Bi-specific Immunotherapy in Myeloma—Opportunities and Challenges

FLASCO SPRING 2023

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

MYELOMA INSTITUTE

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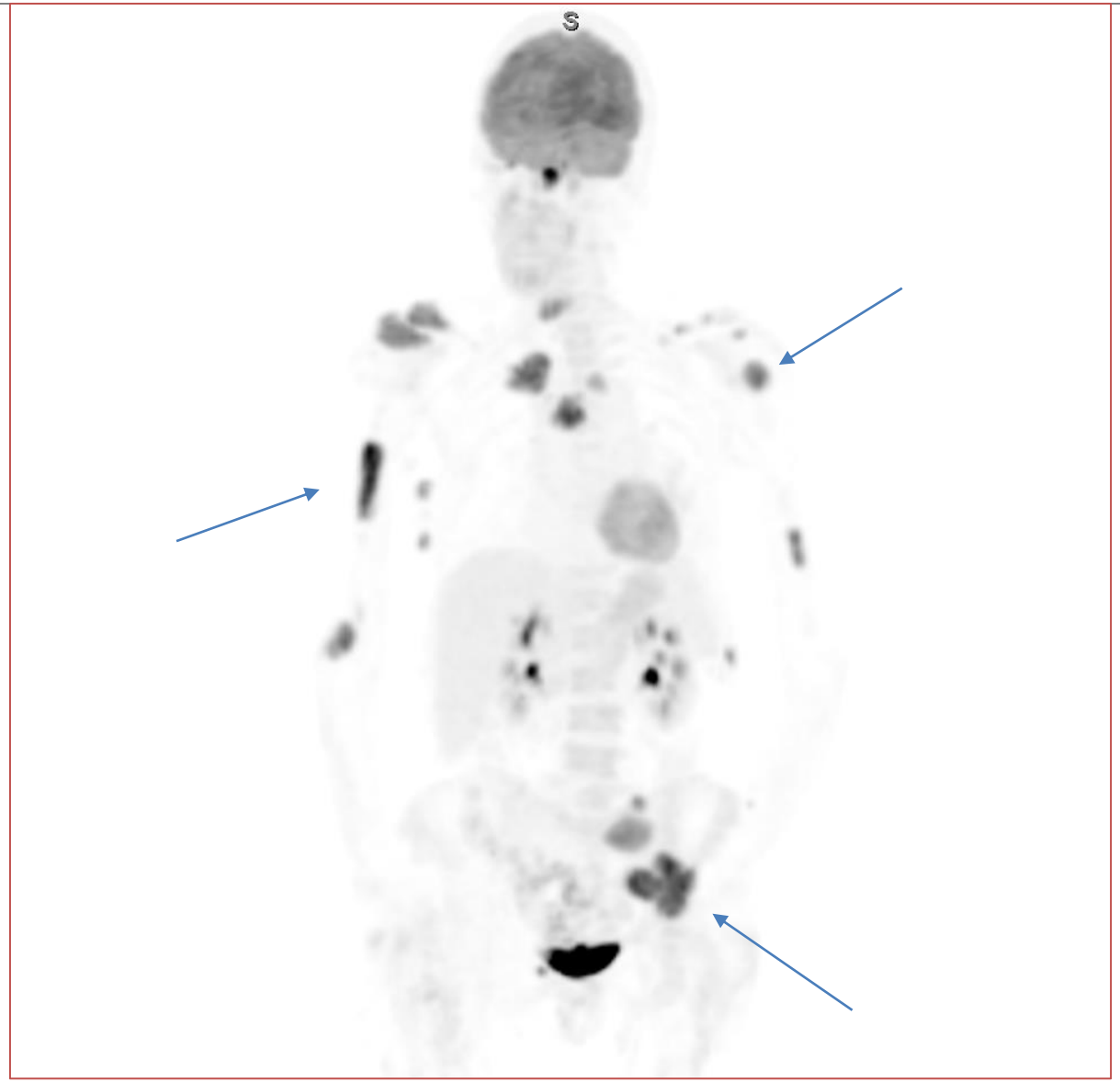
Initial presentation

- 61 yo woman, otherwise healthy, presented to ER with back pain.
- MRI of lumbar spine: multiple lytic lesions in lower T spine + bony pelvis with pathologic fracture of T9.
- Initial laboratory evaluations ultimately showed:
  - SPEP: M-spike 2.85 g/dL
  - FKLC: 1.2 mg/dL
  - FLLC 132 mg/dL
  - sFLCr ratio: 110
  - Hemoglobin: Normal
  - Creatinine: Normal
  - Calcium: Normal
  - Serum Immunoglobulins
    - IgM 23 mg/dl
    - IgA 2431 mg/dl
    - IgG 590 mg/dl

