Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Hematologic Malignancies

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AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE CHAMPION OF THE EMERGENCY PHYSICIAN

ACCC Association of Community Cancer Centers

HOPA Hematology/Oncology Pharmacy Association

Society for Immunotherapy of Cancer

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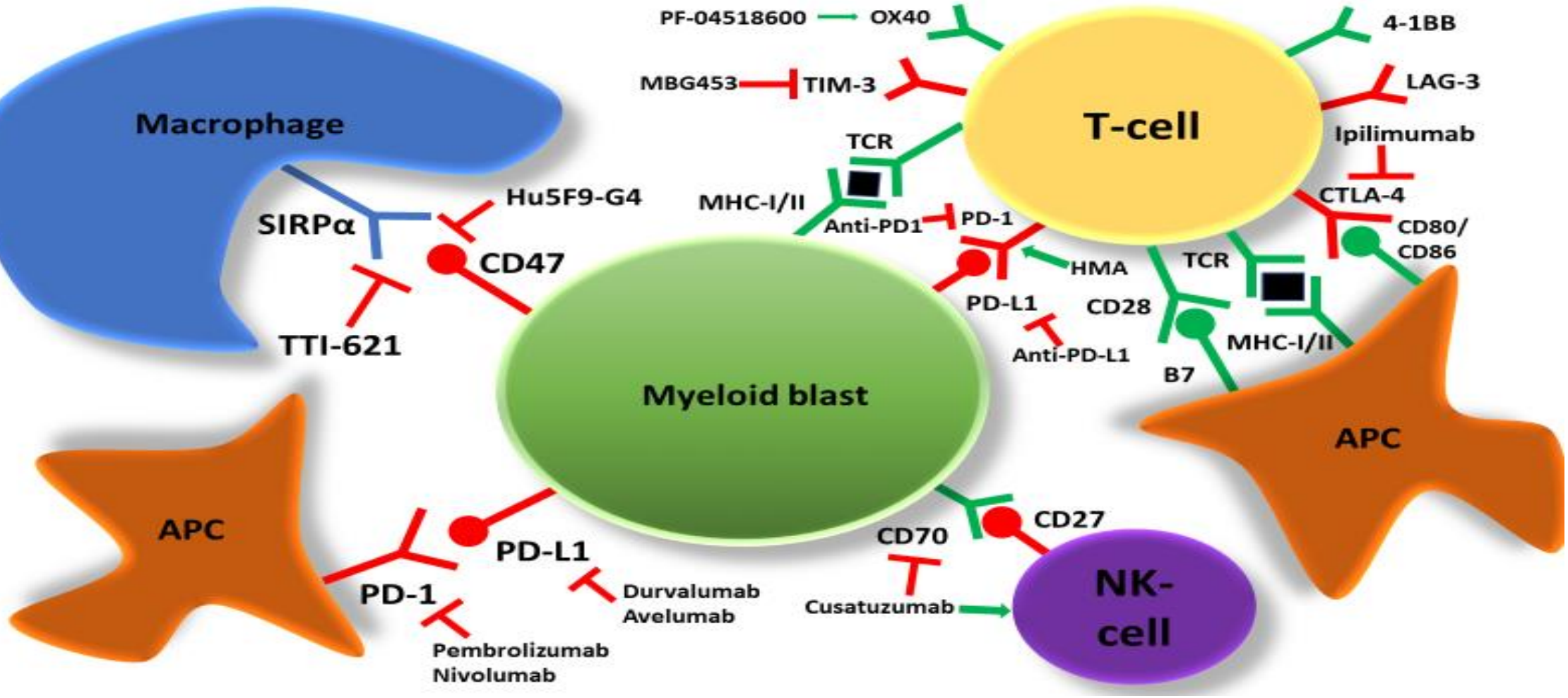
Disclosures

- Consulting Fees: Celgene/BMS, Abbvie, Pfizer, Boehringer-Ingehleim, Trovagene, Incyte, Takeda, Novartis, Otsuka, Jazz, Agios, Acceleron, Astellas, Daiichi Sankyo, Cardinal Health, Taiho, Seattle Genetics, BeyondSpring, Ionis, Epizyme
- Contracted Research: Celgene/BMS, Abbvie, Astex, Pfizer, Medimmune/AstraZeneca, Boehringer-Ingelheim, Trovagene, Incyte, Takeda, Novartis, Aprea, ADC Therapeutics
- I will be discussing non-FDA approved indications during my presentation.

Outline: Major immunotherapies under development

- Immune checkpoint inhibitors
- Antibody-drug conjugates
- Bispecifics
- Cellular therapies

Interaction of leukemic blasts and immune cells in the bone marrow niche as targets for immune checkpoint-mediated therapy



Green: Stimulatory **Red: Inhibitory**

Bewersdorf J, Shallis R, and Zeidan A et al, Blood Reviews, 2020

FDA approved indications of immune checkpoint inhibitors in United States

Squamous Cell Head & Neck Cancer
1L/2L nivolumab after platinum chemotherapy
1L/2L pembrolizumab after platinum chemotherapy

Malignant Melanoma
Adjuvant/1L ipilimumab
1L nivolumab ± ipilimumab
Adjuvant nivolumab
1L pembrolizumab

Merkel Cell Carcinoma
2L avelumab

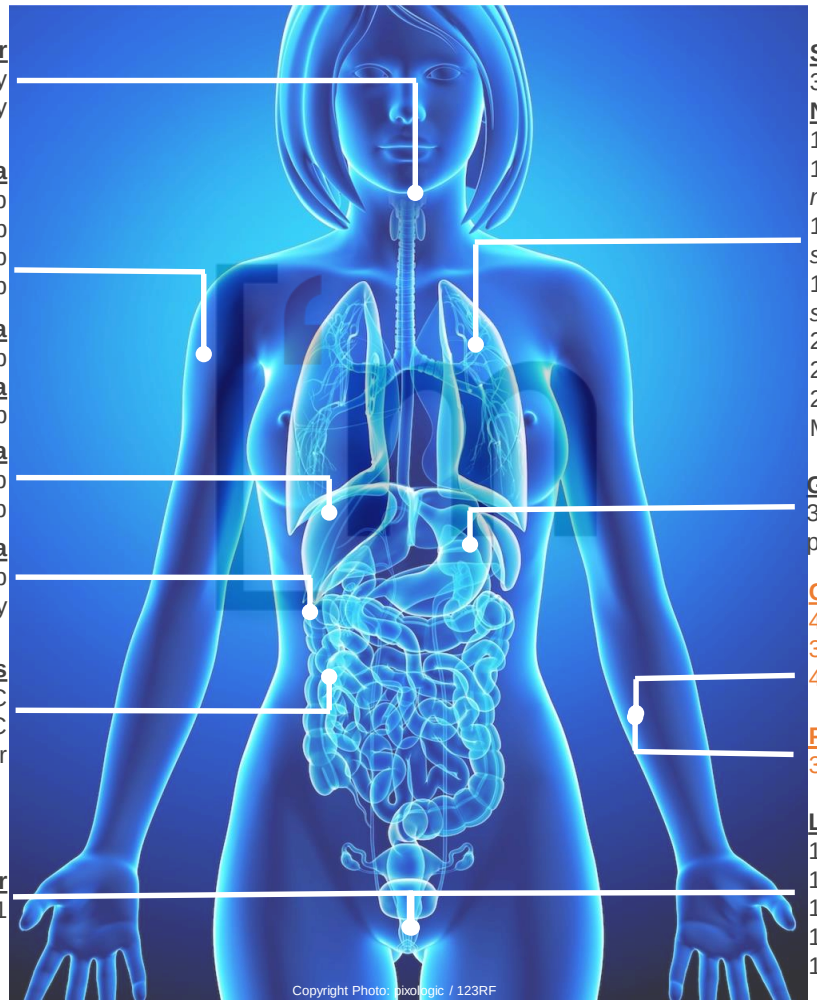
Cutaneous Squamous Cell Carcinoma
1L cemiplimab

Hepatocellular Carcinoma
2L nivolumab after sorafenib
2L pembrolizumab after sorafenib

Adv. Renal Cell Carcinoma
1L nivolumab plus ipilimumab
2L nivolumab after anti-angiogenic therapy

MSI-H or dMMR Cancers
2L nivolumab in CRC
2L nivolumab plus ipilimumab in CRC
2L pembrolizumab in any MSI-H/dMMR cancer

Cervical Cancer
2L pembrolizumab CPS≧1



Small Cell Lung Cancer
3L nivolumab

Non-Small Cell Lung Cancer
1L pembrolizumab TPS≧50%
1L pembrolizumab + pemetrexed & platinum-salt in *non-squamous* NSCLC
1L pembrolizumab + carboplatin & (nab-)paclitaxel in *squamous* NSCLC
1L atezolizumab + bevacizumab, paclitaxel & carboplatin in *non-squamous* NSCLC
2L pembrolizumab TPS≧1%
2L nivolumab
2L atezolizumab
Maintenance durvalumab after chemoradiation

Gastric & GEJ Carcinoma
3L pembrolizumab after fluoropyrimidine- and platinum-chemotherapy +/- HER2 therapy & CPS≧1

Classical Hogdkin Lymphoma
4L pembrolizumab
3L nivolumab after auto-HSCT and BV
4L nivolumab and after auto-HSCT

PMBCL
3L pembrolizumab

Locally Adv. or Met. Urothelial Cancer
1L/2L nivolumab after platinum chemotherapy
1L/2L pembrolizumab
1L/2L atezolizumab after platinum chemotherapy
1L/2L avelumab after platinum chemotherapy
1L/2L durvalumab after platinum chemotherapy

Updated on 11-Dec-2018. Medi-paper.com

FDA-approved checkpoint inhibitors: lymphoma

Drug	Indication	Dose
Nivolumab	Classical **Hodgkin lymphoma**, relapsed after HSCT and brentuximab vedotin or ≥3 previous therapies	240 mg Q2W or 480 mg Q4W
Pembrolizumab	Adult/pediatric refractory classical **Hodgkin lymphoma** or relapsed after 3 previous therapies	200 mg Q3W or 400 mg Q6W adults 2 mg/kg (up to 200 mg) Q3W (pediatric)
Pembrolizumab	Adult/pediatric refractory **primary mediastinal large B-cell lymphoma** or relapsed after 2 previous therapies**	200 mg Q3W or 400 mg Q6W adults 2 mg/kg (up to 200 mg) Q3W (pediatric)

**Not recommended for patients with PBMCL that require urgent cytoreductive therapy.

Efficacy of approved checkpoint inhibitors: lymphoma

Study	Treatment	Patient population	Overall response rate	Complete response rate	Landmark OS
CheckMate 205	Nivolumab	Brentuximab vedotin-naïve **cHL**	65%	29%	1-year: 92%
		Bretuximab vedotin after auto-HCT **cHL**	68%	13%	1-year: 93%
		Bretuximab vedotin before/after auto-HCT **cHL**	73%	12%	1-year: 90%
KEYNOTE-087	Pembrolizumab	**cHL** progressed after ASCT and BV	78.3%	26%	3-year: 86.3%
		cHL after salvage chemo and BV, ineligible for ASCT	64.2%	26%	3-year: 85.7%
		cHL progressed after ASCT without BV treatment	71.7%	31.7%	3-year: 87.6%
KEYNOTE-013	Pembrolizumab	**PMBCL** with relapse/ineligible for ASCT	48%	33%	1-year: 65%
KEYNOTE-170	Pembrolizumab	**PMBCL** ineligible for ASCT with progression on ≥ 2 previous therapies	45%	13%	1-year: 58%

cHL: Classical Hodgkin lymphoma; PMBCL: primary mediastinal B cell lymphoma

Armand, J Clin Oncol 2018; Zinzani, ASH 2019.

