Strategies to strengthen the anti-tumour immune response – from dual targeting therapies to bispecific Antibodies

Professor Tobi Arkenau

Medical Oncologist

Executive Medical Director Sarah Cannon Research UK

Professorial Research Fellow, University College London

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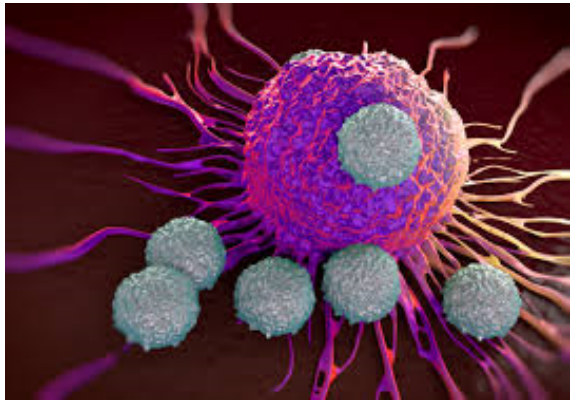
SARAH CANNON

Disclosures

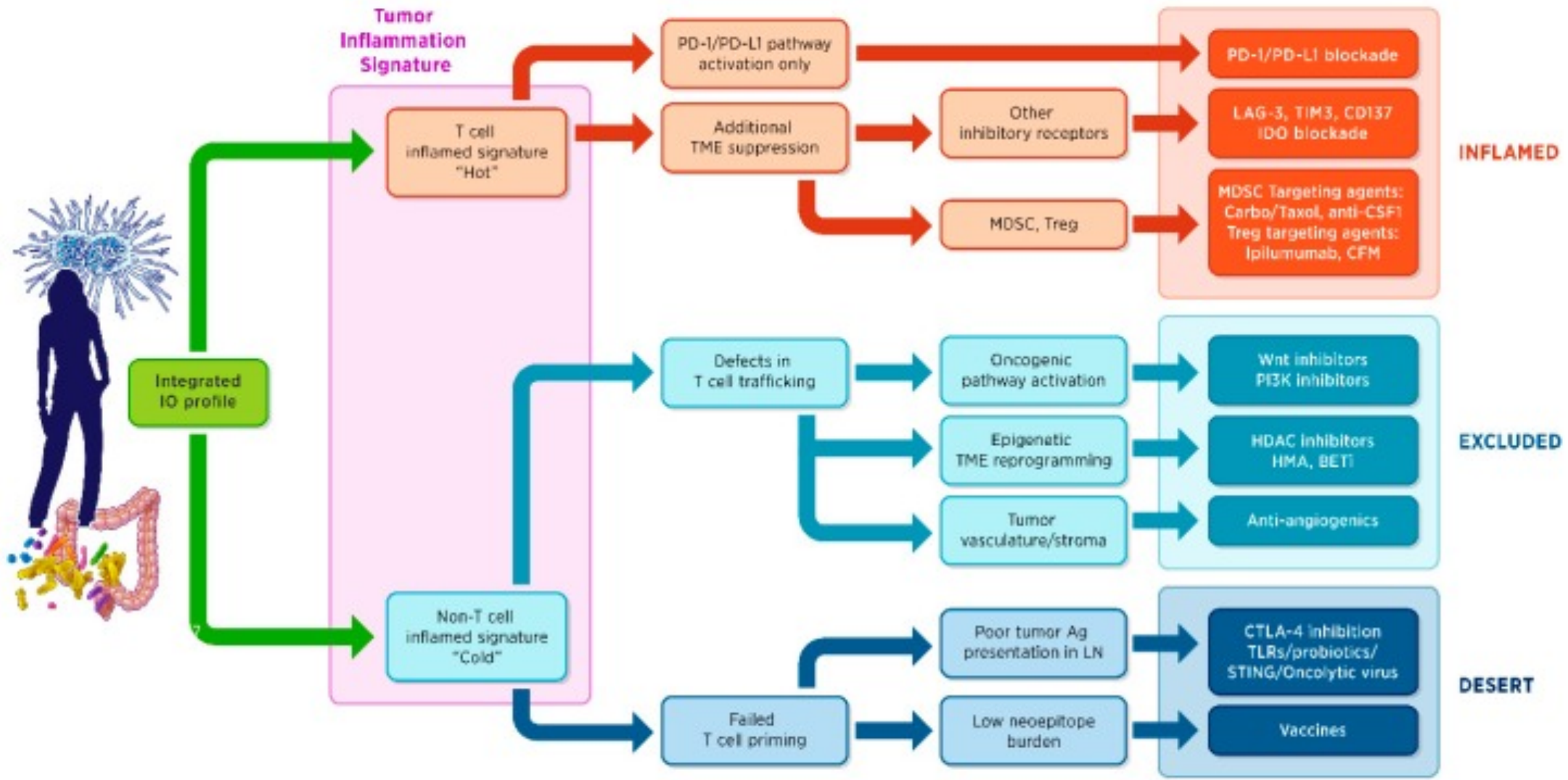
- Employment: Sarah Cannon/HCA
- Advisory Role: Biontech, Bicycle, Guardant, Roche, Bayer, iOncutra, Servier, Pierre Fabre, Array, Beigene, Taiho



