ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for The Treatment of Hematologic Malignancies

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AMERICAN ACADEMY OF EMERGENCY MEDICINE

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Disclosures

- Novartis AG, Contracted Research
- I *will* be discussing non-FDA approved treatments during my presentation.

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Objectives

- Familiarize with clinical data on the efficacy and mechanism of action of approved therapies
- Recognize patient selection criteria for approved therapies
- Select appropriate dosing and sequencing of approved therapies

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Immunotherapy in Heme Malignancies

- Antibody Therapies
  - "naked" antibodies
  - Antibodies with payload
  - Bispecific antibodies
- Cell-based Therapies
  - Allogeneic Stem cell Transplantation
  - CART Cells
  - EBV-CTLs
- Vaccines
- IMiDS
  - Thalidomide
  - Lenalidomide
  - Pomalidomide
- Checkpoint Inhibitors
- Targeted Agents
  - Ibrutinib
  - Ruxolitinib

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Recently Approved Therapies

- NHL/CLL
  - Obinutuzumab
  - Ibrutinib
- Myeloma
  - Daratumumab
- ALL
  - Blinatumumab
- Hodgkin Lymphoma
  - Nivolumab
  - Pembrolizumab

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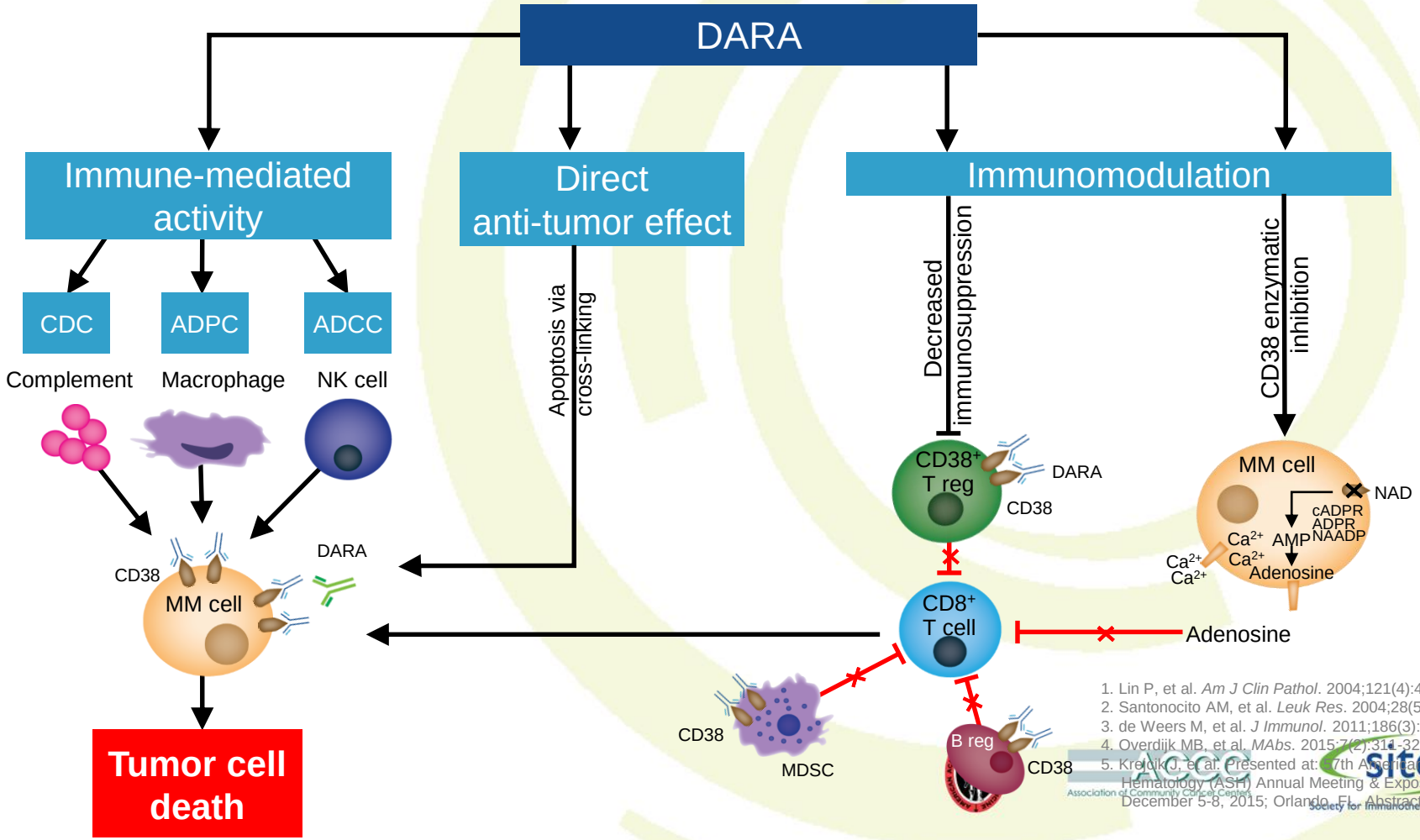
Daratumumab