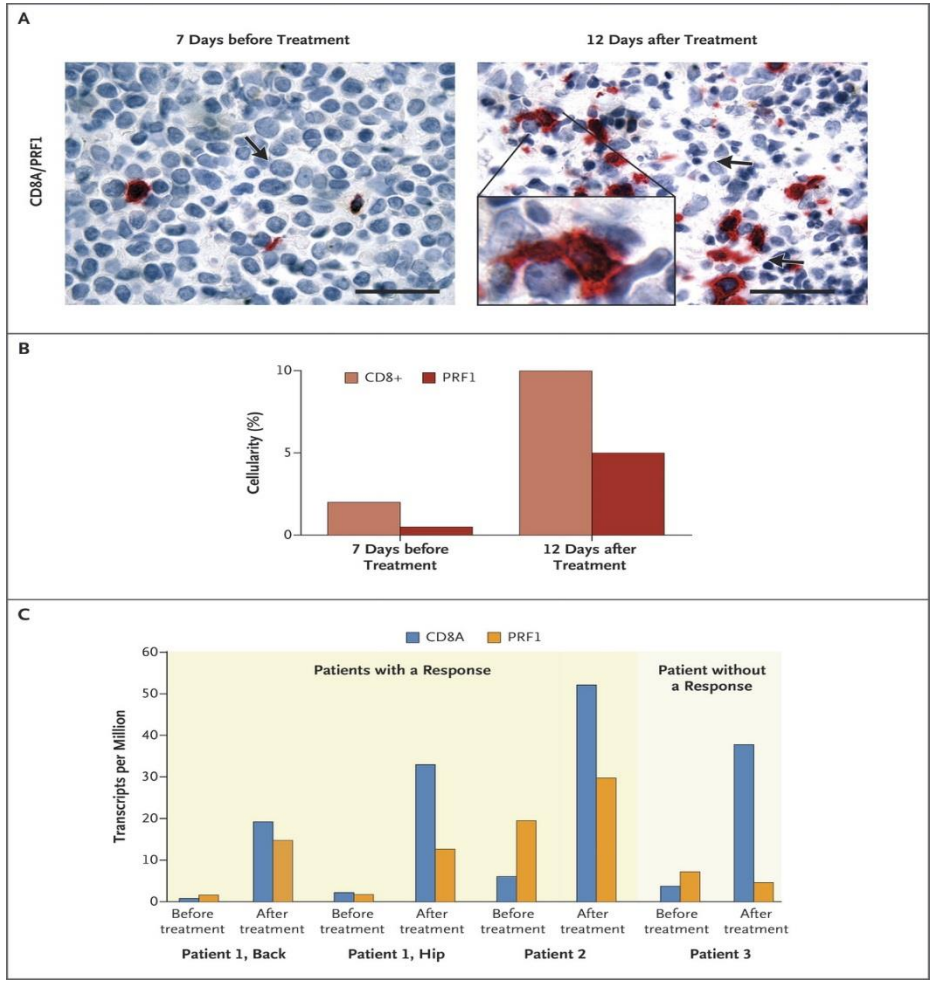
In development: Immune checkpoint inhibitors in AML

Study	Population	Treatment(s)	ORR	Median OS (months)	Status
NCT02775903	Untreated AML	Azacitidine + durvalumab	20%	13.0	Active, not recruiting
		Azacitidine	23%	14.4	
NCT02397720	Relapsed/refractory AML	Azacitidine + nivolumab	33%	6.4	Recruiting
		Azacitidine + nivolumab + ipilimumab	44%	10.5	
NCT02768792	Relapsed/refractory AML	HiDAC followed by pembrolizumab	46%	8.9	Active, not recruiting
NCT02845297	Relapsed/refractory AML	Azacitidine + pembrolizumab	31%	10.8	Recruiting
	Newly diagnosed AML, ≥ 65 years of age		70.5%	13.1	

ASH 2019: Zeidan, Daver, Zeidner, Gojo.

Ipilimumab for Relapsed Hematologic Malignancies after AlloHSCT: A Multicenter Phase I/Ib Study

- 28 patients following allo-SCT; AML=12
- Ipilimumab at: 3 mg/Kg or 10 mg/Kg, every 3 weeks
- Median time from allo-SCT was 19.3 months (late postSCT)
- Efficacy in patients at the higher dose level (5/13 AML CR, median: 3 prior Rx)
- Extramedullary AML more sensitive?
- 6 (23%) cases of immune AE, 1 death



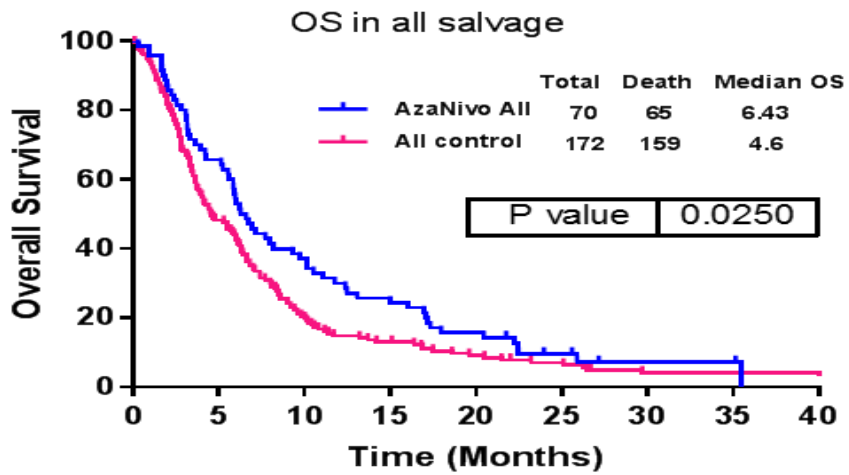
Matthews D et al , NEJM July 2016

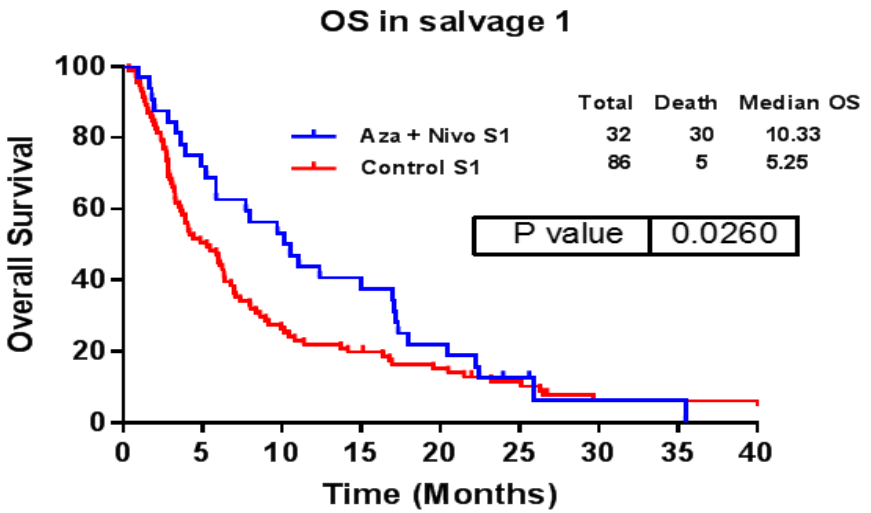
Azacitidine + Nivolumab in Relapsed AML
A Phase Ib/II Study: Responses and survival

Table 2. Best response for azacitidine + nivolumab patients ($N = 70$) and for historic HMA-based clinical trial control ($N = 172$)

	N (%); median (range)	
Best response	Azacitidine/nivolumab	Control
Overall response rate	23 (33)	35 (20)
CR	4 (6)	17 (10)
CRi/CRp	11 (16)	15 (9)
PR	1 (1)	1 (1)
HI[a] (6 months+)	7 (10)	2 (1)
Stable disease (6 months+)[b]	6 (9)	NA
Nonresponders	41 (58)	131 (76)
Median cycles to response	2 (1–13)	2 (1–6)
Median follow-up, in months	13.3 (8.2–25.5)	51 (0.1–64.8)

- How does this compare to HMA's in R/R AML?
  - Single agent Aza/Dec (n=670) in HMA-naïve pts- ORR = 23%, CR/CRi rate = 16%[2]
  - Aza/Dec + Ven: CR/CRi 21%[3]

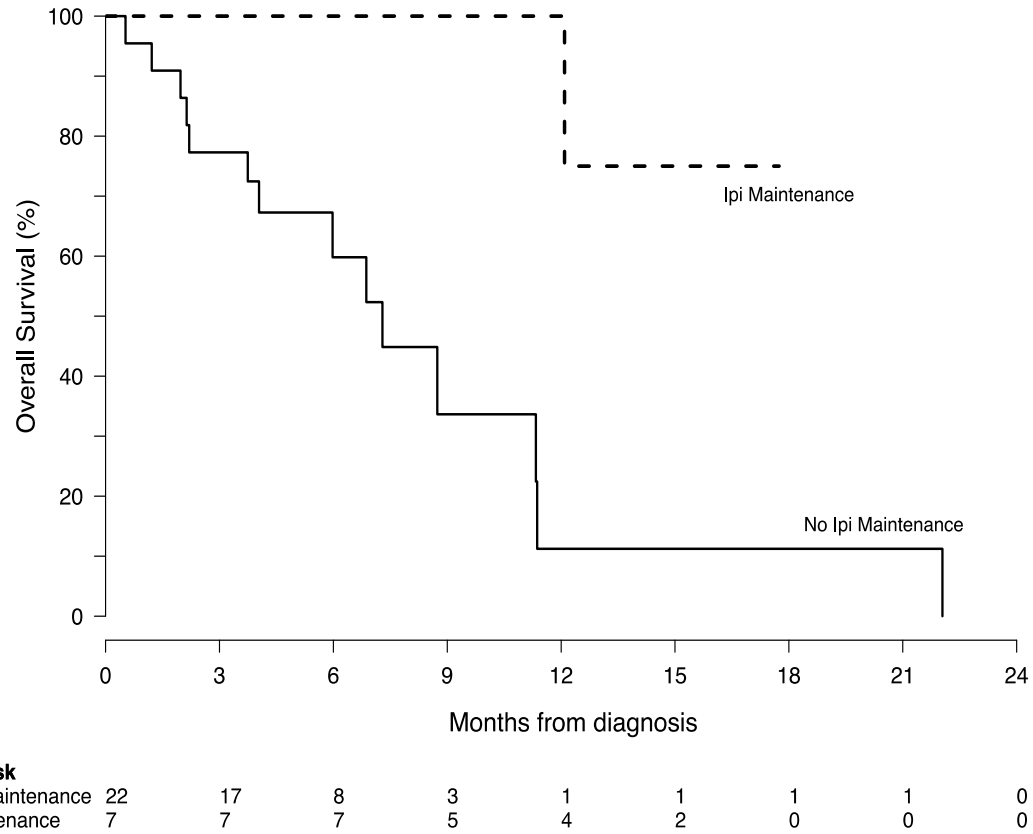




Daver N, et al. Cancer Discovery 2018. 2. Stahl M,,, Zeidan A, Blood Advances 2018. 3. DiNardo, Am J Hematol 2018

Ipilimumab can cause prolonged disease stabilization in some patients with refractory MDS

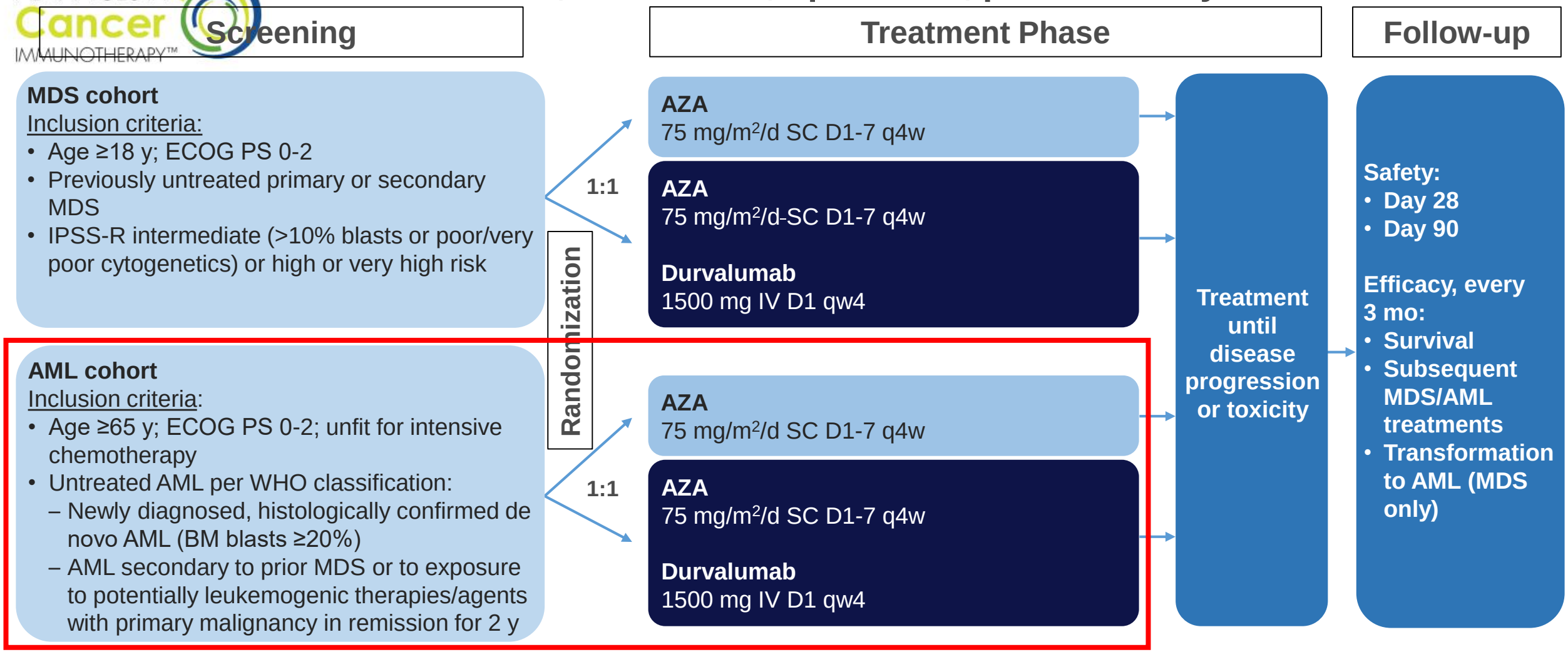
- 29 pts from Yale and 5 other centers
- DL1 (3mg/kg): 3 of 6 pts had G2-4 IRAEs
- DL2 (10mg/kg): 4 of 5 pts had G2-4 IRAEs
- DL1 expanded with no G2-4 IRAEs reported in 18 additional patients.
- All IRAEs were reversible with drug discontinuation or systemic steroids.
- Best responses: mCR in one patient (3.4%). Prolonged stable disease (PSD) for ≥46 weeks (7 pts including 3 with > 1 year).
- 5 pts underwent alloBMT without excessive toxicity.
- Median survival for the group was 9.8 months (294 days, 95%CI, 240-671+).



