2010;116:679-686.
3. Jakubowiak AJ, et al. *Blood*. 2012;120:18011809.

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Phase I/II Study of Weekly Ixazomib Plus Lenalidomide-Dexamethasone (NCT01217957)

- Triplet regimen investigated in an open-label, dose-escalation, phase 1/2 study, conducted in patients with previously untreated MM to:
  - Define the dose of ixazomib to be combined with lenalidomide and dexamethasone
  - Evaluate the efficacy and toxicity of the combination
  - Evaluate the feasibility, efficacy, and safety of long-term maintenance therapy with single-agent ixazomib
- The recommended phase II dose (RP2D) was determined to be ixazomib 4.0 mg weekly, on days 1, 8, 15, with lenalidomide 25 mg on days 1-21, and dexamethasone weekly, in 4-week cycles[1]
  - Results of induction therapy have been previously reported[1]
  - Here we report phase II efficacy and safety data in patients receiving ixazomib maintenance

1. Kumar SK, et al. *Lancet Oncol.* 2014;15:1503-1512.

Kumar SK, et al. *Blood.* 2014;124: Abstract 82.

Patient Eligibility

- Key inclusion criteria:
  - Age ≥18 years
  - ECOG performance status 0-2
  - Adequate hepatic, renal, and hematologic function
  - Measurable disease:
    - Serum M-protein ≥1 g/dL
    - Urine M-protein ≥200 mg/24 hours
    - Involved free light chain ≥10 mg/dL
- Key exclusion criteria:
  - Grade ≥2 PN
  - Prior/concurrent deep vein thrombosis/pulmonary embolism
  - Prior systemic MM therapy

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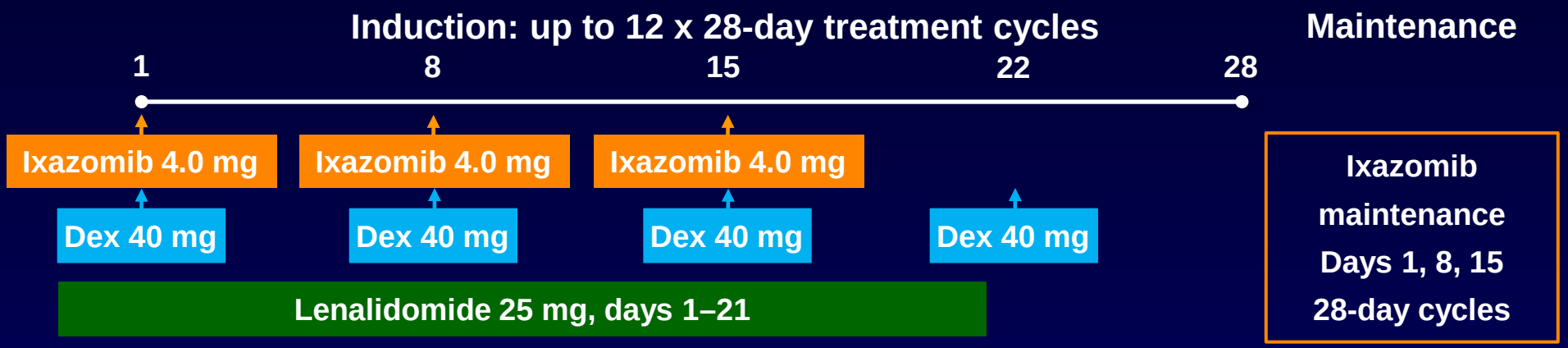
Study Design: Phase II Dosing



- Mandatory thromboembolism prophylaxis with aspirin 81-325 mg QD or low-molecular-weight heparin while receiving lenalidomide–dexamethasone
- Stem cell collection allowed after 3 cycles; patients could proceed to ASCT after 6 cycles
- Ixazomib maintenance continued until progression or unacceptable toxicity
  - Ixazomib administered at last tolerated dose during induction
- Primary objective was CR + VGPR rate

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Enrollment and Disposition

65 patients enrolled[1]
15 phase I, 50 phase II
Median no. of cycles: 7 (range 1-45)

17 patients off treatment before cycle 13 (maintenance)