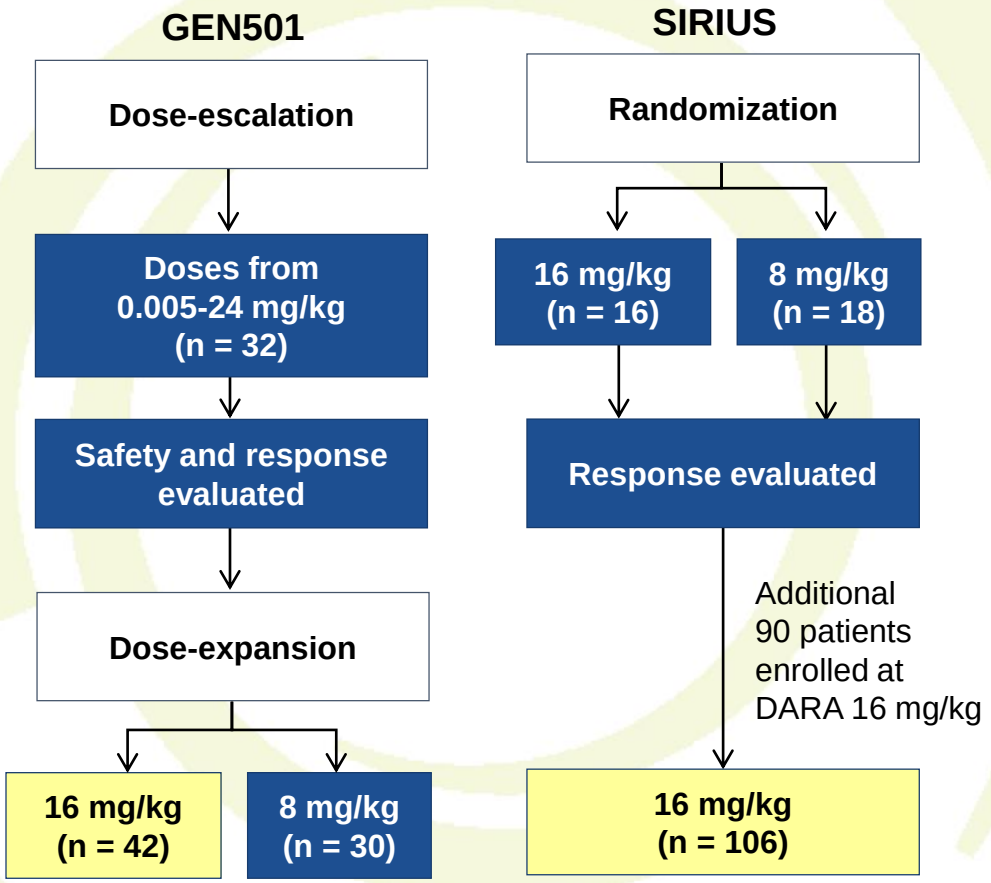
- CD38 is highly and ubiquitously expressed on myeloma cells[1,2]
- DARA is a human IgG1 monoclonal antibody that binds CD38-expressing cells
- DARA binding to CD38 induces tumor cell death through direct and indirect mechanisms[3-5]



1. Lin P, et al. *Am J Clin Pathol*. 2004;121(4):482-488.
2. Santonocito AM, et al. *Leuk Res*. 2004;28(5):469-477.
3. de Weers M, et al. *J Immunol*. 2011;186(3):1840-1848.
4. Overdijk MB, et al. *MAbs*. 2015;7(2):311-321.
5. Kreidk J, et al. Presented at: 57th American Society of Hematology (ASH) Annual Meeting & Exposition; December 5-8, 2015; Orlando, FL. Abstract 3037.

Monotherapy Studies

- DARA was approved by the FDA on November 16, 2015, based on these studies



1. Lokhorst HM, et al. *N Engl J Med*. 2015;373(13):1207-1219.
2. Lonial S, et al. *Lancet*. 2015. In press.

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Clinical Safety

Treatment-emergent adverse event, n (%)	Any grade N = 148	Grade ≥3 N = 148
Fatigue	61 (41)	3 (2)
Nausea	42 (28)	0
Anemia	41 (28)	26 (18)
Back pain	36 (24)	3 (2)
Cough	33 (22)	0
Neutropenia	30 (20)	15 (10)
Thrombocytopenia	30 (20)	21 (14)
Upper respiratory tract infection	30 (20)	1 (<1)

- AEs were consistent with the individual GEN501 and SIRIUS studies; no new safety signals were identified
- **48% of patients had infusion-related reactions**
  - **46%, 4%, and 3% occurred during the first, second, and subsequent infusions, respectively**