Zeidan A et al, Clinical Cancer Research, 2018

Fusion HR-MDS/Older AML 001 study (NCT02775903)

Randomized, multicenter, open-label, phase 2 study



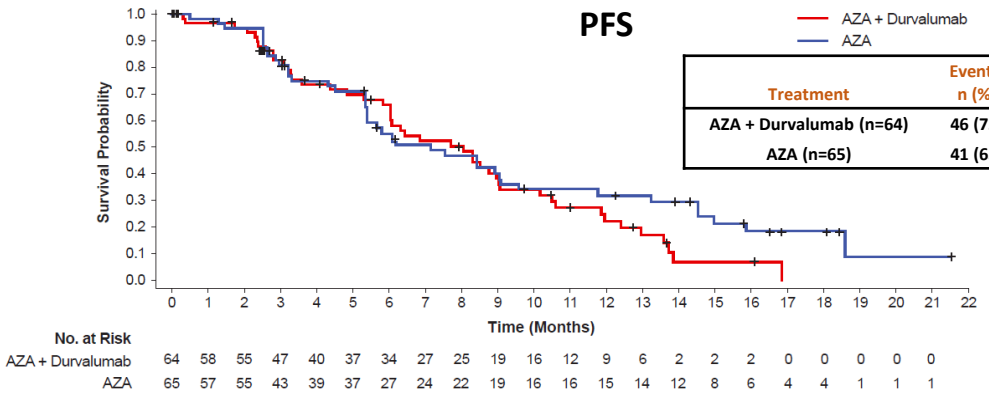
- Last patient randomized: MDS, October 30, 2017; AML, September 29, 2017. Data cutoff: October 31, 2018

BM, bone marrow; ECOG, Eastern Cooperative Oncology Group; IPSS-R, Revised International Prognostic Scoring System; PS, performance status; SC, subcutaneous; WHO, World Healath Organization.

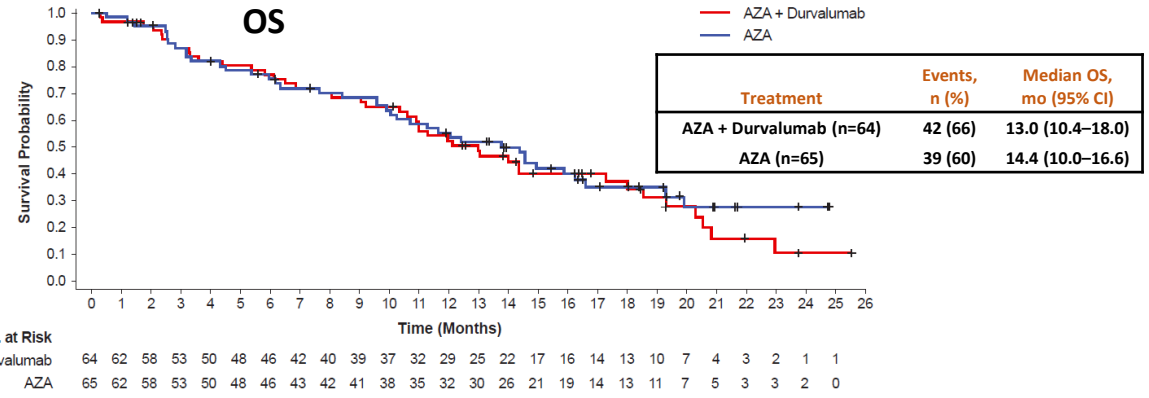
Zeidan AM et al., ASH 2019; Abstract #829

Fusion 001: Response and survival, AML Cohort (ITT Population*)

Response, n (%) [95% CI]	AZA + Durvalumab		AZA
	n=64		n=65
ORR (CR + CRi)	20 (31.3) [19.9, 42.6]		23 (35.4) [23.8, 47.0]
		P=0.6180	
CR	11 (17.2) [7.9, 26.4]		14 (21.5) [11.5, 31.5]
CRi	9 (14.1) [5.6, 22.6]		9 (13.8) [5.5, 22.2]
PR	4 (6.3) [0.3, 12.2]		2 (3.1) [0, 7.3]
SD	23 (35.9)		21 (32.3)
PD	3 (4.7)		3 (4.6)
NE/Missing,† n (%)	12 (18.8)		15 (23.1)



Treatment	Events, n (%)	Median PFS, mo (95% CI)
AZA + Durvalumab (n=64)	46 (72)	8.1 (6.1–9.0)
AZA (n=65)	41 (63)	7.2 (5.4–9.1)



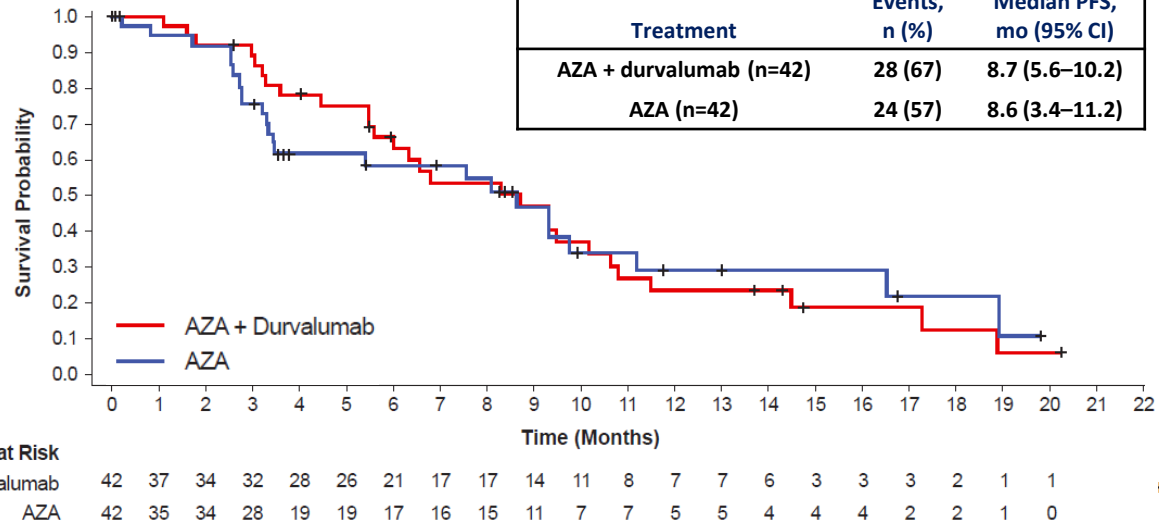
Treatment	Events, n (%)	Median OS, mo (95% CI)
AZA + Durvalumab (n=64)	42 (66)	13.0 (10.4–18.0)
AZA (n=65)	39 (60)	14.4 (10.0–16.6)

Zeidan AM et al., ASH 2019; Abstract #829

PFS and OS in patients with MDS (ITT POPULATION)

Progression-Free Survival*

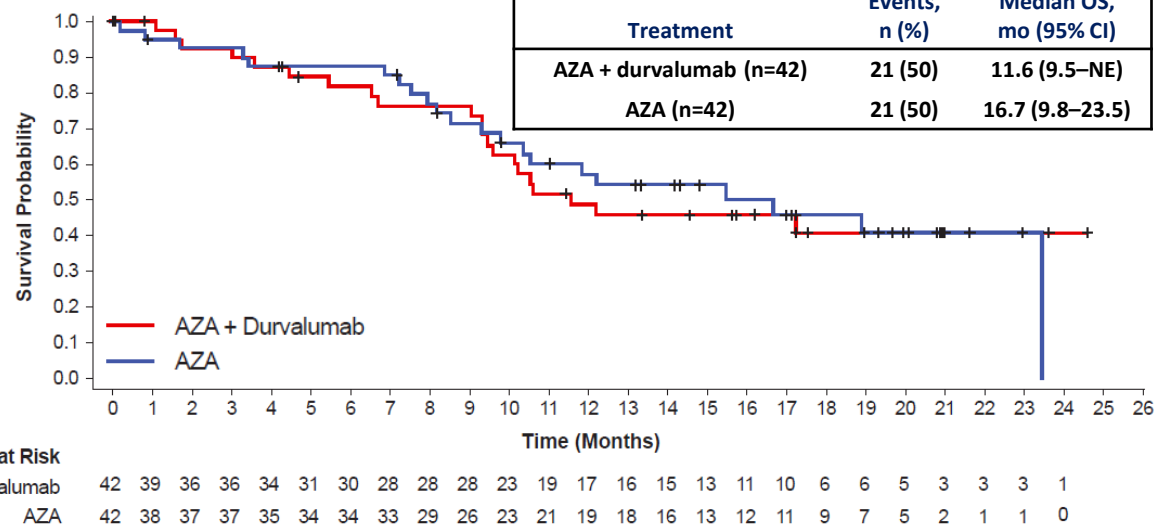
Treatment	Events, n (%)	Median PFS, mo (95% CI)
AZA + durvalumab (n=42)	28 (67)	8.7 (5.6–10.2)
AZA (n=42)	24 (57)	8.6 (3.4–11.2)



No. at Risk																				
AZA + Durvalumab	42	37	34	32	28	26	21	17	17	14	11	8	7	7	6	3	3	3	2	1	1
AZA	42	35	34	28	19	19	17	16	15	11	7	7	5	5	4	4	4	2	2	1	0

Overall Survival†

Treatment	Events, n (%)	Median OS, mo (95% CI)
AZA + durvalumab (n=42)	21 (50)	11.6 (9.5–NE)
AZA (n=42)	21 (50)	16.7 (9.8–23.5)



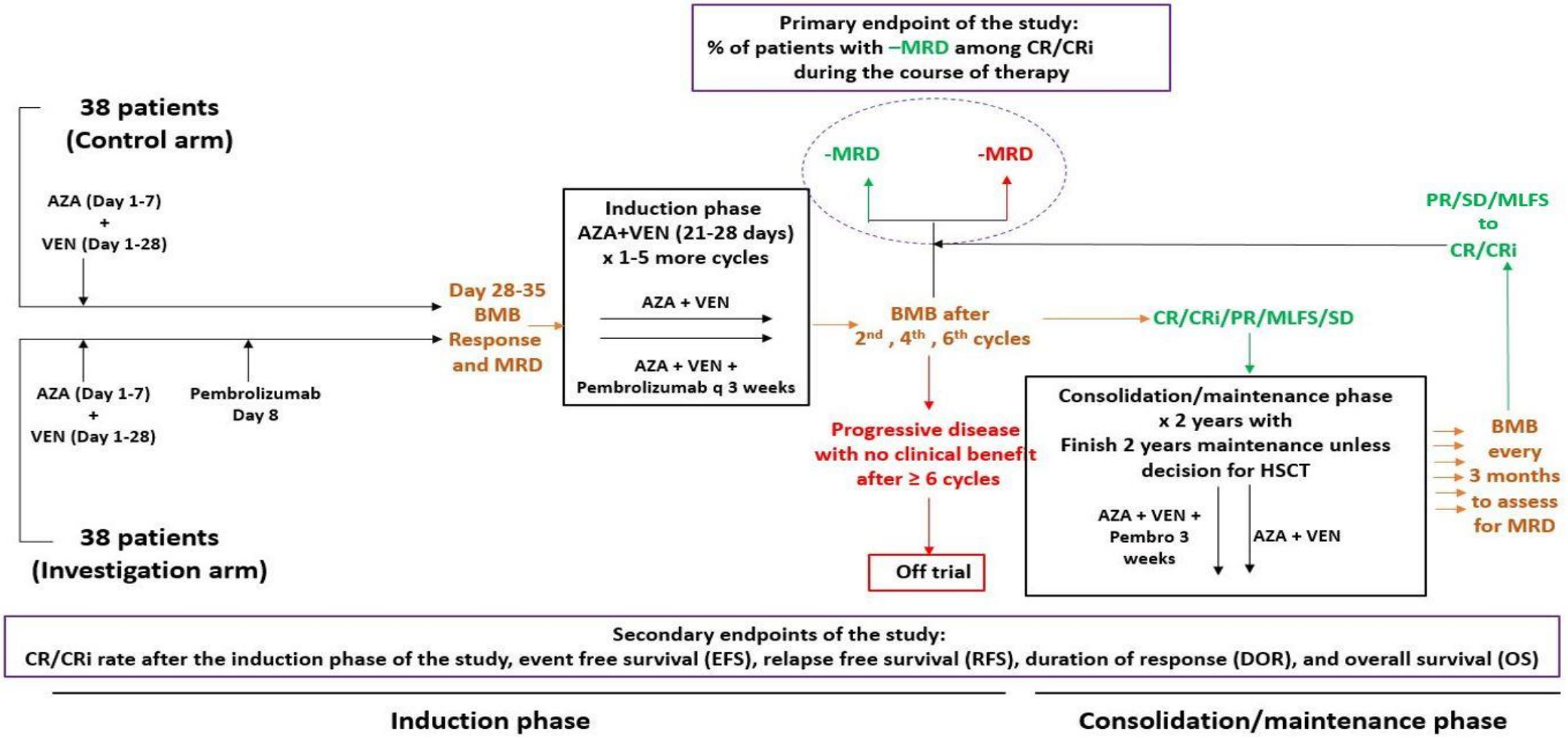
No. at Risk																									
+ Durvalumab	42	39	36	36	34	31	30	28	28	28	23	19	17	16	15	13	11	10	6	6	5	3	3	3	1
AZA	42	38	37	37	35	34	34	33	29	26	23	21	19	18	16	13	12	11	9	7	5	2	1	1	0

- Caution should be used when interpreting results because of the high number of censored patients

*Approximately 33% (combination therapy) and 43% (monotherapy) of patients censored.
†Approximately 50% of patients censored.
Data cutoff: October 31, 2018.

