AntiPD1/PDL1, Ibrutinib

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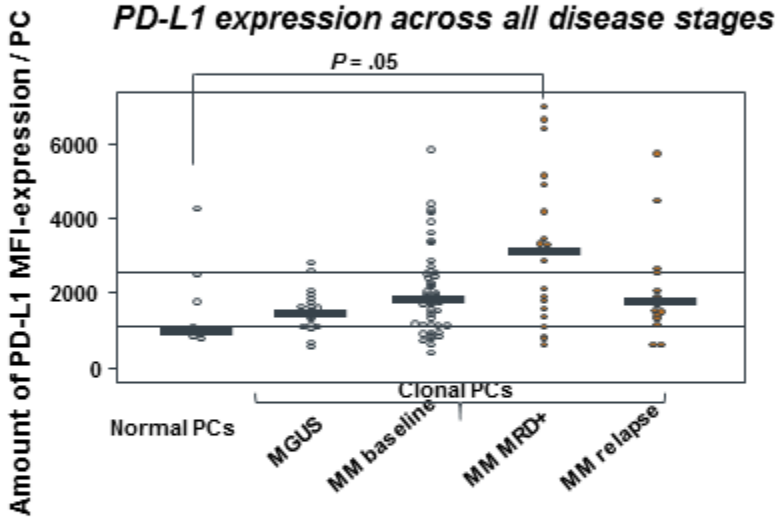
AntiPD1/PDL1

Is There a Role for PD-1 Inhibitors in Multiple Myeloma?

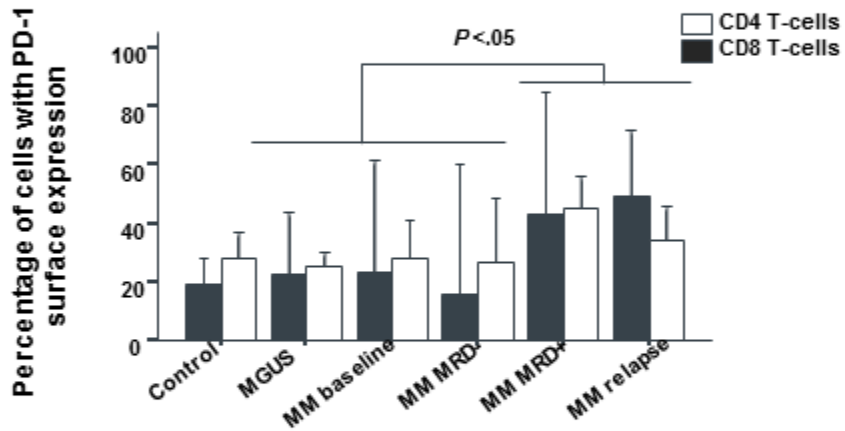
PD-L1 expression is present in PCs[1,2]

[1]Liu J et al, Blood. 2007;110(1):296-304; [2]Tamura H, et al. Leukemia. 2013;27:464-72.

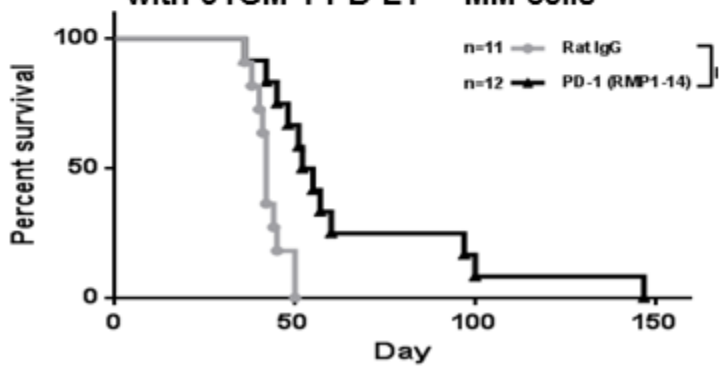
PD-L1 expression across all disease stages

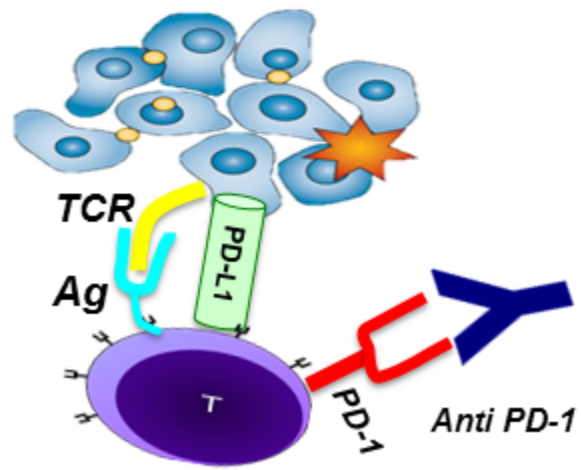


Increase PD-1 among T-cells of MRD/RR pts.



Anti–PD-1 in C57BL/KaLwRijHsd syngeneic mice with 5TGM-1 PD-L1^{+ve} MM cells





Paiva B, et al. *Leukemia*. 2015. 2015;29:2110-3.

Are IMiDs and PD-1 Inhibitors Synergistic in Multiple Myeloma?