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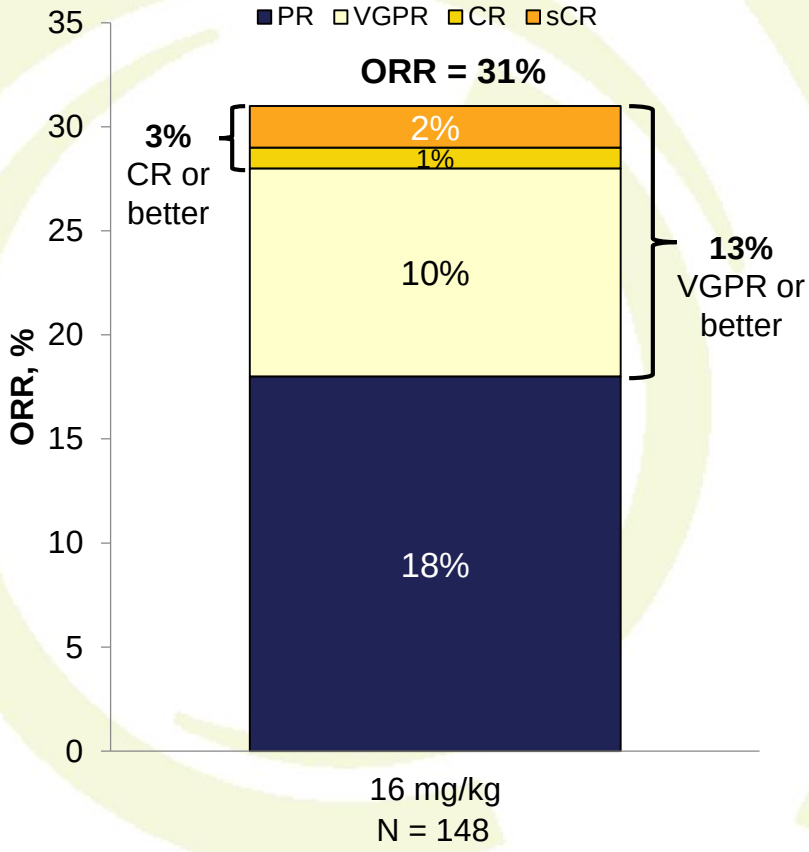
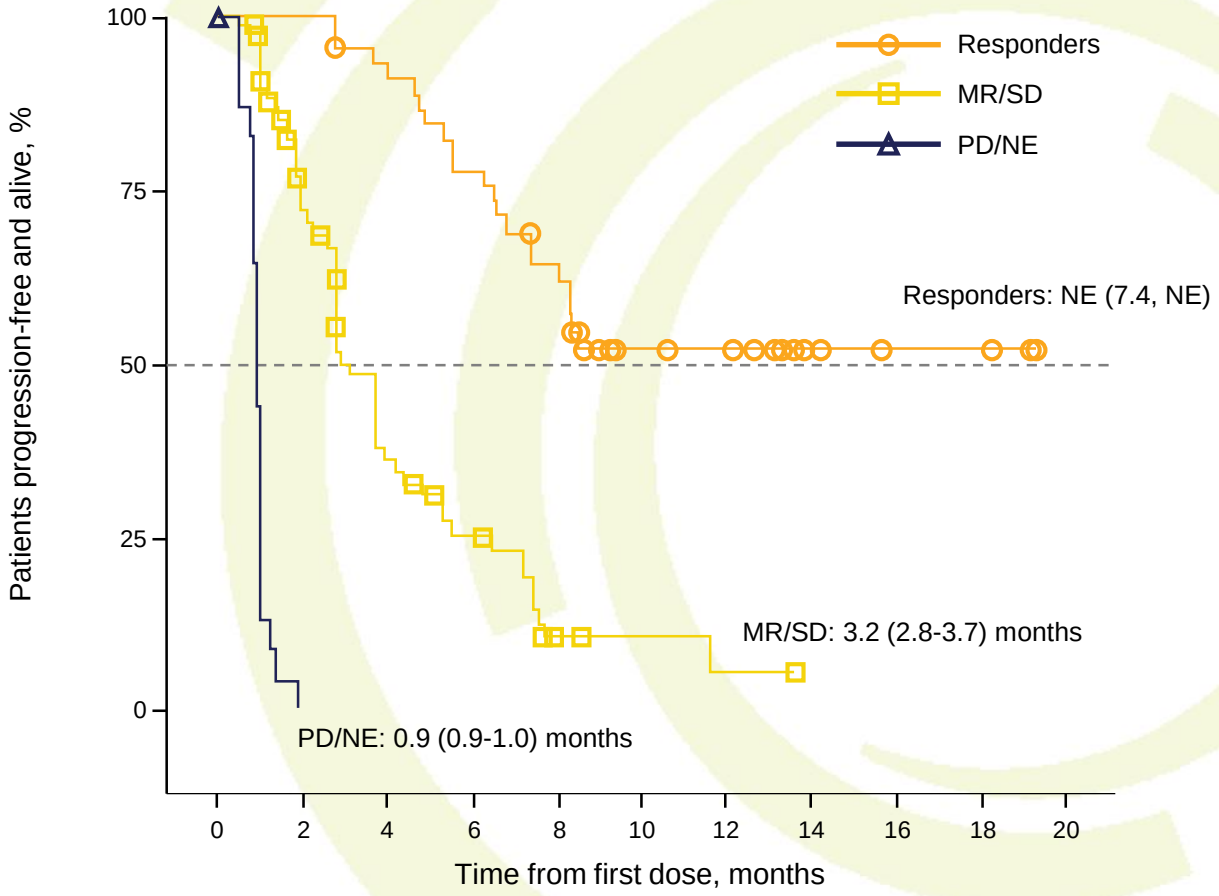
Efficacy in Combined Analysis

	16 mg/kg (N = 148)	
	n (%)	**95% CI**
Overall response rate (sCR+CR+VGPR+PR)	**46 (31)**	**23.7-39.2**
Best response		
sCR	3 (2)	0.4-5.8
CR	2 (1)	0.2-4.8
VGPR	14 (10)	5.3-15.4
PR	27 (18)	12.4-25.4
MR	9 (6)	2.8-11.2
SD	68 (46)	37.7-54.3
PD	18 (12)	7.4-18.5
NE	7 (5)	1.9-9.5
VGPR or better (sCR+CR+VGPR)	19 (13)	7.9-19.3
CR or better (sCR+CR)	5 (3)	1.1-7.7



- ORR = 31%
- ORR was consistent in subgroups including age, number of prior lines of therapy, refractory status, or renal function

Progression-free Survival



Patients at risk											
Responders	46	46	41	35	27	14	13	5	3	3	0
MR/SD	77	45	21	13	3	2	1	0	0	0	0
PD/NE	25	0	0	0	0	0	0	0	0	0	0