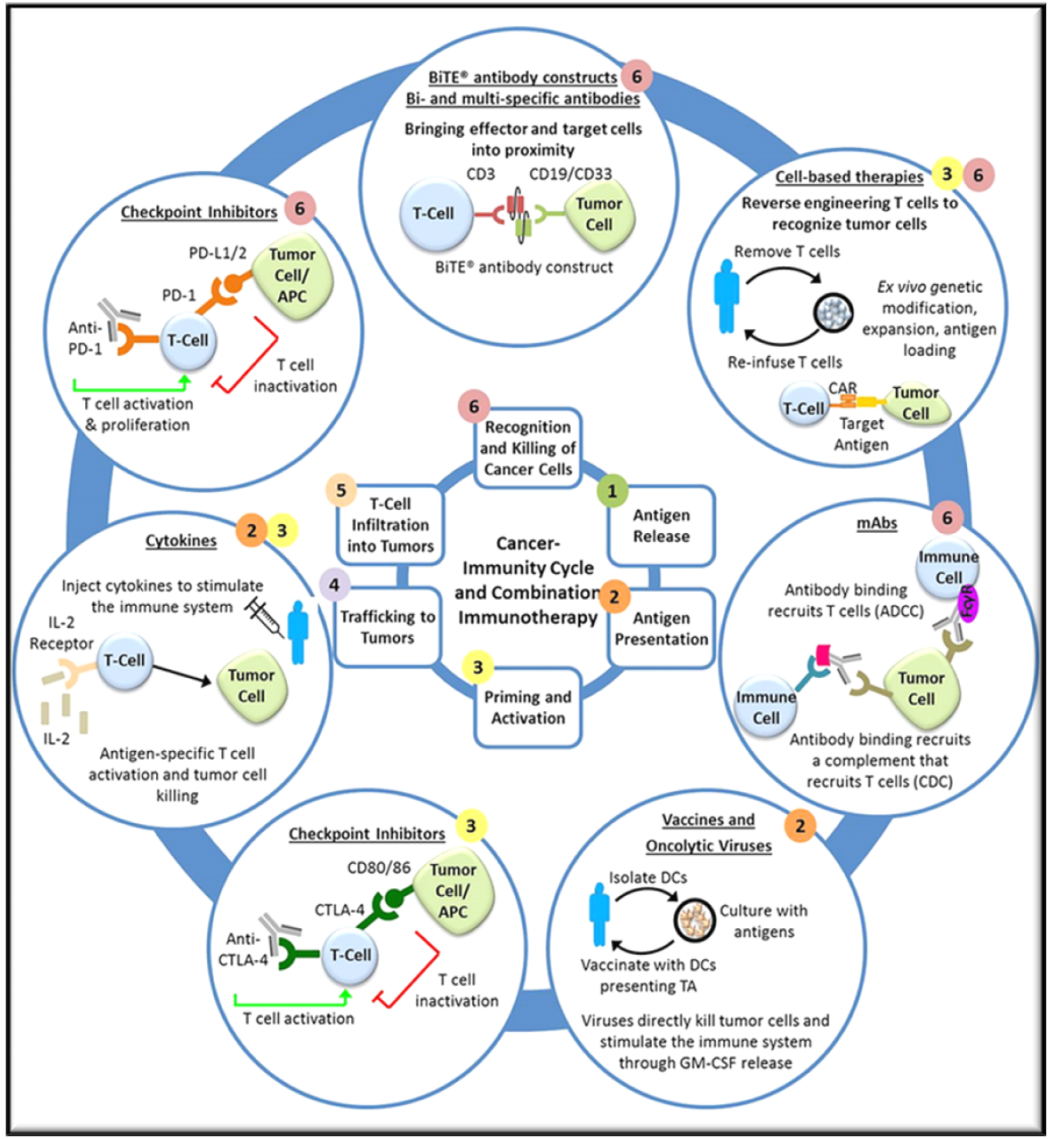
Agenda

- ✓ Targeting the Cancer Immunity Cycle
- ✓ Recent IO-IO combination strategies (PD-1/PDL1 – CTLA4, OX40, TIGIT, LAG3)
- ✓ Evolution of Bispecific Antibodies
- ✓ Future and Challenges

Turning up the heat on non-immunereactive or immune-escaping tumours



Targeting the Cancer Immunity Cycle



Why? single agent checkpoint inhibition often results in low response