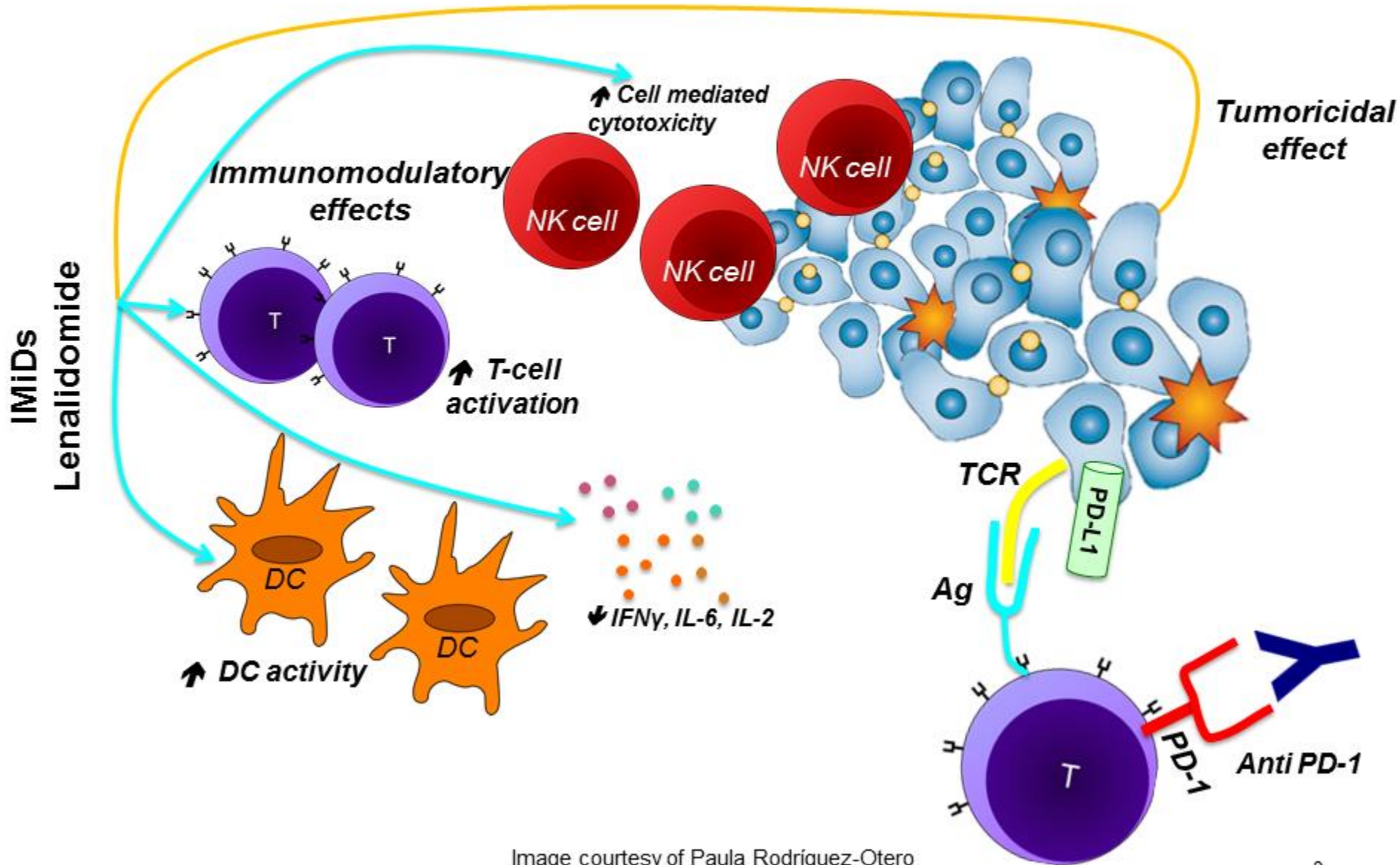


Image courtesy of Paula Rodríguez-Otero

Check-point Blockade +IMIDs

- Phase I KEYNOTE-023 study of pembrolizumab plus lenalidomide and dexamethasone in relapsed MM
  - ORR 76% in 17 evaluable patients
  - 5 patients achieving a PR or better (56%)
- Retrospective series pembrolizumab, pomalidomide, dexamethasone in a heavily pretreated and pomalidomide-exposed population,
  - 89% clinical benefit (3 PR, 2 MR, 3 SD)

San Miguel J, Mateos MV, Shah JJ, et al. Blood 2015;126:505 Wilson L, Cohen AD, Weiss B, et al. Blood 2016;128:2119

blood®
Prepublished online May 1, 2017;
doi:10.1182/blood-2017-03-775122

Pembrolizumab, pomalidomide and low dose dexamethasone for relapsed/refractory multiple myeloma

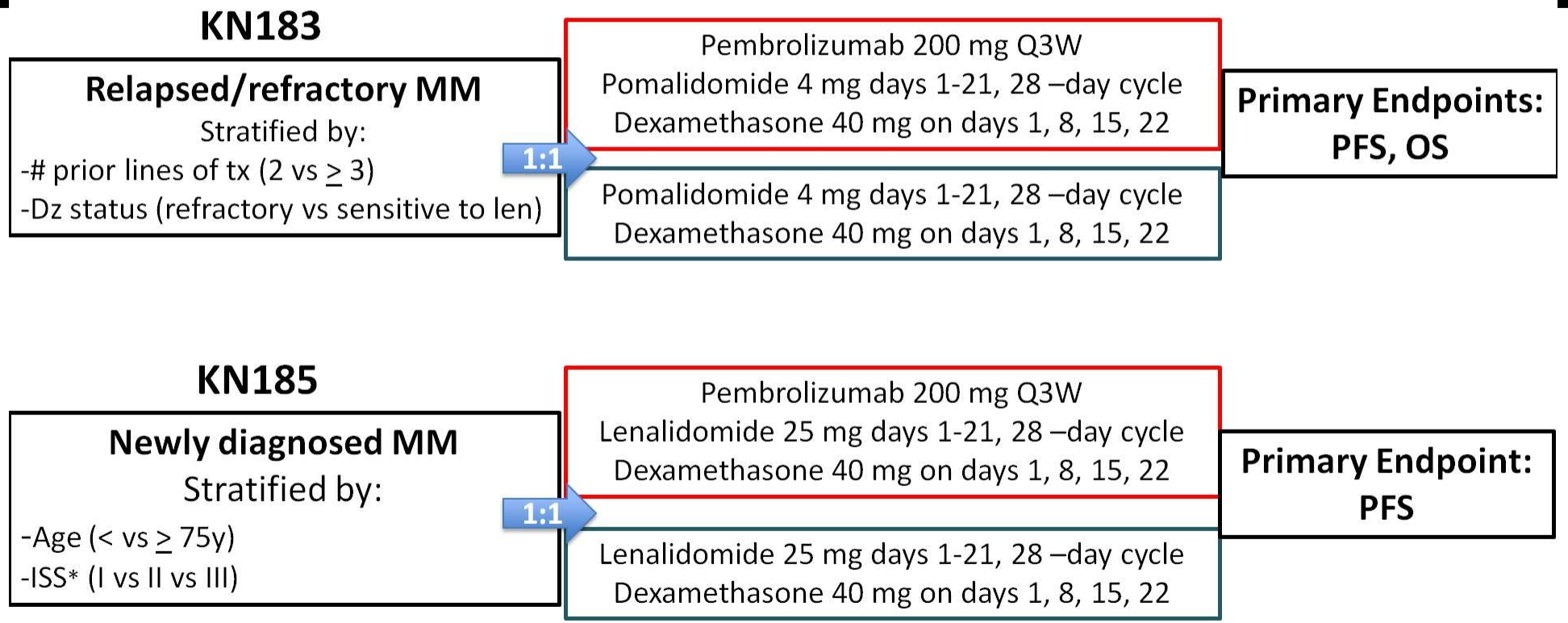
Ashraf Badros, Elizabeth Hyjek, Ning Ma, Alexander Lesokhin, Ahmet Dogan, Aaron P. Rapoport, Mehmet Kocoglu, Emily Lederer, Sunita Philip, Todd Milliron, Cameron Dell, Olga Goloubeva and Zeba Singh

- Phase II, single-center study combined pomalidomide and low-dose dexamethasone, with pembrolizumab
- RRMM after at least 2 lines of prior therapy
- 48 patients with RRMM enrolled

- Treatment-related adverse events of any grade occurred in 35 (73%) of patients
- grade 3 and higher events were observed in 20 (42%) patients,
- Six patients had documented autoimmune interstitial pneumonitis

- ORR was 60%
- median PFS of 17.4 months (95% CI 11.7-18.8); median OS has not been reached