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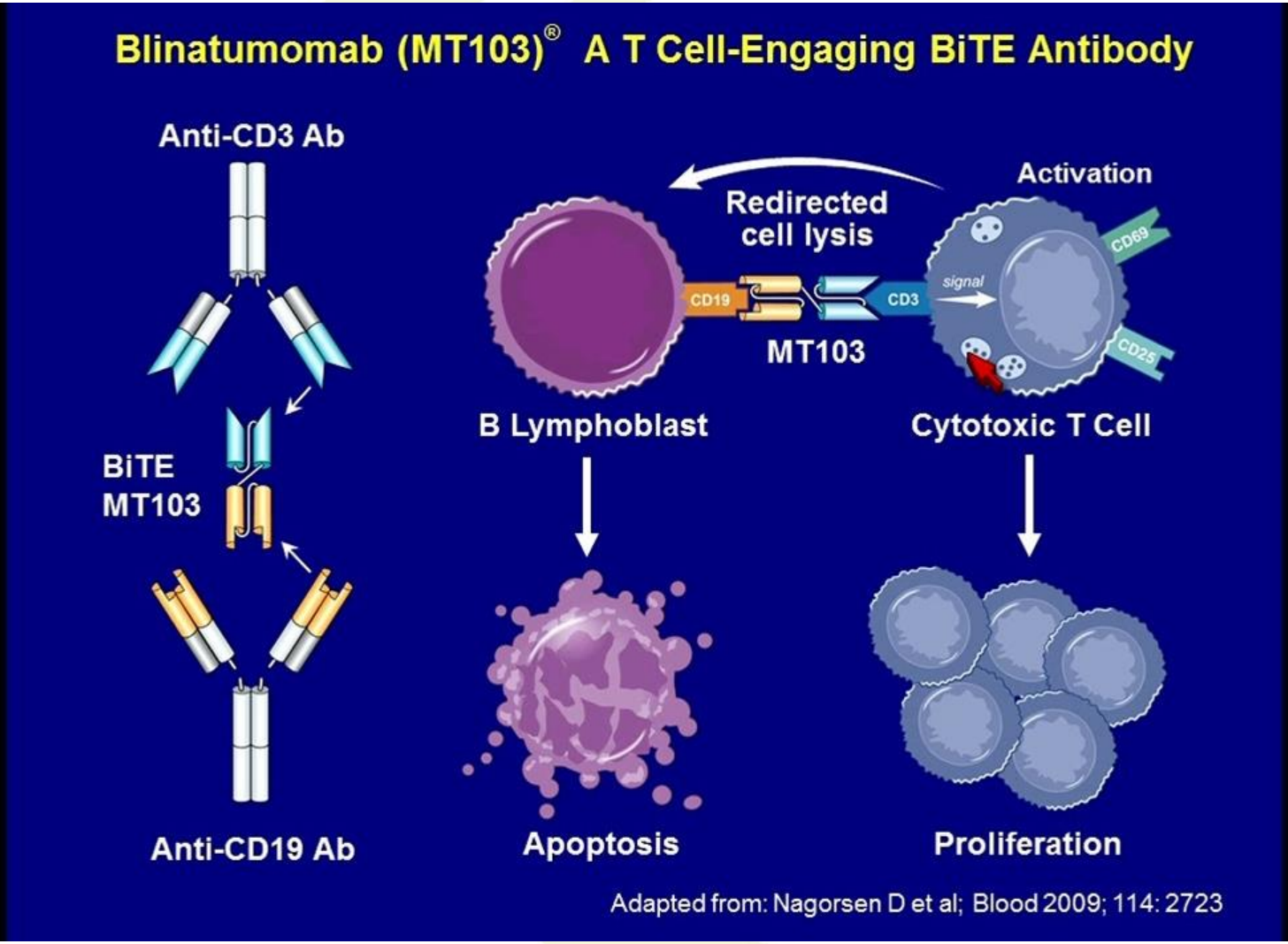
Blinatumumab



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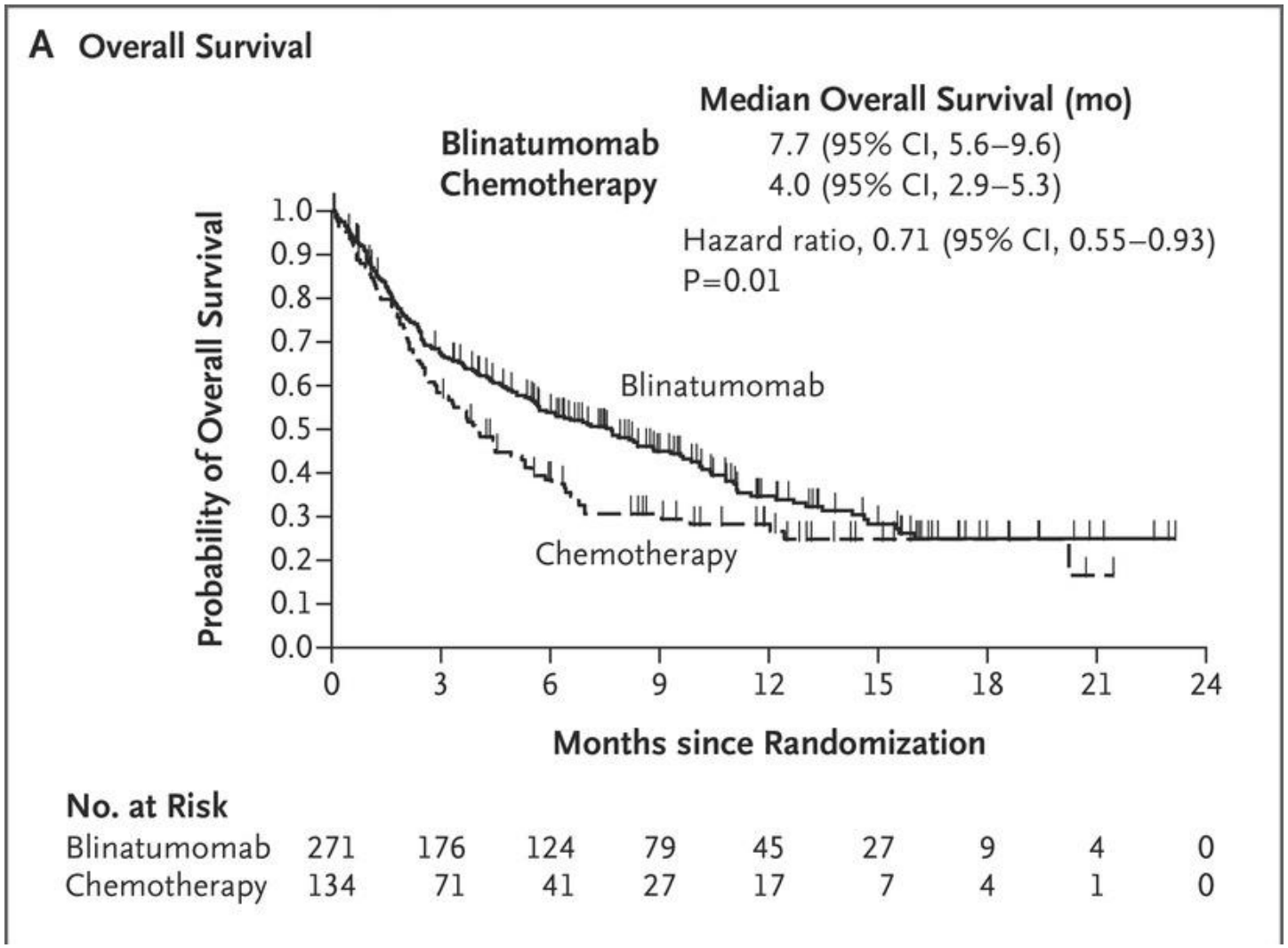
TOWER in B-ALL: Overall Survival



