UNIVERSITY
OF MIAMI

OTHER NOVEL STRATEGIES WITH POTENTIAL TO IMPROVE OUTCOMES IN MULTIPLE MYELOMA

Current practice and future directions

December 4, 2020. San Diego, CA

Professor Ola Landgren, M.D., Ph.D.
University of Miami, Sylvester Comprehensive Cancer Center

UNIVERSITY OF MIAMI

OUTLINE

- Biologic rationale and efficacy/safety findings with Venetoclax
- Next-generation immunomodulatory agents
- Bispecific monoclonal antibodies
- Efficacy/safety data for Melflufen
- New insights on myeloma biology and relapse

Courtesy of Ola Landgren, MD, PhD

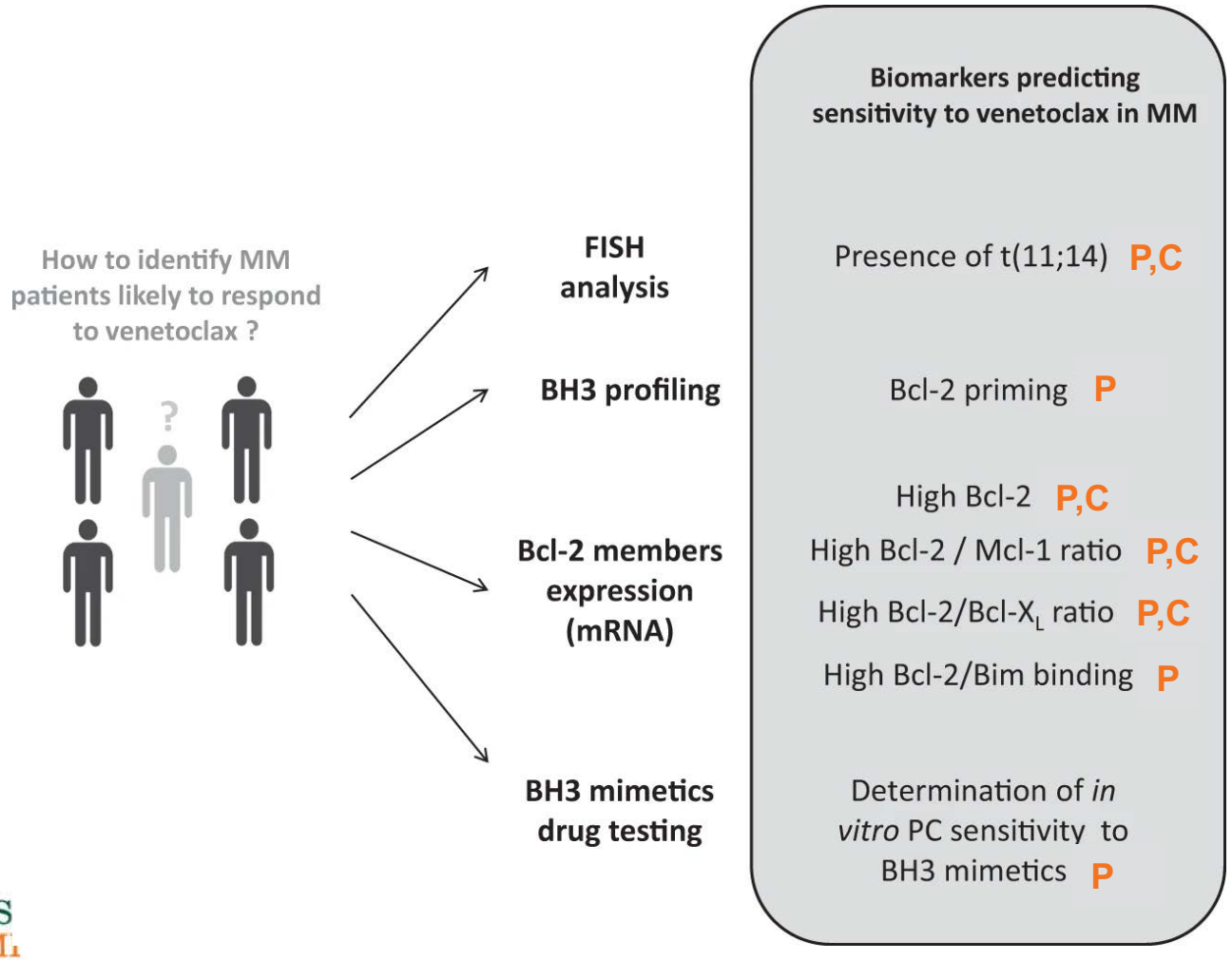
Targeting Bcl-2 for the treatment of multiple myeloma

- Overexpression of anti-apoptotic proteins are hallmarks of cancer
- Tumor cell proliferation is regulated through interactions between anti-apoptotic (Mcl-1, Bcl-2 and Bcl-xL) and pro-apoptotic (Bax and Bak) members
- Subset of myeloma cells with high Bcl-2 expression and low Mcl-1 expression commonly found in CCND1 subset, characterized by the presence of the translocation (11;14)
- Venetoclax binds to Bcl-2 and Bcl-x_L but not to Mcl-1. It induces apoptosis by displacing proapoptotic BH3-only proteins (Bim and Puma) from Bcl-2, leading to caspase-dependent cell death

Bodet L, et al. *Blood*. 2011 Oct 6;118(14):3901-3910

Courtesy of Ola Landgren, MD, PhD

How to identify multiple myeloma likely to respond to venetoclax?



Biomarkers predicting sensitivity to venetoclax in multiple myeloma:

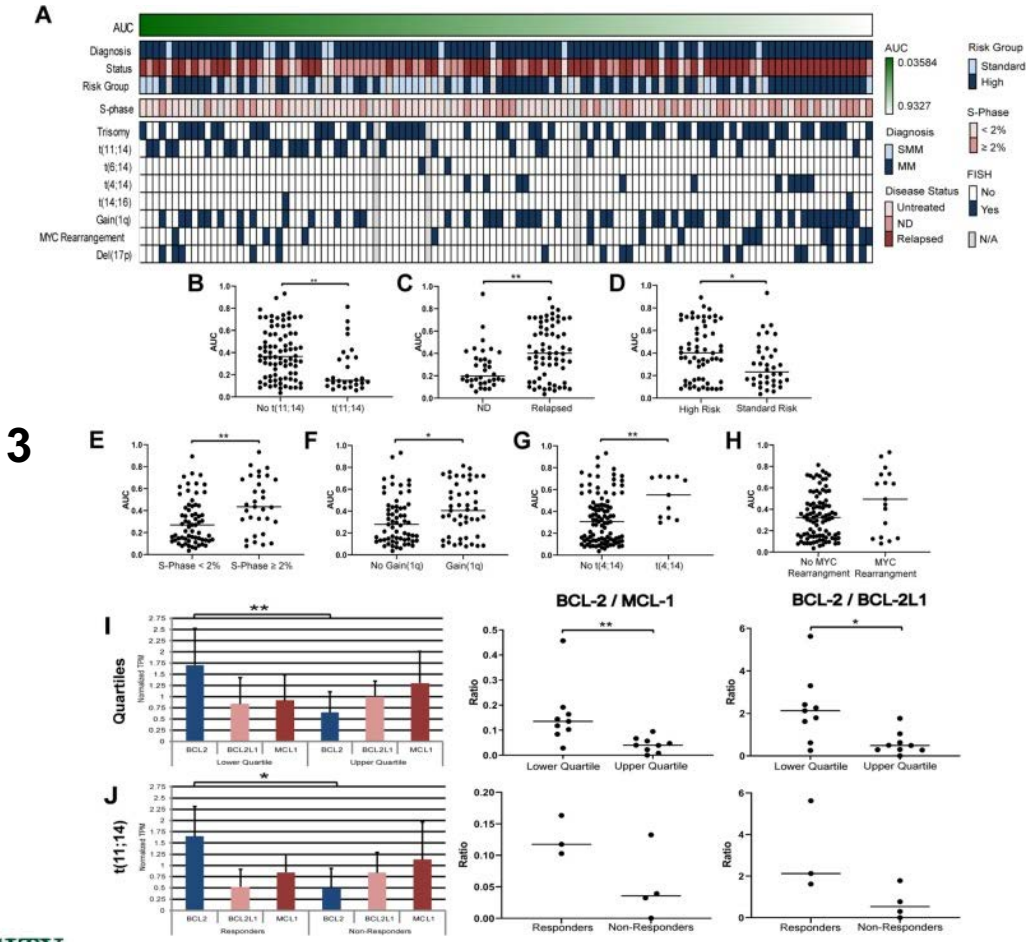
- **C = biomarker demonstrated in clinical trials**
- **P = biomarker demonstrated in preclinical studies**