2 Randomized Controlled Trials of Pembrolizumab Added to SOC in Multiple Myeloma



**International Staging System, Greipp et al JCO 2005*

www.fda.gov

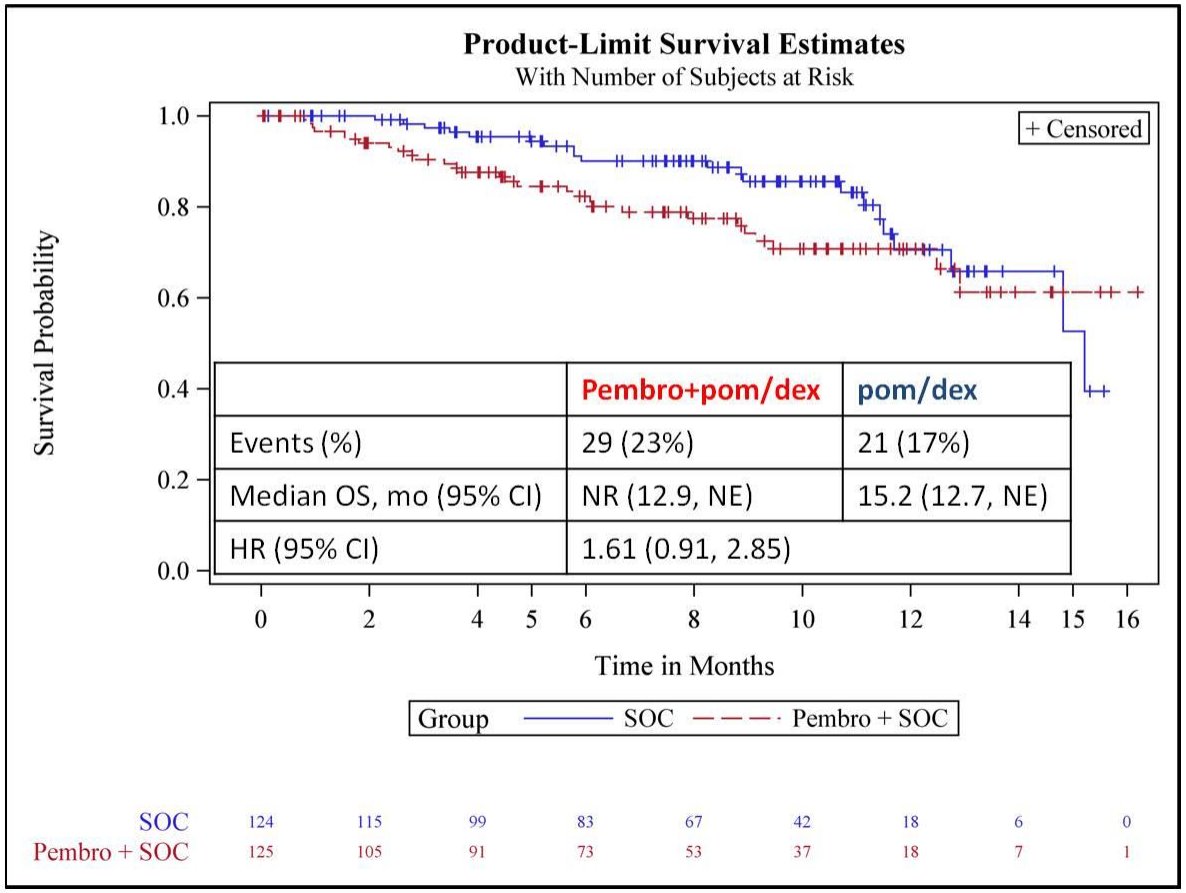
KEYNOTE 183 and 185

FDA Alerts Healthcare Professionals and Oncology Clinical Investigators about Two Clinical Trials on Hold Evaluating KEYTRUDA® (pembrolizumab) in Patients with Multiple Myeloma

[August 31, 2017] Based on data from two recently halted clinical trials, the U.S. Food and Drug Administration today is issuing this statement to inform the public, health care professionals, and oncology clinical investigators about the risks associated with the use of KEYTRUDA® (pembrolizumab) in combination with dexamethasone and an immunomodulatory agent (lenalidomide or pomalidomide) for the treatment of patients with multiple myeloma. KEYTRUDA® (pembrolizumab) is not approved for treatment of multiple myeloma.

https://www.fda.gov/Drugs/DrugSafety/ucm574305.htm

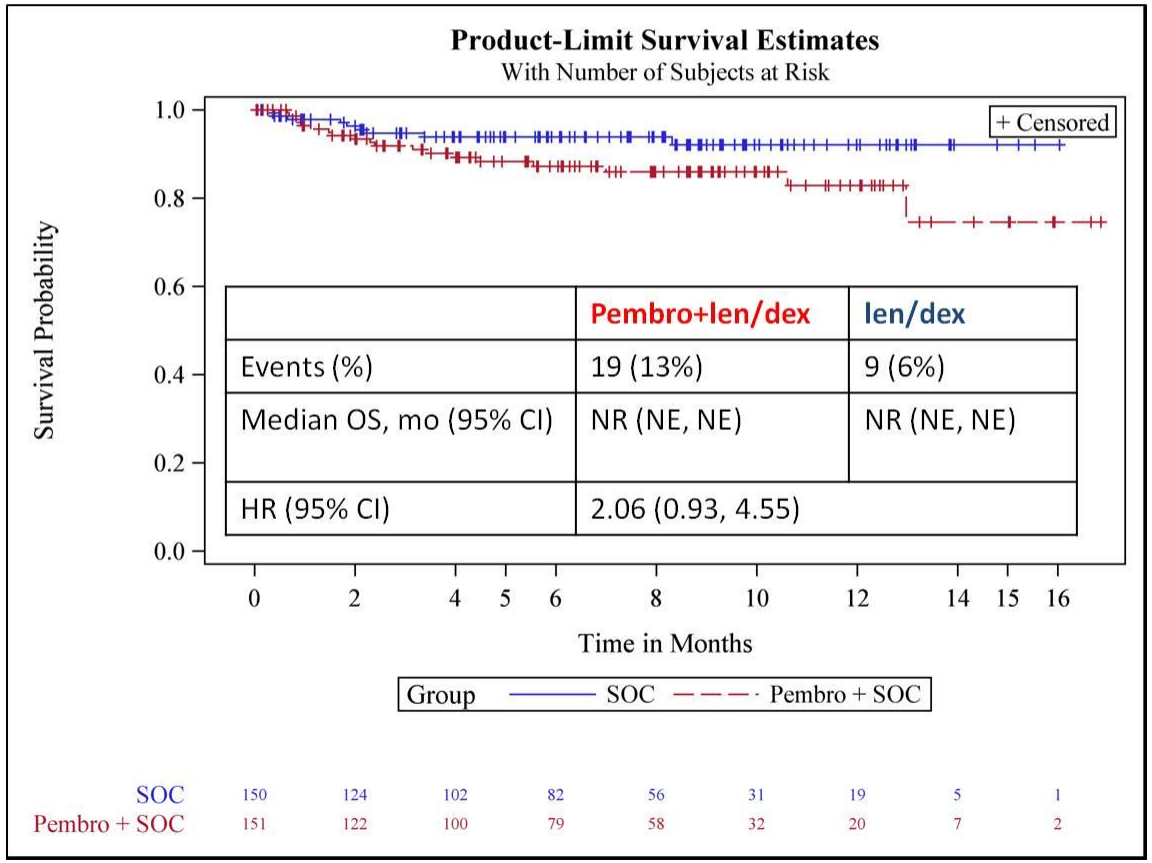
KN183 Results



- N=125 (Pembro-pom-dex), N=124 (pom-dex)
- Median follow-up: 8.1 months
- Causes of death (Pembro-pom-dex): myocarditis, SJS, MI, pericardial hemorrhage, cardiac failure, respiratory tract infection, neutropenic sepsis, sepsis, MOD, respiratory failure, and unknown
- SAEs: 63% vs 46%
- Efficacy:
  - ORR: 34% Pembro-pom-dex arm vs. 40% Pom-dex arm
  - Time-to-progression HR: 1.14 (95% CI: 0.75, 1.74)