Kantarjian H et al. N Engl J Med 2017;376:836-847

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Best Hematologic Response Within 12 Weeks after Treatment Initiation

Table 2. Best Hematologic Response Within 12 Weeks after Treatment Initiation.*

Response Category	Blinatumomab Group (N=271)		Chemotherapy Group (N=134)		Treatment Difference (95% CI)	P Value†
	no.	*% (95% CI)*	*no.*	*% (95% CI)*	*percentage points*	
Complete remission with full hematologic recovery	91	33.6 (28.0–39.5)	21	15.7 (10.0–23.0)	17.9 (9.6–26.2)	<0.001
Complete remission with full, partial, or incomplete hematologic recovery	119	43.9 (37.9–50.0)	33	24.6 (17.6–32.8)	19.3 (9.9–28.7)	<0.001
Complete remission with partial hematologic recovery	24	8.9 (5.8–12.9)	6	4.5 (1.7–9.5)		
Complete remission with incomplete hematologic recovery	4	1.5 (0.4–3.7)	6	4.5 (1.7–9.5)		

* Data are summarized for all patients who underwent randomization (intention-to-treat population). Complete remission was defined as 5% or less bone marrow blasts and no evidence of disease and was further characterized according to the extent of recovery of peripheral blood counts as follows: complete remission with full recovery (platelet count of >100,000 per microliter and absolute neutrophil count of >1000 per microliter), complete remission with partial recovery (platelet count of >50,000 per microliter and absolute neutrophil count of >500 per microliter), or complete remission with incomplete recovery (platelet count of >100,000 per microliter or absolute neutrophil count of >1000 per microliter).

† Rates were compared with the use of a Cochran–Mantel–Haenszel test, with adjustment for the following stratification factors: age (<35 vs. ≥35 years), previous salvage therapy (yes vs. no), and previous allogeneic stem-cell transplantation (yes vs. no).

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Adverse Events

Table 3. Adverse Events.*

Event	Blinatumomab Group (N=267)	Chemotherapy Group (N=109)
	no. of patients (%)	
Any adverse event	263 (98.5)	108 (99.1)
Event leading to premature discontinuation of trial treatment	33 (12.4)	9 (8.3)
Serious adverse event	165 (61.8)	49 (45.0)
Fatal serious adverse event	51 (19.1)	19 (17.4)
Any adverse event of grade ≥3	231 (86.5)	100 (91.7)
Grade ≥3 adverse event of interest reported in at least 3% of patients in either group		
Neutropenia	101 (37.8)	63 (57.8)
Infection	91 (34.1)	57 (52.3)
Elevated liver enzyme	34 (12.7)	16 (14.7)
Neurologic event	25 (9.4)	9 (8.3)
Cytokine release syndrome	13 (4.9)	0
Infusion reaction	9 (3.4)	1 (0.9)
Lymphopenia	4 (1.5)	4 (3.7)
Any decrease in platelet count	17 (6.4)	13 (11.9)
Any decrease in white-cell count	14 (5.2)	6 (5.5)

* Data are summarized for all patients who received at least one dose of trial treatment.

