Please note, these are the actual video-recorded proceedings from the live CME event and may include the use of trade names and other raw, unedited content.

Management of Relapsed/Refractory Multiple Myeloma

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Disclosures

Advisory Committee and Consulting Agreements	Adaptive Biotechnologies, Amgen Inc, Bristol-Myers Squibb Company, Celgene Corporation, Janssen Biotech Inc, Takeda Oncology
Contracted Research	Amgen Inc, Celgene Corporation, Janssen Biotech Inc, Sanofi Genzyme
Data and Safety Monitoring Board	Amgen Inc, Celgene Corporation, Karyopharm Therapeutics, Oncopeptides

Case presentation: Dr Johl

59-year-old man

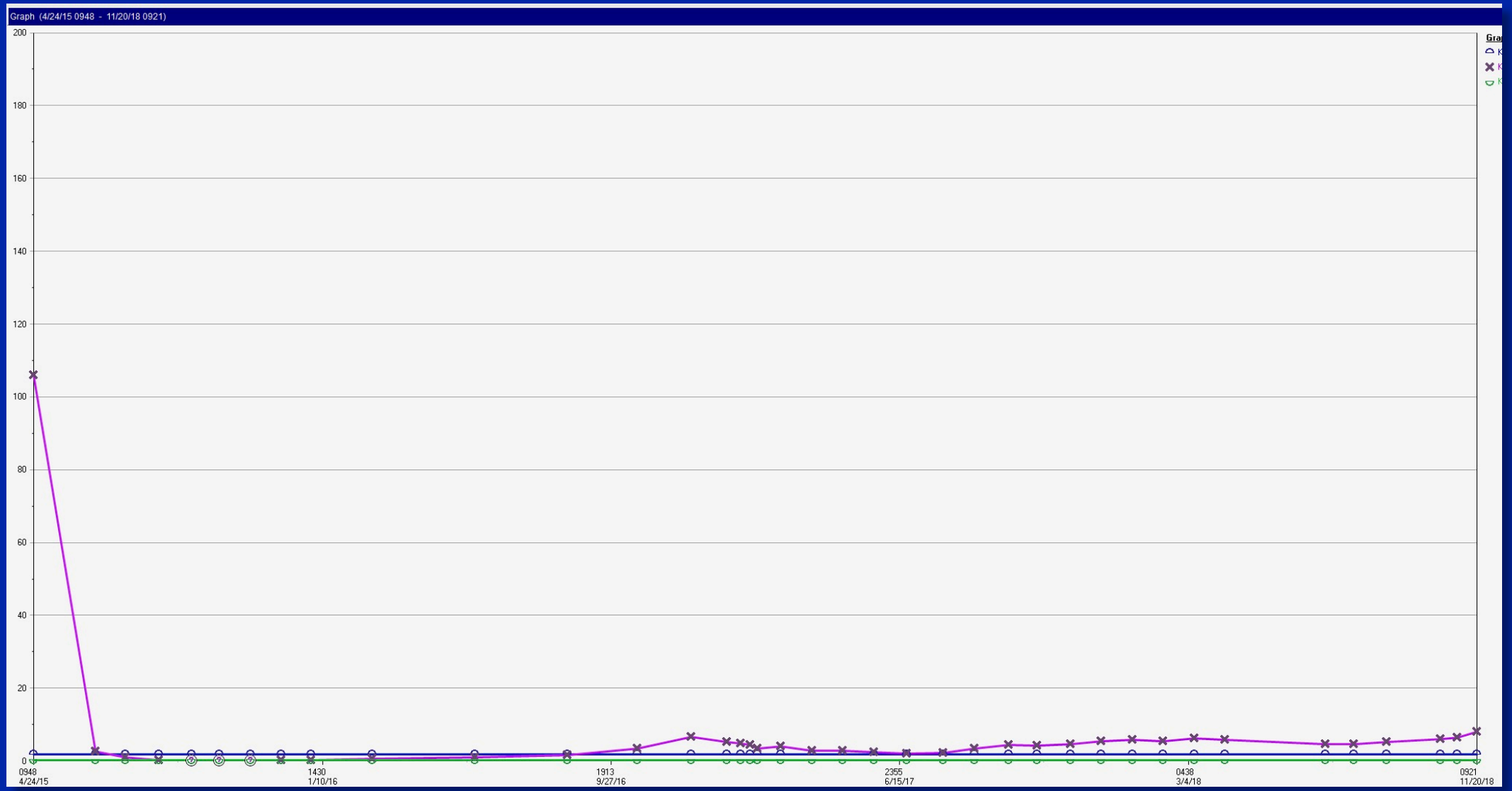
- Presented with knee pain
- Found to have advanced lytic lesions involving proximal tibia and significant anemia, leukopenia and gammopathy
- Bone marrow biopsy: IgG kappa MM
- Radiation therapy to the tibia → RVD → transplant → lenalidomide 10 mg/d (subsequently dose reduced to 5 mg every other day due to neutropenia)
- Now with slowly rising M-spike

Case presentation: Dr Rupard

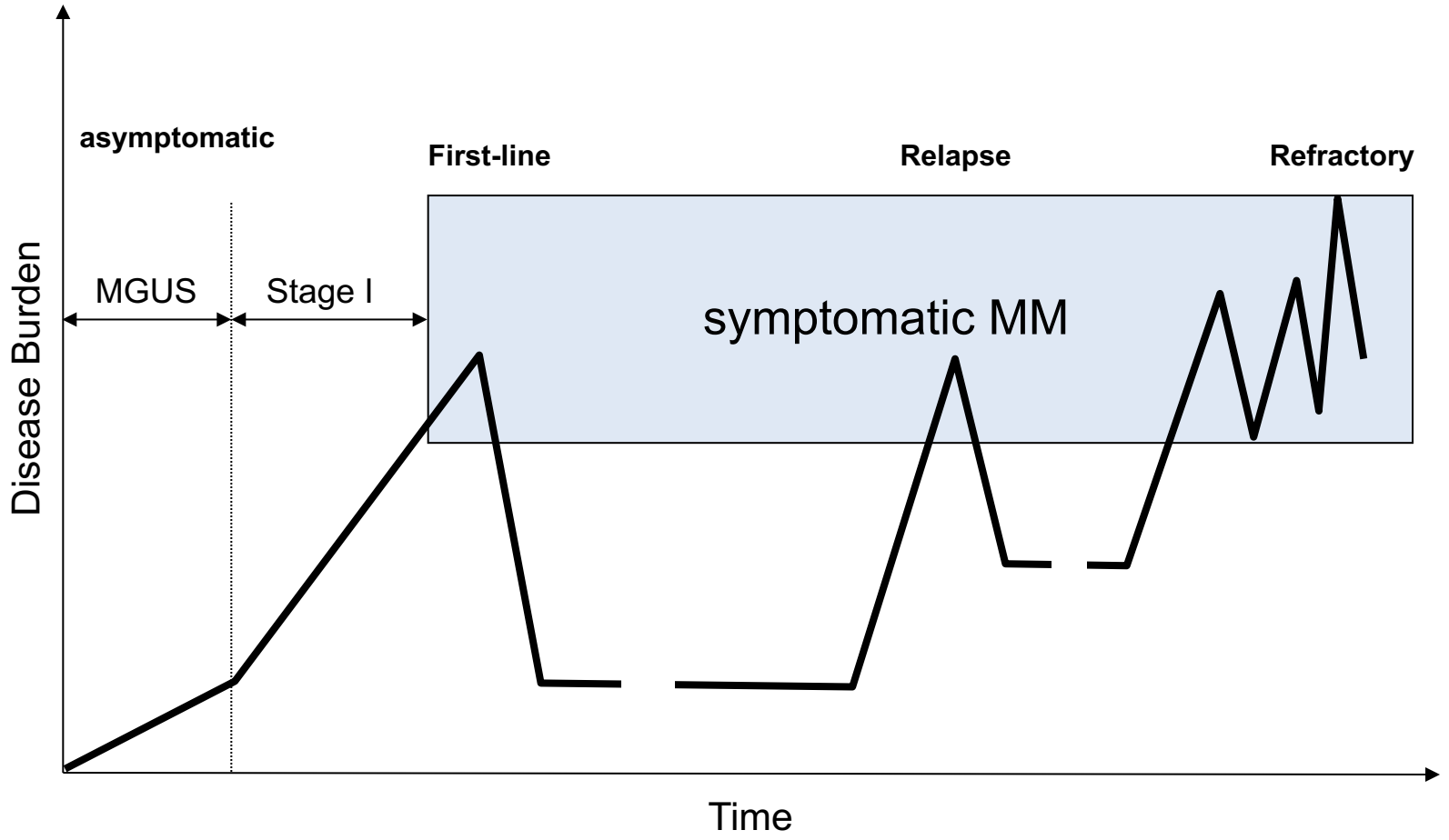
76-year-old woman

- IgG kappa MM: Received KRd on E1A11 (ENDURANCE) clinical trial
- Initial serum free light chains 106 mg/L dropped to 1 mg/L after one cycle of induction treatment