Bone marrow Biopsy

- Plasma cell neoplasm, comprising approximately 10% of marrow cellularity.
- Hypercellular marrow with trilineage hematopoiesis.
- CD138 stains plasma cells which are scattered or in aggregate and are lambda restricted.
- Flow Cytometry: Abnormal plasma cell population with cytoplasmic lambda light chain restriction with abnormal expression of CD27 (decreased) with normal expression of CD19, CD38 and CD138 without CD56 or CD117.
- Cytogenetics: no significant deletions or re-arrangement detected
- FISH: t(14:16), 1q gain

PET/CT



Treatment

- She completed 8 cycles of bortezomib, lenalidomide, dexamethasone (VRd) with a response of VGPR
- Although stem cell harvest was completed. Patient opted to hold off on transplant and save for further down the line
- EOT BMBx: without evidence of plasma cell population-MRD+. Myeloid hyperplasia noted
- EOT PET/CT showed new FDG avid soft tissue densities on right breast. Breast ultrasound showed 3 masses on right breast concerning for malignancy. Breast biopsy pathology revealed TNBC invasive ductal carcinoma.

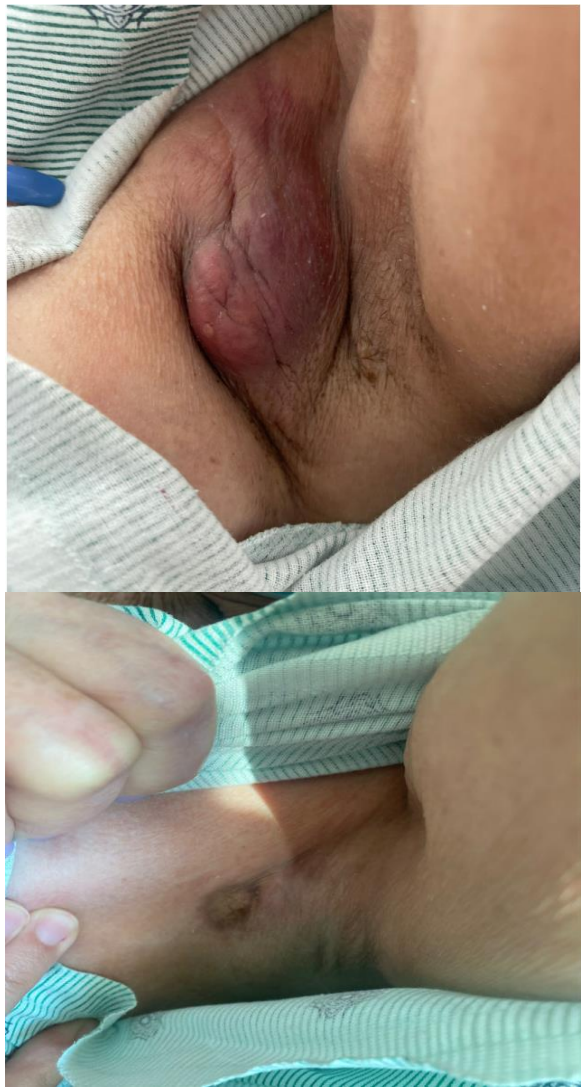
Stage 2 TNBC

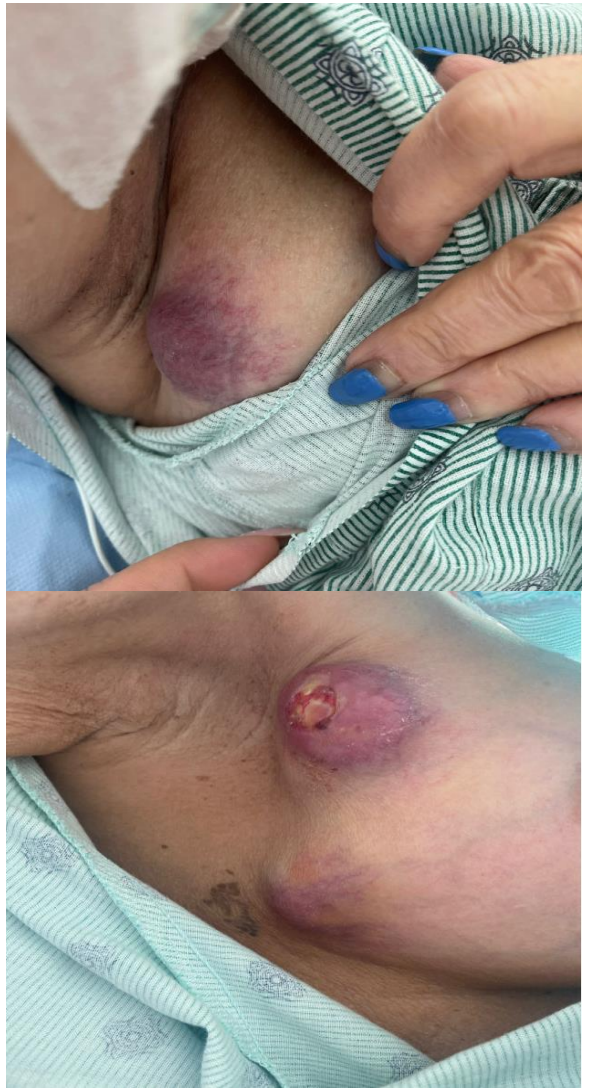
- After receiving one cycle of lenalidomide maintenance. It was stopped to prioritize, curative intent treatment for breast cancer starting with neoadjuvant therapy.
- She was treated with keynote 522, and received pembro-AC.
- As she started pembro-CbT, decision was made that her myeloma was flaring (presentation of new plasmacytomas) and she needed to stop breast NACT and restart myeloma directed treatment and proceeded with 2 cycles of therapy with daratumumab, carfilzomib, dexamethasone (DKd) and pembrolizumab.