rates, short to median term duration of response and survival, development of resistance….

Block other co-inhibitory: LAG3, TIM3, KIR, VISTA, TIGIT

Activate co-stimulatory: 4-1BB, OX-40, GITR, CD27, ICOS

Block inhibitory molecules: IDOi, TGFbi, CSF1Ri, anti-IL-6 or anti-IL-10

Effect trafficking: anti-VEGF, CCL5, CXCR4i

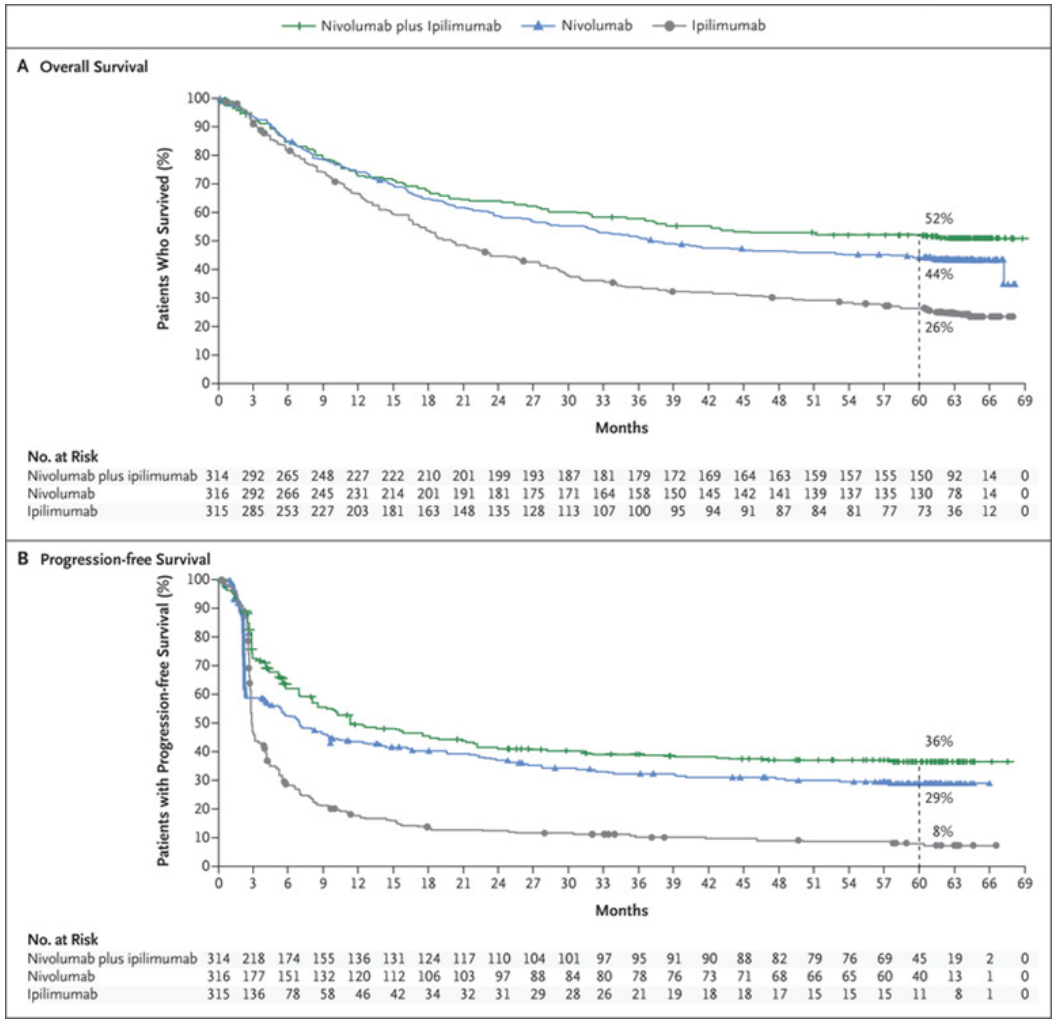
Vaccines: TVEC-oncolytic virus, Neoantigen, other cellular