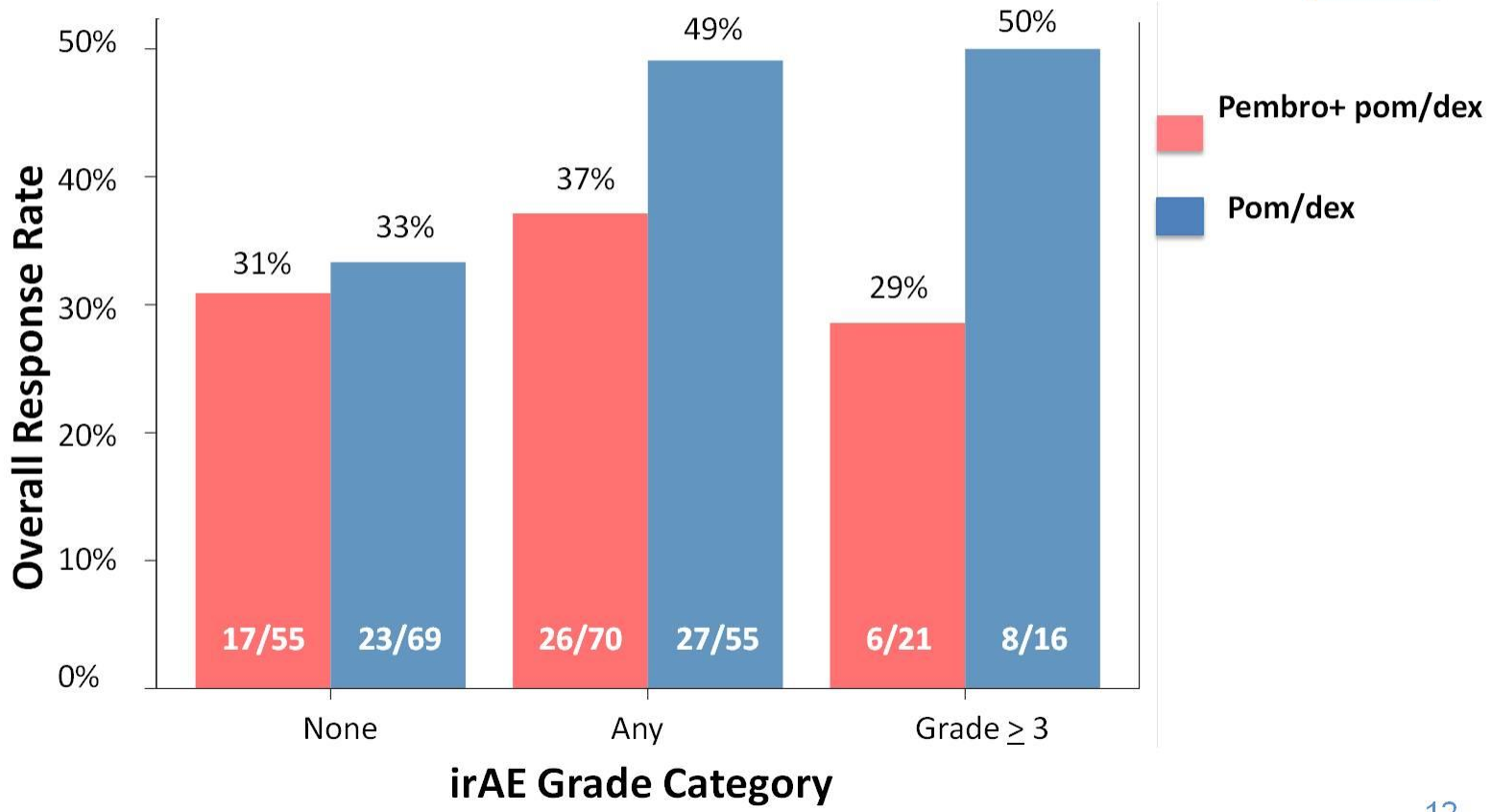
Presented By Aviva Krauss at 2018 ASCO Annual Meeting

KN185 Results

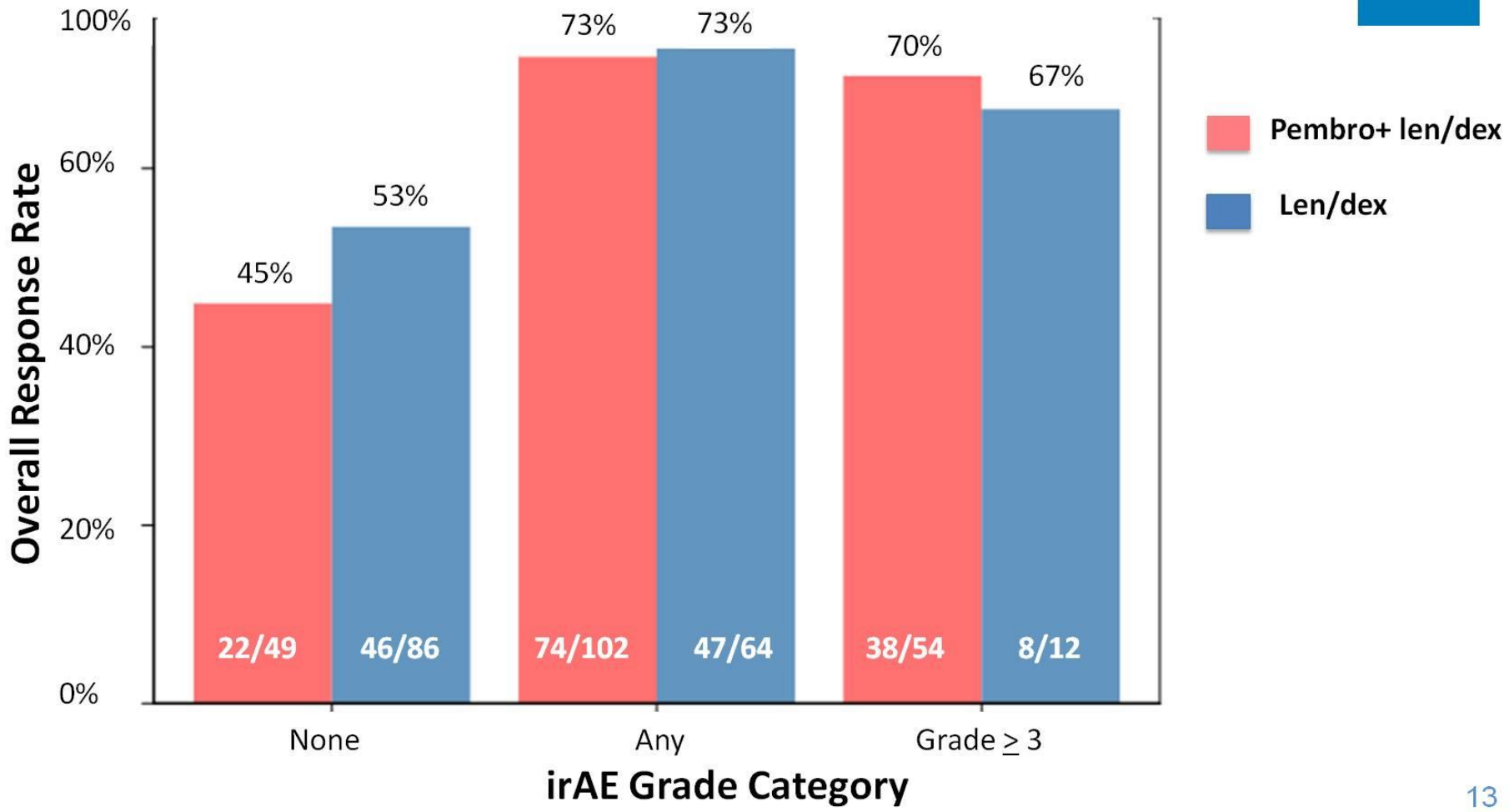


- Median follow-up: 6.6 months
- Causes of death (pembro-len-dex): intestinal ischemia, cardiorespiratory arrest, suicide, PE, cardiac arrest, pneumonia, sudden death, myocarditis, large intestine perforation, and cardiac failure
- SAEs: 54% vs 39%
- Efficacy:
  - ORR: 64% Pembro-len-dex arm vs. 62% Len-dex arm
  - Time-to-progression HR: 0.55 (95% CI: 0.20, 1.50)

KN183: Development of irAE or Grade ≥3 irAE does not significantly change ORR in the pembrolizumab arm



KN185: Development of irAE associated with increased ORR in both arms



Presented By Aviva Krauss at 2018 ASCO Annual Meeting

Higher rate of irAEs and Grade ≥3 irAEs in newly diagnosed multiple myeloma

	KN183 (RRMM)		KN185 (NDMM)	
	Pembro+PomDex	PomDex	Pembro+LenDex	LenDex
Pts with irAE	58%	45%	68%	44%
G≥3 irAE	18%	13%	36%	8%