UNIVERS OF MIAMI

Touzeau C, et al. *Leukemia*. 2018 Sep;32(9):1899-1907

Courtesy of Ola Landgren, MD, PhD

Venetoclax sensitivity *ex vivo* in primary multiple myeloma samples



N=113

- Cellular efficacy of single agent venetoclax response following a 24 h drug exposure
- Increased sensitivity in patient samples with: t(11;14); low plasma cell S-Phase; lack of 1q+; lack of t(4;14); lack of MYC rearrangements
- Transcriptomic ratios of anti-apoptotic Bcl-2 family members, showing Bcl-2 expression significantly increased in responders, with significant difference in Bcl-2/Mcl-1 and Bcl-2/Bcl-2L1 ratios
- Bcl-2 expression significantly increased in the t(11;14) responders compared to the t(11;14) non-responders

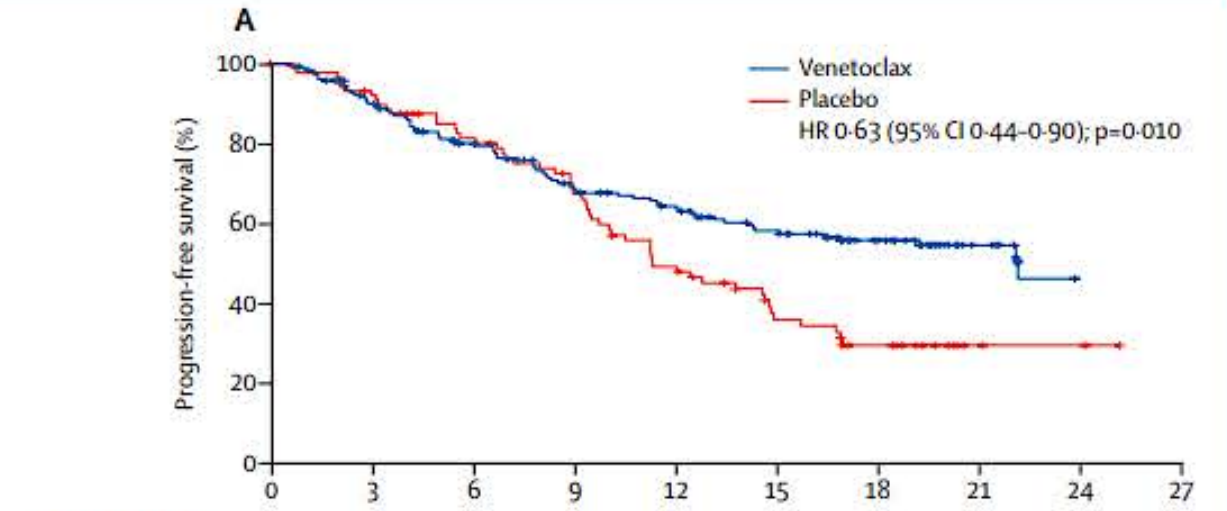
UNIVERSITY OF MIAMI

Bonolo de Campos C, et al. *Blood Cancer Journal*. 2020 May11;10(5):54

Courtesy of Ola Landgren, MD, PhD

Venetoclax in combination with bortezomib and dexamethasone in patients with relapsed or refractory multiple myeloma (BELLINI)

- Venetoclax, bortezomib and dexamethasone have shown encouraging clinical efficacy with acceptable safety and tolerability in phase 1 trial
- 291 patients (1-3 prior lines) randomized to receive venetoclax (n=194) or placebo (n=97), with bortezomib and dexamethasone
- At median follow-up of 18.7 months, median progression-free survival (PFS) was 22.4 versus 11.5 months favoring venetoclax; p=0.010



- Prespecified sub-analysis of t(11;14) patients (N=35) show median PFS not reached versus 9.5 months in venetoclax versus placebo group; similarly, sub-analysis of patients with high Bcl-2 expression (qPCR) levels (N=98) show median PFS of 22.4 versus 9.9 months, respectively

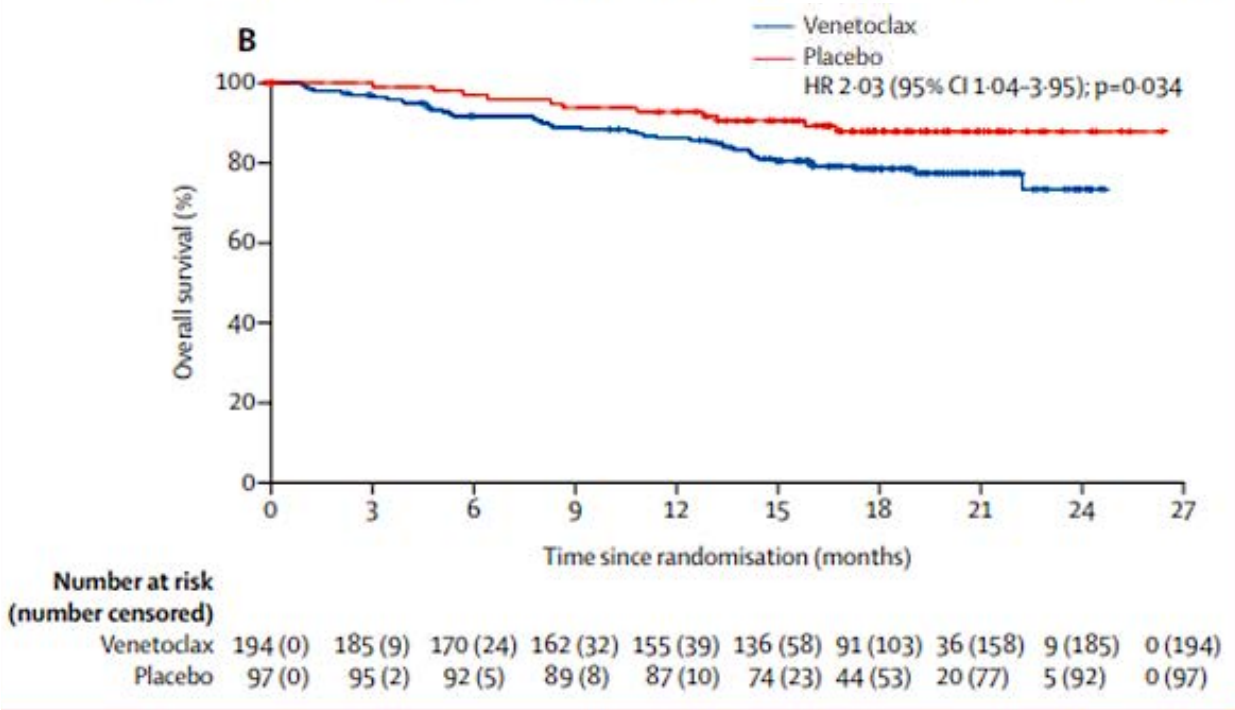
UNIVERSITY
OF MIAMI

Kumar S, et al. *Lancet Oncology*. 2020 Oct 29;S1470-2045

Courtesy of Ola Landgren, MD, PhD

Venetoclax in combination with bortezomib and dexamethasone in patients with relapsed or refractory multiple myeloma (BELLINI)

- However, excess death was found; in safety analysis population, 21% and 11% of pts in the venetoclax and placebo group died, respectively
- 8/13 of treatment-emergent deaths (within 30 days of last dose) in the venetoclax group were infections, including 5 patients who died from sepsis/septic shock and 3 who died from pneumonia
- In venetoclax group, excess mortality primarily seen in patients without t(11;14)



- Authors speculate venetoclax combination may select aggressive malignant clones? Or, treatment-induced immunosuppression may cause susceptibility to life-threatening infections? Or, other explanation(s)?

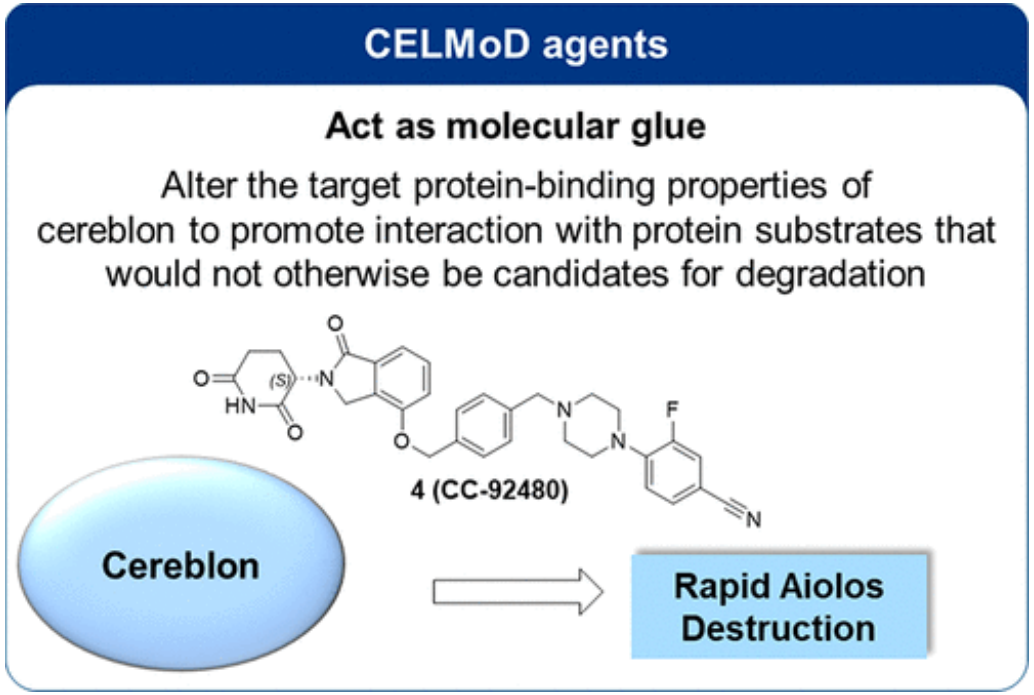
UNIVERSITY OF MIAMI

Kumar S, et al. *Lancet Oncology*. 2020 Oct 29;S1470-2045

Courtesy of Ola Landgren, MD, PhD

Cereblon E3 ligase modulators (CELMoDs)