Adoptive Cellular therapy: TIL, CAR-T cells, TCR T-cells

Dual immunotherapy approaches – PD-1/CTLA4

- By displaying a high degree of T cell infiltration, hot tumours represent a fertile ground for effective CPI-monotherapy or combination therapy
- Exhausted or dysfunctional TILs express a number of inhibitory receptors, most notably cytotoxic T lymphocyte- associated antigen 4 (CTLA4) and PD-1
- CTLA4 inhibits T cells' early activation and differentiation (typically in the lymph nodes) whereas PD-1 modulates their effector functions (mostly within tumours), which can lead to T cell exhaustion
- The non- redundant nature of CTLA4 and PD-1 makes them good targets for dual checkpoint blockade

Ipilimumab (CTLA-4) and Nivolumab (PD-1) FDA approved indications: 1st-line NSCLC, RCC, Melanoma and 2nd-line MSI+ CRC, HCC

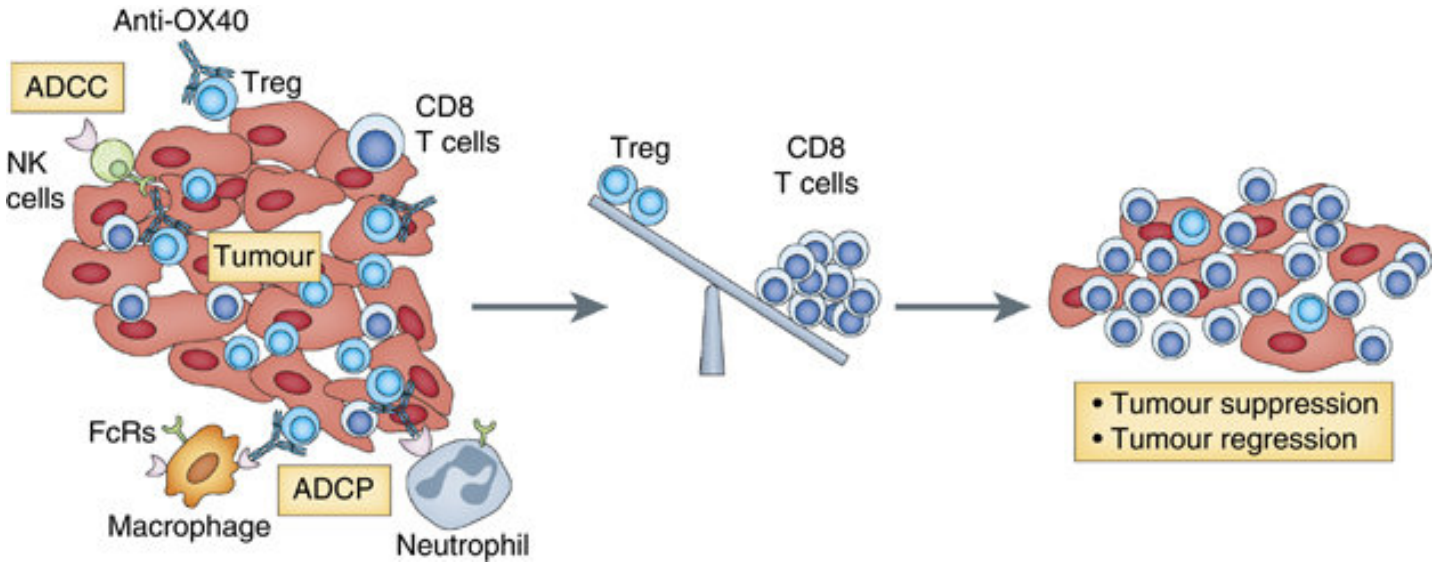


Common irAEs	CTLA-4 Inhibitors	PD-1 Inhibitors	Combination of Nivolumab and Ipilimumab
Cutaneous			
Rash	34%	10–21%	30%
Pruritus	25–30%	11–21%	35%
Vitiligo	4%	11%	9%
Gastrointestinal Disease			
Diarrhea	38%	8–20%	45%
Colitis	8–10%	1–3%	13%
Neurological Disease	4%	6%	12%
Endocrine system			
Hypothyroidism	1–2%	4–10%	17%
Hyperthyroidism	2–3%	Less than 1%	7%
Lung			
Pneumonitis	Less than 1%	1–5%	7%
Liver			
Hepatitis	Less than 1%	1–2%	14–18%

Ikooshaki O et al. Int. J. Mol. Sci. 2020; Larkin et al, N Engl J Med 2019

Change the balance towards T-effector cells – OX40 inhibition

The inhibition of OX40+ regulatory T-cells (Tregs) in tumours by ADCC and ADCP mediated by intratumoural natural killer (NK) cells, macrophages and neutrophils, can swing the balance toward CD8+ T-cell effector function, resulting in tumour regression.



Safety and Tolerability of MEDI0562 in Combination with Durvalumab or Tremelimumab in Patients with Advanced Solid Tumors