Presented By Aviva Krauss at 2018 ASCO Annual Meeting

Phase III trial:Pembro plus IMiDs--- no benefit in terms of ORR, PFS & OS

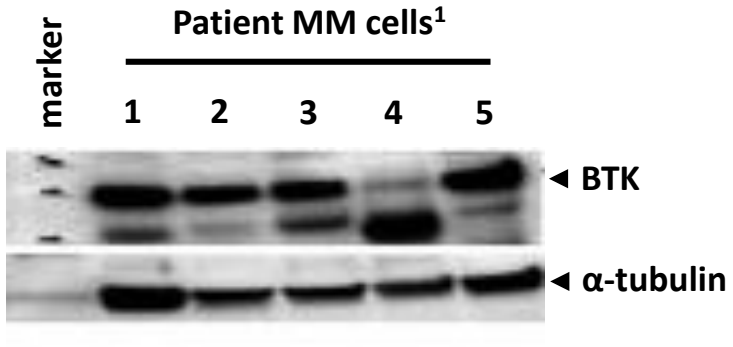
- **ORR 64 vs 62%; PFS (82 vs 87%); OS (87 vs 94%)**
- **Grade 3-5 AEs (72 vs 50%) & irAE (32%)**
- **Death (13 vs 6%)**

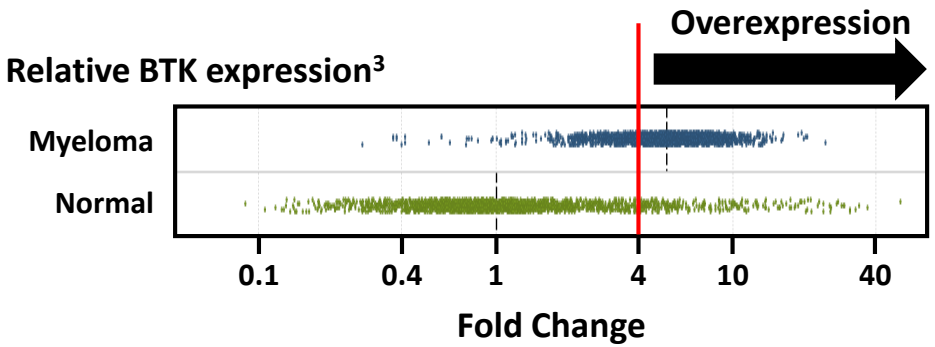
- ***Few observations***
  - **Elderly population:** Median age 74 yrs old (21% ≥ 80yrs)
  - **Pembro arm---more:**
    - Renal insufficiency (14 vs 8%)
    - High risk pts (16 vs 7%)
    - Discontinue (21 vs 8%) …cumulative dose
  - **Very short follow up:** 6.6 m (data cutoff June 2017 ?, no update)

Ibrutinib

BTK Expression in MM Plasma Cells

- BTK is a non-receptor tyrosine kinase that is expressed in many hematopoietic lineages and plays a critical role in B-cell maturation[1,2]
- Increased BTK expression in MM plasma cells compared with normal plasma cells is not expected
- However, recent studies showed robust BTK expression in the majority of MM plasma cells in patients with MM[1,2]

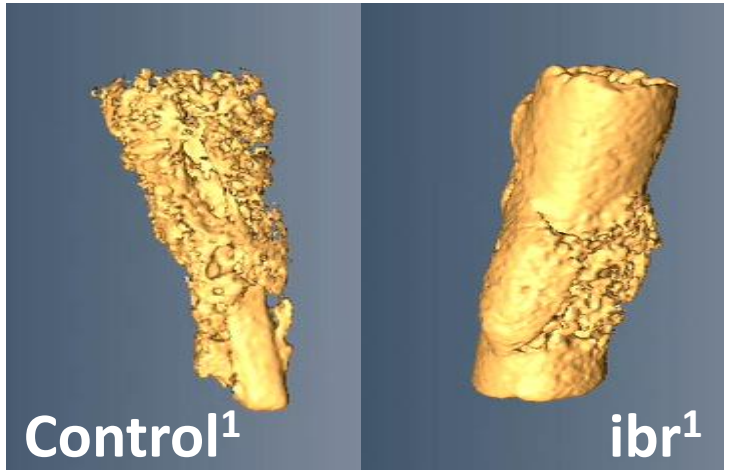


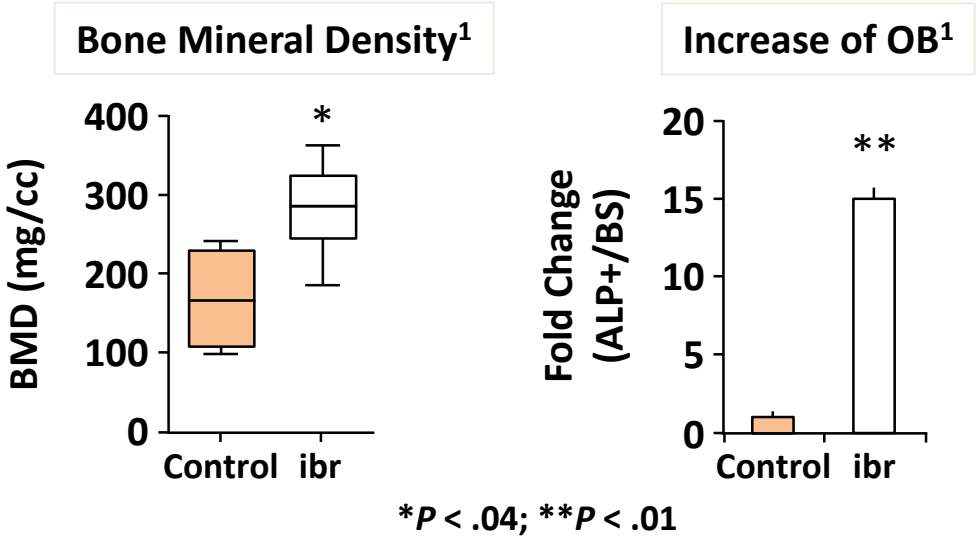


1. Tai YT, et al. *Blood*. 2012;120:1877-1887. 2. Bam R, et al. *Am J Hematol*. 2013; 88:463-471. 3. Unpublished data form Oncomine® by Compendia, Integrated Gene Browser, Quantile normalized, Affymetrix U133 platform - November 2012 (ODA_096).