Zeidan AM et al., ASH 2019; Abstract #829

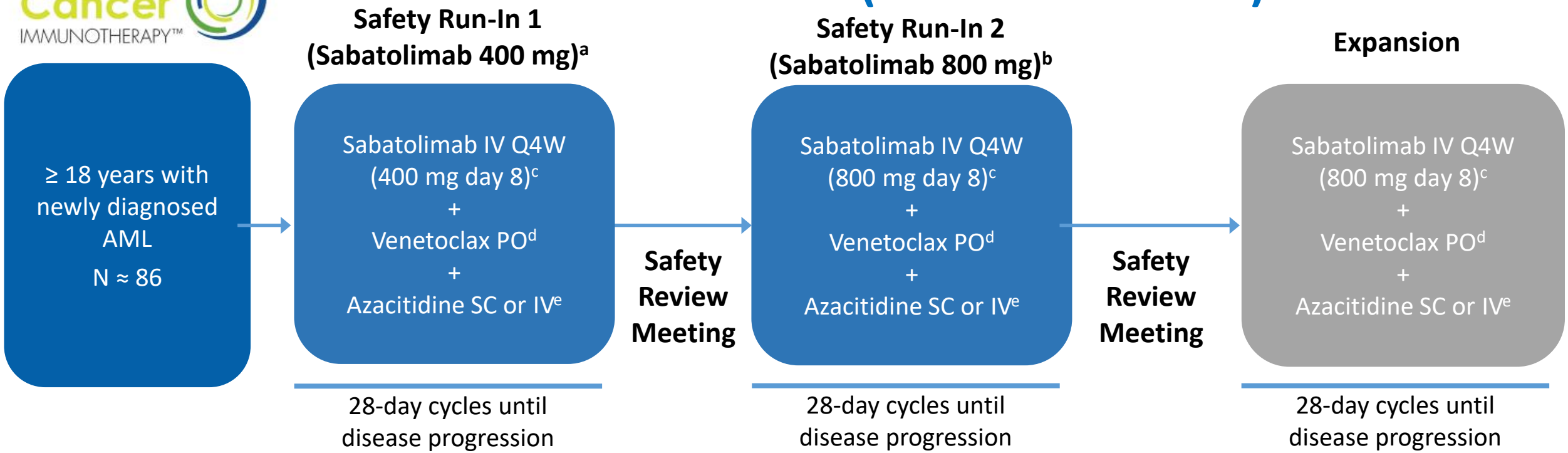
BLAST AML 2: Randomized phase 2 study of azacitidine and venetoclax +/- pembrolizumab for frontline therapy of unfit patients with AML



Study SC chair: Amer Zeidan

Zeidan A, et al, ASH 2020

Sabatolimab (anti-TIM3 inhibitor)+Aza+Ven for frontline unfit AML (STIMULUS-AML1)



[a]Requires 3–6 evaluable patients to have been observed for ≥ 2 cycles. [b]Requires ≥ 9 evaluable patients to have been observed for ≥ 2 cycles. [c]Approximately 6 patients will be enrolled at a starting dose level of 400 mg Q4W. Provided this starting dose is determined to be safe, approximately 12 patients will be enrolled at a dose level of 800 mg Q4W. Each cohort requires evaluable patients to have been observed for ≥ 2 cycles. [d]400 mg daily (following ramp-up). [e]75 mg/m^2/day, days 1-7, or days 1-5 + days 8-9, or days 1-6 + day 8.

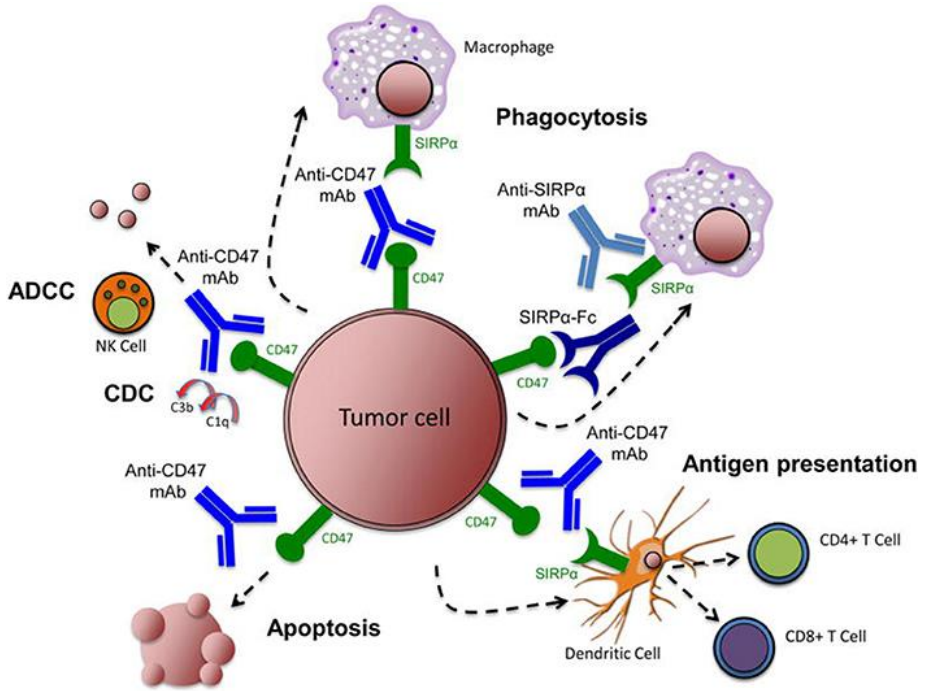
AML, acute myeloid leukemia; IV, intravenously; PO, orally; Q4W, every 4 weeks; SC, subcutaneously.

Zeidan A, et al, SOHO and EHA 2020

In development: Macrophage checkpoint: CD47

Treatment	Populations	ORR	CRR	Median DOR
Azacitidine + magroliumab	Untreated MDS	91.7%	50%	NR (>4.9 months)
	Untreated AML	63.6%	41%	NR (>5.8 months)

- CD47 is expressed on some cancer cells
- CD47 signaling through SIRPα prohibits macrophage phagocytosis of cancer cells – "don't eat me"
- Blocking interaction of CD47 and SIRPα promotes adaptive immune responses and boosts tumor cell phagocytosis



Sallman, ASH 2019.
Zhang, Front Immunol 2020.

Magrolimab Combined with Azacitidine is Effective in Untreated AML Patients Unfit for Intensive Chemotherapy Including TP53 Mutant

Patient Characteristics

Characteristic	1L AML Magro + AZA (N=29)
Median age in years (range)	74 (60–89)
ECOG Performance Status: 0 1 2	7 (24%) 20 (69%) 2 (7%)
Cytogenetic Risk: Favorable Intermediate Poor Unknown/missing	0 2 (7%) 21 (72%) 6 (21%)
WHO AML classification: MRC Therapy related	19 (66%) 3 (10%)
Harboring a *TP53* mutation	13 (45%)

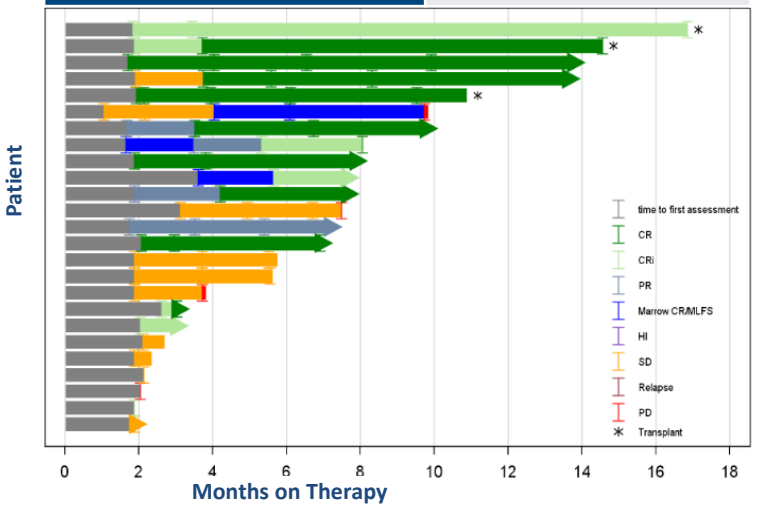
Efficacy: Response

Best Overall Response	1L AML N=25	TP53 Mutant N=12
ORR	16 (64%)	9 (75%)
CR	10 (40%)	5 (42%)
CRi	4 (16%)	4 (33%)
PR	1 (4%)	0
MLFS	1 (4%)	0
SD	8 (32%)	2 (17%)
PD	1 (4%)	1 (8%)
MRD negativity[1]	8/16 (50%)	4/9 (44%)

[1]responses in responders

Efficacy: Durability

Median DOR in mos (range)	Not reached (0.03+ – 15.1+)
Median follow-up in mos (range)	9.4 (1.9–16.9)



- Magrolimab is a first-in-class anti-CD47 antibody, targeting a macrophage immune checkpoint
- Magrolimab + azacitidine well-tolerated, with 64% response rate in unfit AML
- A 75% CR/CRi rate was observed in TP53 mutant AML with clearance of TP53 mutational burden in majority of patients

Slide Courtesy of Naval Daver

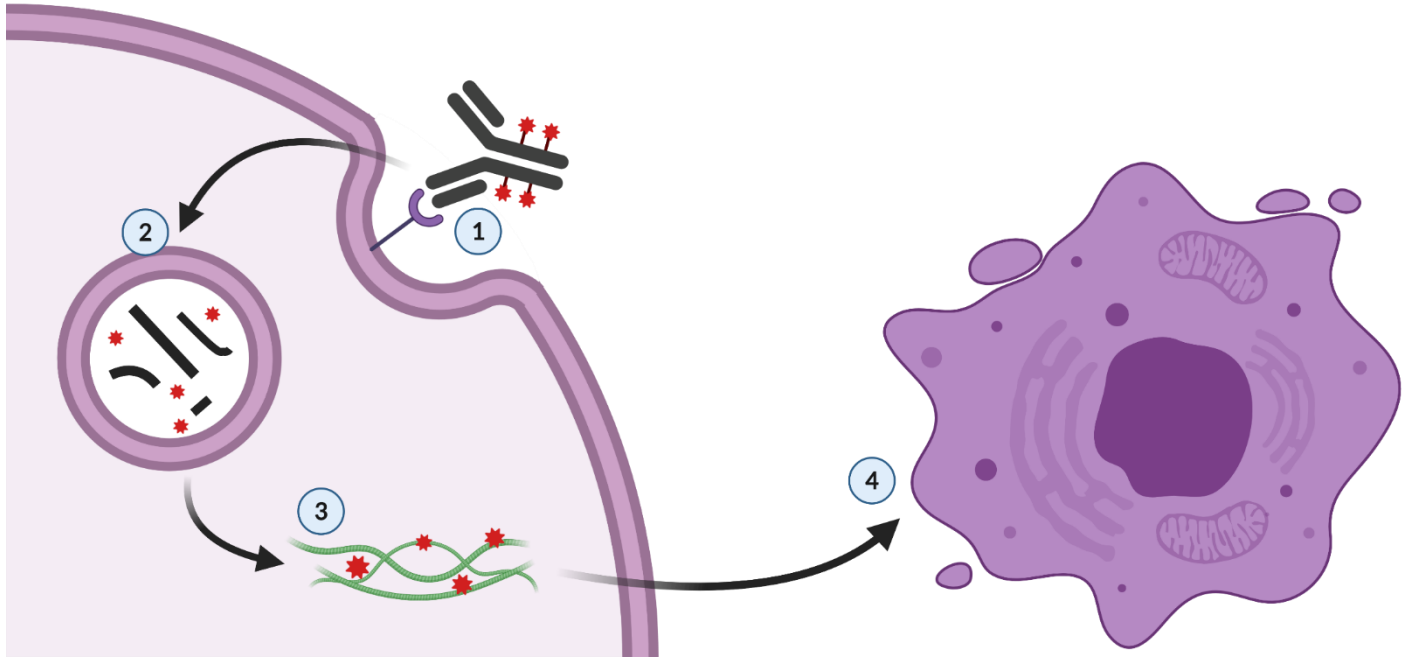
Daver N et al, EHA 2020, S144

Outline

- Immune checkpoint inhibitors
- Antibody-drug conjugates
- Bispecifics
- Cellular therapies