Progression and complications

- After cycle 2 of DKd she was admitted to the hospital for acute compression of the spinal cord with numbness and decreased power of her lower extremities at the beginning, requiring T5-T7 laminectomy (pathology resulted on high grade metastatic myeloma).
- Imaging showed wide-spread abdominal tumor deposits including a large pelvic soft tissue mass, biopsy consistent with plasma cell myeloma.
- Started radiation therapy for symptomatic plasmacytomas and plans for third line treatment

Disease progression





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Repeat Biopsy

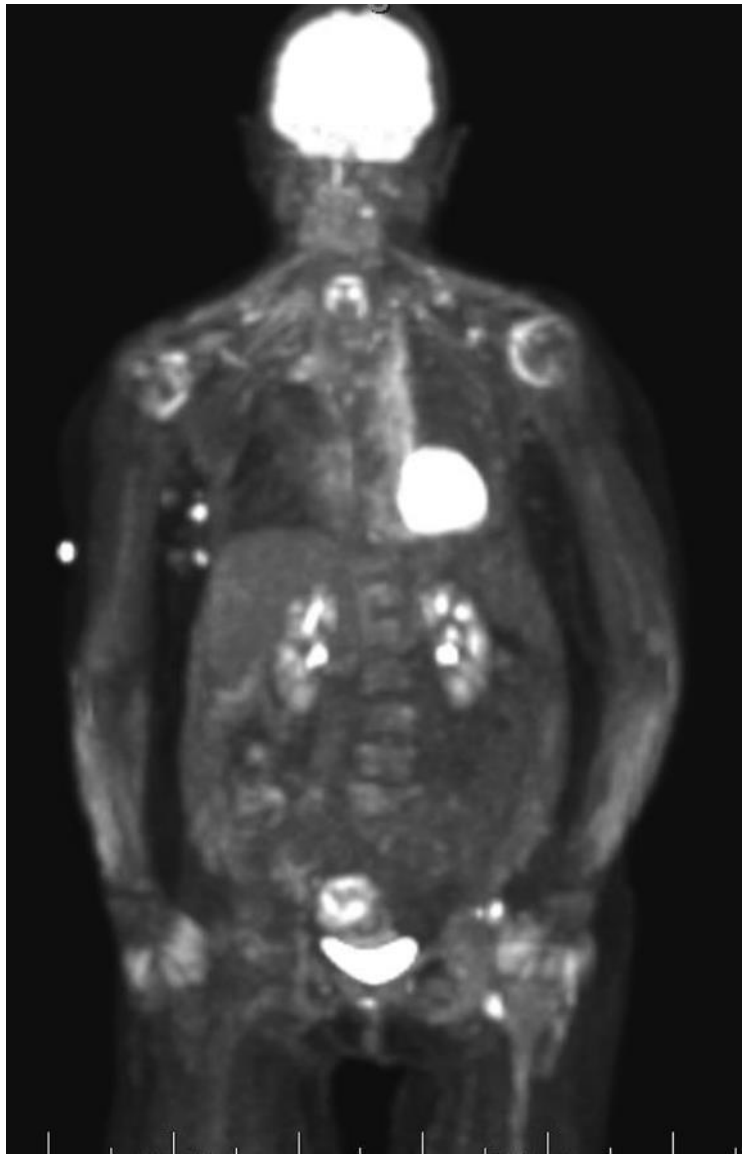
- Superficial tumors were proven to be plasmacytomas by pathology
- Bone marrow biopsy consistent with anaplastic plasma cells
- Patient was very symptomatic and DKd therapy resulted in a mixed response at best.
- Decision was made to “debulk her” with cytotoxic chemotherapy and “immuno-consolidate” with the bispecific T cell directing antibody, teclistamab which had just been FDA approved