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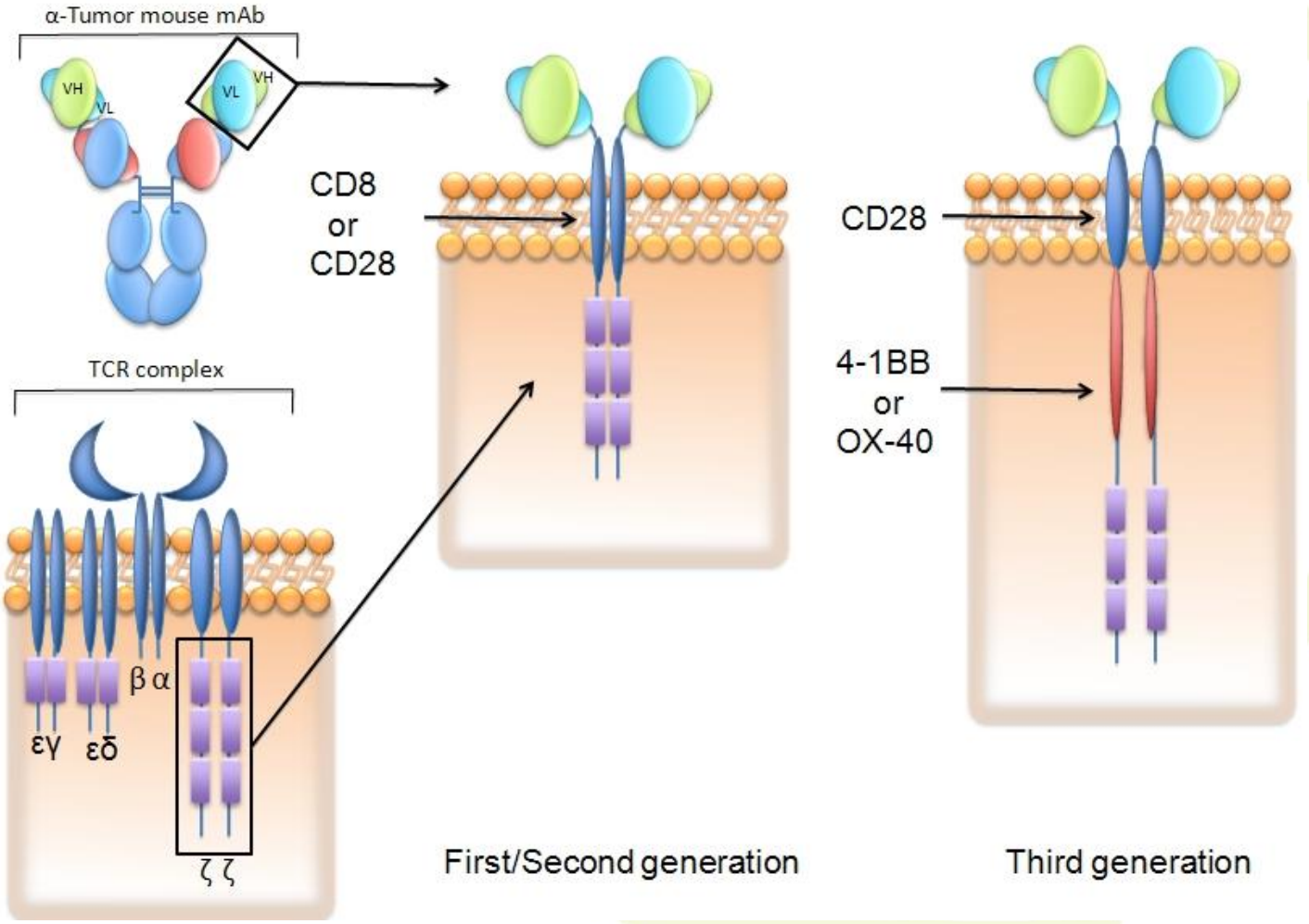
Chimeric Antigen Receptor T-cells



ZUMA-1: Patient Characteristics

Characteristic	DLBCL (n=73)	TFL/PMBCL (n=20)	All Patients (n=93)
Median age (range), years	59 (25-76)	58 (28-76)	59 (25-76)
Age ≥60 years, n (%)	36 (49)	9 (45)	45 (48)
Male, n (%)	47 (64)	15 (75)	62 (67)
ECOG performance status 1, n (%)	48 (66)	8 (40)	56 (60)
Median number of prior therapies (#)	3 (1-7)	4 (2-12)	3 (1-12)
IPI 3-4, n (%)	32 (44)	9 (45)	41 (44)
Disease stage III/IV, n (%)	64 (88)	15 (75)	79 (85)
Refractory subgroup, n (%)*			
Refractory to 2nd or later-line therapy	56 (77)	16 (80)	72 (77)
Relapse post-ASCT	15 (21)	4 (20)	19 (20)

Summary of Adverse Events

Adverse Event, n (%)	Cohort 1 (n=73)	Cohort 2 (n=20)	Total (N=93)
Grade ≥3 adverse event	68 (93)	18 (90)	86 (92)
Grade ≥3 cytokine release syndrome	10 (14)	2 (10)	12 (13)
Grade ≥3 neurologic events (NE)	18 (25)	9 (45)	27 (29)
Fatal events excluding PD 2 of 3 KTE-C19-related	1 (1)	2 (10)	3 (3)

- CRS and NE were generally reversible
  - All CRS events resolved except 1 cardiac arrest (Cohort 2)
  - 3 NEs ongoing at data-cut (Gr 1 memory impairment, Gr 1 tremor, Gr 2 tremor)
  - 1 patient died due to PD with NE ongoing
  - 38% received tocilizumab, 17% received corticosteroids, 17% received both
- No cases of cerebral edema
- Grade 5 events occurred in 3 patients (3%)
  - KTE-C19-related: HLH (Cohort 1) and cardiac arrest (Cohort 2) in the setting of CRS
  - KTE-C19-unrelated: pulmonary embolism (Cohort 2)

ZUMA-1 Pivotal Trial Met Primary Endpoint of ORR At the Interim Analysis (P<0.0001)*