Antibody-drug conjugates

1. Antibody binds to receptor on tumor cell
2. ADC is internalized and broken down
3. Drug payload performs its MOA (here, microtubule disruption)
4. Apoptosis is induced in target cell

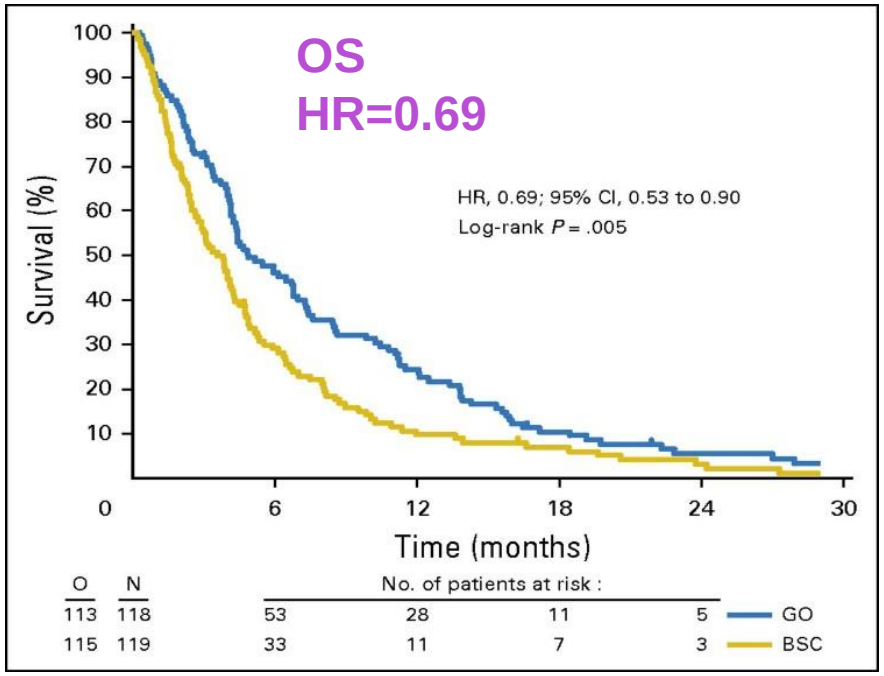


FDA-approved antibody-drug conjugates

Drug	Target antigen	Indication
Brentuximab vedotin	CD30	**Classical Hodgkin lymphoma,** relapsed after HSCT or ≥2 previous therapies
		Cutaneous anaplastic large cell lymphoma or **CD30+ mycosis fungoides** ≥ 1 previous therapies
		Classical Hodgkin lymphoma - first line with combination chemo
		Classical Hodgkin lymphoma consolidation after auto-HSCT
Inotuzumab ozogamicin	CD22	Relapsed/refractory/MRD+ **B-cell ALL**
Polatuzumab vedotin (w/ bendamustine & rituximab)	CD79b	**DLBCL** ≥ 2 previous therapies
Gemtuzumab ozogamicin	CD33	**R/R or newly-diagnosed CD33+ AML** in adults or pediatric patients
Belantamab mafodotin	BCMA	**R/R multiple myeloma** after ≥ 4 prior therapies

Gemtuzumab Ozogamicin
Phase III EORTC-GIMEMA AML-19 Trial

237 patients (≥ 61 yr, unfit for IC) randomized 1:1 to single induction course of GO (6 mg/m^2 on D1 and 3 mg/m^2 on D8) or best supportive care (BSC). Consolidation up to 8 monthly cycles (2 mg/m^2 on D1) for those who did not progress).

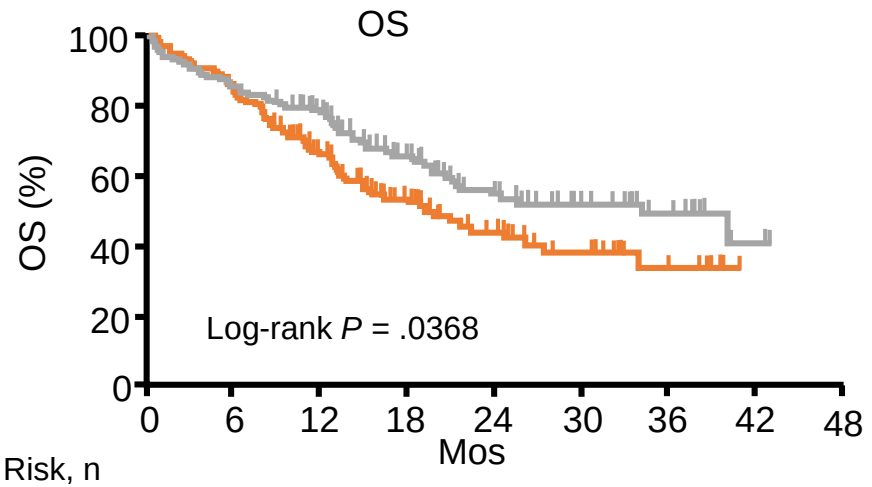


Outcome	GO	BSC
Responses CR/CRi CR CRi PR	 24.3% 8.1% 16.2% 6.3%	
Median OS (months)	4.9 (95%CI, 4.2-6.8)	3.6 (95%CI, 2.6-4.2)
One-year OS %	24.3%	9.7%

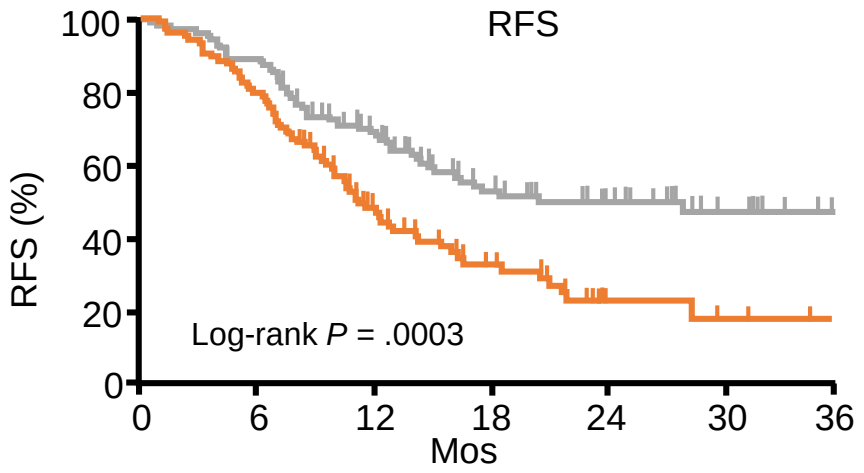
Amadori S et al, JCO 2016, 34, 972-979.

Gemtuzumab Ozogamicin
ALFA-0701 (MF3) Trial: Survival

- GO 3 mg/m^2 on D1, 4, 7 of induction and Day 1 of each consolidation cycle



Pts at Risk, n									
Control	139	117	82	45	26	16	6	0	0
Gemtuzumab	139	118	98	66	43	25	16	4	0



	104	83	39	19	6	3	1
	113	101	68	41	29	16	8

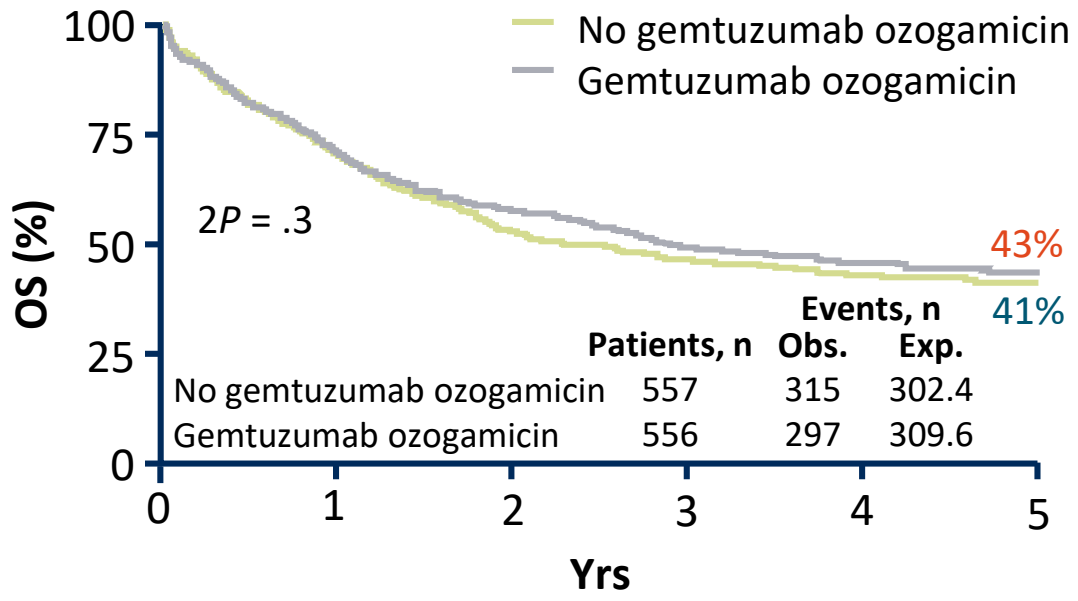
Median time to event, months	**17.3**	**9.5**
HR (95% CI)	**0.56 (0.42, 0.76)**	
p-value	**0.0002**	

- Equivalent CR rates
- Fewer relapses with GO

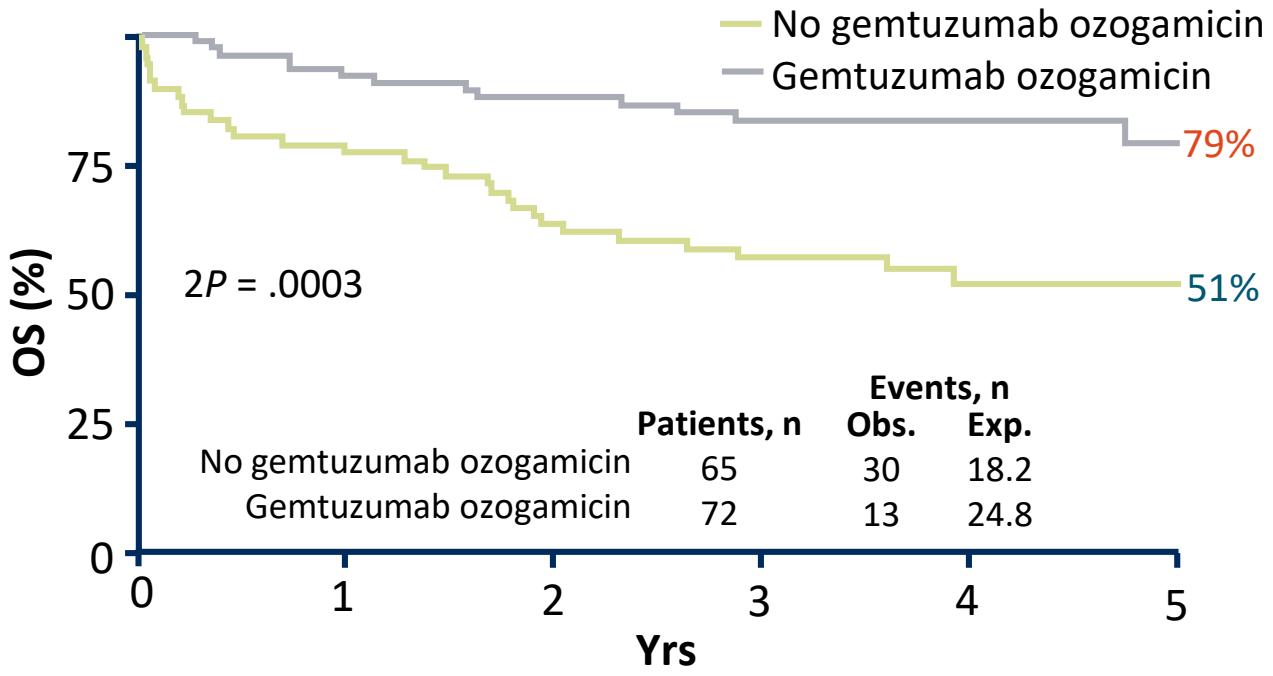
Castaigne S, et al. Lancet. 2012;379:1508-1516.