- CC-92480 binds to cereblon, thereby affecting the ubiquitin E3 ligase activity, and targeting certain substrate proteins for ubiquitination…
- … this induces proteasome-mediated degradation of certain transcription factors, some of which are transcriptional repressors in T cells…
- … this leads to modulation of the immune system, including activation of T lymphocytes; and antiproliferative effects and induction of apoptosis in myeloma cells



Hansen JD, et al. *J Med Chem*. 2020 Jul 9;63(13):6648-6676;

Courtesy of Ola Landgren, MD, PhD

Phase I trial supports CC-92480 for heavily pretreated multiple myeloma

- Patients received escalating doses of CC-92480 + dexamethasone. Parallel dosing schedules: more continuous with 4-day or 7-day breaks *vs.* intensive with longer breaks in a 28-day cycle

- 66 patients received CC-92480 plus dexamethasone; median 6 (range 2-13) prior therapies. Prior therapies: proteasome inhibitors (100%), lenalidomide (97%), pomalidomide (92%), high-dose melphalan (76%). About 50% were considered triple-class refractory

- About 30% of patients remained on CC-92480. Of 51 patients who discontinued treatment, main cause was progressive disease (n=39), withdrawal (n=5), death (n=5), and adverse events (AEs; n=1). No deaths related to CC-92480

Richardson PG, et al. *EHA 2020* (abstract S208)

Courtesy of Ola Landgren, MD, PhD

Phase I trial supports CC-92480 for heavily pretreated multiple myeloma (*cont.*)

- 10 patients had dose-limiting toxicities, most commonly neutropenia. Maximum tolerated dose 1.0 mg for both 10/14-day and 21/28-day schedules

- Most common AEs observed in the study population were neutropenia (74%), infections (71%), and anemia (55%). Neutropenia most common grade 3-4 AE, reported in 49 patients. Neutropenia managed with dose modification and G-CSF; most infections successfully managed with antibiotics

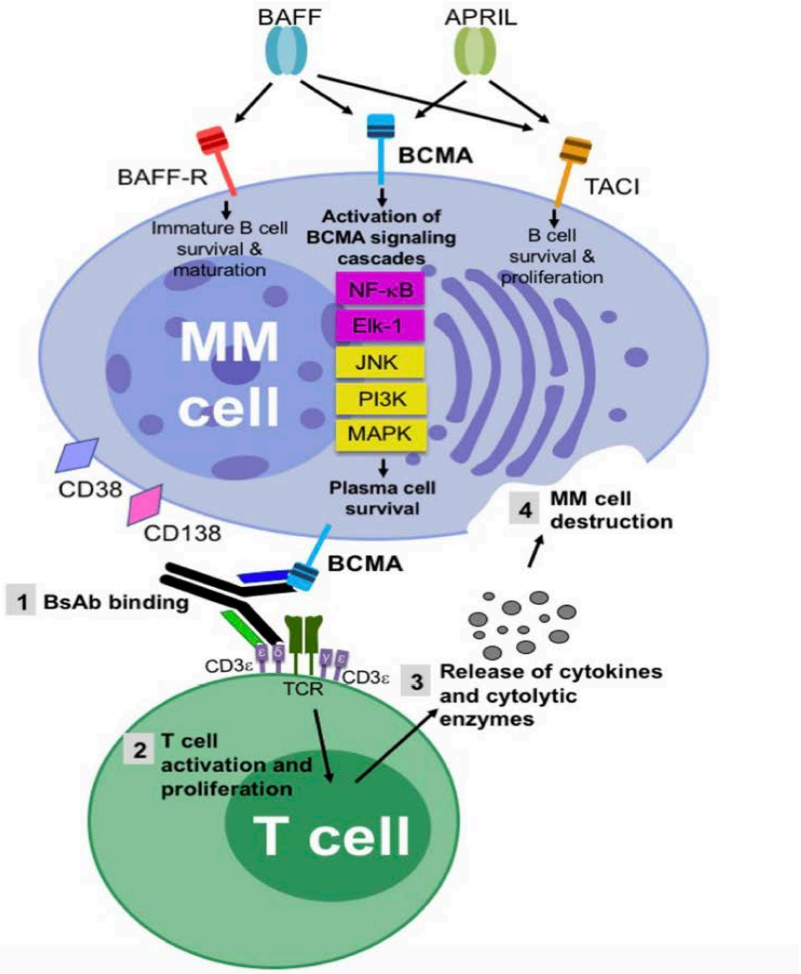
- Preliminary analyses revealed 21% overall response rate (ORR) across all dosing cohorts; 40% ORR among patients treated with maximum tolerated dose (1.0 mg once daily for 10/14 days), and 55% ORR with the recommended phase II dose (1.0 mg once daily for 21/28 days)

Richardson PG, et al. *EHA 2020* (abstract S208)

Courtesy of Ola Landgren, MD, PhD

Targeting BCMA for the treatment of multiple myeloma

- B-cell maturation antigen (BCMA) is a cell-surface receptor in TNF superfamily. Plays key role in B-cell maturation and differentiation
- Promotes myeloma cell growth, chemotherapy resistance, immunosuppression in bone marrow microenvironment
- Antigen expressed specifically on PCs and myeloma cells; higher expression on myeloma cells than normal plasma cells



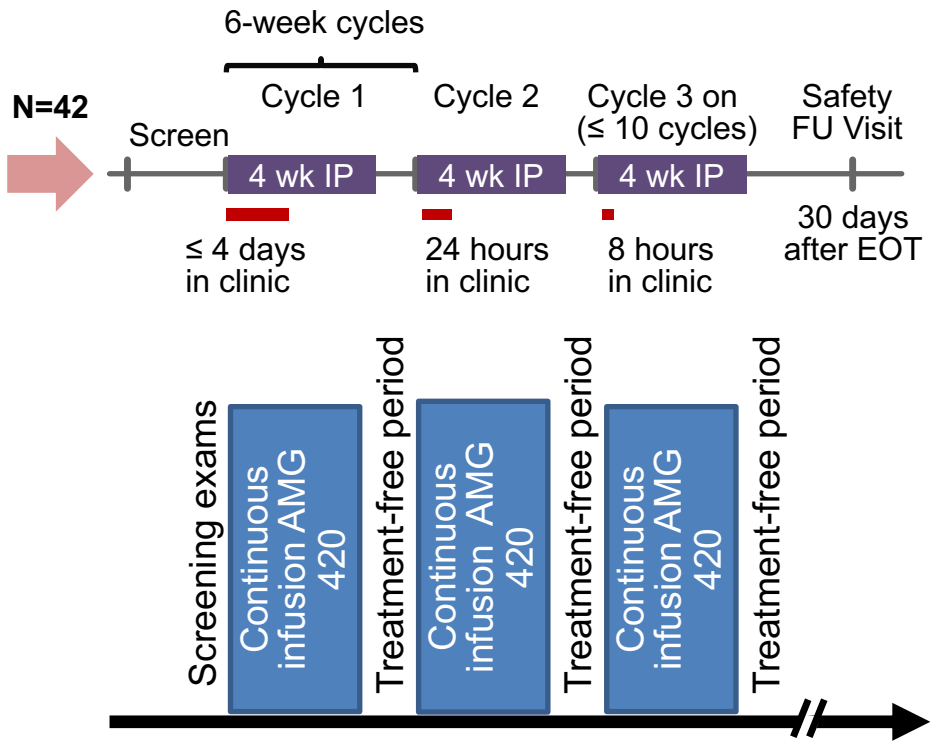
Topp MS, et al. *J Clin Oncol.* 2020 Mar 10;38(8):775-783

Courtesy of Ola Landgren, MD, PhD

Bi-specific BCMA/CD3 for the treatment of multiple myeloma: AMG420

Key Inclusion Criteria:

- Adults ≥ 18 years old
- R/R multiple myeloma with progression after ≥ 2 prior treatment lines, including a PI and an IMiD
- ECOG performance score of ≤ 2



- Single-patient cohorts (**0.2–1.6µg/day)** followed by cohorts of 3–6 patients **(3.2–800 µg/day)**

Primary Endpoints:

- Safety
  - DLTs
  - MTD

Secondary Endpoints:

- Antitumor activity
  - Response, including MRD-negative CR*
  - DOR
- Correlative markers

UNIVERSITY OF MIAMI

Topp MS, et al. *J Clin Oncol.* 2020 Mar 10;38(8):775-783

Courtesy of Ola Landgren, MD, PhD

Bi-specific BCMA/CD3 for the treatment of multiple myeloma: AMG420

- First-in-human study, up to 10 cycles of AMG 420 (4-week infusions/6-week cycles)
- 42 patients received AMG 420 at 0.2-800 µg/d. Median exposure was 1 cycle (range: 1-10) and 7 cycles (range: 1-10) for responders
- Patients discontinued for disease progression (n=25), adverse events (AEs; n=7), death (n=4), completion of 10 cycles (n=3), and consent withdrawal (n=1).