Teclistamab

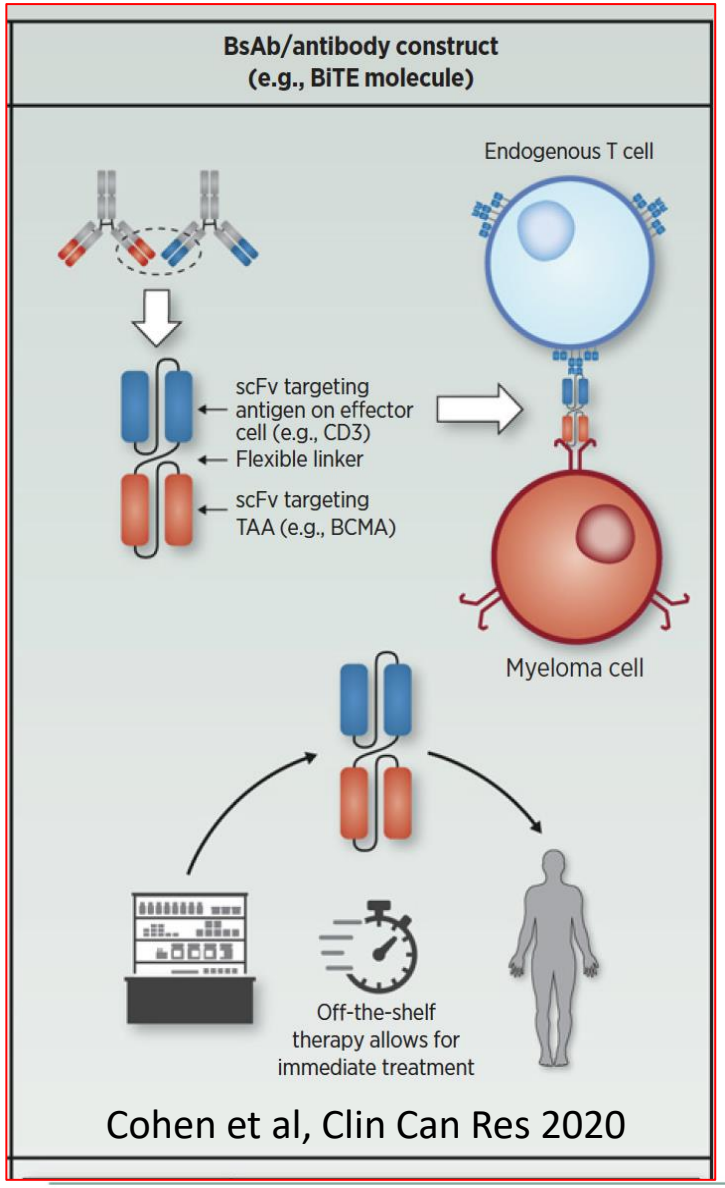
- She received 2 cycles of EPOCH inpatient with significant tumor reduction and was then started on teclistamab
- She received 2 step up doses and 1 full treatment dose of tec over a week inpatient and subsequently moved to weekly treatments as an outpatient
- She immediately reported less pain and reduction of her multiple tumors
- As her myeloma had become anaplastic and mostly extramedullary in manifestation and oligosecretory, myeloma labs not correlated with disease.

Teclistamab Response

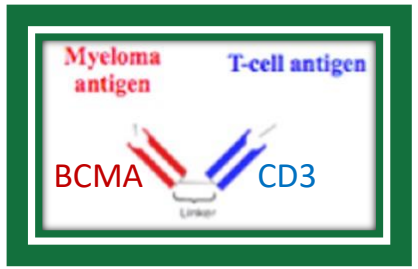
- After 2 cycles of teclistamab, PET/CT:
  - Interval significant improvement of previously seen multiple hypermetabolic osseous lesions
  - Redemonstration of hypermetabolic soft tissue lesions within the right breast overlying the breast implant with two new lesions as detailed above. These findings may represent myelomatous involvement or a second primary, consider tissue sampling if clinically indicated.
- Patient currently being reevaluated for mastectomy at which time pathology of lesions will be evaluated



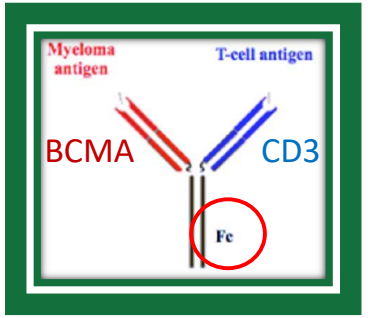
Discussion: BiSpecific T cell directing antibodies