Addition of GO to IC
AML15 Randomized phase 3 trial

OS: All Patients



OS: Favorable Karyotype AML



Burnett AK, et al. J Clin Oncol. 2011;29:369-377

Efficacy of approved ADCs – brentuximab vedotin

Study	Treatment(s)	Patient population	Overall response rate	Complete response rate	Landmark OS
NCT00848926	Brentuximab vedotin	Relapsed/refractory Hodgkin lymphoma after failed auto-SCT	75%	33%	5-year: 41%
NCT00866047	Brentuximab vedotin	Relapsed/refractory systemic anaplastic large cell lymphoma	86%	66%	5-year: 60%
ECHELON-1	Brentuximab vedotin + doxorubicin, vinblastine, and dacarbazine	Previously untreated stage III or IV Hodgkin lymphoma	2-year modified PFS rate: 82.1%		
	Doxorubicin, bleomycin, vinblastine, and dacarbazine		2-year modified PFS rate: 77.2%		
AETHERA	Brentuximab vedotin	Unfavorable-risk relapsed or primary refractory classic Hodgkin lymphoma after auto-SCT	Median PFS: 42.9 months		
	Placebo		Median PFS: 24.1 months		

Chen, Blood 2016; Pro, Blood 2017; Connors, N Engl J Med 2018; Moskowitz, Lancet 2015.

Efficacy of approved ADCs

Study	Treatment(s)	Patient population	Key outcomes
INO-VATE	Inotuzumab ozogamicin	Relapsed/refractory **B cell precursor ALL**	CR/CRi rate: 73.8% vs 30.9% Median OS: 7.7 vs 6.2 months 2-year OS: 22.8% vs 10%
	Standard-of-care chemo		
GO29365	Polatuzumab vedotin + bendamustine & rituximab	Relapsed/refractory **DLBCL**	CRR: 40.0% vs 17.5% Median PFS: 9.5 vs 3.7 months Median OS: 12.4 vs 4.7 months
	Bendamustine & rituximab		
ALFA-0701	Gemtuzumab ozogamicin + daunorubicin + cytarabine	De novo acute **myeloid leukemia**	CR/CRp rate: 81.5% vs 73.6% Median OS: 27.5 vs 21.8 months Median EFS: 17.3 vs 9.5 months
	Daunorubicin + cytarabine		
DREAMM-2	Belantamab mafodotin	R/R **multiple myeloma** after IMiD, PI, and anti-CD38	ORR: 31% Median PFS: 2.9 months

Sehn, J Clin Oncol 2020; Kantarjian, Cancer 2019; Lambert, Haematologica 2018.

In development: Novel ADCs in clinical trials

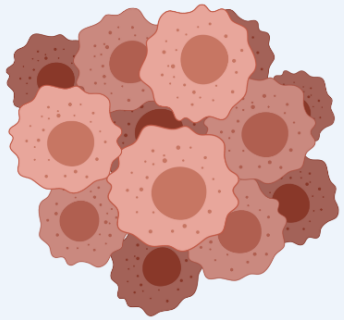
Trial	Indication	Treatment(s)	ADC target antigen	Phase
NCT03544281	R/R multiple myeloma	GSK2857916 + lenaolidomide + dexamethasone	BCMA	2
		GSK2857916 + bortezomib + dexamethasone		
NCT03386513	CD123+ AML, BPDCN or ALL	IMGN632	CD123	1/2
NCT03424603	R/R B cell malignancies	STRO-001	CD74	1
NCT03682796	R/R B cell lymphoma	TRPH-222	CD22	1
NCT04240704	CLL or NHL	JBH492	CCR7	1
NCT03833180	Pre-treated hematologic malignancies	VLS-101	ROR1	1

Outline

- Immune checkpoint inhibitors
- Antibody-drug conjugates
- Bispecifics
- Cellular therapies

Bispecifics in immunotherapy

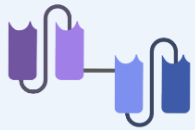
Target 1: Tumor



Explored targets include:
CD19, CD20, EGFR, BCMA, CEA, FAP, EpCAM, CD123 …

Immune cell engagers

Bispecific killer cell engagers



Bispecific T cell engagers

Bispecific antibodies

Nanobody-scFv

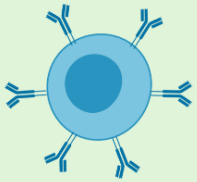
Target 2: Immune cell

T cells

NK cells

Macrophages

B cells



Commonly CD3 on T cells, CD16 for NK and macrophages, etc

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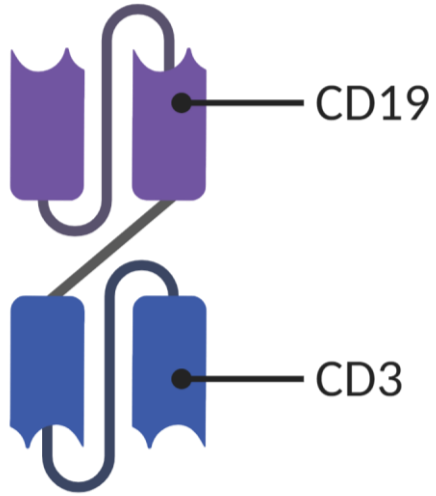
Clinical use of immune cell engagers

Drug	Indications
Blinatumomab	Relapsed/refractory B-ALL
	B-ALL in 1st or 2nd complete response with MRD ≥ 0.1%

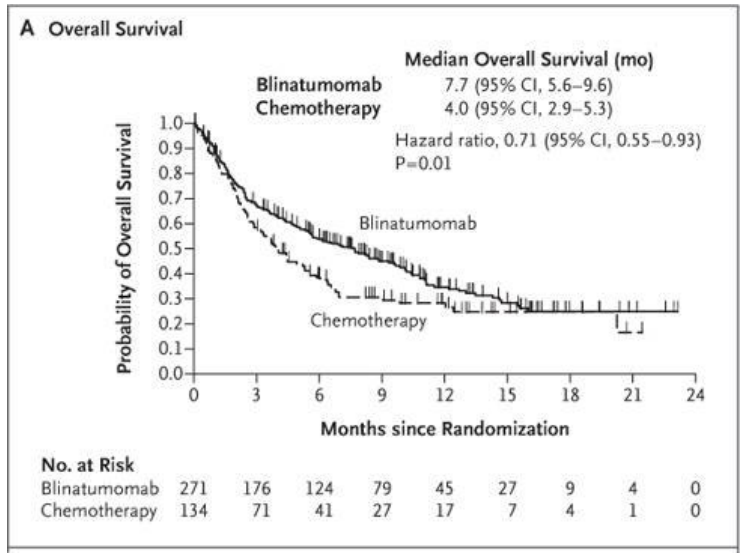


Blinatumomab prescribing information.

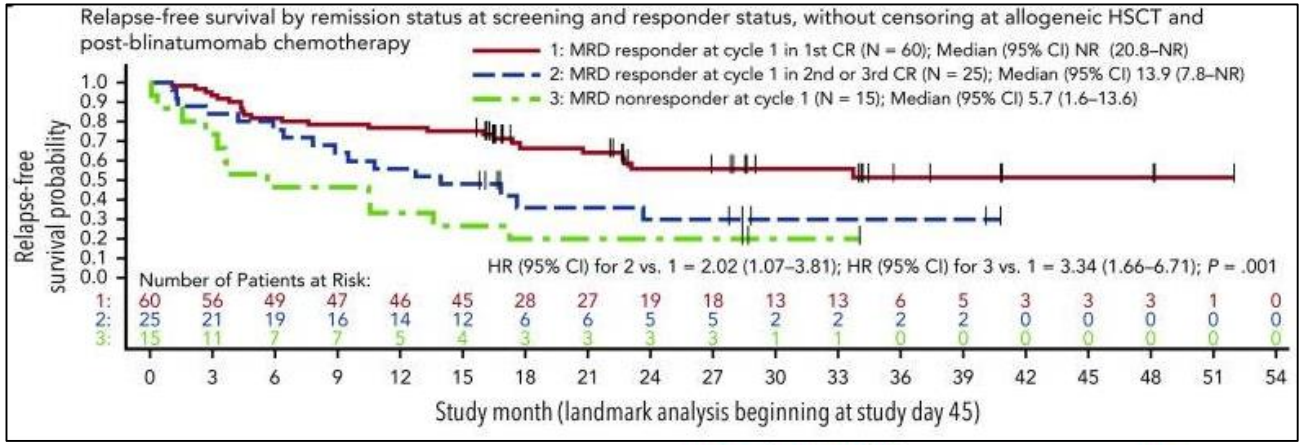
Blinatumomab in R/R B-ALL

Trial	Patient population	Treatment	Key outcomes
NCT02013167	Adults with R/R B-ALL	Blinatumomab	Median OS: 7.7 vs 4.0 months Median DOR: 7.3 vs 4.6 months
		Chemotherapy	
NCT01207388	Adults with MRD+ B-ALL	Blinatumomab	Complete MRD response rate: 78% Median OS: 36.5 months

R/R B-ALL



MRD+ B-ALL



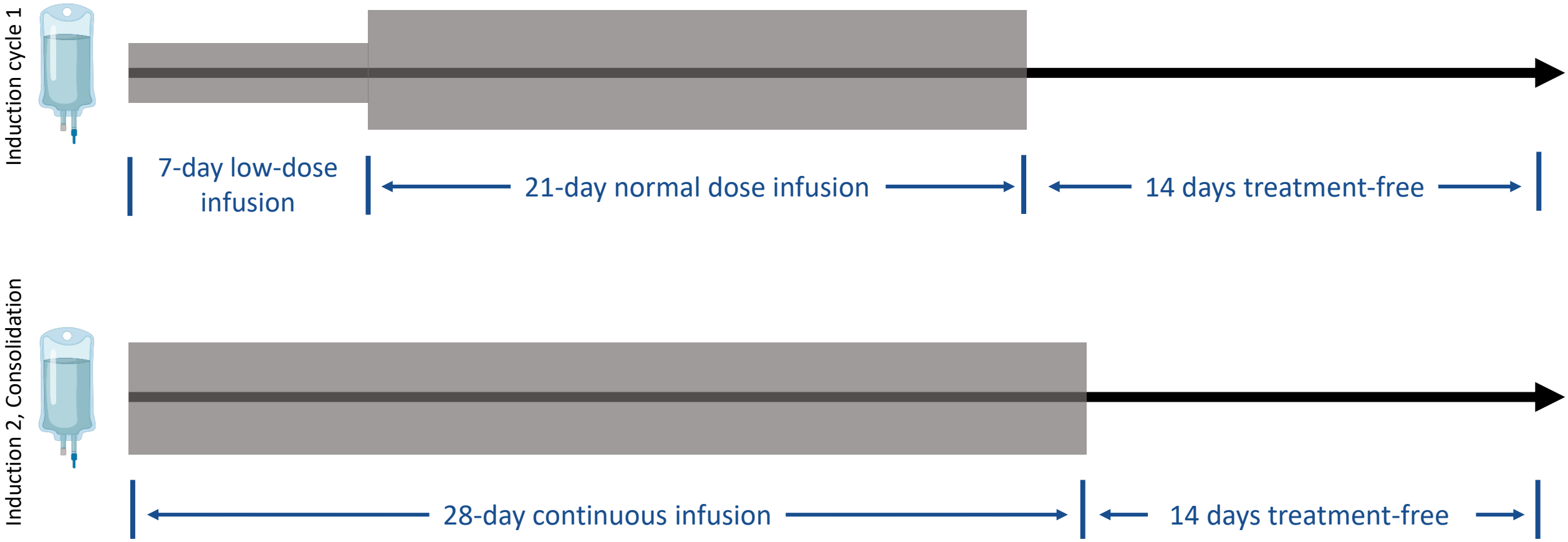
Dosing regimens for blinatumomab

	Cycle		Patients weighing 45 kg or more (Fixed-dose)	Patients weighing less than 45 kg (BSA-based dose)
MRD-positive B-ALL	Induction cycle 1	Days 1-28	28 mcg/day	15 mcg/m^2/day (not to exceed 28 mcg/day)
		Days 29-42	14-day treatment-free interval	14-day treatment-free interval
	Consolidation cycles 2-4	Days 1-28	28 mcg/day	15 mcg/m^2/day (not to exceed 28 mcg/day)
		Days 29-42	14-day treatment-free interval	14-day treatment-free interval

	Cycle		Patients weighing 45 kg or more (Fixed-dose)	Patients weighing less than 45 kg (BSA-based dose)
R/R B-ALL	Induction cycle 1	Days 1-7	9 mcg/day	5 mcg/m^2/day (not to exceed 9 mcg/day)
		Days 8-28	28 mcg/day	15 mcg/m^2/day (not to exceed 28 mcg/day)
		Days 29-42	14-day treatment-free interval	14-day treatment-free interval
	Induction cycle 2	Days 1-28	28 mcg/day	15 mcg/m^2/day (not to exceed 28 mcg/day)
		Days 29-42	14-day treatment-free interval	14-day treatment-free interval
	Consolidation cycles 3-5	Days 1-28	28 mcg/day	15 mcg/m^2/day (not to exceed 28 mcg/day)
		Days 29-42	14-day treatment-free interval	14-day treatment-free interval
	Continued therapy cycles 6-9	Days 1-28	28 mcg/day	15 mcg/m^2/day (not to exceed 28 mcg/day)
		Days 29-42	56-day treatment-free interval	56-day treatment-free interval

Blinatumomab prescribing information.

Dosing regimens for blinatumomab – R/R B-ALL



Blinatumomab prescribing information.