- 2 phase I patients
  - Both due to AEs
- 15 phase II patients
  - 6 due to AEs
  - 4 patient withdrawals
  - 2 disease progression
  - 1 unsatisfactory response
  - 2 other

23 withdrew to initiate ASCT
9 phase I, 14 phase II

25 patients entered maintenance phase

- 4 phase I patients (BSA-based dosing)
  - Received actual doses of 4.0, 4.0, 3.6, and 3.4 mg
- 21 phase II patients (fixed dosing[2])
  - 16 entered at 4.0 mg
  - 4 entered at 3.0 mg
  - 1 entered at 2.4 mg
  - **Focus of the current presentation**

1. Kumar SK, et al. *Lancet Oncol.* 2014;15:1503-1512.
2. Gupta N, et al. *Br J Clin Pharmacol.* 2014. [Epub ahead of print]

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Patient Characteristics

	All phase II patients, n = 50	Patients receiving maintenance, n = 21
Median age, years (range)	65 (34-86)	68 (34-77)
Age ≥65 years, n (%)	25 (50)	12 (57)
Age ≥75 years, n (%)	9 (18)	2 (10)
Male, n (%)	30 (60)	13 (62)
White, n (%)	42 (84)	16 (76)
ISS disease stage at diagnosis, n (%)		
I	25 (50)	14 (67)
II	19 (38)	7 (33)
III	6 (12)	0
MM subtype, n (%)		
IgG	34 (68)	16 (76)
IgA	9 (18)	3 (14)
IgD	1 (2)	0
Light chain	6 (12)	2 (10)
Median creatinine clearance, mL/min	85.3	83.5

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Cytogenetics

	All phase II patients, n = 50	Patients receiving maintenance, n = 21
Patients with cytogenetic assessment, N*	47	19
Conventional/karyotype	7 (15)	3 (16)
Molecular/FISH	15 (32)	6 (32)
Both	25 (53)	10 (53)
Unfavorable cytogenetics†, n (%)	6 (13)	3 (16)
Type of cytogenetic abnormality, n (%)		
del 13 (by metaphase cytogenetics)	2 (4)	2 (11)
del 17	2 (4)	1 (5)
t(4;14)	1 (2)	0
t(14;16)	1 (2)	1 (5)
1q amplification	1 (2)	0

*No sample collected for 3 patients. †Unfavorable cytogenetics includes del 17, t(4;14), t(14;16), and 1q amplification abnormalities detected by FISH or metaphase cytogenetics and del 13 detected by metaphase cytogenetics.

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Treatment exposure

At data cut-off (October 2, 2014)	Patients receiving maintenance, n = 21
Median cycles of ixazomib received, n (range)	
Total (including induction and maintenance cycles)	31 (15-35)
Maintenance cycles	19 (3-23)
Median treatment duration, months (range)	29.0 (16.3-33.3)
Maintenance duration, months (range)	19.8 (2.3-22.9)
Mean relative dose intensity* of ixazomib overall / during induction / during maintenance, %	92 / 95 / 89.5
Patients remaining on ixazomib maintenance, n (%)	11 (52%)

*Dose taken/dose prescribed

- Among the 29 patients in phase 2 who did not proceed to maintenance, median number of cycles of ixazomib received was 6 (1-12)
  - Median cycle of first stem cell mobilization (n = 14) was cycle 4 (3-9), and patients who received ASCT received a median of 6 (3-12) cycles of ixazomib