Topp MS, et al. *J Clin Oncol.* 2020 Mar 10;38(8):775-783

Courtesy of Ola Landgren, MD, PhD

Bi-specific BCMA/CD3 for the treatment of multiple myeloma: AMG420

- Patients discontinued for disease progression (n=25), adverse events (AEs; n=7), death (n=4), completion of 10 cycles (n=3), and consent withdrawal (n=1)

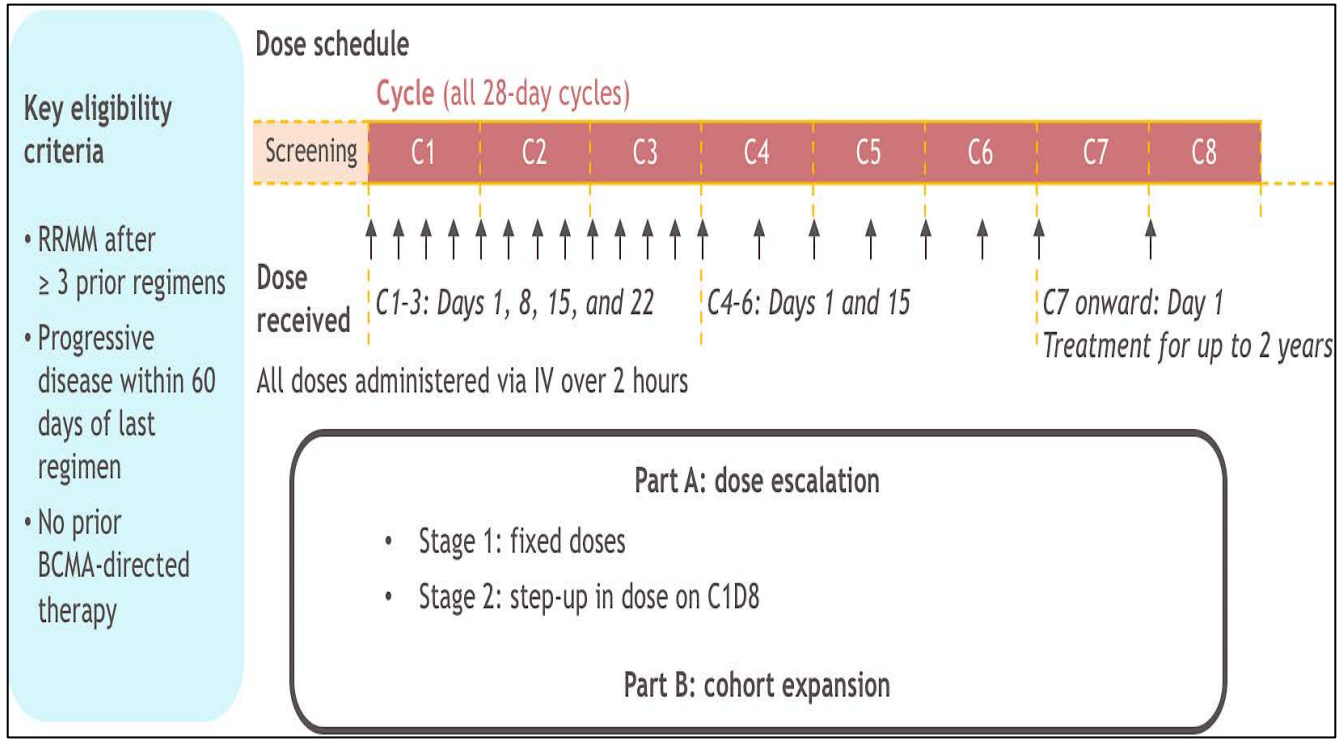
- Serious AEs (n=20; 48%) included infections (n=14) and polyneuropathy (n=2); treatment-related serious AEs included 2 grade 3 polyneuropathies and 1 grade 3 edema. There were no grade ≥ 3 CNS toxicities or anti-AMG 420 antibodies

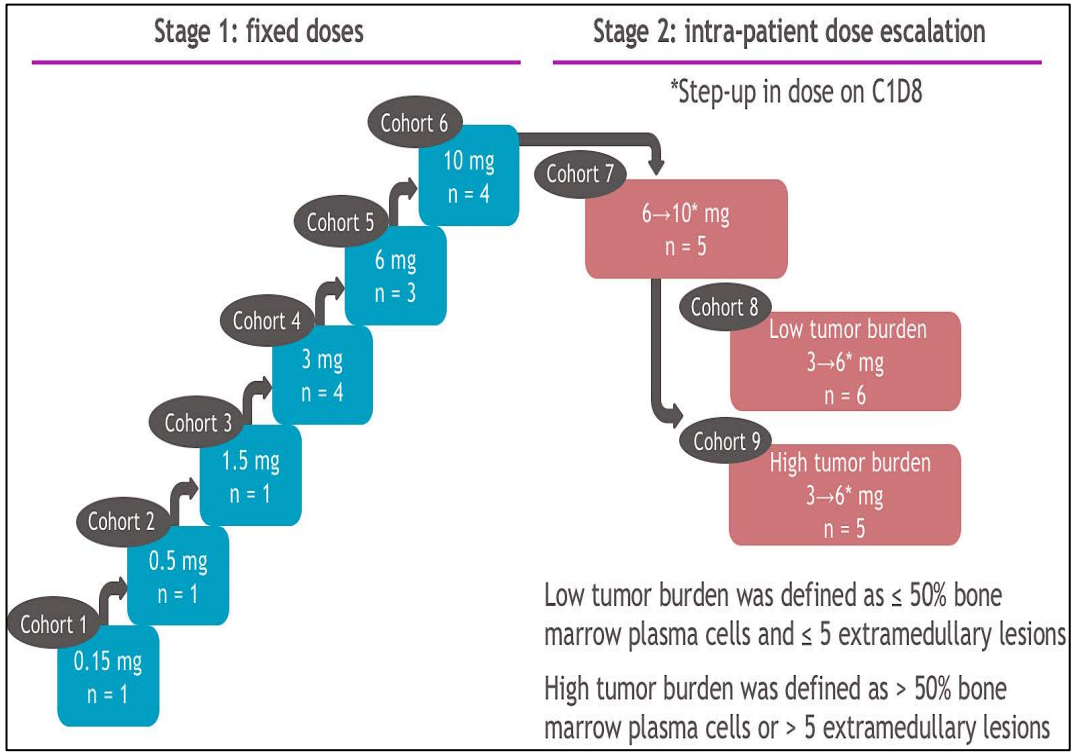
- Maximum tolerated dose (MTD) of 400 µg/d had overall response rate of 70% (7 of 10). Of these, five patients experienced MRD-negative complete responses, and 1 had a partial response, and 1 had a very good partial response; all 7 patients responded during the first cycle, and some responses lasted > 1 year

Topp MS, et al. *J Clin Oncol.* 2020 Mar 10;38(8):775-783

Courtesy of Ola Landgren, MD, PhD

Bi-specific BCMA/CD3 for the treatment of multiple myeloma: CC-93269: study design





UNIVERSITY OF MIAMI

Costa L, et al. *EHA 2020* (abstract S205)

Courtesy of Ola Landgren, MD, PhD

Bi-specific BCMA/CD3 for the treatment of multiple myeloma: CC-93269: prior regimens

	All patients (N = 30)	
	Exposed	Refractory
Prior regimens, median (range), n	**5 (3-13)**	
PIs, n (%)	**30 (100)**	**23 (76.7)**
Bortezomib	30 (100)	13 (43.3)
Carfilzomib	23 (76.7)	17 (56.7)
Ixazomib	5 (16.7)	3 (10.0)
IMiDs, n (%)	**30 (100)**	**24 (80.0)**
Lenalidomide	30 (100)	14 (46.7)
Pomalidomide	26 (86.7)	22 (73.3)
Anti-CD38 monoclonal antibodies, n (%)	**29 (96.7)**	**24 (80.0)**
Daratumumab	28 (93.3)	23 (76.7)
Isatuximab	4 (13.3)	2 (6.7)
Prior PI, IMiD, and anti-CD38 antibody, n (%)	**29 (96.7)**	**20 (66.7)**
Stem cell transplantation, n (%)		
Autologous	23 (76.7)	
Allogeneic	3 (10.0)	