Common side effects of T cell engagers

Cytokine release syndrome

- Characterized by initial flu-like symptoms, which progress into a shock-like syndrome with elevation in cytokine levels
- Patients display fever, vascular leakage, and organ dysfunction
- Variable onset and course
- Pre-treatment with dexamethasone required
- Management:
  - IL-6 and IL-6R antagonism
  - Corticosteroids
  - Other cytokine receptor antagonists

B cell aplasia

- Due to current clinical agents targeting CD19, which is expressed by both normal and neoplastic B cells
- May result in hypogammaglobulinemia
- Increased risk of infection
- Managed through administration of intravenous immunoglobulin

Stay tuned: more information on toxicity management later in this program

Neurotoxicity

- Also known as "immune effector cell-associated neurotoxicity syndrome" (ICANS)
- Manifests as confusion, delirium, seizures, cerebral edema
- Largely unknown mechanisms
- Incidence increases with more doses, increased age, more prior therapies
- Management:
  - Supportive care for low-grade
  - Corticosteroids for higher-grade

In development: Novel immune cell engagers in clinical trials

Trial	Indication	Treatment	Target antigens	Phase
NCT03214666	HR myelodysplastic syndromes, R/R AML, systemic mastocytosis	GTB-3550 (TriKE)	CD16, IL-15, CD33	1/2
NCT03516591	High-risk myelodysplastic syndromes	AMV564	CD33, CD3	1
NCT03739606	CD123+ R/R blood cancers	Flotetuzumab	CD123, CD3	2
NCT02730312	CD123+ R/R blood cancers	XmAb14045	CD123, CD3	1
NCT03888105	R/R B cell NHL	Odronextamab	CD20, CD3	2
NCT03309111	Previously treated multiple myeloma	GBR 1342	CD38, CD3	1/2
NCT03761108	R/R multiple myeloma	REGN5458	BCMA, CD3	1/2

Outline

- Immune checkpoint inhibitors
- Antibody-drug conjugates
- Bispecifics
- Cellular therapies

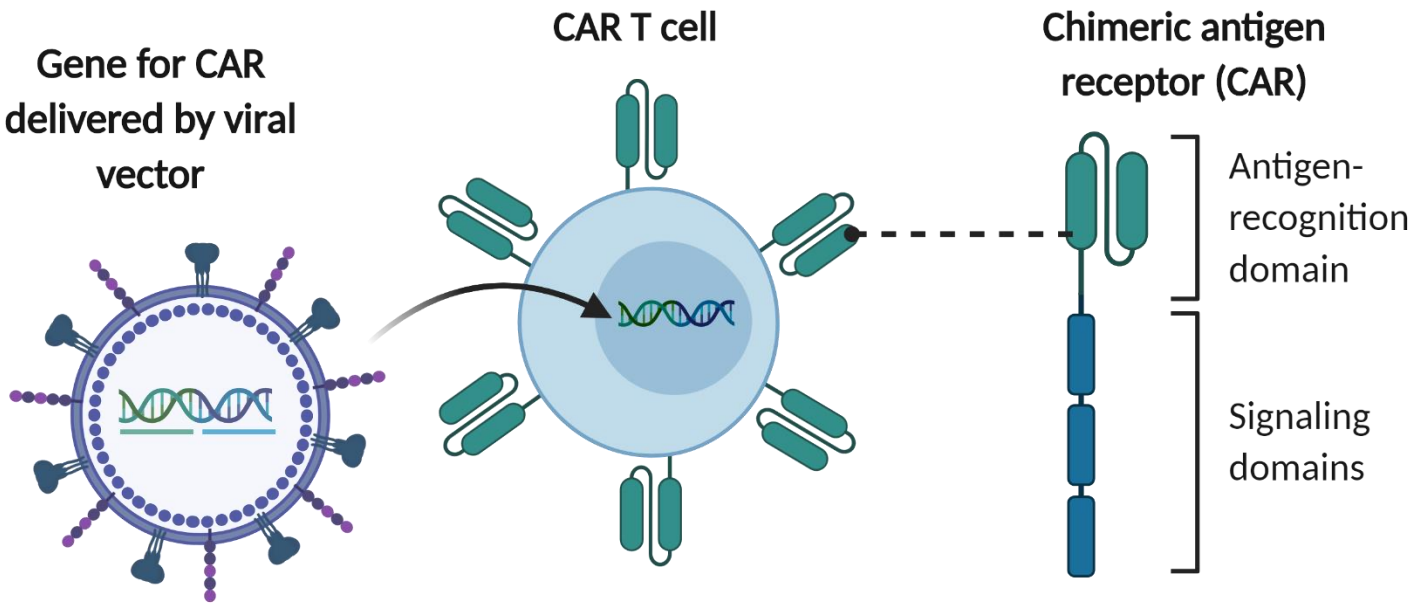
Comparing T cell engagers and CAR T therapy

	CAR T cells	T cell engagers (BiTEs)
Structure	Synthetic gene construct encoding an scFv against tumor antigen linked to activation/costimulatory motifs	Recombinant protein with two specificities: one for tumor antigen and one for T cell antigen (usually CD3)
Effector cell types	Engineered CD8+ and CD4+ T cells	Endogenous CD8+ and CD4+ T cells
Immune synapse	Atypical	Typical
Serial killing	Yes	Yes
Killing mechanisms	Perforin and granzyme B, Fas-Fas-L, or TNF/TNF-R	Perforin and granzyme B
Trafficking	Active	Passive
Clinical applications	Pre-treatment lymphodepletion followed by a single infusion	No lymphodepletion; repeat administration and continuous infusions.
Specificity	Manufactured for each patient	"Off-the-shelf"

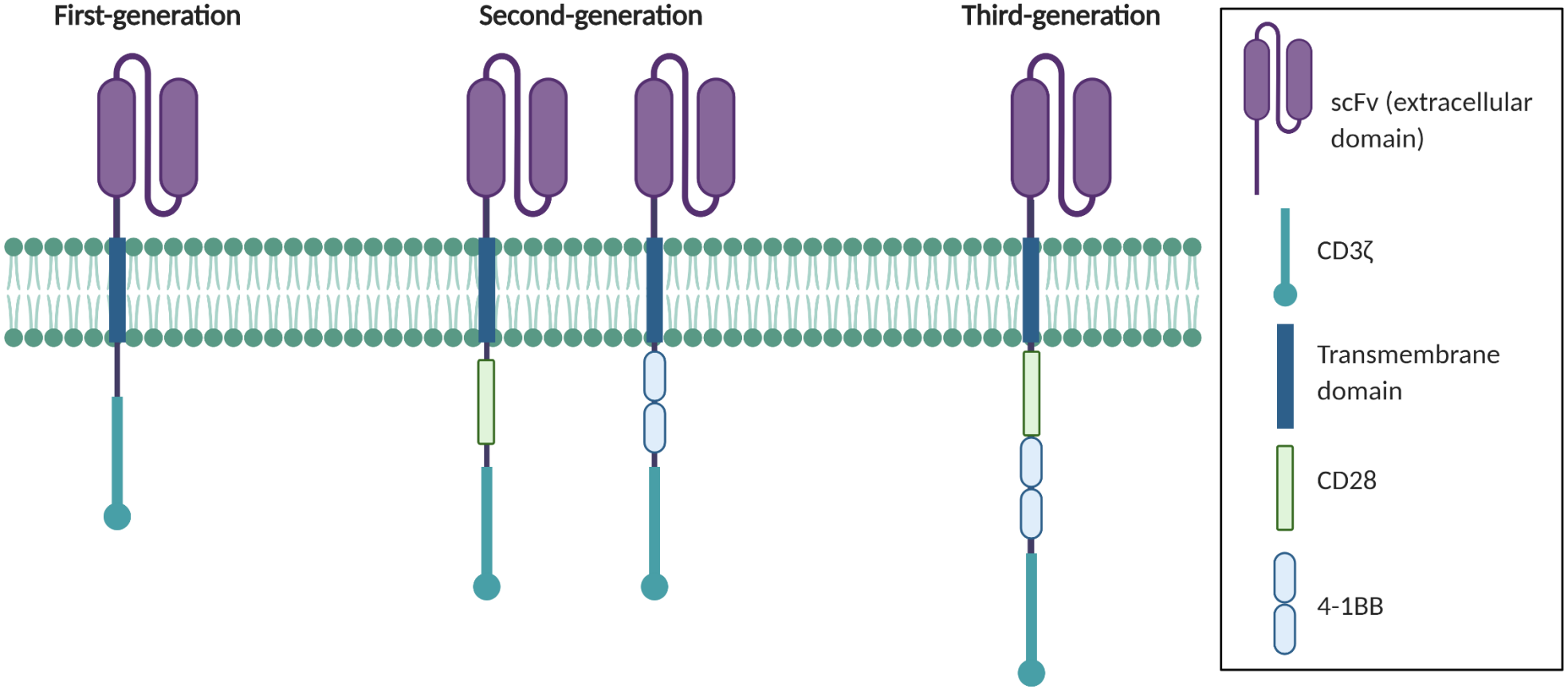
Slaney, Cancer Disc 2018.

Chimeric antigen receptors

- Overcome immune tolerance
- Targets surface molecules in native conformation
- Independent of antigen presenting cell and MHC complex



Evolution of CAR constructs



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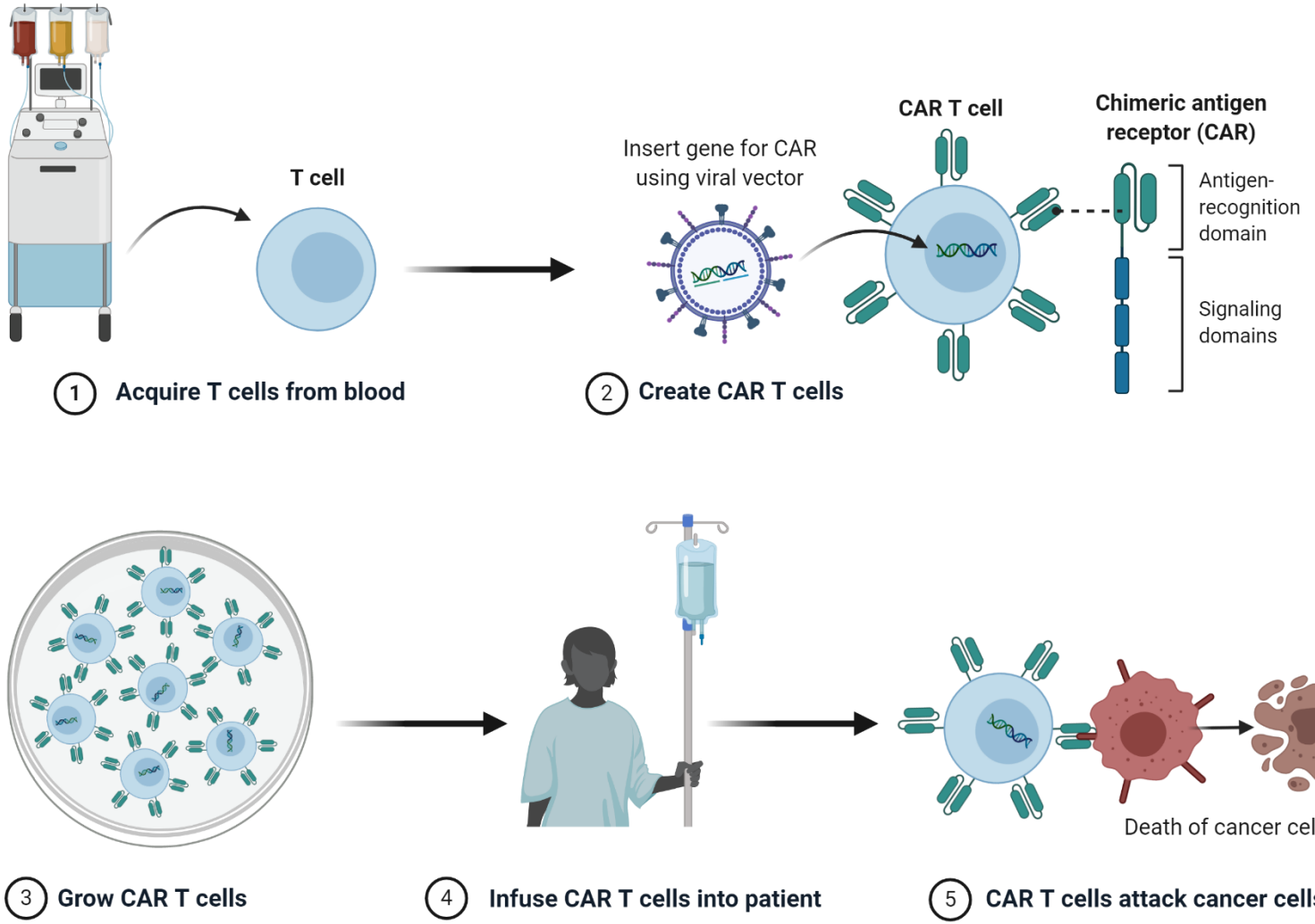
CAR T manufacturing and administration



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FDA-approved CAR T cell therapies

Drug	Target/co-stimulatory domain	Indication	Dose
Axicabtagene ciloleucel	CD19/CD28	Adults with r/r large B-cell lymphoma, Including diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma	2 x 10^6 CAR-positive, viable T cells per kg bodyweight (up to 2x10^8)
Tisagenlecleucel	CD19/4-1BB	Patients ≤25 yr with refractory B-cell acute lymphoblastic leukemia or in 2+ relapse	0.2-0.5x10^6 CAR-positive, viable T cells per kg if under 50 kg 0.1-2.5x10^8 CAR-positive, viable T-cells if over 50 kg
Tisagenlecleucel	CD19/4-1BB	Adults with r/r large B-cell lymphoma after 2+ therapies Including DLBCL, high-grade B-cell lymphoma, DLBCL arising from follicular lymphoma	0.6-6.0 x 10^8 CAR-positive, viable T cells
Brexucabtagene autoleucel	CD19/CD28	Adults with mantle cell lymphoma (MCL) who have not responded to or who have relapsed following other treatments	2 x 10^6 CAR-positive, viable T cells per kg bodyweight (up to 2x10^8)

Comparing clinical trials of CAR T therapies

Trial	Indication	Treatment(s)	ORR	Landmark OS	Grade 3+ toxicity rates
ZUMA-2	R/R mantle cell lymphoma	Brexucabtagene autoleucel (KTE-X19)	86% CRR: 57%	1-year: 86%	CRS: 18% NE: 46%
ZUMA-1	Refractory large B cell lymphoma	Axicabtagene ciloleucel	83% CRR: 58%	2-year: 50%	CRS: 11% NE: 32%
JULIET	R/R diffuse large B cell lymphoma	Tisagenlecleucel	52% CRR: 40%	1-year: 49%	CRS: 22% NE: 12%
ELIANA	R/R B cell acute lymphoblastic leukemia	Tisagenlecleucel	82% CRR: 62%	18-month: 70%	CRS: 48% NE: 13%

Wang, ASH 2019; Locke, Lancet Oncol 2019; Schuster, N Engl J Med 2019; Grupp, Biol Blood Mar Trans 2019.