Case presentation: Dr Rupard (Continued)



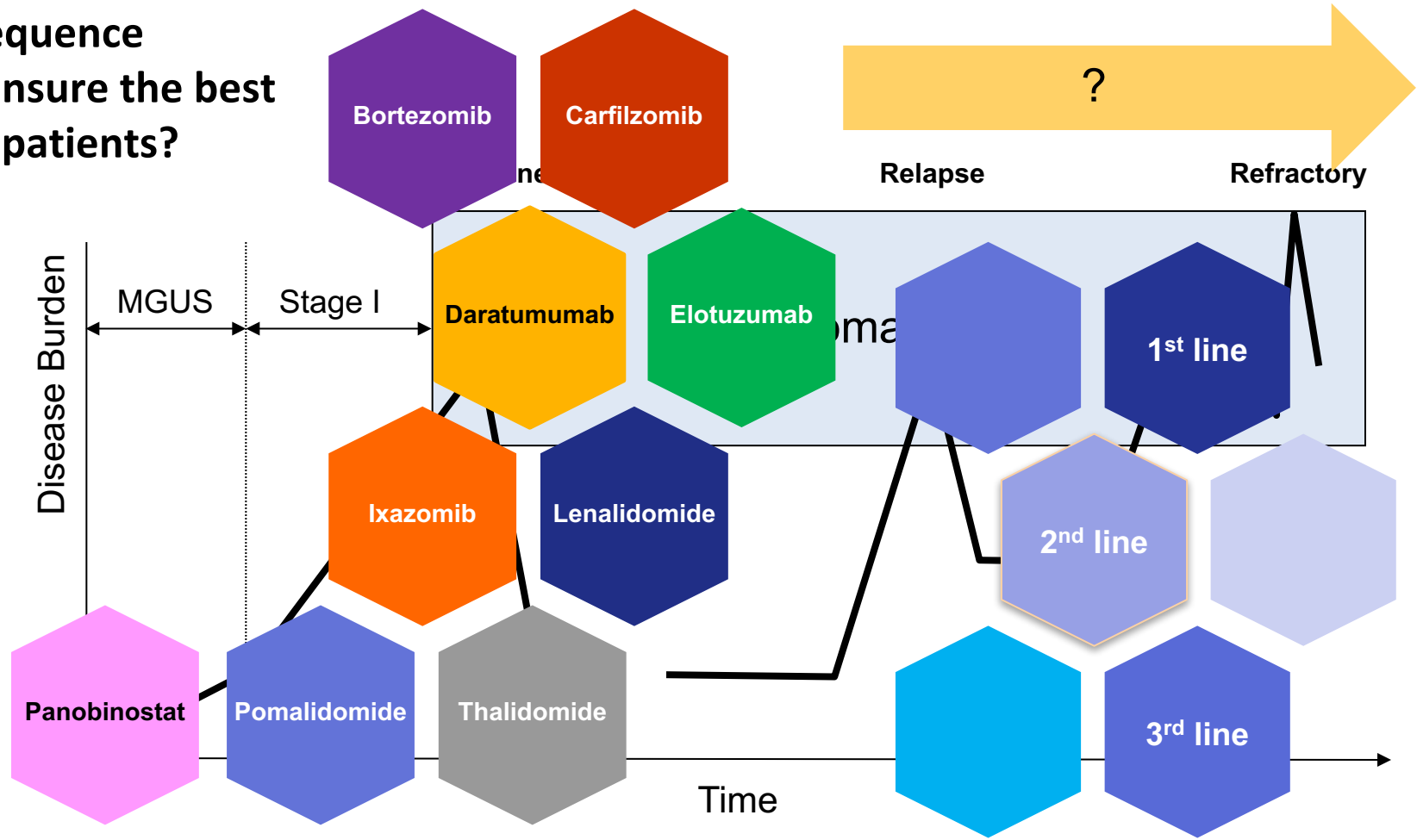
Multiple myeloma – Not a sprint but a marathon



Adapted from Laubach JP, et al. *Leukemia* 2016;30:1005–17.

Multiple myeloma – Not a sprint but a marathon

How do we sequence therapies to ensure the best outcomes for patients?



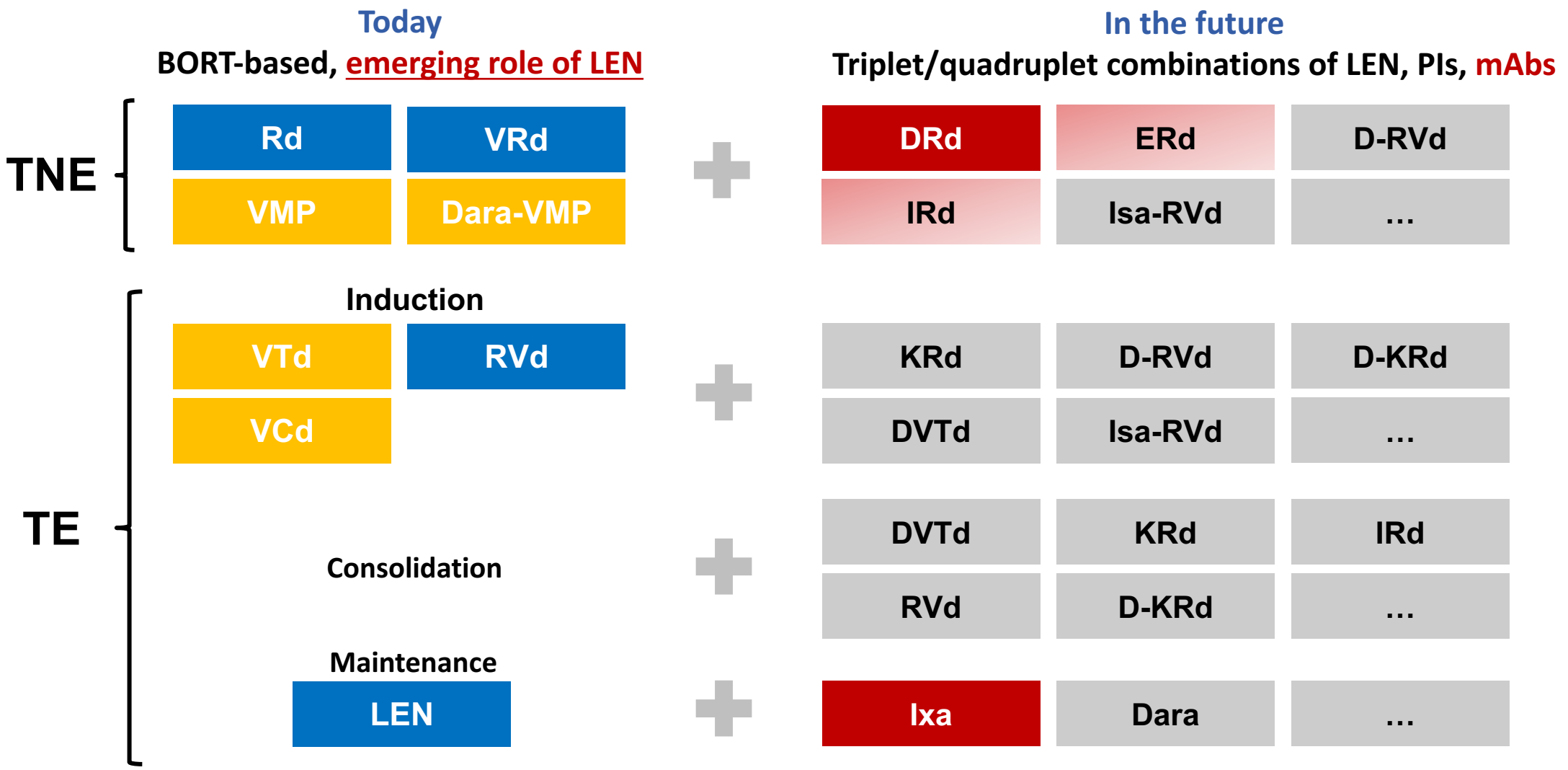
Adapted from Laubach JP, et al. *Leukemia* 2016;30:1005–17.