UNIVERSITY OF MIAMI

Costa L, et al. *EHA 2020* (abstract S205)

Courtesy of Ola Landgren, MD, PhD

Bi-specific BCMA/CD3 for the treatment of multiple myeloma: CC-93269: adverse events

Common (≥ 20% all grade) TEAEs[a], n (%)	All patients (N = 30)	
	All grade	Grade ≥ 3
Patients with ≥ 1 TEAE	29 (96.7)	22 (73.3)
Hematologic TEAEs		
Neutropenia	14 (46.7)	13 (43.3)
Anemia	13 (43.3)	11 (36.7)
Thrombocytopenia	9 (30.0)	5 (16.7)
Nonhematologic TEAEs		
Cytokine release syndrome	23 (76.7)	1 (3.3)
Infections and infestations	17 (56.7)	9 (30.0)
Diarrhea	8 (26.7)	1 (3.3)
Vomiting	8 (26.7)	0
Back pain	7 (23.3)	0
Fatigue	6 (20.0)	0
Infusion-related reaction	6 (20.0)	0
Nausea	6 (20.0)	0

Parameter	All patients (N = 30)
Patients with a CRS event, n (%)	**23 (76.7)**
After first dose	23 (76.7)
After second dose	7 (23.3)
After third dose	2 (7.4)[a]
Maximum CRS grade, n (%)	
1	15 (50.0)
2	7 (23.3)
≥ 3	1 (3.3)
Time to onset, median (range), days	1 (1–9)
Duration, median (range), days	2 (1–6)
Tocilizumab use, n (%)	13 (43.3)
Corticosteroid use, n (%)	22 (73.3)

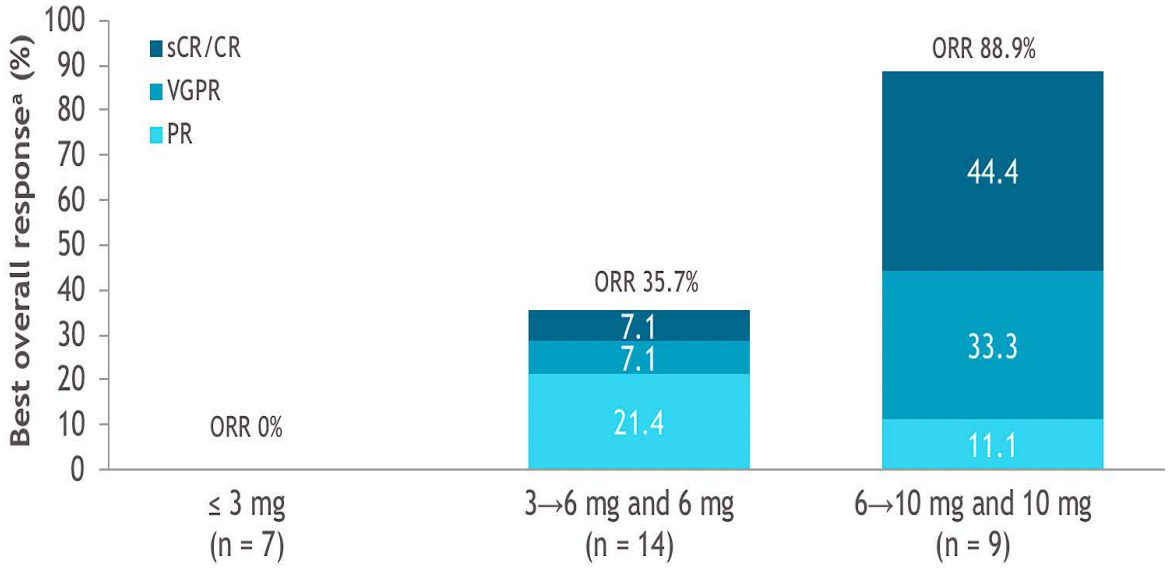
UNIVERSITY OF MIAMI

In cohort 7 (6 →10 mg), 1 patient experienced grade 3 (6 mg) followed by grade 5 CRS (10 mg); contributing factors included myeloma progression with extensive extramedullary disease, and concomitant infection

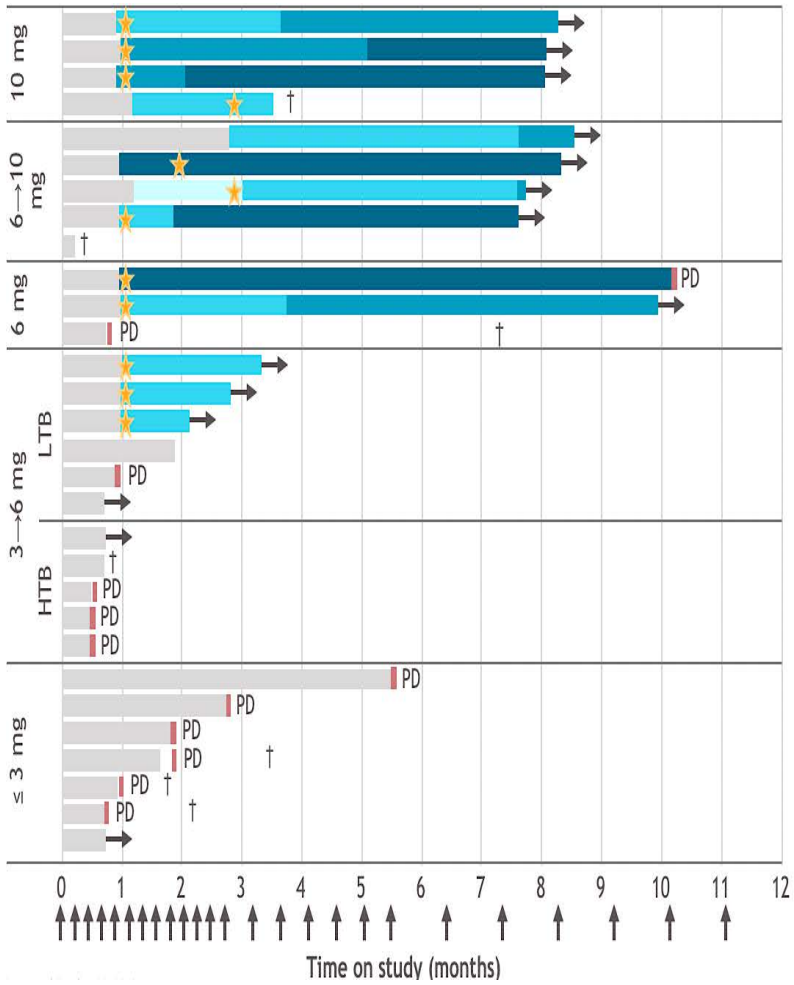
Costa L, et al. *EHA 2020* (abstract S205)

Courtesy of Ola Landgren, MD, PhD

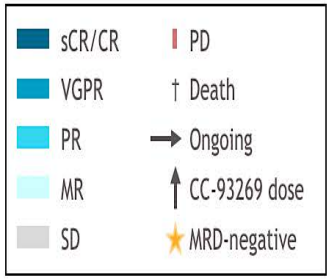
Bi-specific BCMA/CD3 for the treatment of multiple myeloma: CC-93269: efficacy



In all patients (N=30), 43% ORR and 17% sCR/CR; among patients receiving 10 mg (N=9), 89% ORR and 44% sCR/CR



- Median time to first response was 4.1 weeks (range 4.0-13.1)
- 11 of 13 responses are ongoing
- 5 of 30 (16.7%) patients achieved an MRD-negative sCR/CR
  - 12 of 13 (92.3%) responding patients achieved MRD negativity (≤ $1/10^5$) in the bone marrow on or before C4D1 by Euroflow[a]



UNIVERSITY OF MIAMI

Costa L, et al. *EHA 2020* (abstract S205)

Courtesy of Ola Landgren, MD, PhD

Bi-specific BCMA/CD3 for the treatment of multiple myeloma: teclistamab: study design

Key Objectives

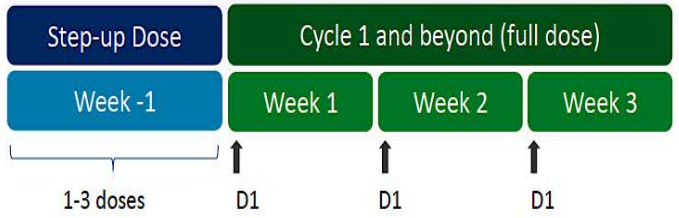
- Part 1: Identify RP2D
- Part 2: Safety and tolerability
- Antitumor activity, PK, PD