Jonathan W. Goldman,[1] Sarina A. Piha-Paul,[2] Brendan Curti,[3] Katrina S. Pedersen,[4] Todd M. Bauer,[5] Stefanie L. Groenland,[6] Richard Carvajal,[7] Vaishali Chhaya,[8] Scott A. Hammond,[8] Katie Streicher,[8] Danielle M. Townsley,[8] Young Kwang Chae,[9] Jens Voortman,[10] Aurelien Marabelle,[11] John Powderly[12]

[1]David Geffen School of Medicine, UCLA, Los Angeles, CA, USA; [2]University of Texas, MD Anderson Cancer Center, Houston, TX, USA;
[3]Providence Cancer Center and Earle A. Chiles Research Institute, Portland, OR, USA; [4]Washington University School of Medicine, St. Louis, MO, USA;
[5]Sarah Cannon Research Institute/Tennessee Oncology, PLLC, Nashville, TN, USA; [6]The Netherlands Cancer Institute–Antoni van Leeuwenhoek, Amsterdam, The Netherlands;
[7]Columbia University Medical Center, New York, NY, USA; [8]AstraZeneca, Gaithersburg, MD, USA;
[9]Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL, USA;
[10]Amsterdam UMC, Vrije Universiteit Amsterdam, Department of Medical Oncology, Cancer Center Amsterdam, The Netherlands;
[11]Gustave Roussy, Université Paris-Saclay, Villejuif, France; [12]Carolina BioOncology Institute, Huntersville, NC, USA

Baseline Characteristics

Baseline characteristic	Treatment Arm A MEDI0562 + durvalumab N= 27	Treatment Arm B MEDI0562 + tremelimumab N=31	Total study population N=58
Median age, years	58.0	55.0	56.5
(range)	(31, 90)	(25, 79)	(25, 90)
Male, n (%)	10 (37.0)	18 (58.1)	28 (48.3)
Race*, n (%)			
White	20 (74.1)	21 (67.8)	41 (70.7)
Black or African American	3 (11.1)	1 (3.2)	4 (6.9)
Asian	2 (7.4)	1 (3.2)	3 (5.2)
Other	0	5 (16.1)	5 (8.6)
Unknown	2 (7.4)	3 (9.7)	5 (8.6)
ECOG performance status, n (%)			
0	12 (44.4)	11 (35.5)	23 (39.7)
1	15 (55.6)	20 (64.5)	35 (60.3)
Most common tumor type, n (%)			
Cervical	7 (25.9)	2 (6.5)	9 (15.5)
Colon/Rectum	3 (11.1)	4 (12.9)	7 (12.1)
Bladder	3 (11.1)	1 (3.2)	4 (6.9)
Pancreatic	0	3 (9.7)	3 (5.2)
Prior IO therapy, n (%)			
Atezolizumab	1 (3.7)	1 (3.2)	2 (3.4)
Pembrolizumab	0	1 (3.2)	1 (1.7)