Options in RRMM: NCCN Guidelines 2018 (USA)

Preferred	Repeat primary induction therapy (if relapse >6 months) (2A)			
	RVD (2A) KD (1) KRD (1)	Dara VD (1) Dara RD (1) Elo RD (1)		Ixa RD (1)
Recommended	Benda VD (2A) Benda RD (2A) Liposomal Doxo VD (1) VCD (2A) KCD (2A) KD (2A)	RCD (2A) VD (1) Dara (2A) Dara Pom D (2A) Elo VD (2A) Ixa D (2A)	RD (1) Pano VD (1) Pano KD (2A) Pano RD (2A)	Pom CD (2A) Pom D (1) Pom VD (2A) Pom KD (2A) Ixa Pom D (2A)
Useful	Benda DCEP	DT-PACE +/- V (VTD-PACE) High-dose cyclophosphamide		

NCCN Clinical Practice Guidelines in Oncology. Multiple Myeloma V4.2018 Feb 2018.

Treatment landscape in front-line therapy of NDMM is evolving



BORT, bortezomib; LEN, lenalidomide; mAb, monoclonal antibody; PI, proteasome inhibitor; TE, transplant eligible; TNE, transplant non-eligible.

Treatment landscape in front-line therapy of NDMM is evolving

Today

BORT-based, emerging role of LEN

TNE

Rd	VRd
VMP	Dara-VMP

TE

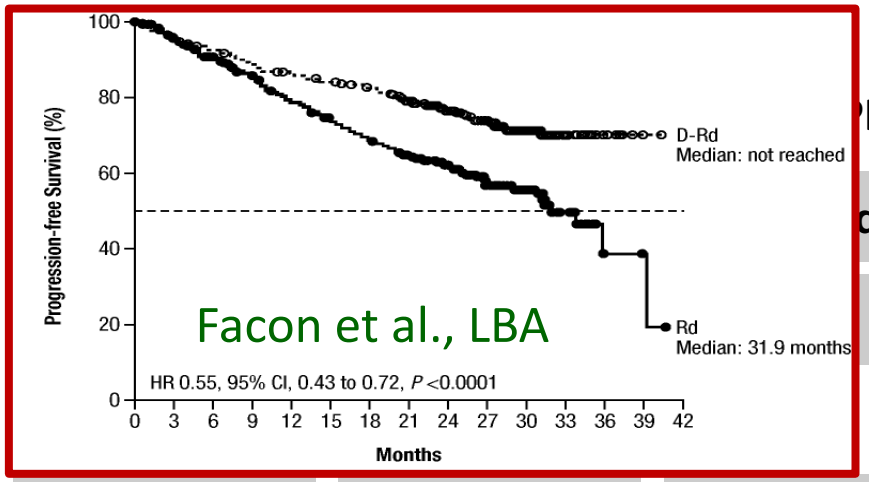
Induction

VTd	RVd
VCd	

Consolidation

Maintenance

LEN	

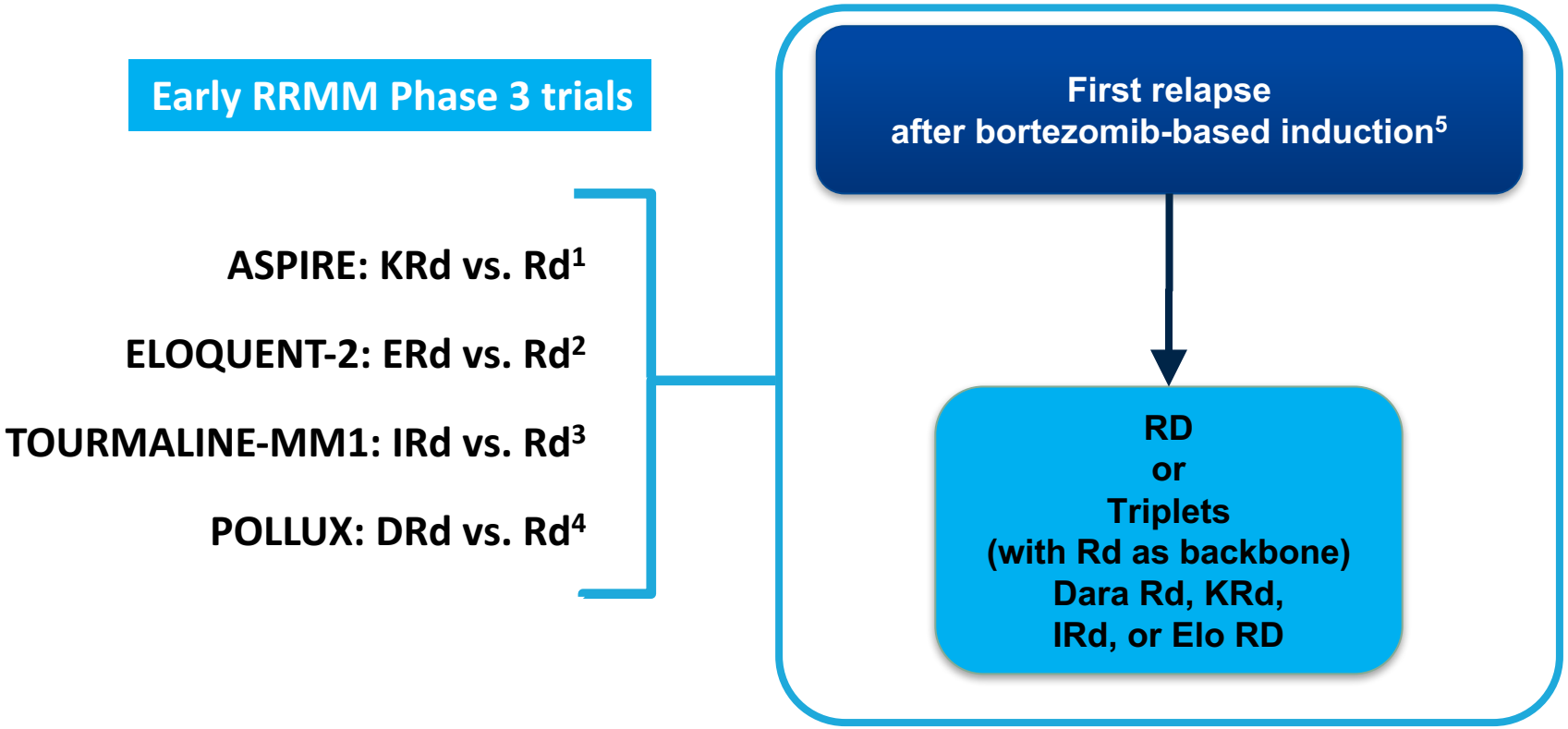


PIs, mAbs

		d
KRd	D-RVd	D-KRd
DVTd	Isa-RVd	…
DVTd	KRd	IRd
RVd	D-KRd	…
Ixa	Dara	…

BORT, bortezomib; LEN, lenalidomide; mAb, monoclonal antibody; PI, proteasome inhibitor; TE, transplant eligible; TNE, transplant non-eligible.