Impact of BTK Inhibition on Bone

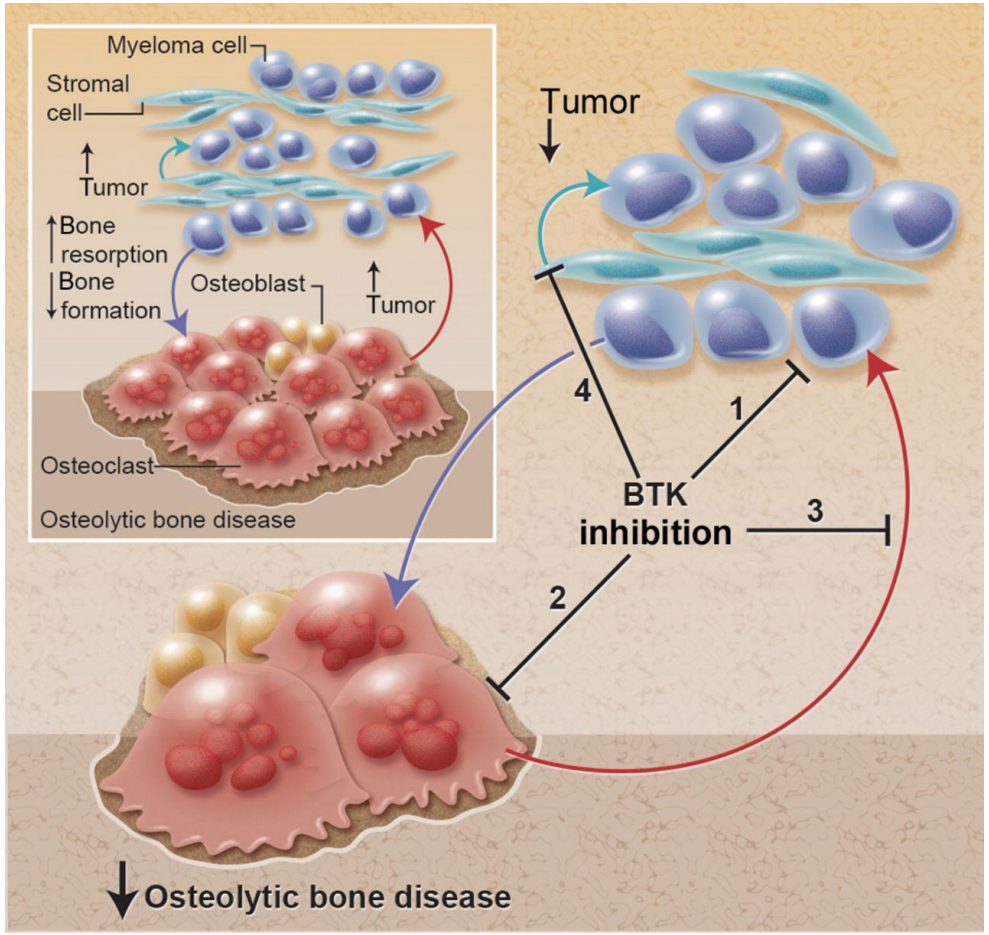
- BTK is expressed on osteoclasts (OC) but not osteoblasts (OB)[1]
- BTK activation mediates osteoclastogenesis induced by M-CSF and RANKL[1,2]
- Ibrutinib inhibited osteolytic activity by OC in vitro and decreased OC cytokine secretion[1]
- Ibrutinib suppressed bone resorption activity by OC in SCID-hu animals implanted with MM cells[1]





1. Tai YT, et al. *Blood.* 2012;120:1877-1887. 2. Bam R, et al. *Am J Hematol*. 2013; 88:463-471.

Effect of BTK Inhibition in the MM Microenvironment



1. Inhibits tumor growth
   - Reduced downstream NF-κB and STAT3
   - ERK1/2 and AKT signaling
2. Directly inhibits osteoclastic bone resorption and OC formation
3. Inhibits the release of osteoclast-derived tumor growth factors
4. Prevents adhesion to bone marrow stromal cells (BMSCs) and release of BMSC-derived growth factors
   - Reduced IL-6, SDF-1, BAFF, IL-8, M-CSF, and MIP-1

Edwards C M *Blood.* 2012;120:1757-1759

Ibrutinib +/-dexamethasone for relapsed or R/R MM: phase 2 trial

- Cohorts 1 and 3 assessed activity of ibrutinib monotherapy (420 and 840 mg/day, respectively, with 40 mg of dex once weekly allowed on disease progression at the discretion of the investigator);
- Cohorts 2 and 4 assessed ibrutinib (560 and 840 mg/day respectively) in combination with 40 mg of oral dex onceweekly (LD dex).

Richardson et al, British Journal of Haematology, 2018, 180, 821–830

Patient characteristics

Characteristic	Cohort 1 (n = 13)	Cohort 2 (n = 18)	Cohort 3 (n = 18)	Cohort 4 (n = 43)	Overall (N = 92)
Median age – years (range)	62 (49–74)	66 (46–77)	66 (54–81)	65 (43–81)	65 (43–81)
Male – n (%)	8 (62)	9 (50)	13 (72)	26 (60)	56 (61)
ECOG PS – %					
0	54	33	44	47	45
1	46	67	56	53	55
Median time since diagnosis – years	3.9	5.0	6.3	6.5	5.9
Measurable disease – n (%)					
SPEP/UPEP	11 (85)	14 (78)	16 (89)	33 (77)	74 (80)
sFLC	2 (15)	4 (22)	2 (11)	10 (23)	18 (20)
Disease status to last treatment* – n (%)					
Relapsed	4 (31)	2 (11)	4 (22)	13 (30)	23 (25)
Relapsed and refractory	9 (69)	16 (89)	13 (72)	30 (70)	68 (74)
Last line of therapy – n (%)					
PI and/or IMiD	11 (85)	14 (78)	13 (72)	39 (91)	77 (84)
No PI or IMiD	2 (15)	4 (22)	5 (28)	4 (9)	15 (16)
Chromosomal abnormalities by FISH – n (%)					
t(11;14)	1 (8)	1 (6)	5 (28)	8 (19)	15 (16)
del13q14	5 (38)	3 (17)	3 (17)	4 (9)	15 (16)
t(4;14)	2 (15)	5 (28)	5 (28)	1 (2)	13 (14)
del17p	3 (23)	5 (28)	0 (0)	4 (9)	12 (13)
High-risk cytogenetics† – n (%)	5 (38)	8 (44)	5 (28)	5 (12)	23 (50)
ISS stage – n (%)					
I	6 (46)	6 (33)	8 (44)	23 (54)	43 (47)
II	6 (46)	8 (44)	8 (44)	16 (37)	38 (41)
III	1 (8)	4 (22)	2 (11)	4 (9)	11 (12)

Richardson et al, British Journal of Haematology, 2018, 180, 821–830

Efficacy

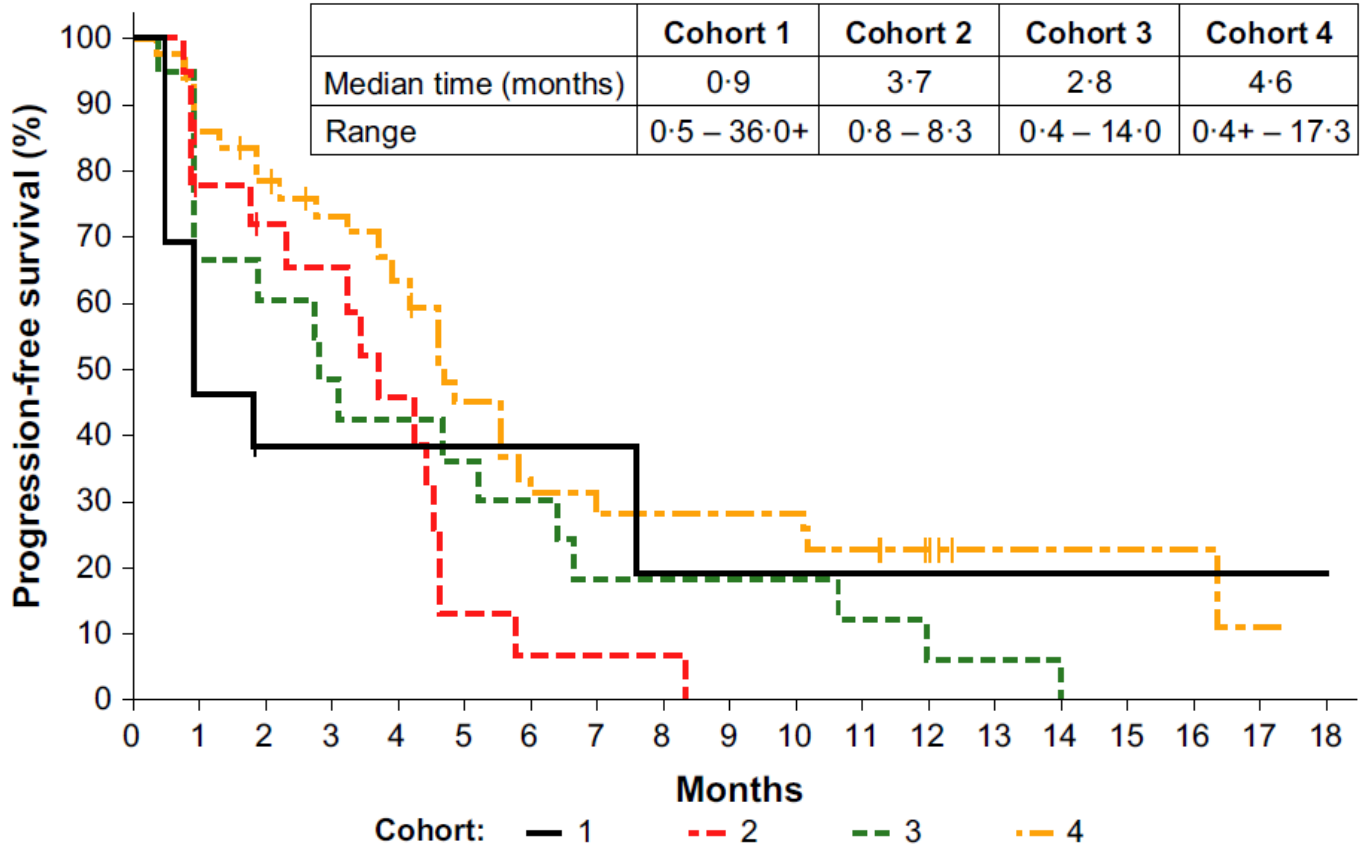
Table III. Overall response by IMWG criteria