Key Eligibility Criteria

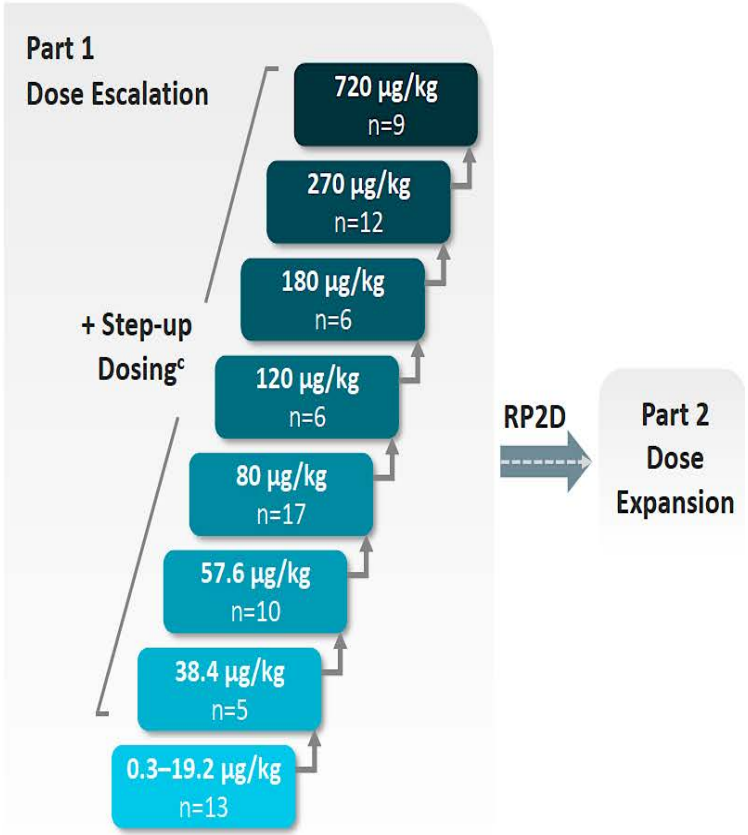
- Measurable MM
- RR or intolerant to established MM therapies
- Hb ≥8 g/dL, platelets[a] ≥75x10^9/L, ANC ≥1.0x10^9/L
- No prior BCMA-targeted therapy

Intravenous Dosing

- Initial Q2W dosing switched to weekly ± step-up dosing
- Pre-medications[b] limited to step-up doses and 1st full dose



- **Results from Part 1 intravenous dose escalation are presented**



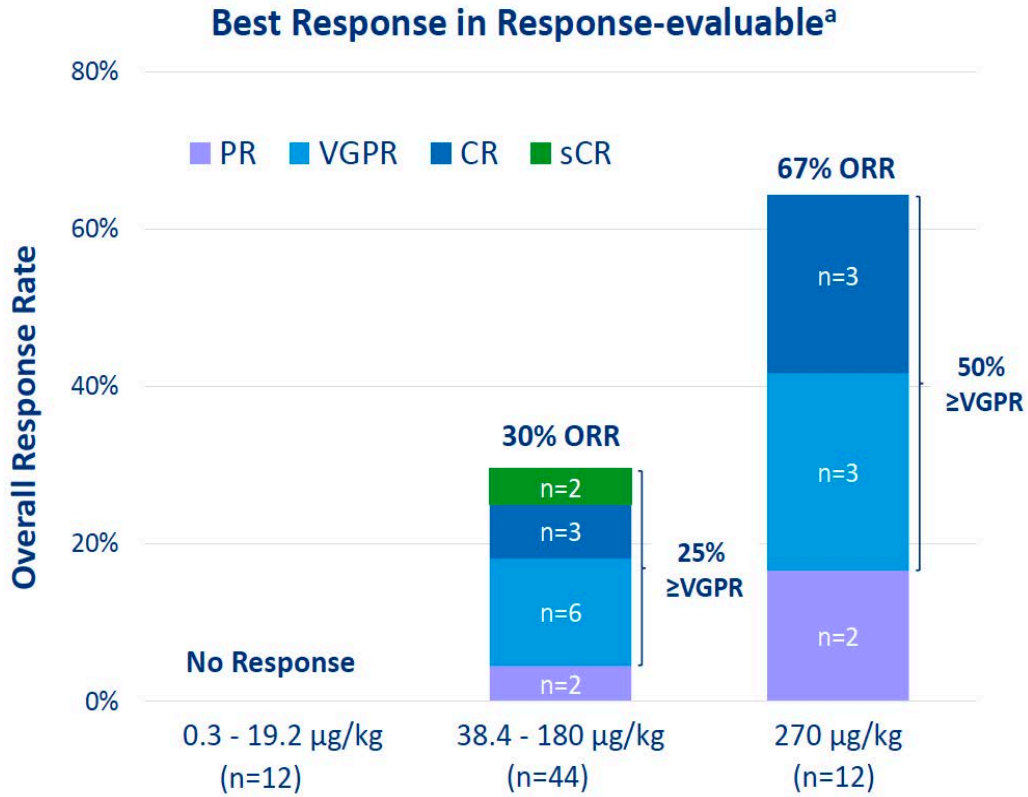
UNIVERSITY OF MIAMI

Mateos MV, et al. *EHA 2020* (abstract S206)

Courtesy of Ola Landgren, MD, PhD

Bi-specific BCMA/CD3 for the treatment of multiple myeloma: teclistamab: prior therapies and efficacy

Characteristic	Total (N = 78)
Prior lines of therapy, median (range)	6 (2–14)
Triple-class exposed, n (%)[c]	72 (92)
Penta-drug exposed, n (%)[d]	51 (65)
Refractory status, n (%)	
Carfilzomib	48 (62)
Pomalidomide	56 (72)
Anti-CD38[e]	68 (87)
Triple-class refractory[c]	62 (80)
Penta-drug refractory[d]	32 (41)
Refractory to last line of therapy,[f] n (%)	67 (86)



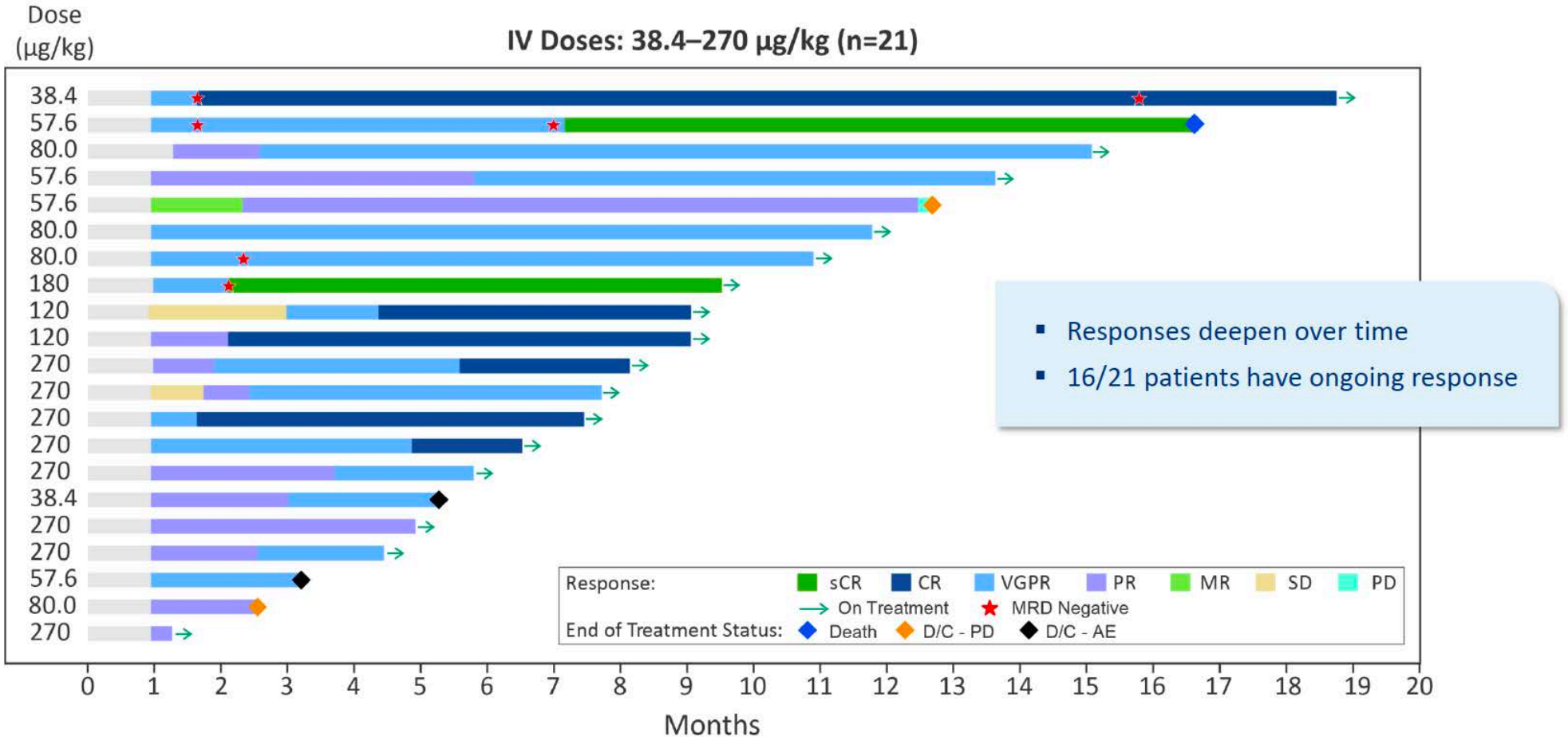
- At 270 µg/L. 7/8 responders were triple class refractory; 5/8 were penta-refractory.
- 4/5 evaluable patients were MRD neg at 10^{-6}
- 2/2 evaluable patients maintained MRD neg for 5m (VGPR) and 14m (CR)