CAR T side effects

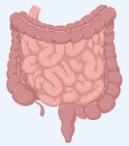
- Cytokine Release Syndrome (CRS)
- Neurotoxicity
  - ICANS: Immune effector cell-associated neurotoxicity syndrome
  - NE: Neurologic events
- B cell aplasia
- Macrophage Activation Syndrome (MAS)/HLH

Stay tuned: more information on toxicity management later in this program

CAR T side effects - CRS

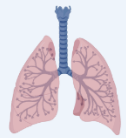
Cytokine Release Syndrome symptoms

Gastrointestinal
- Nausea/vomiting
- Diarrhea
- Anorexia



Skin
- Rash

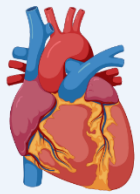
Respiratory
- Tachypnea
- Hypoxia
- Pulmonary edema



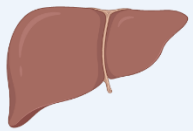
Constitutional
- Fever +/- rigors
- Malaise/fatigue
- Myalgias
- Arthralgias
- Headache

Coagulation
- Elevated D-dimer
- Hypofibrinogenemia +/- bleeding

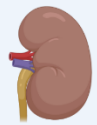
Cardiovascular
- Tachycardia
- Hypotension
- Capillary leak
- Widened pulse presssure
- Increased cardiac output (early)
- Potentially diminished cardiac output (late)



Hepatic dysfunction
- Transaminitis
- Hyperbilirubinemia



Renal function
- Azotemia



Symptoms often mimic sepsis, but treatment of CRS is quite different

Eligibility considerations for CAR

- Disease
  - Relative stability during CAR T manufacturing (~2-6 weeks)
  - Bridging therapy (chemo, RT, steroids, lenalidomide, ibrutinib)
  - CNS control
- Patient
  - Adequate cell counts
  - DVT, bleeding, infection, neuro disorders
  - Functional status: at screen vs. day of CAR T infusion
- Other
  - Social support, reimbursement
  - Availability of tocilizumab for CRS management

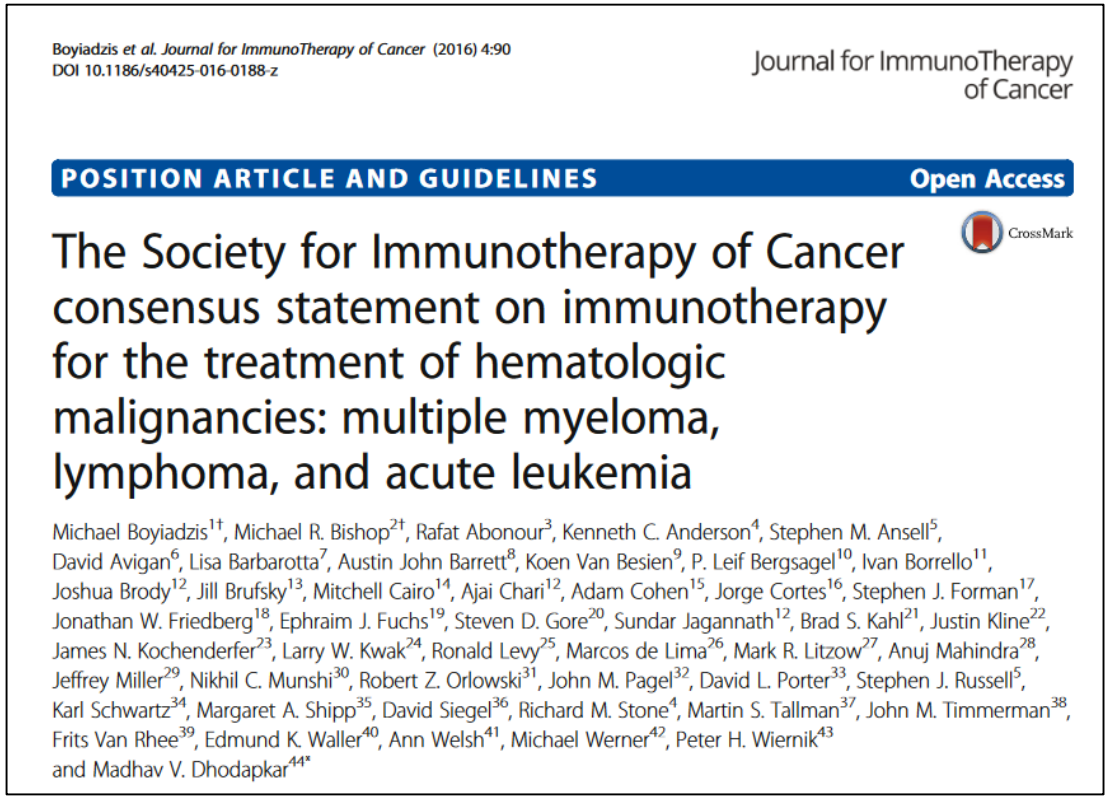
In development: Novel CAR T therapies in clinical trials

Trial	Indication	Treatment	Target antigen	Phase
NCT03651128	R/R multiple myeloma	bb2121	BCMA	3
NCT03971799	R/R pediatric AML	CD33CART	CD33	1/2
NCT04186520	R/R B cell malignancies	CAR-20/19 T cells	CD19, CD20	1/2
NCT04109482	R/R BPDCN, AML, HR MDS	MB-102	CD123	1/2
NCT03287817	Diffuse large B cell lymphoma	AUTO3	CD19, CD22	1/2
NCT02690545	R/R HL and NHL	ATLCAR.CD30	CD30	1/2

Conclusions

- Many immunotherapy options for hematological malignancies
- Checkpoint inhibitors for Hodgkin lymphoma and PMBCL – high response rate, excellent tolerance, durable responses if CR
- Blinatumomab and inotuzumab for ALL – effective salvage, deeper remissions
- Polatuzumab vedotin for DLBCL – effective salvage, potential to become frontline
- CAR T therapy – ever-increasing indications; patient selection and toxicity management still concerns

Additional Resources



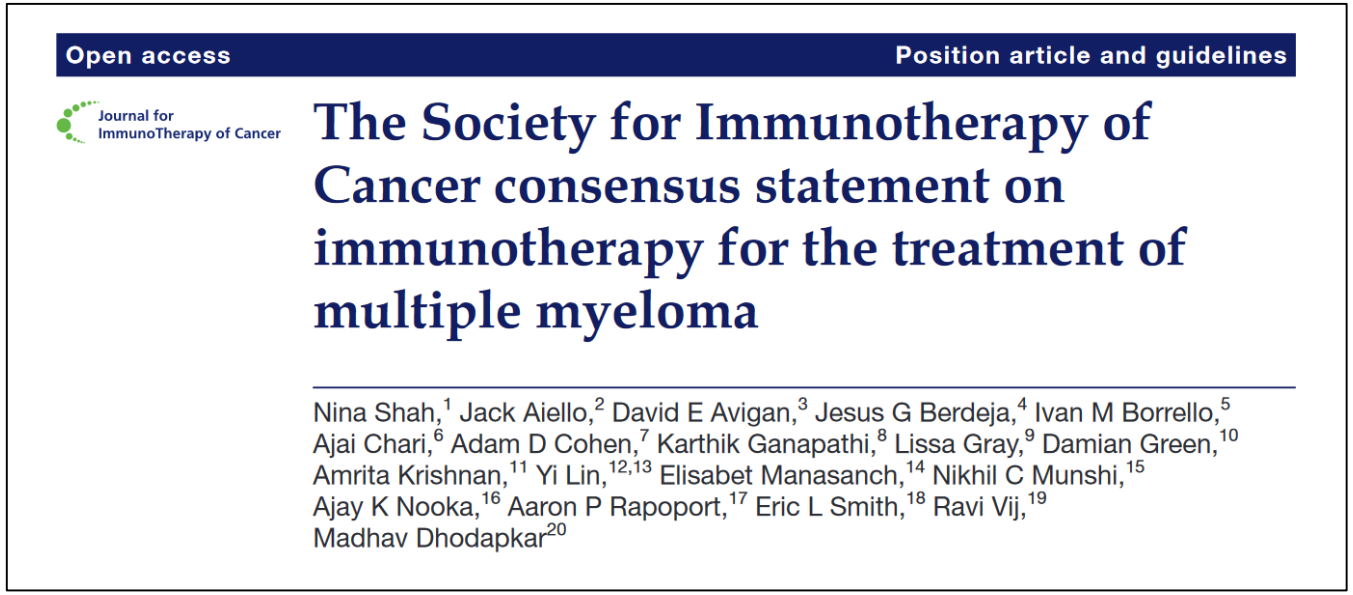
Boyiadzis *et al. Journal for ImmunoTherapy of Cancer* (2016) 4:90
DOI 10.1186/s40425-016-0188-z

Journal for ImmunoTherapy of Cancer

POSITION ARTICLE AND GUIDELINES **Open Access**

The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of hematologic malignancies: multiple myeloma, lymphoma, and acute leukemia

Michael Boyiadzis[1†], Michael R. Bishop[2†], Rafat Abonour[3], Kenneth C. Anderson[4], Stephen M. Ansell[5], David Avigan[6], Lisa Barbarotta[7], Austin John Barrett[8], Koen Van Besien[9], P. Leif Bergsagel[10], Ivan Borrello[11], Joshua Brody[12], Jill Brufsky[13], Mitchell Cairo[14], Ajai Chari[12], Adam Cohen[15], Jorge Cortes[16], Stephen J. Forman[17], Jonathan W. Friedberg[18], Ephraim J. Fuchs[19], Steven D. Gore[20], Sundar Jagannath[12], Brad S. Kahl[21], Justin Kline[22], James N. Kochenderfer[23], Larry W. Kwak[24], Ronald Levy[25], Marcos de Lima[26], Mark R. Litzow[27], Anuj Mahindra[28], Jeffrey Miller[29], Nikhil C. Munshi[30], Robert Z. Orlowski[31], John M. Pagel[32], David L. Porter[33], Stephen J. Russell[5], Karl Schwartz[34], Margaret A. Shipp[35], David Siegel[36], Richard M. Stone[4], Martin S. Tallman[37], John M. Timmerman[38], Frits Van Rhee[39], Edmund K. Waller[40], Ann Welsh[41], Michael Werner[42], Peter H. Wiernik[43] and Madhav V. Dhodapkar[44*]



Open access **Position article and guidelines**

Journal for ImmunoTherapy of Cancer

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Acknowledgements

- Some figures created using Biorender.com

Case Study

- A 60 year old with relapsed advanced Hodgkins lymphoma after several lines of therapy has started receiving nivolumab. He received first dose of nivolumab 2 weeks ago and comes to office to receive the second dose. He reports he started experiencing significant high volume diarrhea with bloody stools and abdominal pain for last 3 days. Which of the following is wrong:

A) We need to rule out infectious causes by stool studies and cultures

B) Once infectious causes ruled out, this is likely an immune mediated related event (colitis) related to nivolumab

C) If nivolumab-related colitis is confirmed, would hold nivolumab and start high dose steroids

D) If symptoms are significant or worsened despite initial therapy, the patient might need admission, imaging and surgical consult, and stronger immunosuppression

E) Would immediately proceed with nivolumab dose as these symptoms are unrelated