Best Overall Response in Patients with ≥3 Month Follow-up

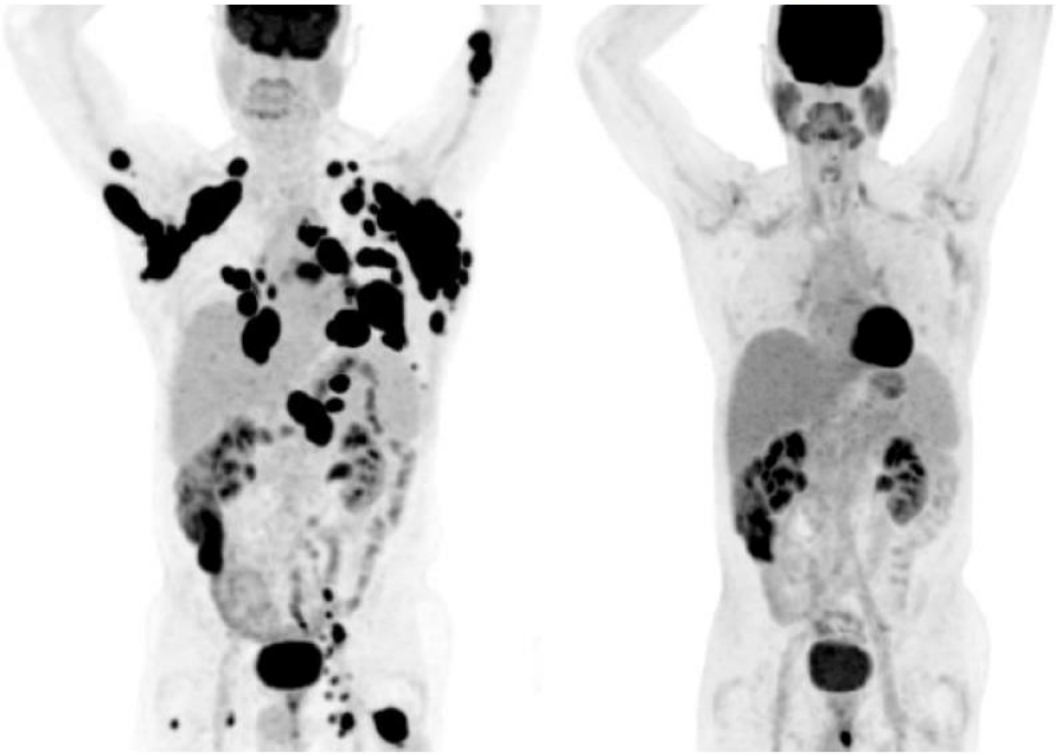
Subgroup	n	ORR	CR
DLBCL	51	76%*	47%
TFL / PMBCL	11	91%	73%
Total	**62**	**79%**	**52%**

**P*<0.0001 (exact binomial test comparing observed ORR to a historical control assumption of 20%)

- At month 3 assessment the CR rate was 39%
- 7 patients with SD/PR at 1 mo converted to CR at 3 mo
- Complete Response in key subgroups:
  - 75% (n=9/12) CR relapsed post-ASCT
  - 47% (n=23/49) CR refractory to ≥2nd line

Patient Case: Ongoing 9+ mo Durable CR in Refractory DLBCL

- 62-yo M with DLBCL
- Prior therapies
  - R-CHOP
  - R-GDP
  - R-ICE
  - R-lenalidomide
- No response to last 3 lines of therapy



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Adverse Events in CD19-trageted therapies

- Cytokine release syndrome (CRS)
  - Fever
  - Hypotension
  - Respiratory insufficiency
- Neurological changes
  - Delirium
  - Global encephalopathy
  - Aphasia
  - Seizure-like activities/seizure