Response	Cohort 1* (n = 13)	Cohort 2 (n = 18)	Cohort 3* (n = 18)	Cohort 4 (n = 43)
PR – n (%)	0 (0)	1 (6)	0 (0)	2 (5)
MR – n (%)	1 (8)	0 (0)	0 (0)	10 (23)
SD ≥4 cycles – n (%)	1 (8)	4 (22)	6 (33)	10 (23)
SD <4 cycles – n (%)	5 (38)	10 (56)	5 (28)	12 (28)
PD – n (%)	5 (38)	2 (11)	4 (22)	6 (14)
NE – n (%)	0 (0)	1 (6)	1 (6)	0 (0)
CBR (≥MR) – %	8	6	0	28
ORR (≥PR) – %	0	6	0	5

Richardson et al, British Journal of Haematology, 2018, 180, 821–830

PFS

	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Median time (months)	0·9	3·7	2·8	4·6
Range	0·5 – 36·0+	0·8 – 8·3	0·4 – 14·0	0·4+ – 17·3



Richardson et al, British Journal of Haematology, 2018, 180, 821–830

Phase 1 trial of ibrutinib and carfilzomib for relapsed or R/R MM

Table 1. Cohort descriptions ($N = 43$).

Treatment	Cohort 1 ($n = 3$)	Cohort 2a ($n = 5$)	Cohort 2b ($n = 17$)	Cohort 3b ($n = 18$)
Ibrutinib	560 mg	560 mg	560 mg	840 mg
Carfilzomib	27 mg/m^2	36 mg/m^2	36 mg/m^2	36 mg/m^2
Dexamethasone	–	–	+	+

Cohort 3a not opened based on PCYC-1111 outcomes noted with the inclusion of dexamethasone to study treatment [8].

Chari et al, LEUKEMIA & LYMPHOMA, 2018
https://doi.org/10.1080/10428194.2018.1443337

Patient characteristics

Characteristic	Cohort 1 ($n=3$)	Cohort 2a ($n=5$)	Cohort 2b ($n=17$)	Cohort 3b ($n=18$)	Total ($N=43$)
Median age, years (range)	69 (68–71)	72 (60–82)	60 (47–83)	59 (44–76)	63 (44–83)
Median time from diagnosis, years (range)	8.2 (1.7–18.6)	4.2 (2.0–12.5)	5.0 (2.1–25.3)	4.0 (0.5–9.7)	4.2 (0.5–25.3)
Male, %	67	80	35	50	49
ECOG performance status, %					
0	33	20	24	33	28
1	67	80	71	50	63
2	0	0	6	17	9
Chromosomal abnormalities by FISH, %					
t(11;14)	33	20	6	6	9
t(4;14)	0	20	12	28	19
del17p	0	0	6	11	7
High-risk cytogenetics[a]	0	20	18	33	23
ISS stage at baseline, *n*					
I	3	1	10	8	22
II	0	2	3	6	11
III	0	2	3[b]	3[b]	8
Median prior lines of therapy, *n* (range)	3 (2–9)	3 (2–7)	3 (2–5)	2.5 (2–7)	3 (2–9)
Disease status to last treatment, %					
Relapsed	0	40	12	6	12
Refractory	100	60	88	94	88
Autologous stem cell transplant, %	100	60	76	61	70
Alkylator, %	100	100	76	94	88
IMiD,[c] %					
Thalidomide	0	40	29	22	26
Thalidomide refractory	0	20	0	11	7
Lenalidomide	100	100	94	100	98
Lenalidomide refractory	100	60	71	72	72
Pomalidomide	33	20	41	22	30
Pomalidomide refractory	33	20	35	22	28
PI,[c] %					
Bortezomib	100	100	100	100	100
Bortezomib refractory	67	60	76	78	74
Carfilzomib	0	0	6	17	9
Carfilzomib refractory	0	0	0	0	0

Chari et al, LEUKEMIA & LYMPHOMA, 2018
https://doi.org/10.1080/10428194.2018.1443337

Adverse Events

	Cohort 1 ($n=3$)		Cohort 2a ($n=5$)		Cohort 2b ($n=17$)		Cohort 3b ($n=18$)		Total ($N=43$)	
Adverse event, %	All	Grade ≥3	All	Grade ≥3	All	Grade ≥3	All	Grade ≥3	All	Grade ≥3
Fatigue	0	0	80	40	65	18	44	11	53	16
Diarrhea	0	0	60	20	65	24	39	6	49	14
Cough	33	0	40	0	41	0	56	0	47	0
Constipation	33	0	60	0	35	0	44	0	42	0
Nausea	0	0	0	0	41	6	50	0	37	2
Anemia	33	33	60	40	35	24	28	6	35	19
Pyrexia	33	0	60	0	41	24	17	0	33	9
Upper respiratory tract infection	33	0	0	0	41	12	33	0	33	5
Dyspnea	0	0	60	20	35	6	22	6	30	7
Headache	33	0	40	0	47	6	11	0	30	2
Hypertension	33	33	40	40	35	29	22	11	30	23
Insomnia	0	0	0	0	41	0	33	0	30	0
Epistaxis	0	0	60	0	29	0	22	0	28	0
Hypokalemia	0	0	40	0	41	12	17	6	28	7
Thrombocytopenia	33	33	20	0	18	6	39	17	28	12
Urinary tract infection	0	0	20	0	29	12	28	6	26	7
Arthralgia	0	0	60	0	24	0	11	0	21	0
Peripheral edema	0	0	20	0	18	0	28	0	21	0
Abdominal pain	0	0	20	0	24	0	17	0	19	0
Acute kidney injury	33	0	20	0	24	12	56	6	19	7
Muscle spasms	0	0	20	0	18	0	22	0	19	0
Pneumonia	33	33	40	40	12	12	17	17	19	19
Rash maculo-papular	0	0	0	0	24	18	17	0	16	7
Vomiting	0	0	20	0	24	12	11	0	16	5
Back pain	0	0	0	0	24	12	11	6	14	7
Hyperglycemia	0	0	0	0	18	12	17	11	14	9
Neutropenia	0	0	20	20	12	6	6	6	9	7
Sepsis	0	0	0	0	18	18	0	0	7	7