UNIVERSITY OF MIAMI

Mateos MV, et al. *EHA 2020* (abstract S206)

Courtesy of Ola Landgren, MD, PhD

Bi-specific BCMA/CD3 for the treatment of multiple myeloma: teclistamab: duration of response



UNIVERSITY OF MIAMI

Mateos MV, et al. *EHA 2020* (abstract S206)

Courtesy of Ola Landgren, MD, PhD

Bispecific antibodies in development for the treatment of multiple myeloma

Target	Agent	Type	Comments	Clinical trials no.*
BCMA	AMG 420 (BI 836909)	BiTE	7 of 10 (70%) ORR in phase 1 expansion at MTD; single-agent phase 1b/2 ongoing	NCT02514239, NCT03836053
BCMA	PF-06863135	Bispecific	Single-agent phase 1	NCT03269136
BCMA	JNJ-64007957	Bispecific	Single-agent phase 1	NCT03145181
BCMA	TNB-383B	Bispecific	Single-agent phase 1	NCT03933735
BCMA	REGN5458	Bispecific	Single-agent phase 1	NCT03761108
BCMA	CC-93269 (EM901)	Bispecific	Single-agent phase 1	NCT03486067
BCMA	AMG 701	Bispecific	Single-agent phase 1	NCT03287908
BCMA	AFM26	Bispecific	CD16 × BCMA, targets NK cells, preclinical	
BCMA	HPN217	Bispecific	Preclinical	
BCMA	EM801	Bispecific	Preclinical	
CD38	AMG 424	Bispecific	Single-agent phase 1	NCT03445663
CD38	GBR 1342	Bispecific	Single-agent phase 1	NCT03309111
FcRH5	BFCR4350A	Bispecific	Single-agent phase 1	NCT03275103
GPRC5D	JNJ-64407564	Bispecific	Single-agent phase 1	NCT03399799

Cohen A. *ASH 2019* (Educational session)

Courtesy of Ola Landgren, MD, PhD

Melflufen: a novel peptide-drug conjugate that rapidly delivers cytotoxic payload into tumor cells

- HORIZON single arm study (N=95), melflufen + low-dose dex in pts refractory to pom and/or daratumumab. Pts must have received ≥2 prior lines. ORR primary endpoint.
  - 30% ORR: 1 pt achieved sCR, 11% VGPR, and 18% PR. Median PFS: 4 months
  - Treatment-related grade 3/4 AEs were reported in 68 pts (72%), most commonly (>20%) neutropenia (55%), thrombocytopenia (52%), and anemia (26%). The most common treatment-related nonhematologic grade 3/4 AE was pneumonia (3%)

Richardson PG, et al. *EHA 2019* (abstract S1605)

Courtesy of Ola Landgren, MD, PhD

Melflufen: a novel peptide-drug conjugate that rapidly delivers cytotoxic payload into tumor cells

- OCEAN, randomized, global, Phase III study evaluating the efficacy and safety of melflufen + dexamethasone *versus* pomalidomide + dexamethasone
  - Eligible patients cannot be primary refractory, they should have received 2-4 prior lines of therapy; patients refractory to both their last line of therapy and lenalidomide within 18 months of randomization

Table 1. OCEAN study dose schedule.

Group	Drug	Dose	Schedule (/28-day cycle)
Arm A	Melflufen	40 mg IV	Day 1
	Dexamethasone	40 mg oral tablets†	Days 1, 8, 15 and 22
Arm B	Pomalidomide	4 mg oral capsule	Days 1–21 (inclusive)
	Dexamethasone	40 mg oral tablets†	Days 1, 8, 15 and 22

†The dexamethasone dose will be reduced to 20 mg for patients aged ≥75 years. In the USA only, oral dexamethasone may be substituted with IV dexamethasone at the investigator's discretion.

IV: Intravenous.

UNIVERSITY OF MIAMI

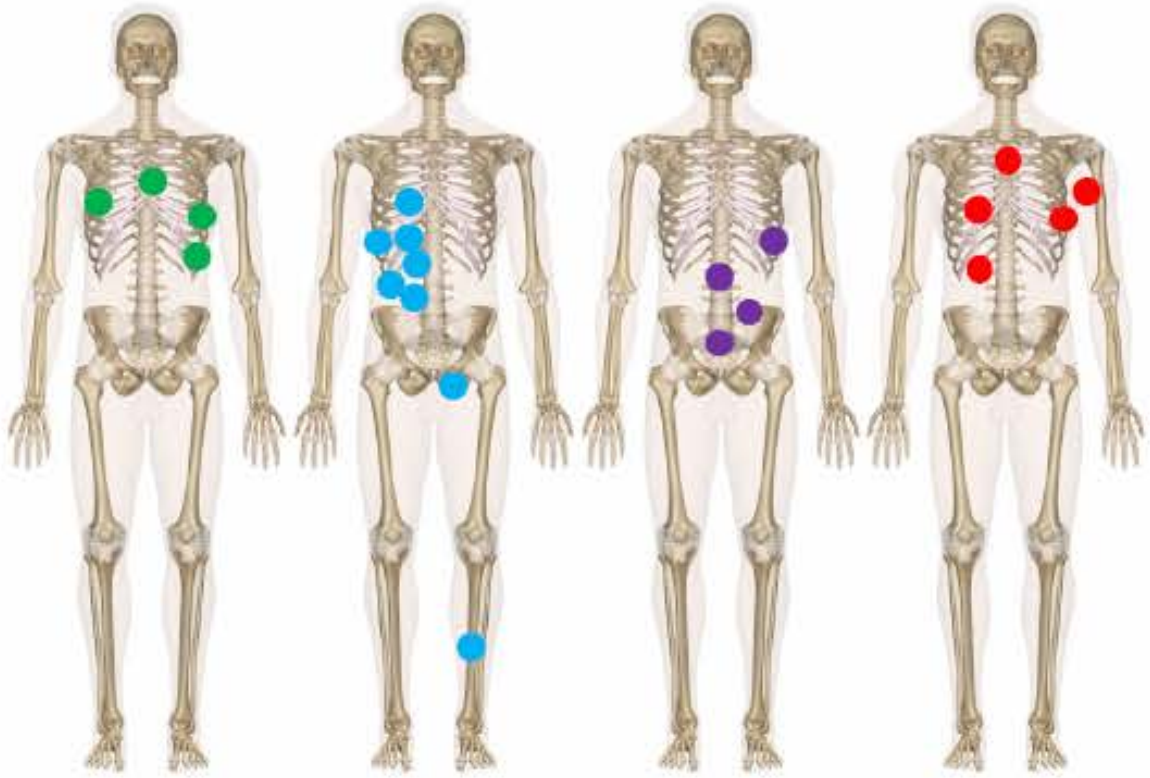
Schjesvold F, et al. *Future Oncol.* 2020 Apr;16(11):631-641

Courtesy of Ola Landgren, MD, PhD

Genomic profiling of multiple myeloma at relapse

- Whole genome sequencing on concurrent samples obtained from several – rarely biopsied – anatomical sites, obtained by warm autopsy in relapsed/refractory myeloma patients

Sample ID	Specimen Source
I-H-106917-T2-1	Right 5th rib
I-H-106917-T2-2	Left 6th rib
I-H-106917-T2-3	Left 9th rib
I-H-106917-T2-4	Sternum
I-H-130718-T1-1	Left inferior calf
I-H-130718-T1-2	Left inguinal
I-H-130718-T1-4	Right pleural cavity
I-H-130718-T1-6	Right lung
I-H-130718-T1-9	Liver
I-H-130718-T1-10	Gallbladder
I-H-130718-T1-11	Right chest wall
I-H-130718-T1-12	Epigastric subcutaneous
I-H-130719-T1-2	Lower left rib 10th
I-H-130719-T1-4	Spinal
I-H-130719-T1-5	Left psoas
I-H-130719-T1-6	Sacrum
I-H-130720-T1-2	Left arm subcutaneous
I-H-130720-T1-3	6th rib mass
I-H-130720-T1-4	Upper sternum mass
I-H-130720-T1-5	Liver
I-H-130720-T1-8	Right lung middle lobe