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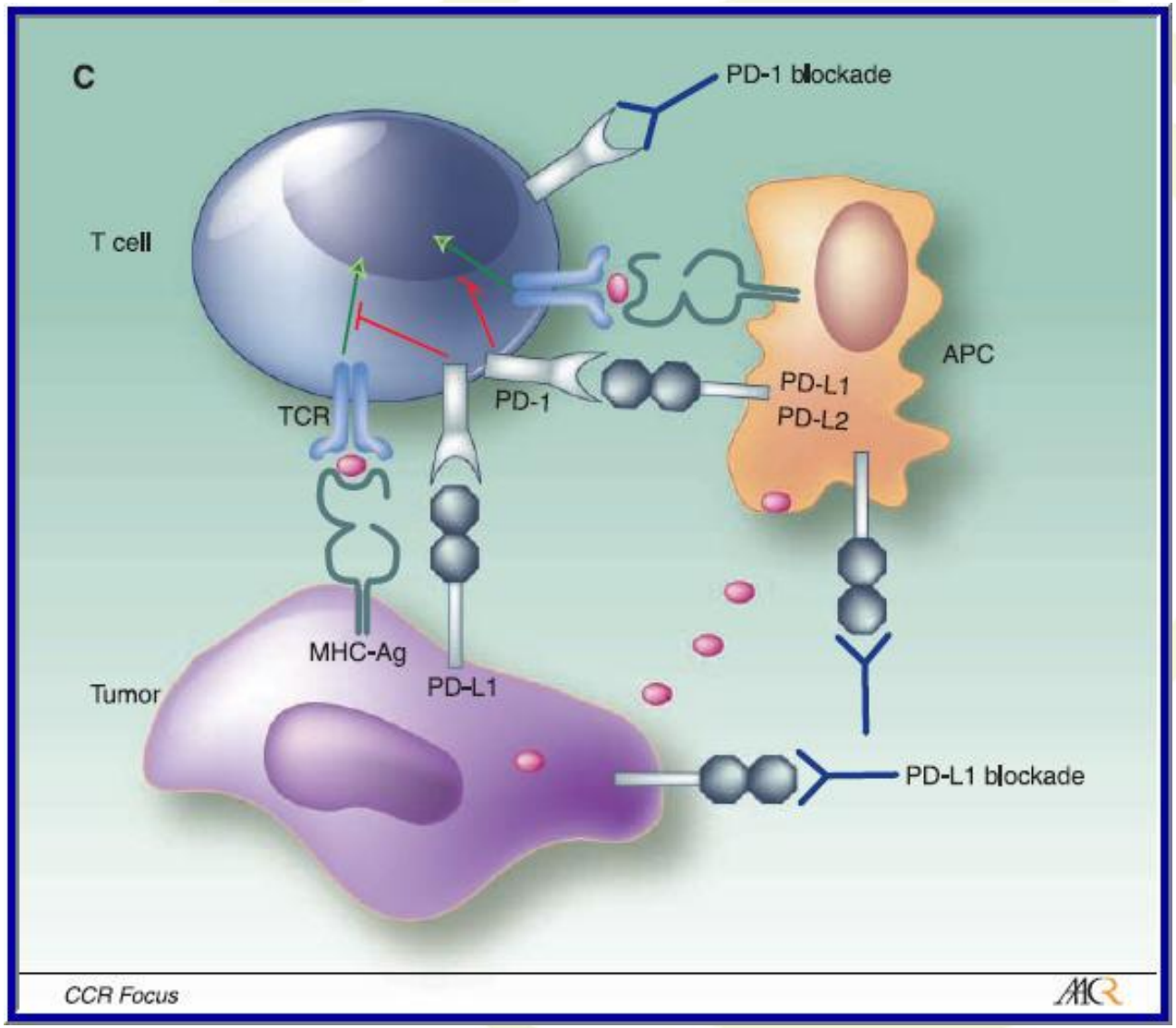
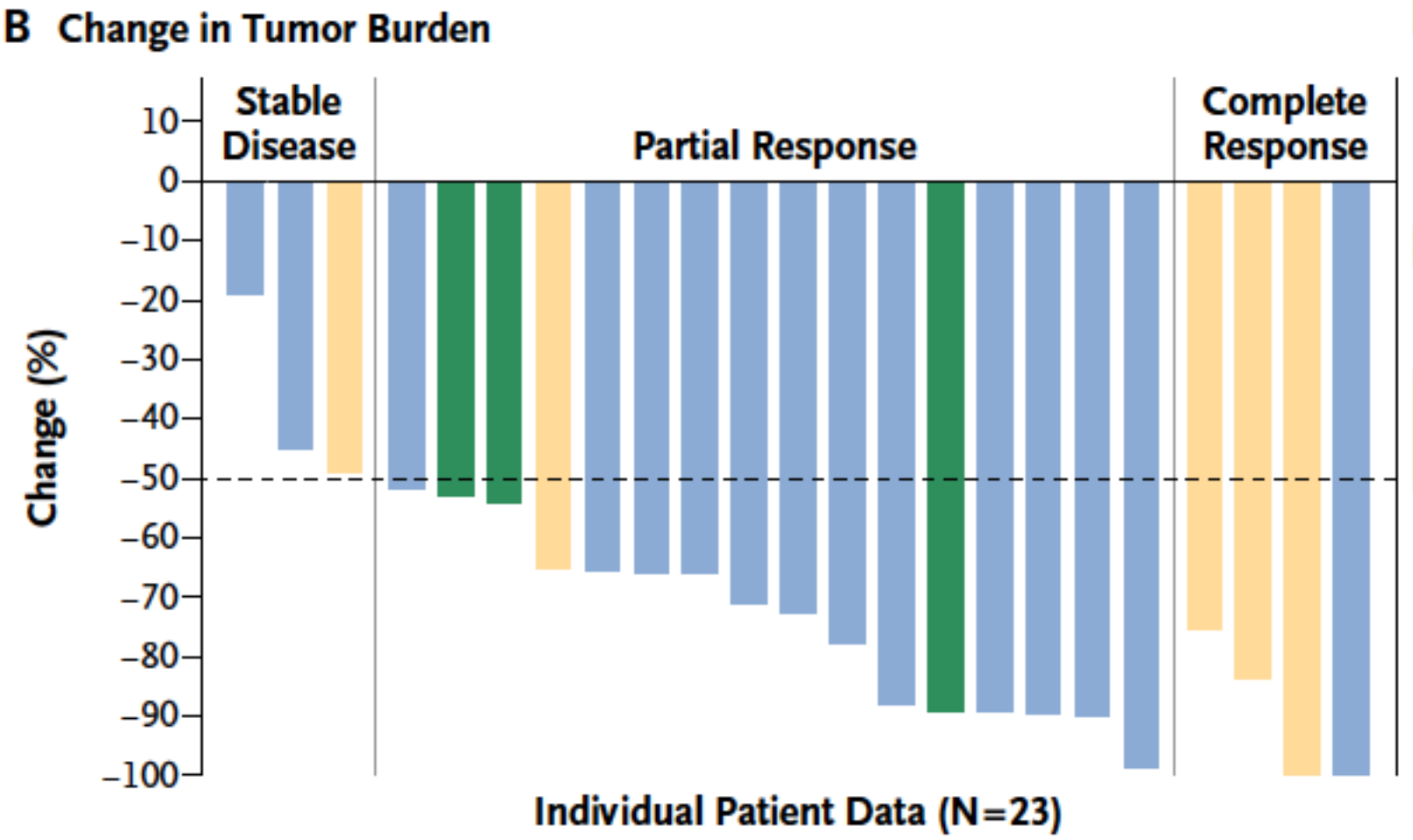
Immune Checkpoint Inhibition



Response In Hodgkin Lymphoma



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Conclusions

- As new therapies enter the clinic, it is important to understand their emerging toxicity profiles
- Appropriate patient selection is key to safe and effective delivery
- Traditional chemotherapy sensitivity no longer applies to downstream treatment selection
- Limited information on comparative therapy selection and sequencing

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Where to begin?

- http://www.sitcancer.org/research/cancer-immunotherapy-guidelines/hematologic

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