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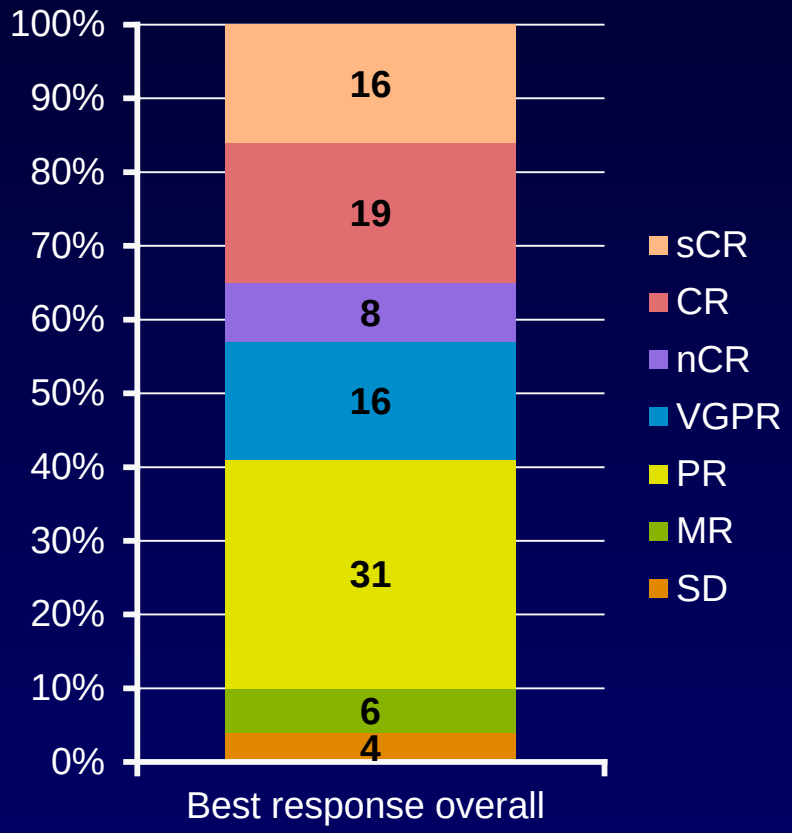
Best Response to Treatment, All Patients (n = 49)*



Best response, n (%)	All patients, n = 49* To induction	Overall
CR+VGPR+PR	44 (90)	44 (90)
CR	11 (22)	17 (35)
sCR	5 (10)	8 (16)
VGPR	18 (37)	12 (24)
nCR	2 (4)	4 (8)
CR+VGPR	29 (59)	29 (59)
PR	15 (31)	15 (31)
MR	3 (6)	3 (6)
SD	2 (4)	2 (4)

*1 patient in phase 2 not response-evaluable

- Among the 14 patients who discontinued induction to undergo ASCT, best response to induction included 4 (29%) sCR, 4 (29%) VGPR, and 6 (43%) PR
  - Response following ASCT are not included in the above data