ESMO treatment guidelines for RRMM patients after BORT-based induction



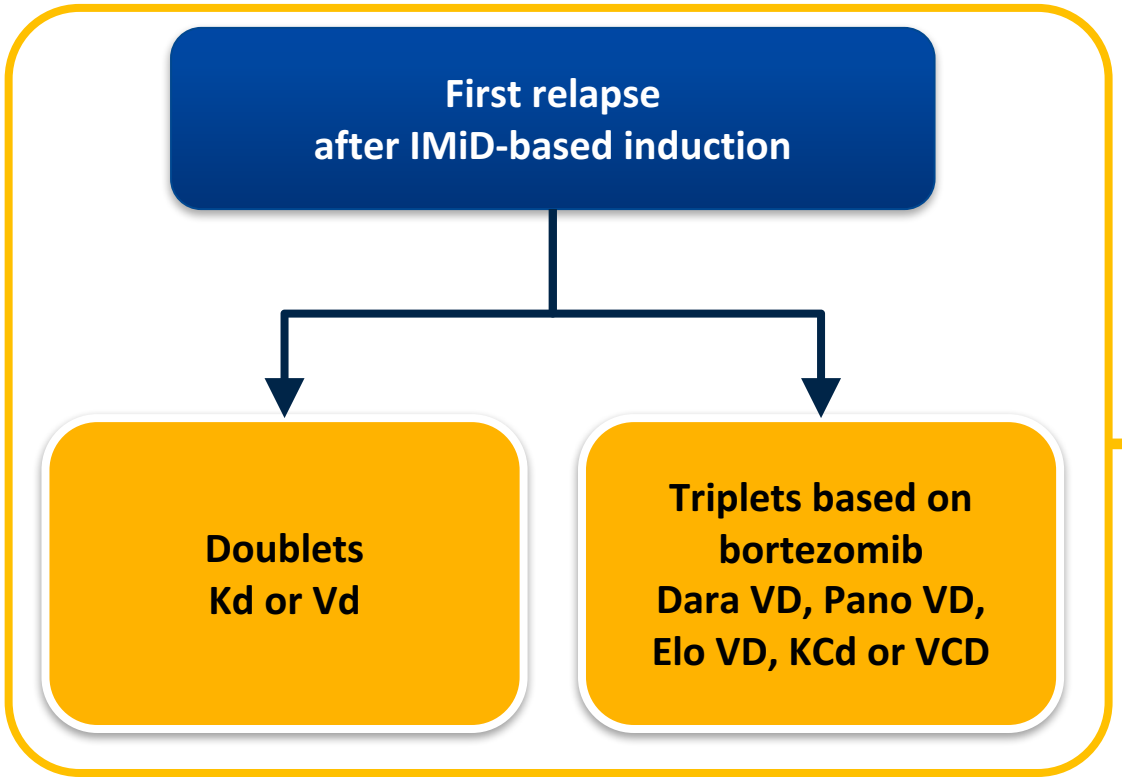
[1] Stewart AK et al. *N Engl J Med* 2015;372(2):142-52; Dimopoulos M et al. *J Hematol Oncol* 2018;11(1):49; Siegel DS et al. *J Clin Oncol* 2018;36(8):728-34.
[2] Lonial S et al. *N Engl J Med* 2015;373(7):621-31; Dimopoulos MA et al. *Cancer* 2018;124(20):4032-43.
[3] Moreau P et al. *N Engl J Med* 2016;374(17):1621-34.
[4] Dimopoulos MA et al. *Haematologica* 2018;[Epub ahead of print]; Dimopoulos MA et al. *N Engl J Med* 2016;375(14):1319-31.

Clinical phase 3 trials with Rd Backbone treatment

Clinical Trial	ORR (CR)		PFS (mo)		OS (mo)	
	Triplet	Rd	Triplet	Rd	Triplet	Rd
ASPIRE: KRd vs. Rd	KRd 87.1% (31.8%)	66.7% (9.3%)	KRd 26.3	17.6	KRd 48.3	40.4
ELOQUENT-2: ERd vs. Rd	ERd 79.0% (4.0%)	66.0% (7.0%)	ERd 19.4	14.9	ERd 48.0 (HR 0.78)	40.0
TOURMALINE-MM1: IRd vs. Rd	IRd 92.9% (12.0%)	76.4% (7.0%)	IRd 20.6	14.7	IRd NR	NR
POLLUX-MMY3008: DRd vs. Rd	DRd 92.9% (43.1%)	76.4% (19.2%)	DRd NR	17.5	DRd 92.1 % 1y	86.8% 1y

Stewart AK, et al. *N Engl J Med* 2015;372:142–152; Siegel DS, et al. *J Clin Oncol*. 2018; 36:728-734; . Lonial S, et al. *N Engl J Med* 2015;373:621-31; 2. Dimopoulos MA, et al. *Cancer*. 2018; 124:4032-4043. Moreau P, et al. *N Engl J Med* 2016;374:1621–1634.
Dimopoulos MA, et al. *N Engl J Med* 2016;375:1319–1331, Dimopoulos MA, et al. *Haematologica* 2018.

ESMO treatment guidelines for RRMM patients after IMiD-based induction



Early RRMM Phase 3 trials

ENDEAVOR: Kd vs. Vd[1]

CASTOR: DVd vs. Vd[2]

PANORAMA-1: Pano Vd vs. Vd[3]

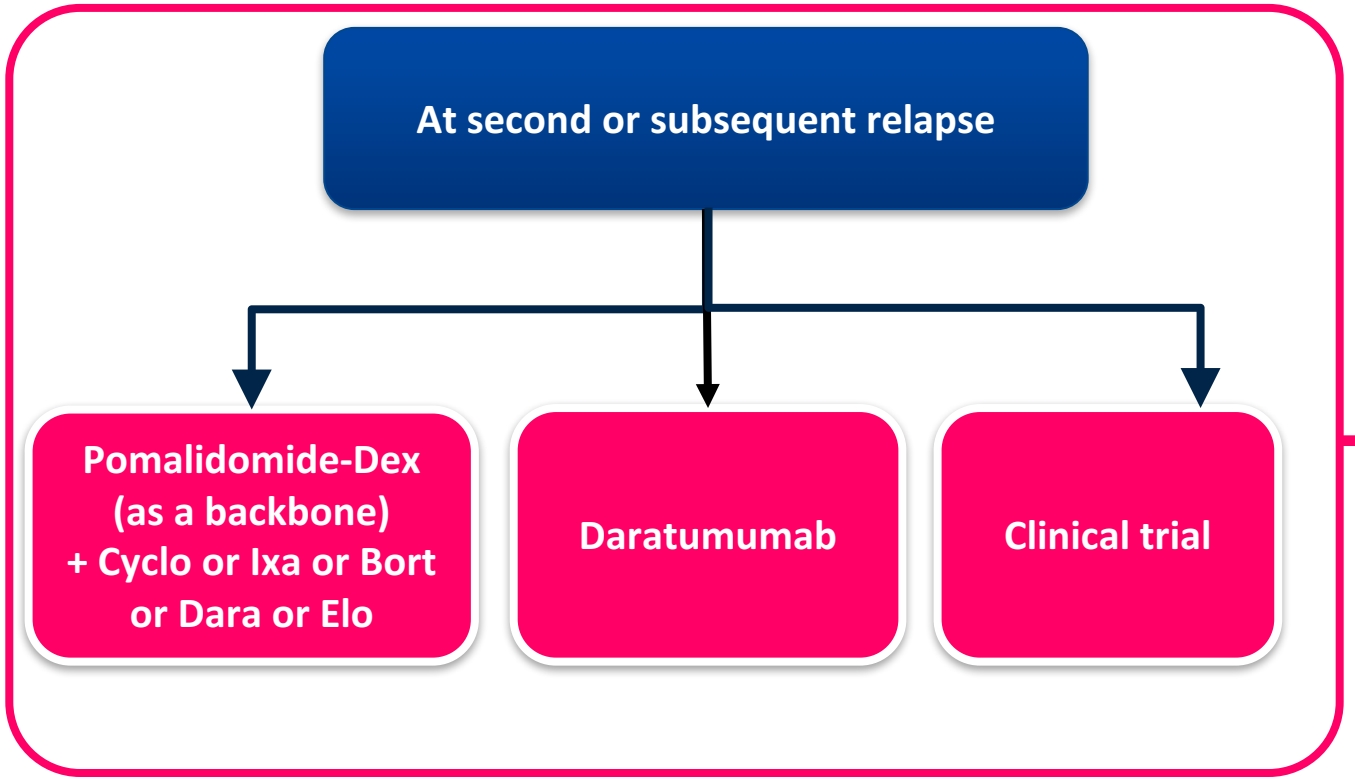
1. Dimopoulos MA, et al. *Lancet Oncol* 2016 ;17:27–38;
2. Palumbo A, et al. *N Engl J Med* 2016;375:754–766; 3. San-Miguel JF, et al. *Lancet Oncol* 2014;15:1195–2067.