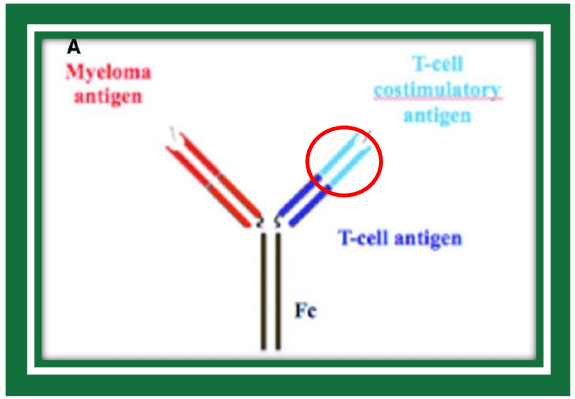
Cohen et al, Clin Can Res 2020



BiTE: Bispecific T cell Engager, AMG401
Short half-life



Bispecific Antibody: incorporation of Fc domain to extend half-life



Trispecific Antibodies: incorporation of both T cell antigen and costimulatory domain

Teclistamab, Furthest Developed Bispecific Ab Representative

The NEW ENGLAND JOURNAL of MEDICINE

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ORIGINAL ARTICLE

Teclistamab in Relapsed or Refractory Multiple Myeloma

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Study Design: Phase 1/2

- A BCMA x CD3 BiSAb
- Weekly teclistamab after step-up doses
- Primary end point was ORR

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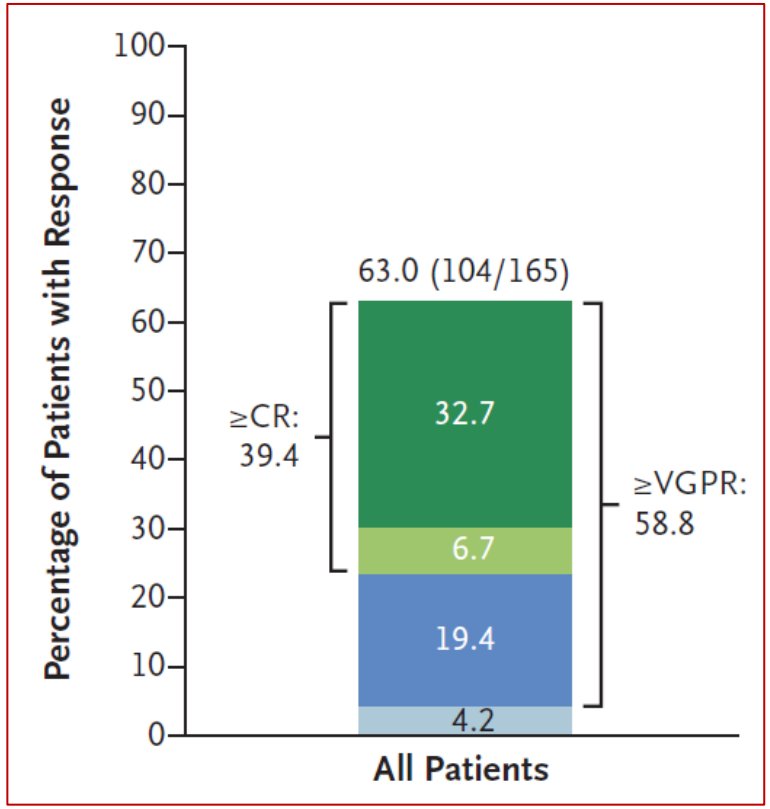
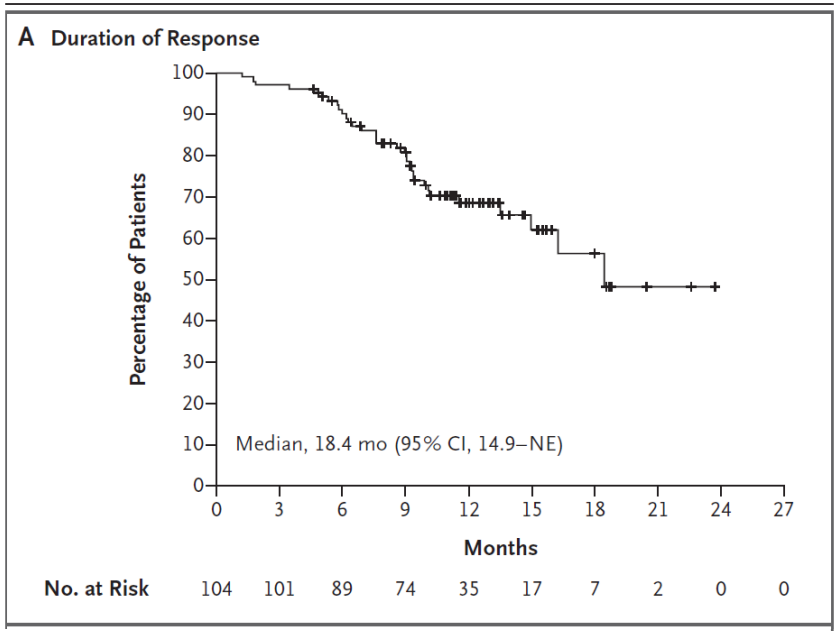
Table 1. Characteristics of the Patients at Baseline.