Chari et al, LEUKEMIA & LYMPHOMA, 2018
https://doi.org/10.1080/10428194.2018.1443337

Efficacy

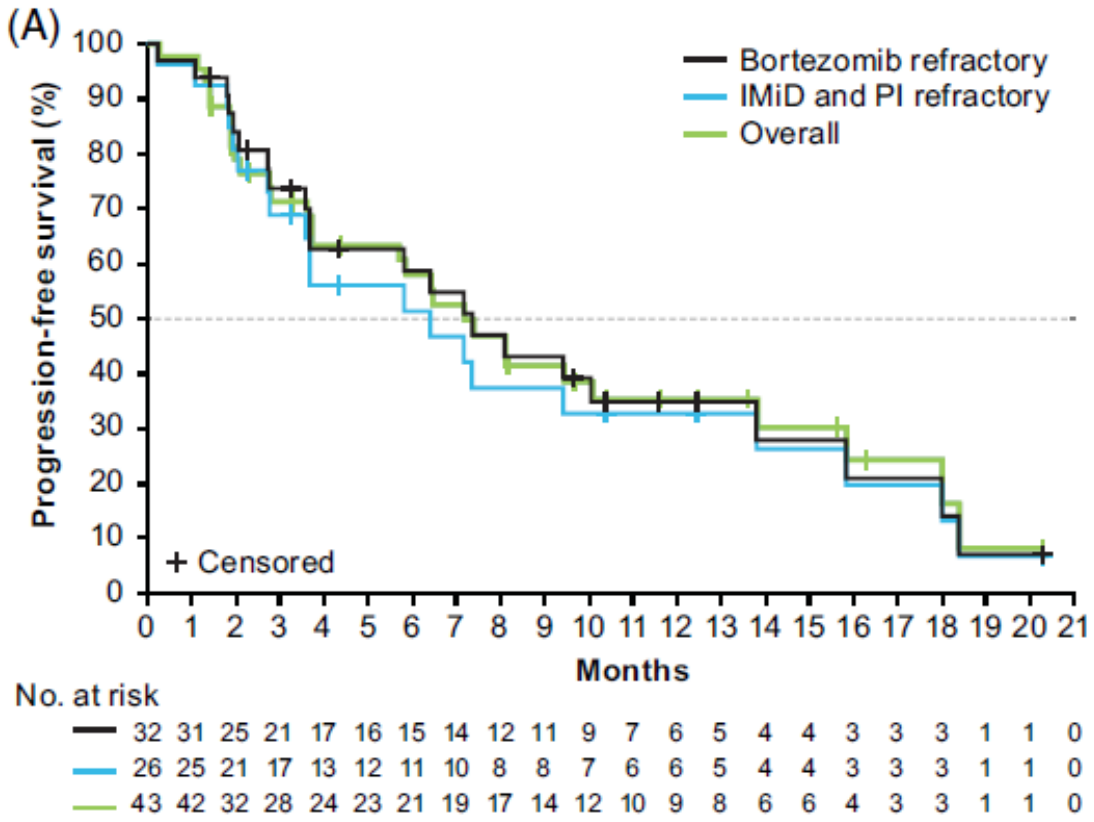
Table 4. Best response by IMWG response criteria.

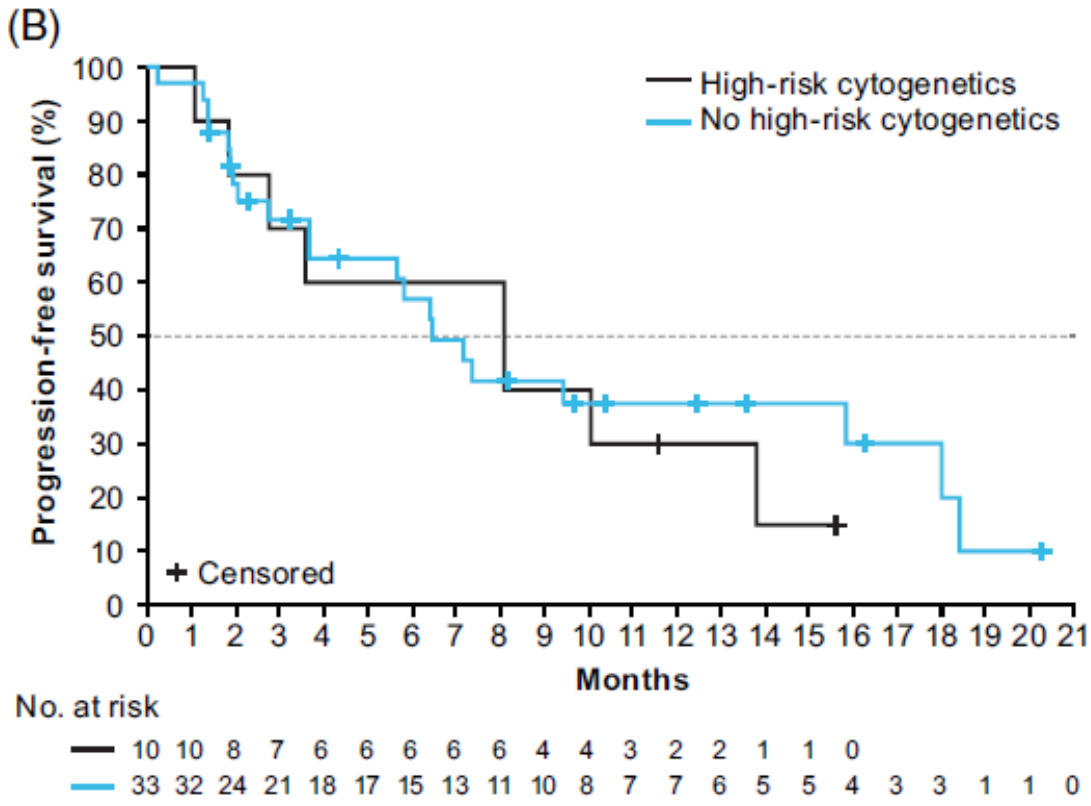
Treatment, %	Cohort 1 ($n = 3$)	Cohort 2a ($n = 5$)	Cohort 2b ($n = 17$)	Cohort 3b[a] ($n = 17$)	Total ($N = 42$)
sCR/CR	0	0	0	6	2
VGPR	0	0	29	24	21
PR	67	40	41	41	43
MR	0	0	12	12	10
ORR ($\geq$PR)	67	40	71	71	67
CBR ($\geq$MR)	67	40	82	82	76

CBR defined as $\geq$ MR by International Myeloma Working Group criteria.
CBR: clinical benefit rate; CR: complete response; MR: minimal response; ORR: overall response rate; PR: partial response; sCR: stringent complete response; VGPR: very good partial response.
[a]One patient not evaluable for response because of early discontinuation.

Chari et al, LEUKEMIA & LYMPHOMA, 2018
https://doi.org/10.1080/10428194.2018.1443337

PFS





Chari et al, LEUKEMIA & LYMPHOMA, 2018
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Alliance Studies (Activation Pending)

- AFT15: Phase I/II Ibrutinib + Rd in RR MM – Yvonne Efebera, Jacob Laubach

Conclusions

- Trials of Pembrolizumab with ImIds have raised concerns regarding toxixity of the combination.
- However trials with other Pd1/PDL1 inhibitors in combination with ImIds and other drugs are ongoing and data is awaited.
- Ibrutinib showed modest efficacy as a single agent.
- However, the best potential for the drug lies in combination therapy.

Questions?