Proteasome inhibitor based clinical phase 3 trials

Clinical Trial	ORR (CR)		PFS (mo)		OS (mo)	
	Novel Doublet/ Triplet	Vd	Novel Doublet/ Triplet	Vd	Novel Doublet/ Triplet	Vd
ENDEAVOR: Kd vs. Vd	Kd 77.0% (13.0%)	63.0% (6.0%)	Kd 17.6	9.4	Kd* 47.6	40.0
CASTOR: DVd vs. Vd	DVd 82.9% (19.2%)	63.2% (9.0%)	DVd 16.7	7.1	DVd NR	NR
PANORAMA-1: PanoVd vs. Vd	PanoVd 60.7% (11.0%)	54.6% (6.0%)	PanoVd 12.0	8.1	PanoVd 40.3	35.8

Dimopoulos MA, et al. *Lancet Oncol* 2016 ;17:27–38; . Dimopoulos MA, et al. *Lancet Oncol* 2017 ; 18:1327-13373. Palumbo A, et al. *N Engl J Med* 2016;375:754–766; San-Miguel JF, et al. *Lancet Oncol* 2014;15:1195–2067. San-Miguel JF, et al. Lancet Haematol. 2016 Nov;3(11):e506-e515

ESMO treatment guidelines for RRMM patients at second or subsequent relapse



Pom-Dex based RRMM randomized trials

ELOQUENT-3: EPd vs. Pd[1]

OPTIMISMM: PVd vs. Pd[2*]

*1.-3. relapse

1. Dimopoulos et al. N Engl J Med 2018; 2. Richardson et al. ASCO 2018

ELOQUENT-3 Study Design

An international, open-label, randomized, phase 2 trial (NCT02654132); n= 105 patients

Patients with MM

- ≥2 prior lines of therapy
- Refractory to last therapy
- Refractory or relapsed and refractory to lenalidomide and a proteasome inhibitor
- Prior pomalidomide not permitted

Cycles 1–2 | **Cycles 3+** | **Follow-up every 4 weeks**

→ **EPd**

- **Elotuzumab** 10 mg/kg IV Weekly
- **Elotuzumab** 20 mg/kg IV Every 4 weeks
- **Pomalidomide** 4 mg orally; Days 1–21
- **Dexamethasone** 40 mg equivalent; weekly

Cycles are 28 days

→ **Pd**

- **Pomalidomide** 4 mg orally; Days 1–21
- **Dexamethasone** 40 mg orally; weekly

Endpoints

Primary

- PFS by investigator

Secondary

- Overall response rate (ORR)
- Overall survival (OS)

Exploratory

- Safety
- Duration of response (DOR)

Characteristic	EPd (n=60)	Pd (n=57)
Prior lines of therapy, median (range)	3 (2–8)	3 (2–8)
Refractory to lenalidomide, n (%)	54 (90)	48 (84)
Refractory to a proteasome inhibitor, n (%)	47 (78)	47 (82)
Refractory to lenalidomide and a proteasome inhibitor, n (%)	**41 (68)**	**41 (72)**

Dimopoulos et al. N Engl J Med 2018;

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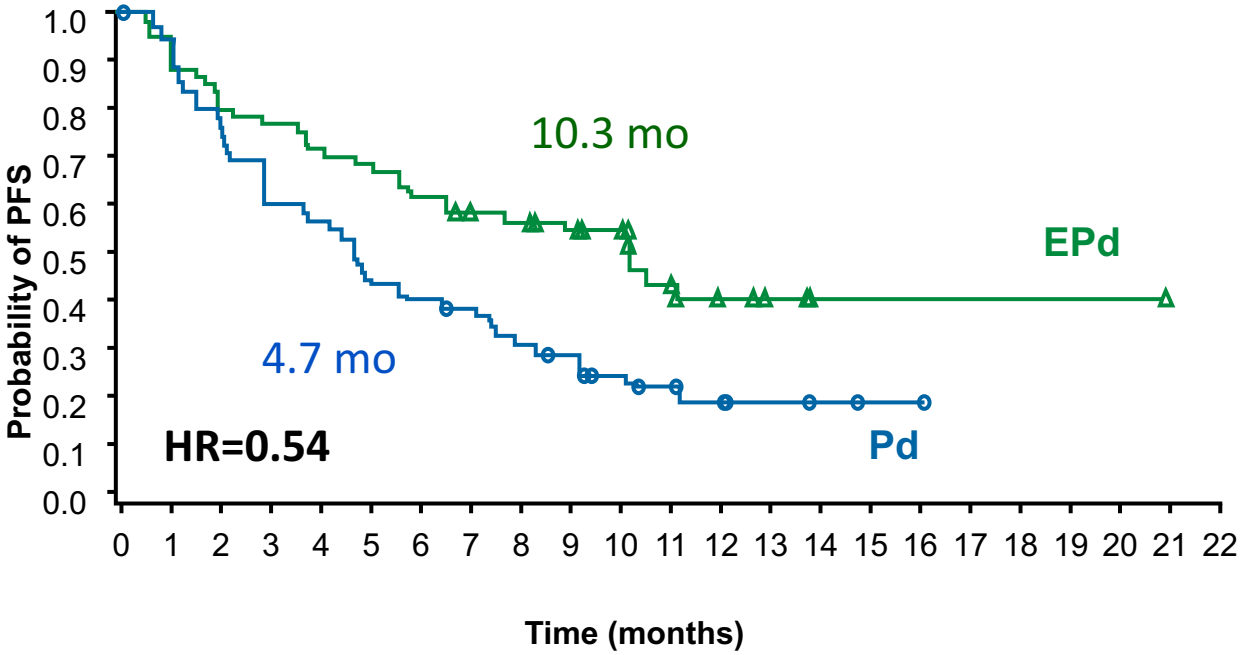
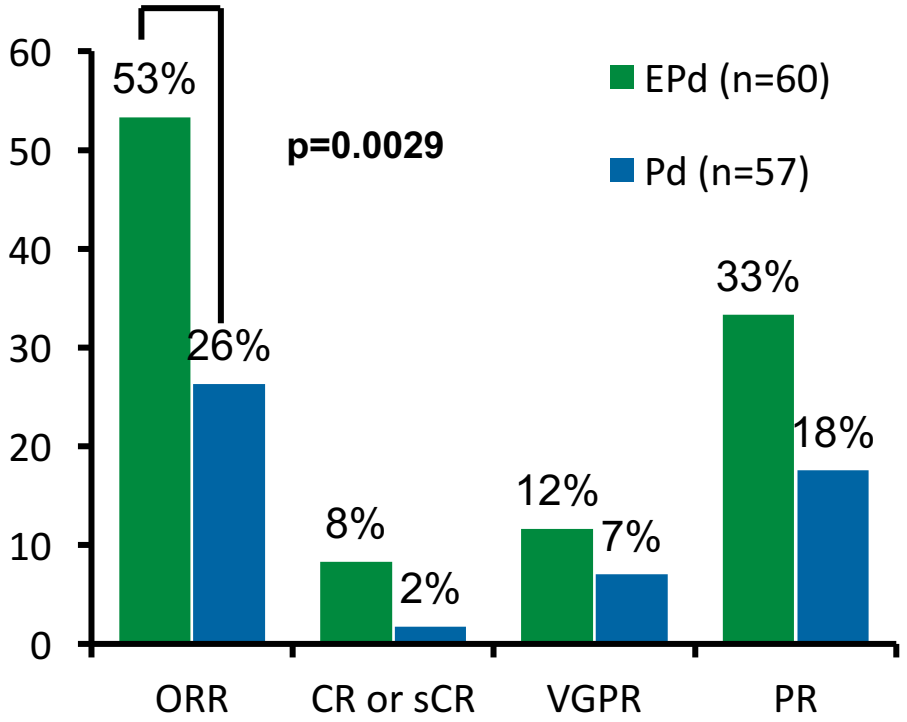
ELOQUENT-3: Progression-Free Survival and Response





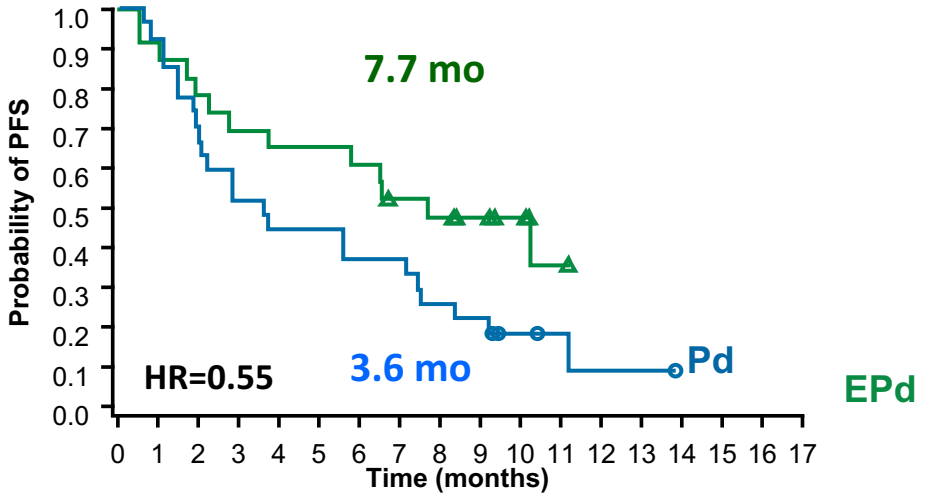
- 46% reduction in the risk of progression or death with EPd
- Median PFS was more than twice as long with EPd vs Pd