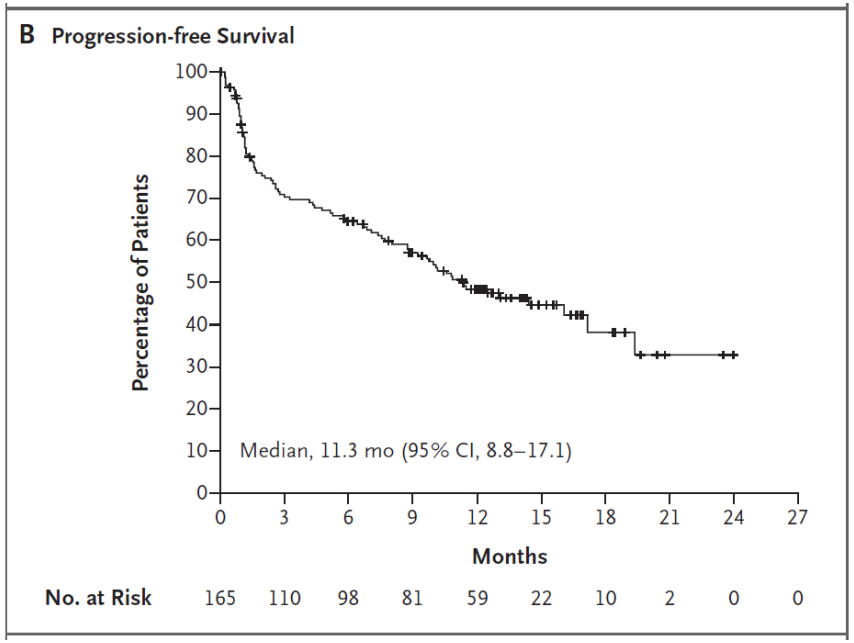
Characteristic	Phase 1 (N=40)	Phase 2 (N=125)	Total (N=165)
Age			
Median (range) — yr	62.5 (39.0–84.0)	64.0 (33.0–83.0)	64.0 (33.0–84.0)
≥75 yr — no. (%)	5 (12.5)	19 (15.2)	24 (14.5)
Sex — no. (%)			
Male	26 (65.0)	70 (56.0)	96 (58.2)
Female	14 (35.0)	55 (44.0)	69 (41.8)
Race — no. (%)*			
White	34 (85.0)	100 (80.0)	134 (81.2)
Black	1 (2.5)	20 (16.0)	21 (12.7)
Asian	0	3 (2.4)	3 (1.8)
Other	5 (12.5)	2 (1.6)	7 (4.2)
Median time since diagnosis (range) — yr	5.6 (0.8–17.4)	6.2 (0.9–22.7)	6.0 (0.8–22.7)
≥1 Extramedullary plasmacytoma — no. (%)†	8 (20.0)	20 (16.0)	28 (17.0)
≥60% Plasma cells in bone marrow — no./total no. (%)	3/38 (7.9)	15/122 (12.3)	18/160 (11.2)
ECOG performance-status score — no. (%)‡			
0	17 (42.5)	38 (30.4)	55 (33.3)
≥1	23 (57.5)	87 (69.6)	110 (66.7)
International Staging System class — no./total no. (%)			
I	24/39 (61.5)	61/123 (49.6)	85/162 (52.5)
II	11/39 (28.2)	46/123 (37.4)	57/162 (35.2)
III	4/39 (10.3)	16/123 (13.0)	20/162 (12.3)
High-risk cytogenetic profile — no./total no. (%)	12/37 (32.4)	26/111 (23.4)	38/148 (25.7)
del(17p)	9/37 (24.3)	14/111 (12.6)	23/148 (15.5)
t(4:14)	4/37 (10.8)	12/111 (10.8)	16/148 (10.8)
t(14;16)	1/37 (2.7)	3/111 (2.7)	4/148 (2.7)
Median no. of lines of previous therapy (range)	5 (2–11)	5 (2–14)	5 (2–14)
Previous stem-cell transplantation — no. (%)	34 (85.0)	101 (80.8)	135 (81.8)
Previous therapy exposure — no. (%)			
Triple-class§	40 (100.0)	125 (100.0)	165 (100.0)
Penta-drug¶	26 (65.0)	90 (72.0)	116 (70.3)
Refractory status — no. (%)			
Immunomodulatory agent‖	38 (95.0)	114 (91.2)	152 (92.1)
Proteasome inhibitor**	34 (85.0)	108 (86.4)	142 (86.1)
Anti-CD38 monoclonal antibody††	39 (97.5)	109 (87.2)	148 (89.7)
Triple-class§	32 (80.0)	96 (76.8)	128 (77.6)
Penta-drug¶	16 (40.0)	34 (27.2)	50 (30.3)
Refractory to last line of therapy	33 (82.5)	115 (92.0)	148 (89.7)