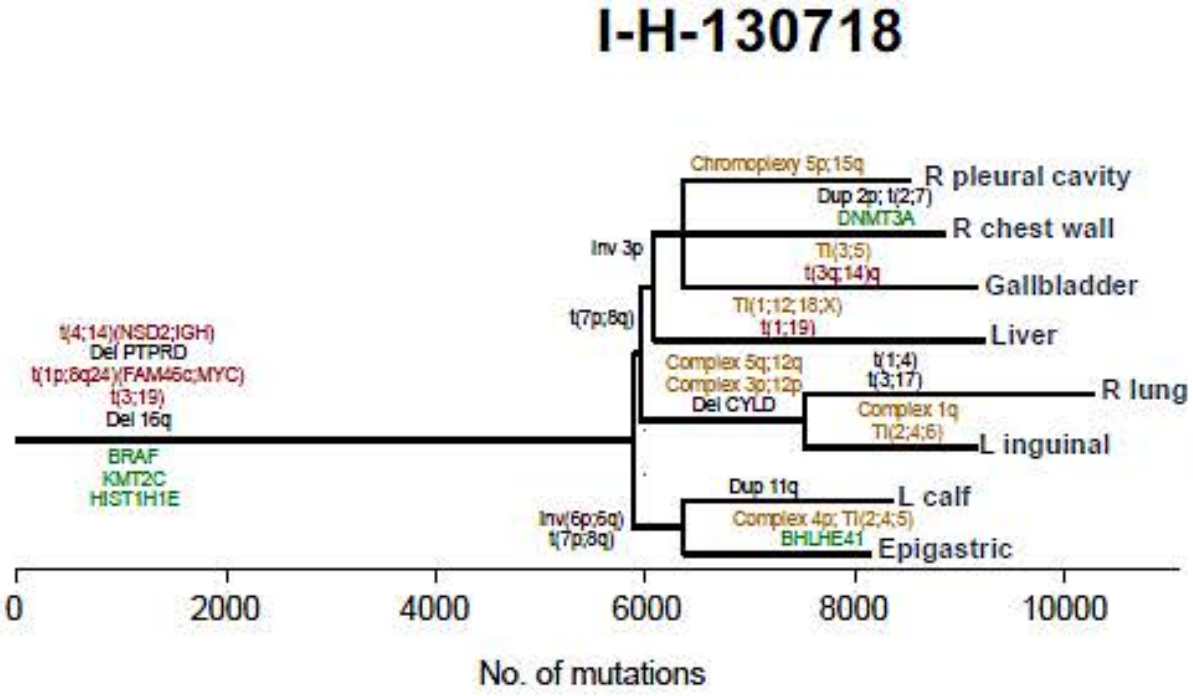
UNIVERSITY OF MIAMI

Landau H, et al. *Nature Comm* 2020 Jul 17;11(1):3617

Courtesy of Ola Landgren, MD, PhD

Reconstruction of myeloma evolutionary trajectories

- Median of 10,938 (range 6977-13,239) mutations detected by WGS
- We defined key evolutionary trajectories and drivers of myeloma seeding
- We reconstructed phylogenetic tree solution (trunk and branches) for each patient and defined the main evolutionary trajectories

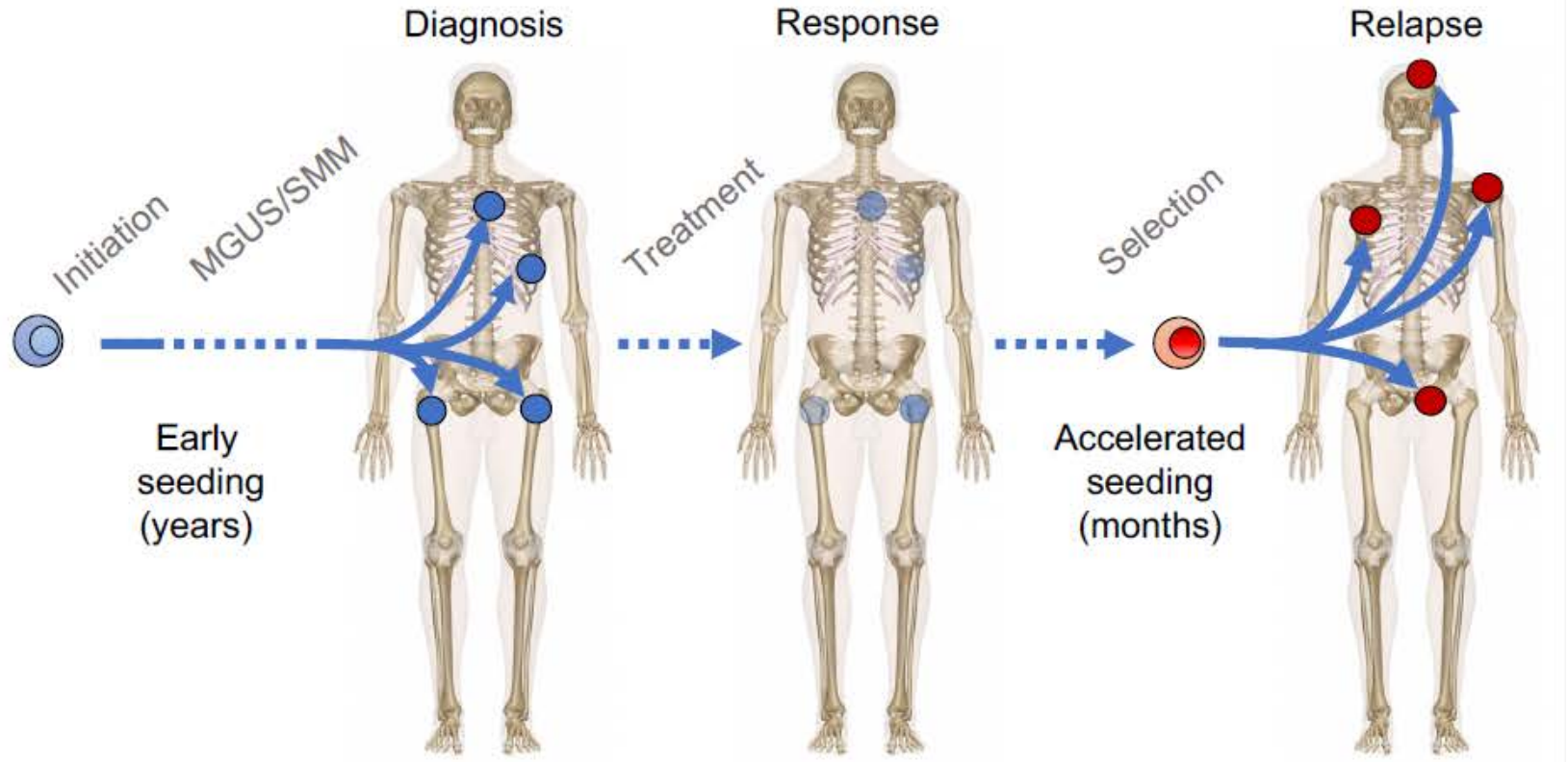


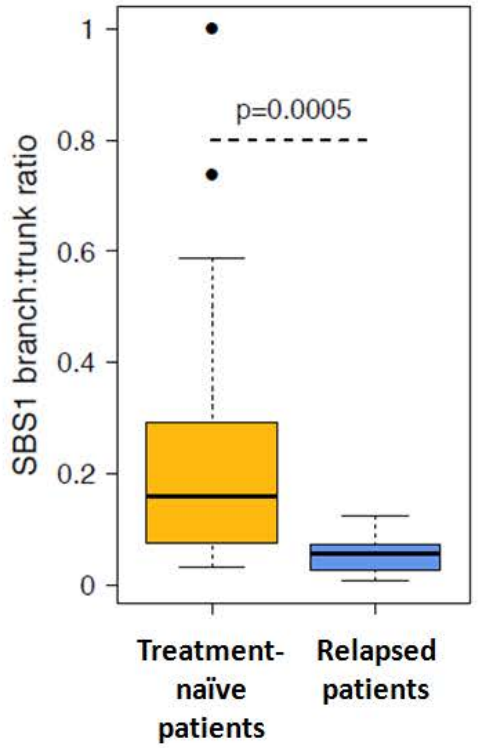
UNIVERSITY OF MIAMI

Landau H, et al. *Nature Comm* 2020 Jul 17;11(1):3617

Courtesy of Ola Landgren, MD, PhD

Reconstruction of myeloma evolutionary trajectories





Contribution of mutational signatures associated with aging (SBS1 described as "clock-like"), in the branches versus the trunk

Accelerated seeding within months, similar to metastasis in solid tumors

UNIVERSITY OF MIAMI

Landau H, et al. *Nature Comm* 2020 Jul 17;11(1):3617

Courtesy of Ola Landgren, MD, PhD

Thank you for your attention!

Ola Landgren, M.D, Ph.D.
Professor of Medicine
Chief, Myeloma Program
Chief, Experimental Therapeutics Program
Sylvester Comprehensive Cancer Center
University of Miami
Email: col15@miami.edu