- Patient demographics and baseline characteristics were well-balanced between treatment arms

*Patients who selected multiple categories are classed as 'unknown'.
IO, immuno-oncology

Safety Summary: AEs

	Treatment Arm A MEDI0562 + durvalumab N=27	Treatment Arm B MEDI0562 + tremelimumab N=31	Total study population N=58
Any event, n (%)			
Any AE	26 (96.3)	31 (100)	57 (98.3)
Grade ≥3 AE	20 (74.1)	21 (67.7)	41 (70.7)
Serious AE	14 (51.9)	16 (51.6)	30 (51.7)
Death*	1 (3.7)	1 (3.2)	2 (3.4)
AEs leading to discontinuation of treatment	6 (22.2)	6 (19.4)	12 (20.7)
MEDI0562-related events, n (%)			
Any AE	20 (74.1)	24 (77.4)	44 (75.9)
Grade ≥3 AE	6 (22.2)	10 (32.3)	16 (27.6)
Serious AE	3 (11.1)	5 (16.1)	8 (13.8)
AEs leading to discontinuation of MEDI0562	6 (22.2)	6 (19.4)	12 (20.7)
Durvalumab-related events, n (%)			
Any AE	20 (74.1)	-	20 (34.5)
Grade ≥3 AE	6 (22.2)	-	6 (10.3)
Serious AE	3 (11.1)	-	3 (5.2)
AEs leading to discontinuation of durvalumab	6 (22.2)	-	6 (10.3)
Tremelimumab-related events, n (%)			
Any AE	-	22 (71.0)	22 (37.9)
Grade ≥3 AE	-	11 (35.5)	11 (19.0)
Serious AE	-	5 (16.1)	5 (8.6)
AEs leading to discontinuation of tremelimumab	-	5 (16.1)	5 (8.6)

- Median duration of exposure to MEDI0562 was 12.0 (range 2.0–80.9) weeks in the MEDI0562 + durvalumab arm and 8.0 (range 2.0–42.0) weeks in the MEDI0562 + tremelimumab arm

Safety data are assessed in the as-treated population.

*AEs leading to death were renal failure (7.5 mg MEDI0562 + 1500 mg durvalumab) and Grade 4 colitis leading to Grade 5 multiple organ dysfunction syndrome (22.5 mg MEDI0562 + 225 mg tremelimumab)

AE, adverse event

Preliminary Clinical Activity

	Treatment Arm A MEDI0562 + durvalumab N=26	Treatment Arm B MEDI0562 + tremelimumab N=31	Total study population N=57
ORR, n (%)	3 (11.5)	0	3 (5.3)
(95% CI)	(2.4, 30.2)	(0.0, 11.2)	(1.1, 14.6)
Best overall response, n (%)			
PR†	3 (11.5)	0	3 (5.3)
SD	9 (34.6)	9 (29.0)	18 (31.6)
PD	9 (34.6)	16 (51.6)	25 (43.9)
NE	5 (19.2)	6 (19.4)	11 (19.3)
Median PFS (RECIST), months	2.4	1.8	1.9
(95% CI)	(1.8, 5.6)	(1.7, 1.9)	(1.8, 2.6)
PFS rate at 6 months (RECIST), %	25.0	17.1	20.5
(95% CI)	(10.3, 42.9)	(5.9, 33.1)	(10.8, 32.4)
Median OS, months, n	17.4	8.5	11.9
(95% CI)	(6.7, NA)	(4.9, 25.5)	(7.2, 25.5)
OS rate at 12 months (%)	59.2	38.9	48.9
(95% CI)	(37.3, 75.7)	(20.0, 57.5)	(34.3, 62.0)