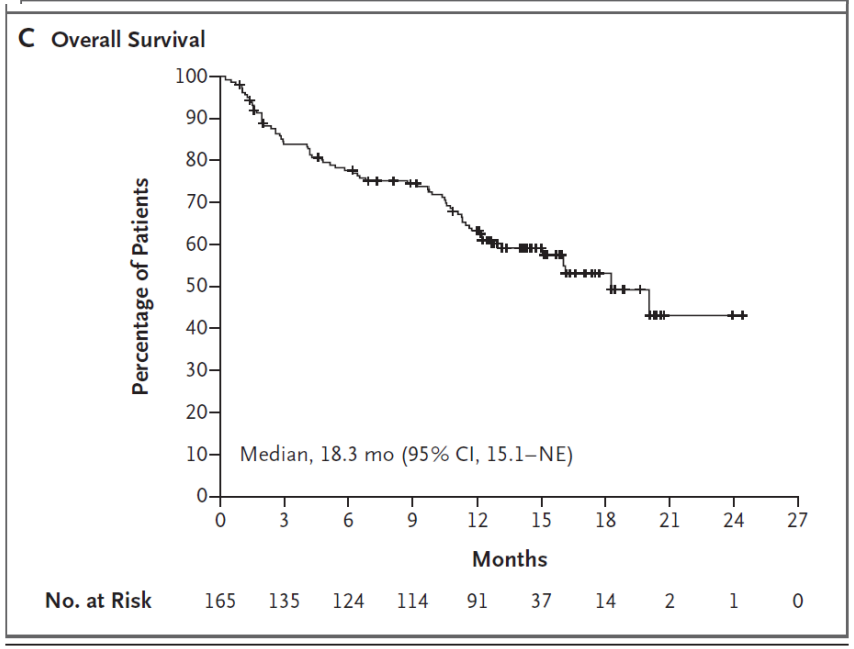
Teclistamab: Efficacy

- N=165;
- Follow up 14.1 months
- ORR 63%
- DoR 18.4 months
- MRD negativity rate 26.7%









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Teclistamab: Adverse Reactions

Table 2. Adverse Events in 165 Patients (Safety Population).*

Event	Any Grade	Grade 3 or 4
	no. of patients (%)	
Any adverse event	165 (100)	156 (94.5)
Hematologic		
Neutropenia	117 (70.9)	106 (64.2)
Anemia	86 (52.1)	61 (37.0)
Thrombocytopenia	66 (40.0)	35 (21.2)
Lymphopenia	57 (34.5)	54 (32.7)
Leukopenia	29 (17.6)	12 (7.3)
Nonhematologic		
Diarrhea	47 (28.5)	6 (3.6)
Fatigue	46 (27.9)	4 (2.4)
Nausea	45 (27.3)	1 (0.6)
Injection-site erythema	43 (26.1)	0
Pyrexia	45 (27.3)	1 (0.6)
Headache	39 (23.6)	1 (0.6)
Arthralgia	36 (21.8)	1 (0.6)
Constipation	34 (20.6)	0
Cough	33 (20.0)	0
Pneumonia	30 (18.2)	21 (12.7)
Covid-19	29 (17.6)	20 (12.1)
Bone pain	29 (17.6)	6 (3.6)
Back pain	27 (16.4)	4 (2.4)
Cytokine release syndrome†	119 (72.1)	1 (0.6)
Neurotoxic event	24 (14.5)	1 (0.6)

Infections were frequent: 76.4%; Grade 3 or 4, 44.8%)

Efficacy Data of Bispecific Antibodies in Early Development

Table 1. Efficacy of selected bispecific therapies (Abbreviations: CR, complete response; DoR, duration of response; IMiD, immunomodulatory drug; MTD, maximum tolerated dose; NA, not reported; NR, not reached; ORR, overall response rate; PI, proteasome inhibitor; Q, every; RP2D, recommended phase 2 dose; W, week).