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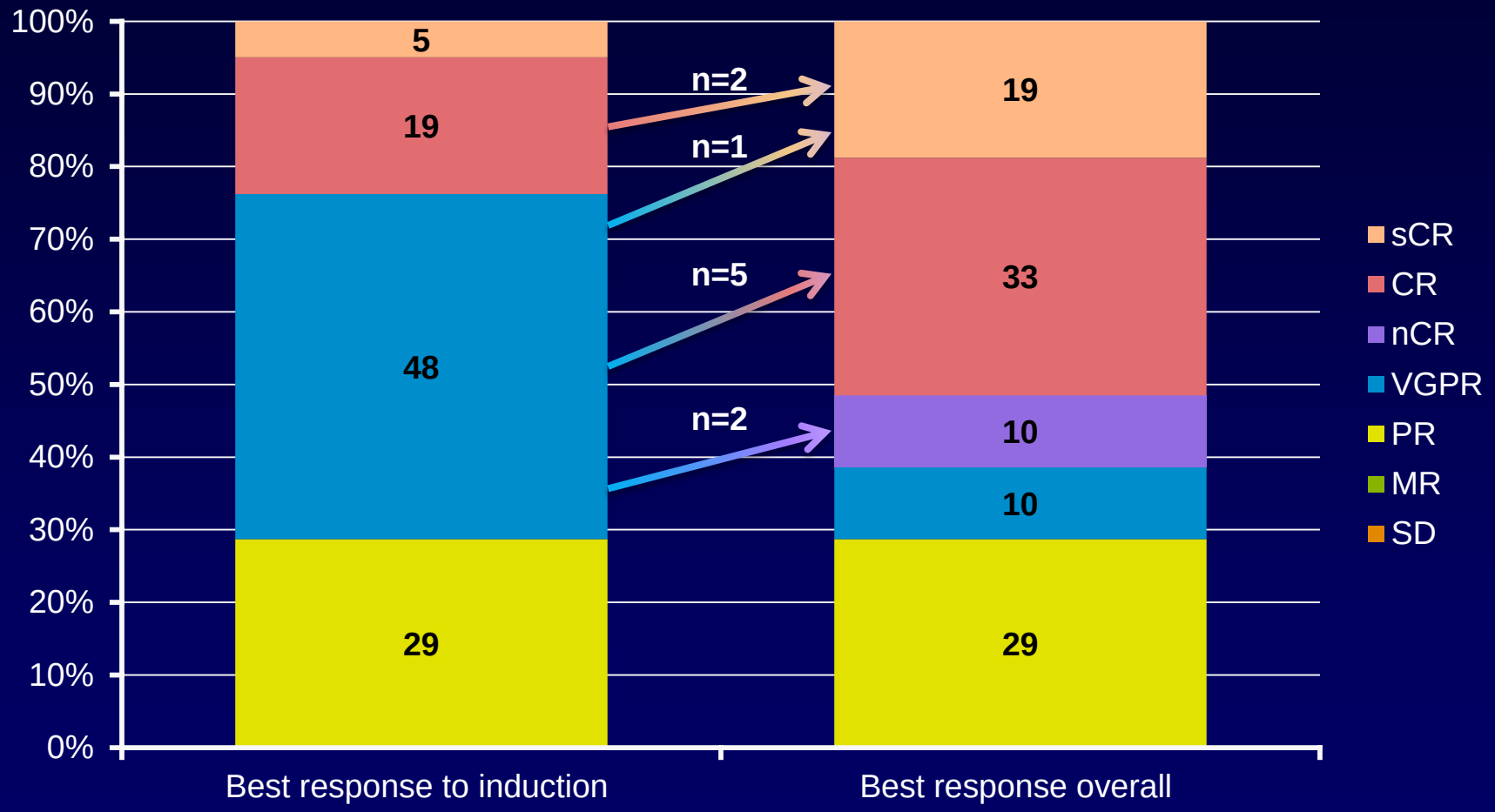
Best Response to Treatment in Phase II Patients Receiving Maintenance (n = 21)



- **10 (48%) patients improved their response during maintenance:**
  - **2 VGPR to nCR, 5 VGPR to CR, 1 VGPR to sCR, and 2 CR to sCR**