Dimopoulos et al. N Engl J Med 2018;

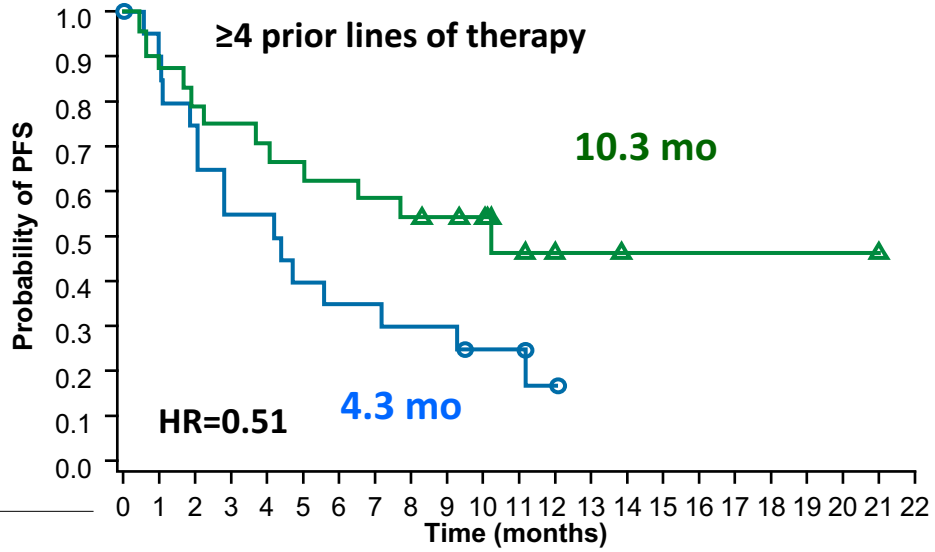
Progression-Free Survival: High Risk, ≥4 prior lines of therapy

Overall Survival

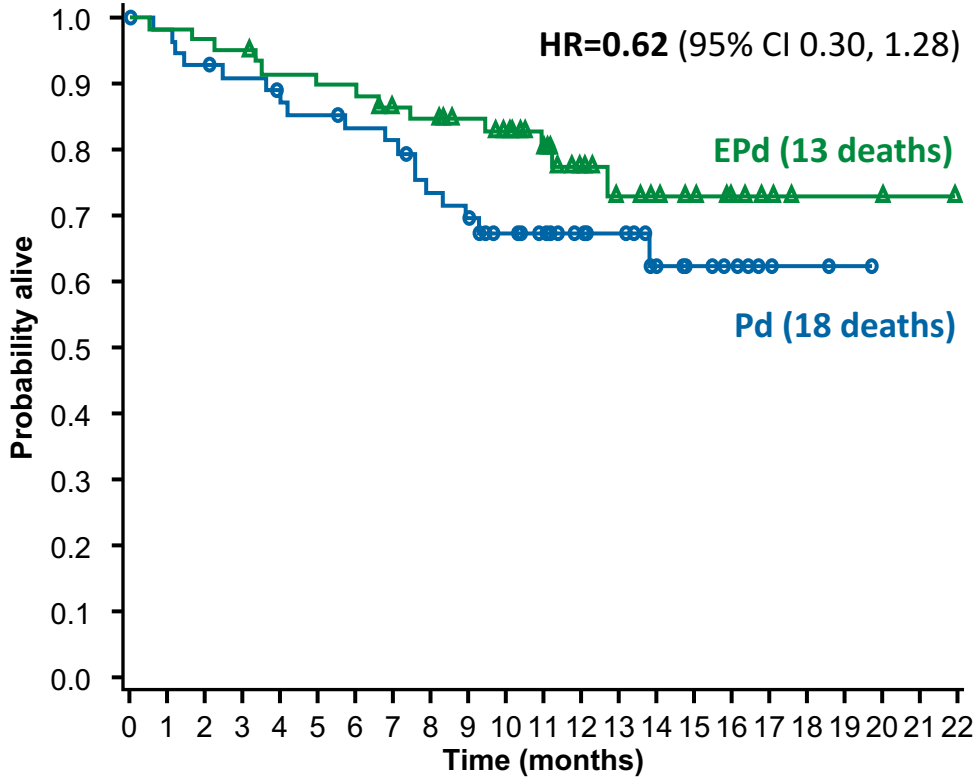
High risk: del(17p), t(4;14), or t(14;16) present or LDH ≥300 IU/L



≥4 prior lines of therapy



Overall survival



Dimopoulos et al. N Engl J Med 2018;

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ELOQUENT-3: All-Cause Hematologic and Special Interest Adverse Events

	EPd (n=60)			Pd (n=55)		
Exposure adjustment	**No**		**PY=47.7**	**No**		**PY=34.3**
AEs, n (%)[a]	**Any grade**	**Grade 3–4**	**Events/100 PY**	**Any grade**	**Grade 3–4**	**Events/100 PY**
Hematologic AEs[b]	31 (52)	23 (38)	178	30 (55)	23 (42)	224
Anemia	15 (25)	6 (10)	46	20 (36)	11 (20)	85
Neutropenia	14 (23)	8 (13)	52	17 (31)	15 (27)	73
Thrombocytopenia	9 (15)	5 (8)	23	10 (18)	3 (5)	35
Lymphopenia	6 (10)	5 (8)	21	1 (2)	1 (2)	3
Special interest AEs						
Infections	39 (65)	8 (13)	182	36 (65)	12 (22)	230
Vascular disorders	8 (13)	2 (3)	NR	5 (9)	0	NR
Cardiac disorders	7 (12)	4 (7)	17	6 (11)	2 (4)	17
Neoplasms[c]	1 (2)	1 (2)	2	12 (22)	6 (11)	38
Second primary malignancy	0	0	NR	1 (2)	1 (2)	NR

[a]Includes AEs reported between first dose and 60 days after last dose of study therapy; [b]Includes hematologic AEs in ≥10% of patients; [c]Includes malignant, benign, and unspecified neoplasms
NR, not reported

Dimopoulos et al. N Engl J Med 2018;

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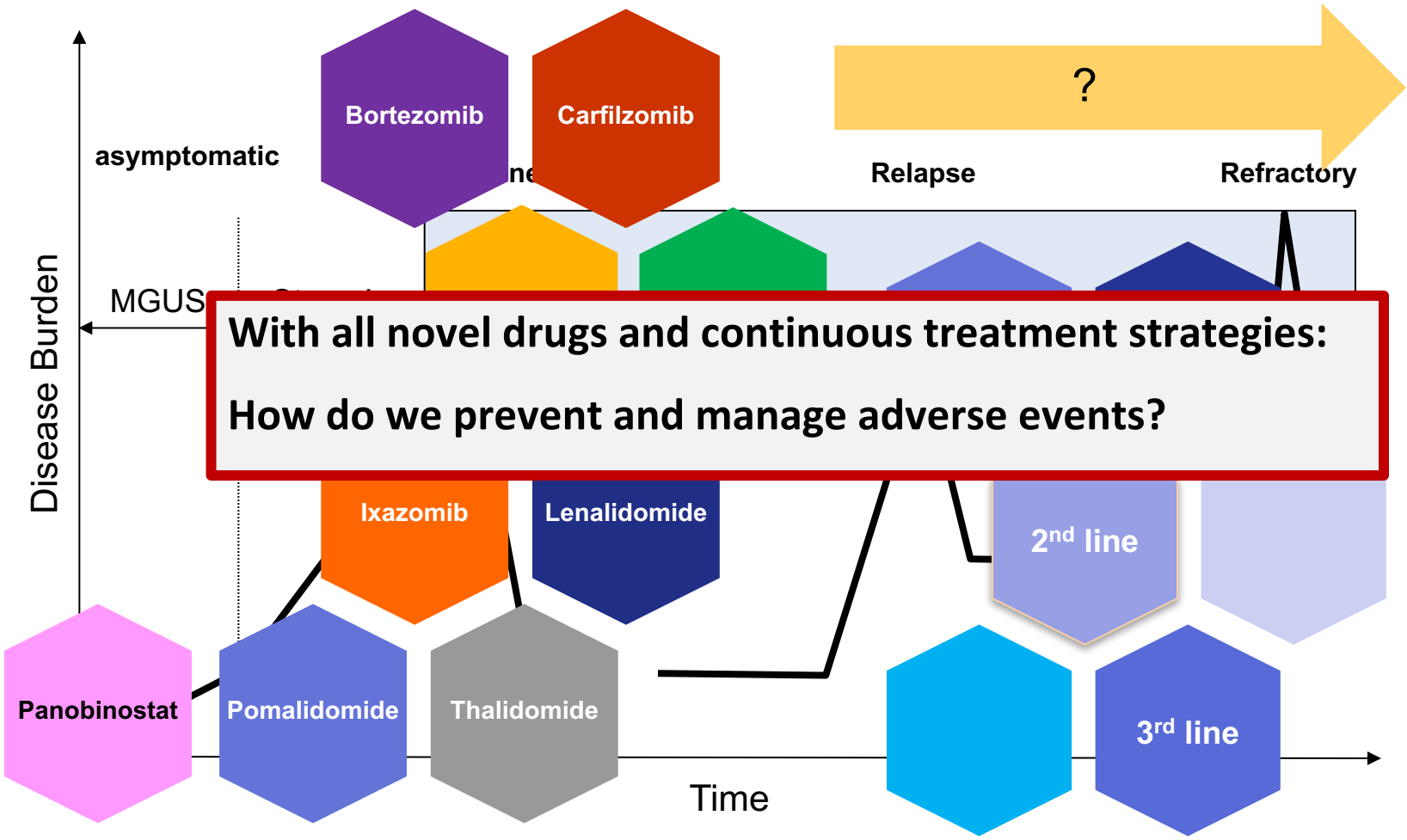
Multiple myeloma – Not a sprint but a marathon