Drug	Target	Sponsor	Phase (Total N)	Design	Dosage: MTD/RP2D (*n*)	Eligibility	Patient characteristics	ORR (@RP2D)	CR	Median DoR, months	6-Month DoR
ABBV-383 (TNB-383B) [31]	BCMA	AbbVie	I (103)	Infusion Q3W; 0.025–120 mg dose range	60 mg q3W (44 ≥ 40mg)	Inclusion: ≥3 prior lines (PI, IMiD, anti-CD38) Exclusion: Prior BCMA therapy	Median age: 67 years High risk: NA Median # of prior lines: 5	64%	16%	NA	NA
Alnuctamab (CC-93269) [32]	BCMA	Celgene	I (19)	Step-up dosing Q1W; 0.15–10 mg dose range	≥6 mg (12)	Inclusion: ≥3 prior lines Exclusion: Prior BCMA therapy	Median age: 67 years High risk: NA Median # of prior lines: 6	83%	33%	NA	NA
Elranatamab (PF-06863135) [23]	BCMA	Pfizer	I (58)	Step-up dosing Q1W or Q2W SC; 0.08–1 mg/kg dose range	0.215–100 mg/kg (20)	Inclusion: NA Exclusion: NA	Median age: NA High risk: NA Median # of prior lines: 6	70%	30%	NR	92.3%
Linvoseltamab (REGN 5458) [29]	BCMA	Regeneron	I (68)	Infusion Q1W→Q2W; 3–400 mg dose range	96/200 mg (15)	Inclusion: prior PI, IMiD, anti-CD38) Exclusion: NA	Median age: 64 years High risk: 23.5% Median # of prior lines: 5	73.	48%	≥ 8.4	92.1% (8-month)
Pacanalotamab (AMG 420) [16]	BCMA	Amgen	I (42)	Continuous Infusion 4 W on, 2 W off; 0.2 ug-700 ug/day dose range	400 mg/d (10)	Inclusion: ≥2 prior lines (PI & IMiD) Exclusion: PCL, EMD, CNS disease, allogeneic SCT	Median age: 65 years High risk: 33% Median # of prior lines: 5	70%	50%	≥ 8	NA
Pavurutamab (AMG 701) [21]	BCMA	Amgen	I (75)	Step-up Infusion Q1W; 0.14–12 mg dose range	3–12 mg (45)	Inclusion: ≥3 prior lines (PI, IMiD, anti-CD38) Exclusion: EMD, CNS, allogeneic SCT, prior BCMA	Median age: 63 years High risk: NA Median # of prior lines: 6	36%	9%	≥3.8	NA
Teclistamab (JNJ-64007957) [60]	BCMA	Janssen	II (165)	2 step-up SC doses Q1W	1.5 mg/kg (165)	Inclusion: ≥3 prior lines (PI, IMiD, anti-CD38) Exclusion: prior BCMA	Median age: 64 years High risk: 26% Median # of 5 prior lines:	63%	39%	18.4	90%
Talquetamab (JNJ-64407564) [34]	GPRC5D	Janssen	I (95)	Step-up dosing Q1W or Q2W SC; 5–800 ug/kg dose range	405 ug/kg QW (30) 800 ug/kg Q2W (17)	Inclusion: no available therapies Exclusion: prior BCMA allowed	Median age: 62/60 years High risk: NA Median # of prior lines: NA	70% (QW) 71% (Q2W)	NR	NR	67% NR
Cevostamab (RG6160) [39]	FcRH5	Roche	I (160)	Step-up dosing Q1W or Q2W SC	90 mg QW 160 mg QW	Inclusion: no available therapies Exclusion: NA	Median age: 64 years High risk: NA Median # of prior lines: 6	37% 55%	NA	15.6	NA

Division

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Safety Data of Bispecific Antibodies in Early Development

Table 2. Safety of Selected Bispecific Therapies (Abbreviations: CRS, cytokine release syndrome; ICANS, immune effector cell associated neurotoxicity syndrome; NA, not reported).

	CRS		ICANS	Infections		Neutropenia	Peripheral neuropathy	
Drug	All grade	Grade ≥3	All grade	All grade	Grade ≥3	All grade	All grade	Grade ≥3
ABBV-383 (TNB-383B) $N = 103$	52%	2%	NA	28%	NA	17%	NA	NA
Alnuctamab (CC-93269) $N = 19$	90%	5%	NA	NA	26%	53% (Grade 3/4)	NA	NA
Elranatamab (PF-06863135) $N = 58$	83%	0	NA	NA	NA	64%	NA	NA
Linvoseltamab (REGN 5458) $N = 68$	38%	0	NA	NA	NA	16%	0	0
Pacanalotamab (AMG 420) $N = 42$	38%	2%	NA	33%	24%	NA	5%	5%
Pavurutamab (AMG 701) $N = 75$	61%	7%	8%	NA	17%	23%	8%	NA
Teclistamab (JNJ-64007957) $N = 165$	72%	1%	15%	76%	45%	71%	NA	NA
Talquetamab (JNJ-64407564) $N = 95$	73% (weekly) 78% (biweekly)	3% (weekly) 0 (biweekly)	NA	37% 13%	3% 4%	67% 44%	NA	NA
Cevostamab (RG6160) $N = 160$	80%	1%	13%	43%	19%	18%	NA	NA

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Summary and conclusions

- Complicated case with a patient dealing with three different malignancies. Prioritizing which malignancy to treat was at the utmost importance
- Teclistamab use has thus far showed promising results in this aggressive case of multiple myeloma
- The use of teclistamab has provided enough disease control, to allow the patient to resume breast cancer management
- Bi-Specific T cell directing antibodies has significantly changed the landscape of myeloma treatment

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