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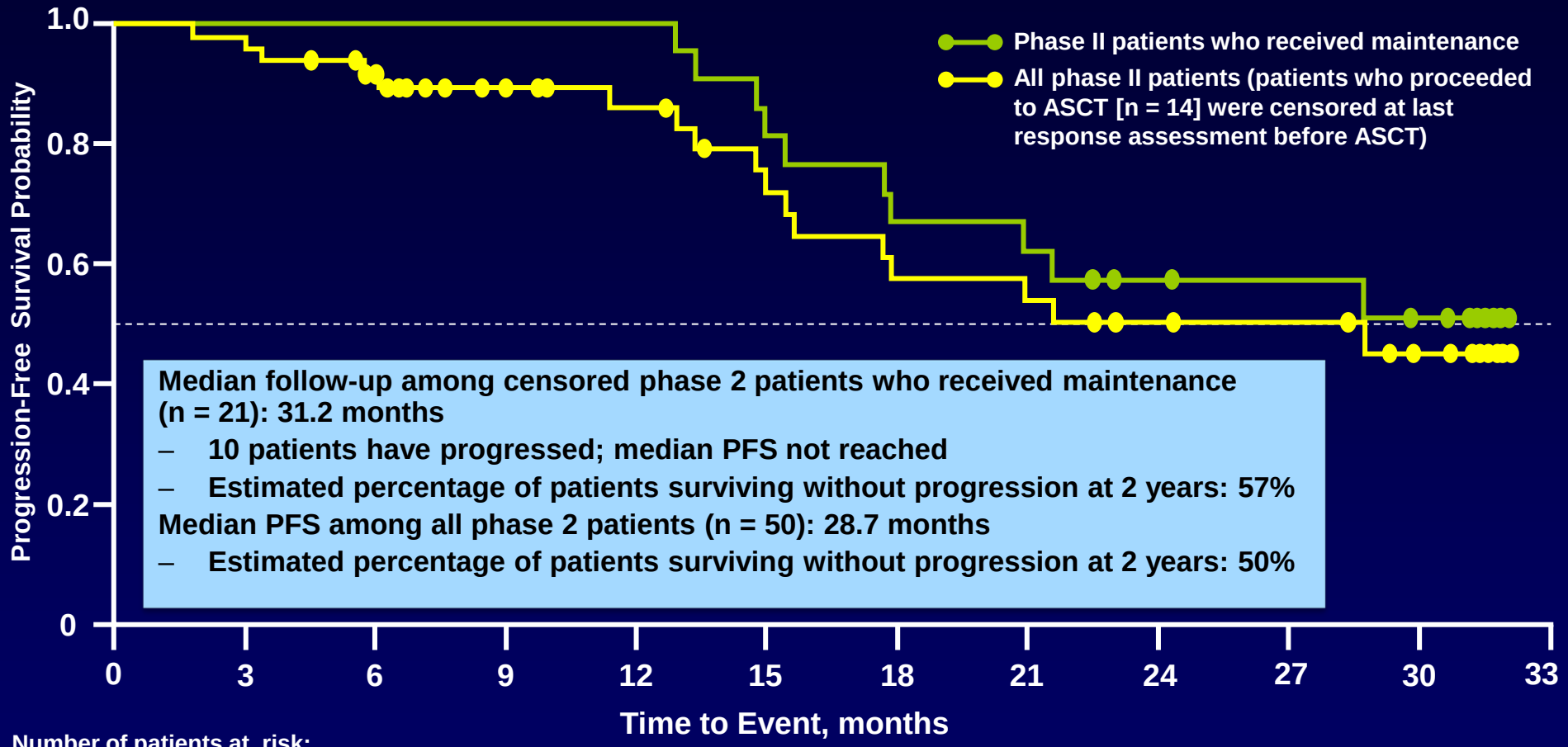
PFS



- All 21 patients who received ixazomib maintenance were alive after follow-up of 25.1-33.9 months, including a median follow-up from start of maintenance of 19.9 months (range 13.4-22.2)

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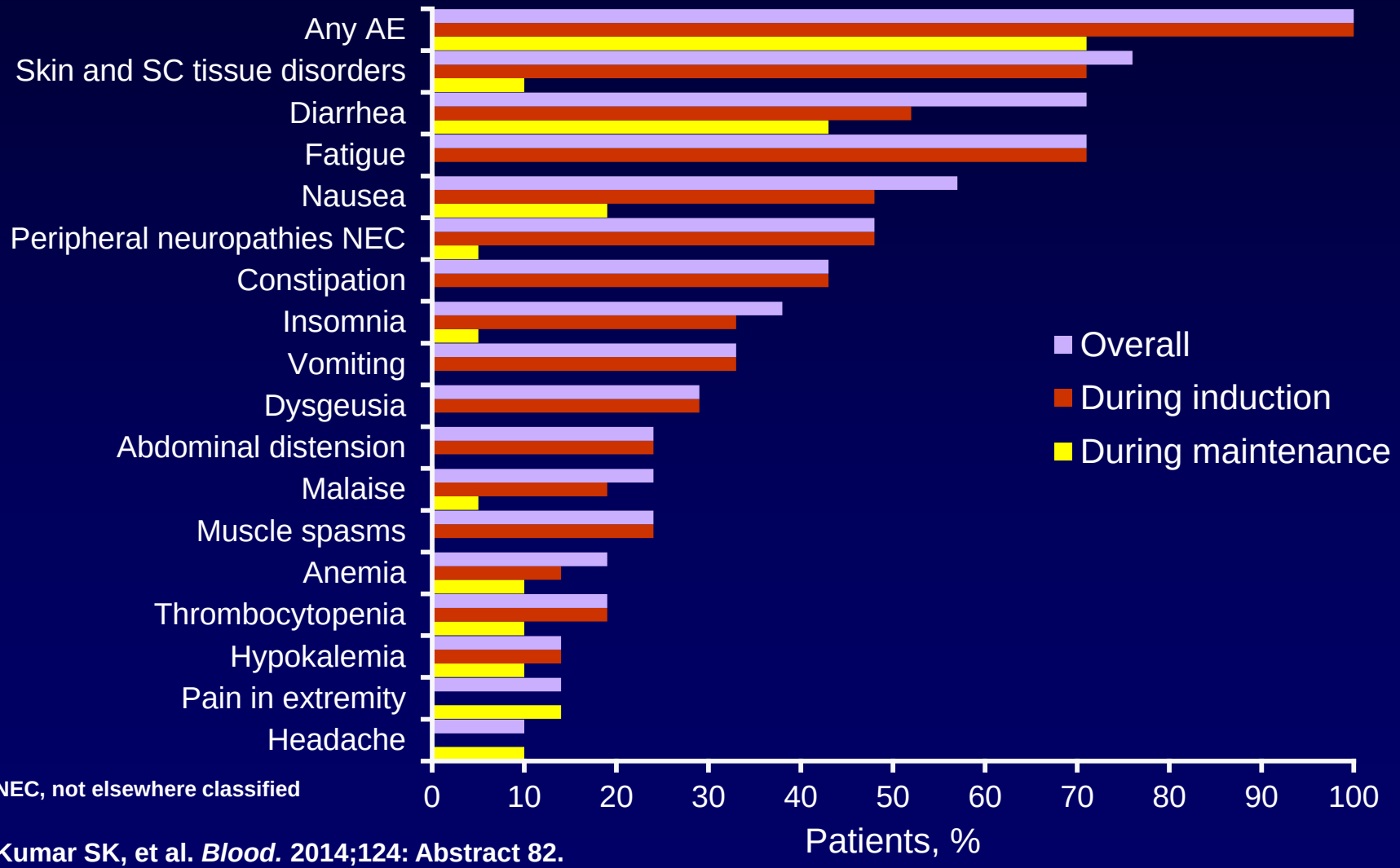
Most Common Drug-Related AEs (>20% Patients Overall, or With New Onset in >1 Patient During Maintenance)