Adapted from Laubach JP, et al. *Leukemia* 2016;30:1005–17.

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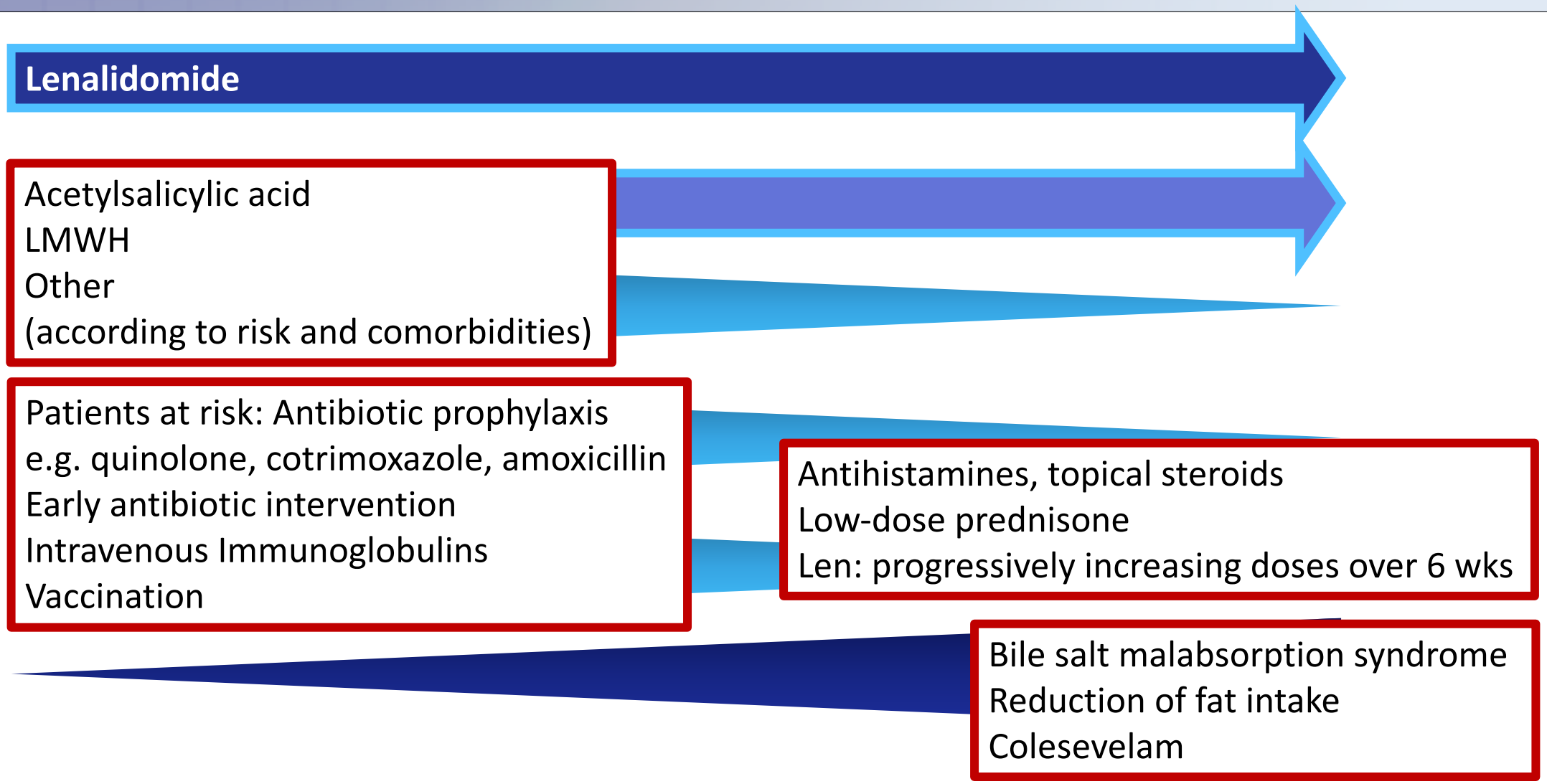
Side effect management of novel therapeutics – Immunomodulatory Agents