NEC, not elsewhere classified

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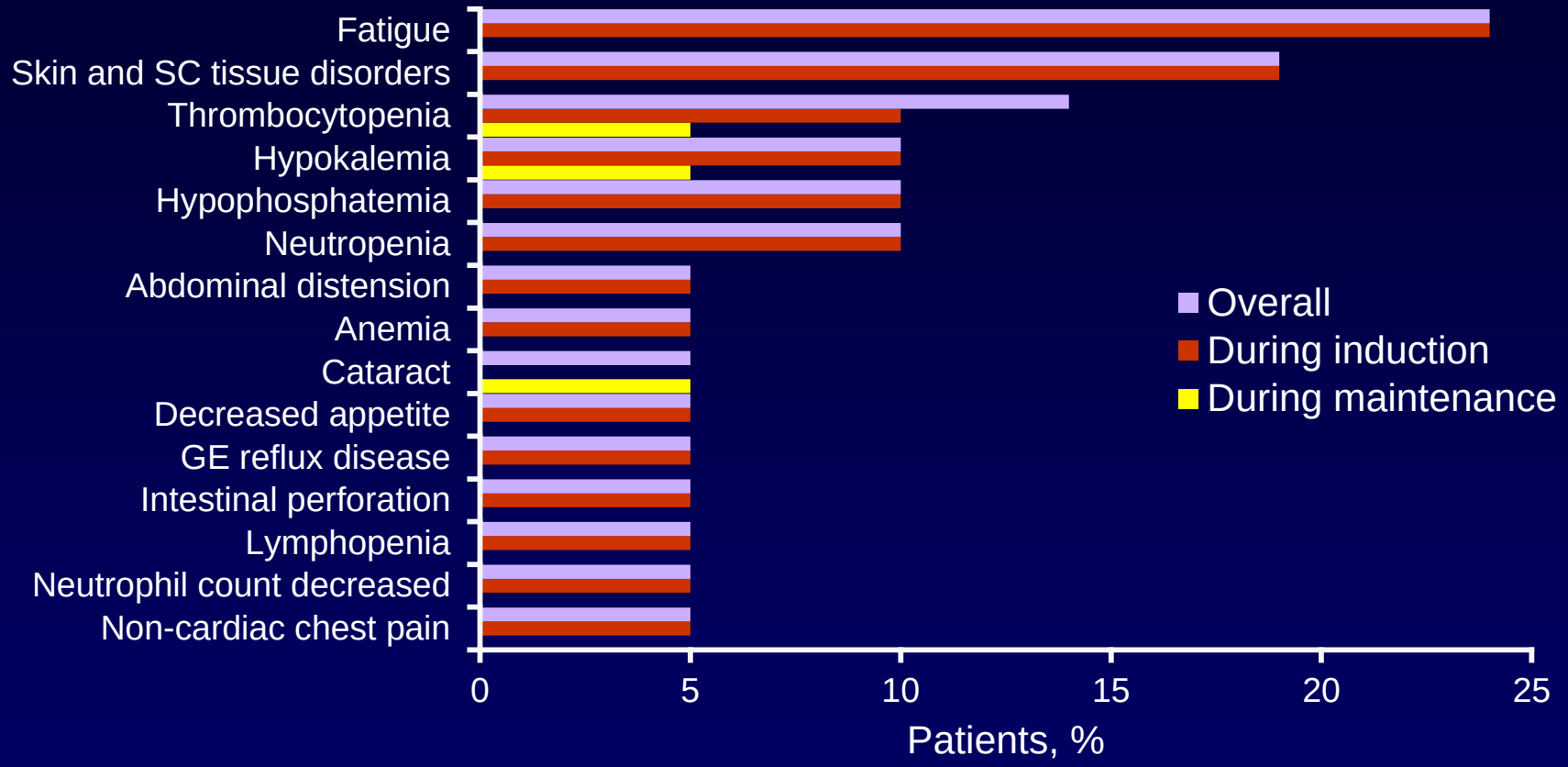
Grade 3 Drug-Related AEs, Overall and by Treatment Phase