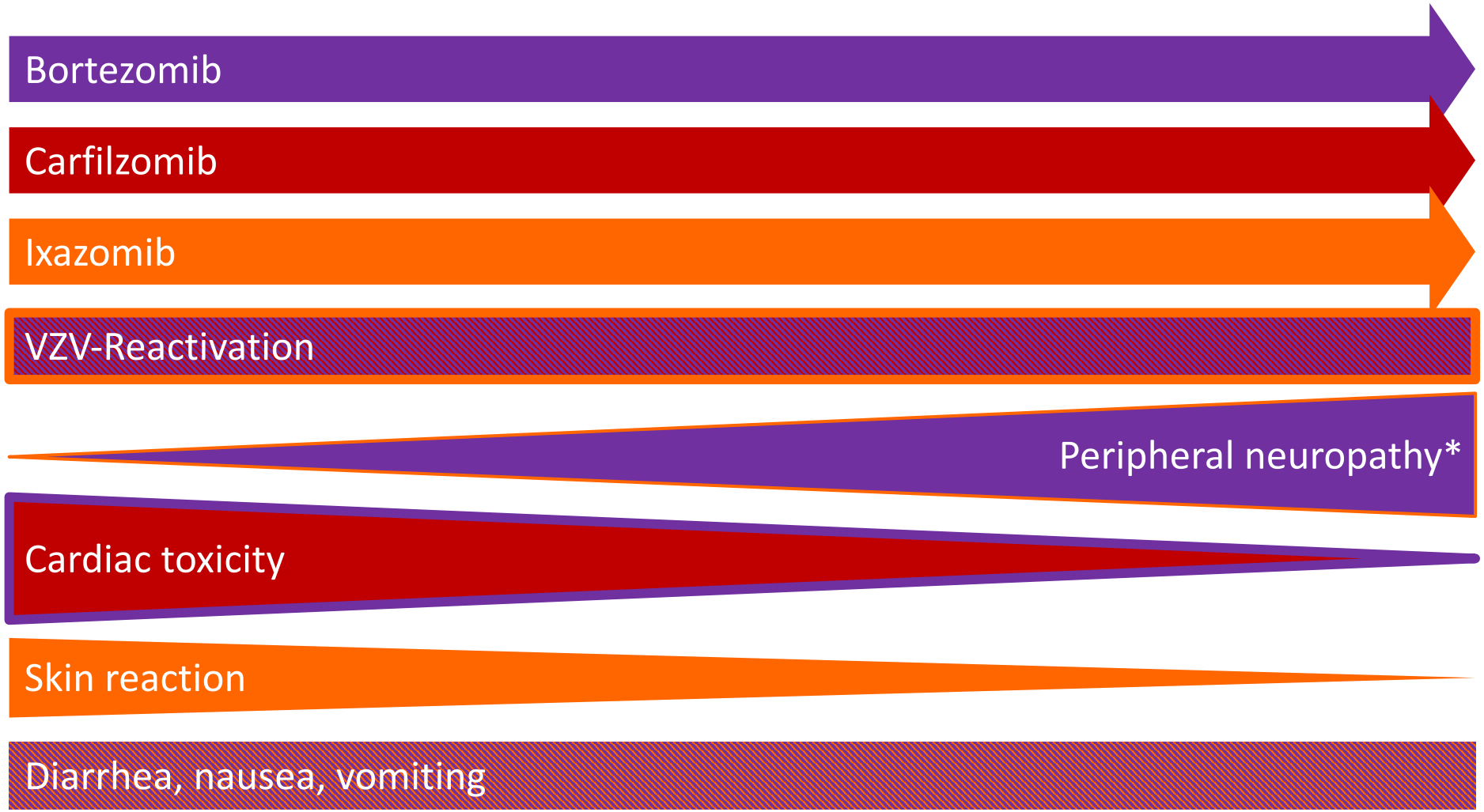
Ludwig, H. et al., Leukemia 2018

Side effect management of novel therapeutics – Immunomodulatory Agents



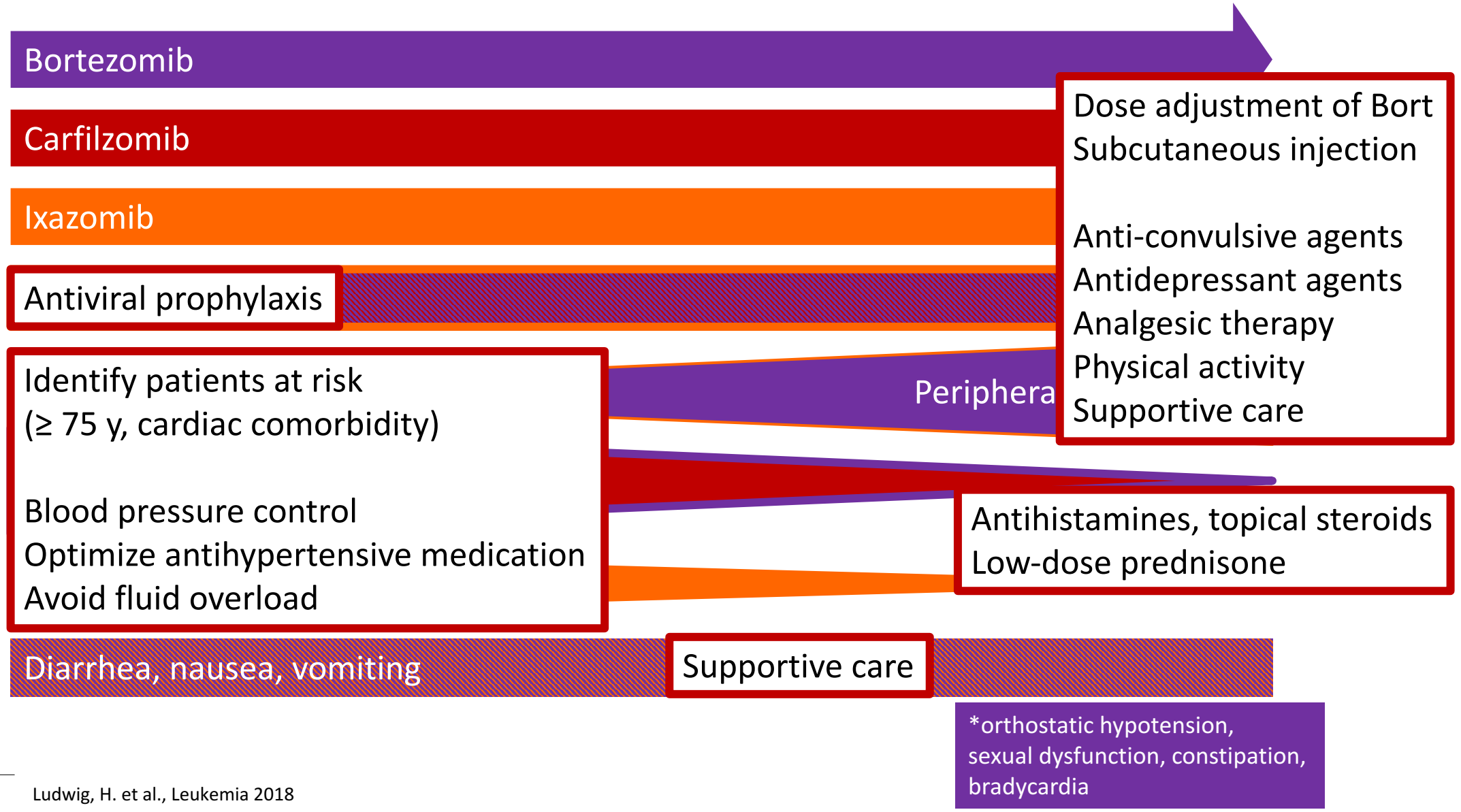
Ludwig, H. et al., Leukemia 2018

Side effect management of novel therapeutics – Proteasome Inhibitors



Ludwig, H. et al., Leukemia 2018

Side effect management of novel therapeutics – Proteasome Inhibitors



Ludwig, H. et al., Leukemia 2018

Side effect management of novel therapeutics – monoclonal Antibodies

Ludwig, H. et al., Leukemia 2018

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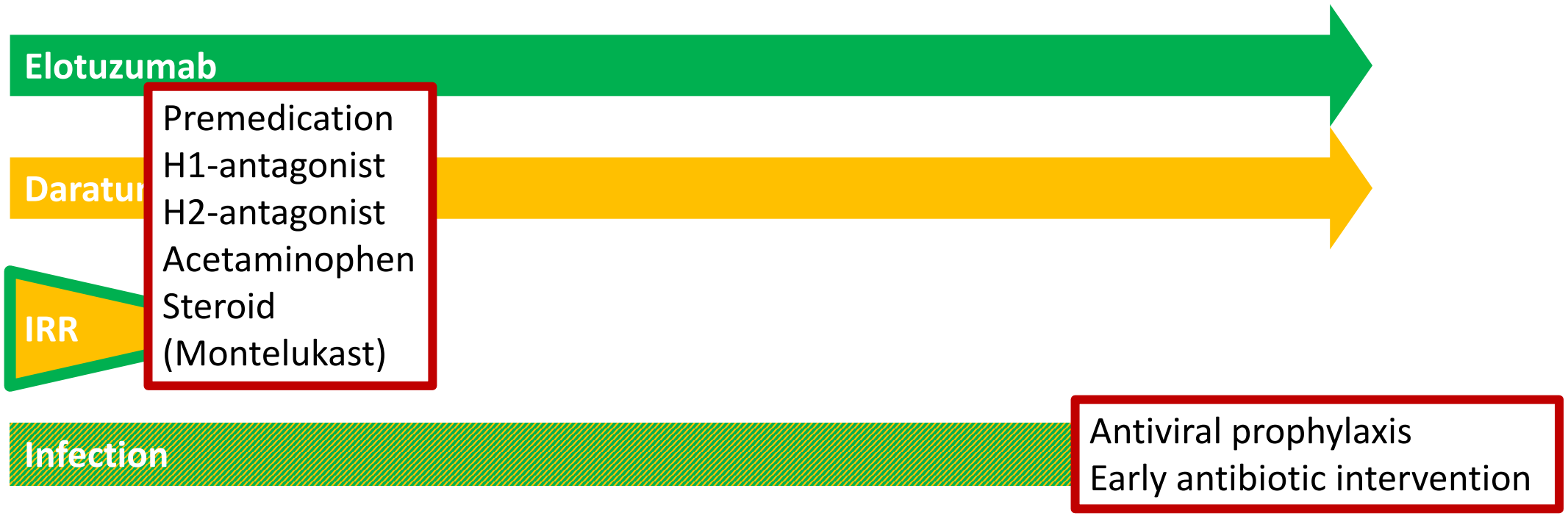
Side effect management of novel therapeutics – monoclonal Antibodies



Ludwig, H. et al., Leukemia 2018

Summary and Future Directions

- RRMM remains an area of primary challenge in improving patient outcome
- Treatment sequence requires consideration of pretreatment, but also of patient individual variables
- Rd should if possible be extended to a triplet, Vd is not anymore standard for treatment of relapsed disease and should be extended or replaced
- With the emerging use of Lenalidomide in first-line treatment, Pomalidomide + Dexamethasone based treatments are gaining importance
- The recently FDA approved triplet of Elotuzumab, Pomalidomide and Dexamethasone demonstrates significant and clinically meaningful efficacy
- With the emerging treatment options and long-term and continuous treatment of patients with myeloma, prevention and management of adverse events is crucial