- **Drug-related grade 3 AEs were reported in 13 (62%) patients overall, including in 11 (52%) during induction and in 3 (14%) patients during maintenance**
- **There were no grade 4 drug-related AEs reported at any time during induction and maintenance among the 21 patients who received ixazomib maintenance**

GE, gastro-esophageal

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Serious AEs (SAEs) and Dose Reductions

- Of the 21 patients who received maintenance therapy, 10 (48%) reported an SAE at any time during induction and maintenance treatment
  - Including 3 (14%) with drug-related SAEs
- SAEs were reported in 4 (19%) patients during ixazomib maintenance:
  - Grade 3 acute myocardial infarction; grade 3 pneumonia; grade 3 orthostatic hypotension; grade 2 ventricular extrasystoles
  - All were considered not related to treatment
- In total, 17 (81%) patients required any study drug dose reduction due to an AE during induction
  - Only 2 (10%) patients required ixazomib dose reduction during maintenance, due to PN and neuralgia, respectively
- There were no discontinuations due to AEs and no on-study deaths

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Conclusions

- The all-oral combination of ixazomib, lenalidomide, and dexamethasone is active as induction therapy, with a manageable safety profile, at the RP2D in previously untreated MM patients
  - 90% of patients achieved PR or better, including a ≥VGPR rate of 59% and a CR rate of 22%, after up to 12 cycles of induction
  - Common AEs included skin and SC tissue disorders, diarrhea, fatigue, nausea, and peripheral neuropathy
- Data on 21 patients who received maintenance therapy indicate that single-agent ixazomib maintenance for up to 1.9 years was feasible, with a generally manageable safety profile, in patients not undergoing ASCT
  - Ixazomib maintenance improved responses following triplet induction therapy, with 48% of patients showing increased response depth during maintenance
  - Rate of CR+nCR increased from 24% after induction to 62%, with 71% ≥VGPR
  - Ixazomib maintenance contributed to durable responses
  - New-onset toxicity during single-agent ixazomib maintenance was limited
- A phase 3 trial of ixazomib plus lenalidomide–dexamethasone versus placebo plus lenalidomide–dexamethasone in patients with previously untreated MM is currently enrolling (TOURMALINE-MM2; NCT01850524)

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