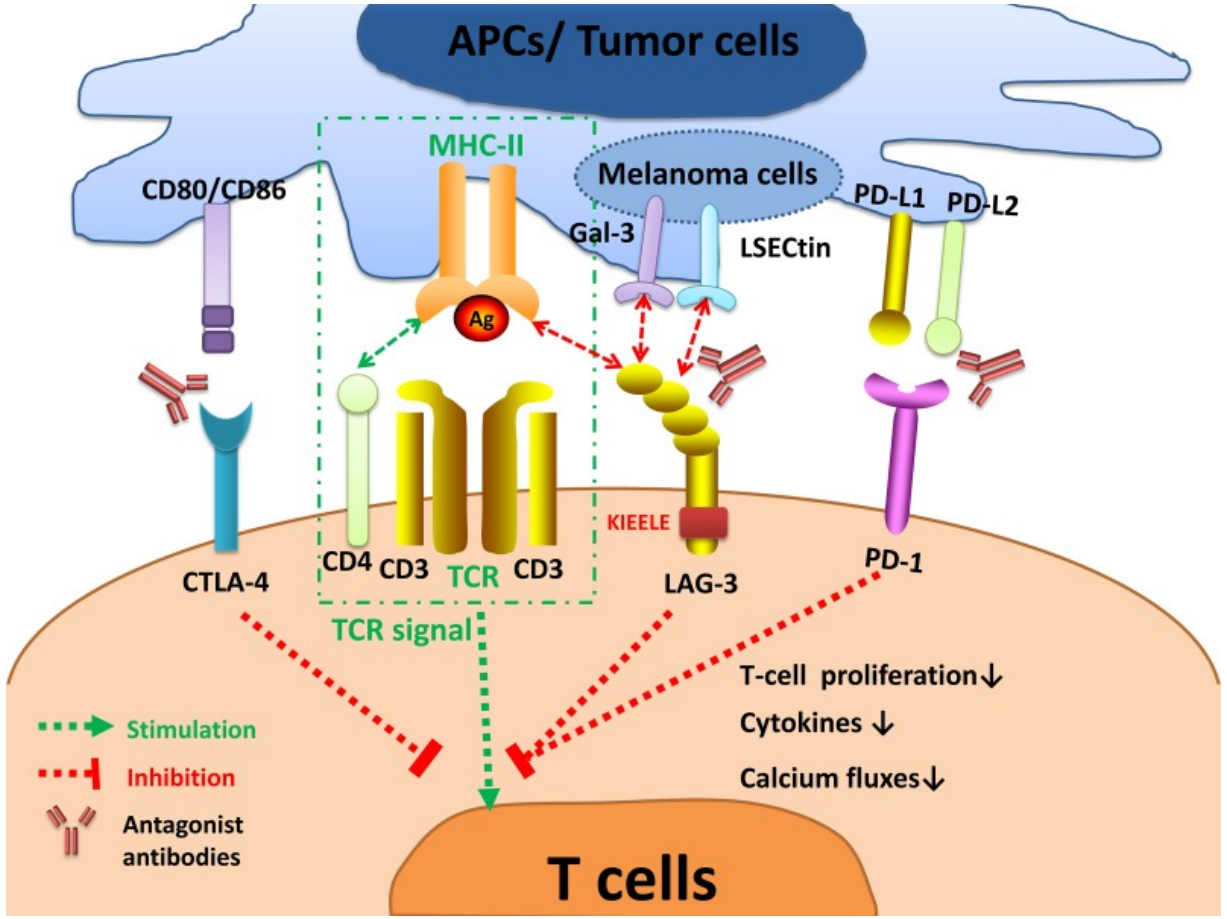
- The DCR at ≥24 weeks post treatment in the MEDI0562 + durvalumab arm was 30.8% (95% CI, 14.3–51.8) versus 16.1% (95% CI, 5.5–33.7) in the MEDI0562 + tremelimumab arm

All responses are reported for the response-evaluable population (all patients in the as-treated population with ≥1 post-baseline tumor assessment or who died from any cause or discontinued due to clinical PD, prior to any post-baseline tumor assessment)
Responders consisted of two patients with cervical squamous cell carcinoma (7.5 mg MEDI0562 + 1500 mg durvalumab and 22.5 mg MEDI0562 + 1500 mg durvalumab) and one patient with cervical clear-cell carcinoma (7.5 mg MEDI0562 + 1500 mg durvalumab).

CI, confidence interval; DCR, disease control rate; NA, not available; NE, not evaluable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial disease; PD, progressive disease; RECIST, Response Evaluable Criteria in Solid Tumors; SD, stable disease; TTR, time to response

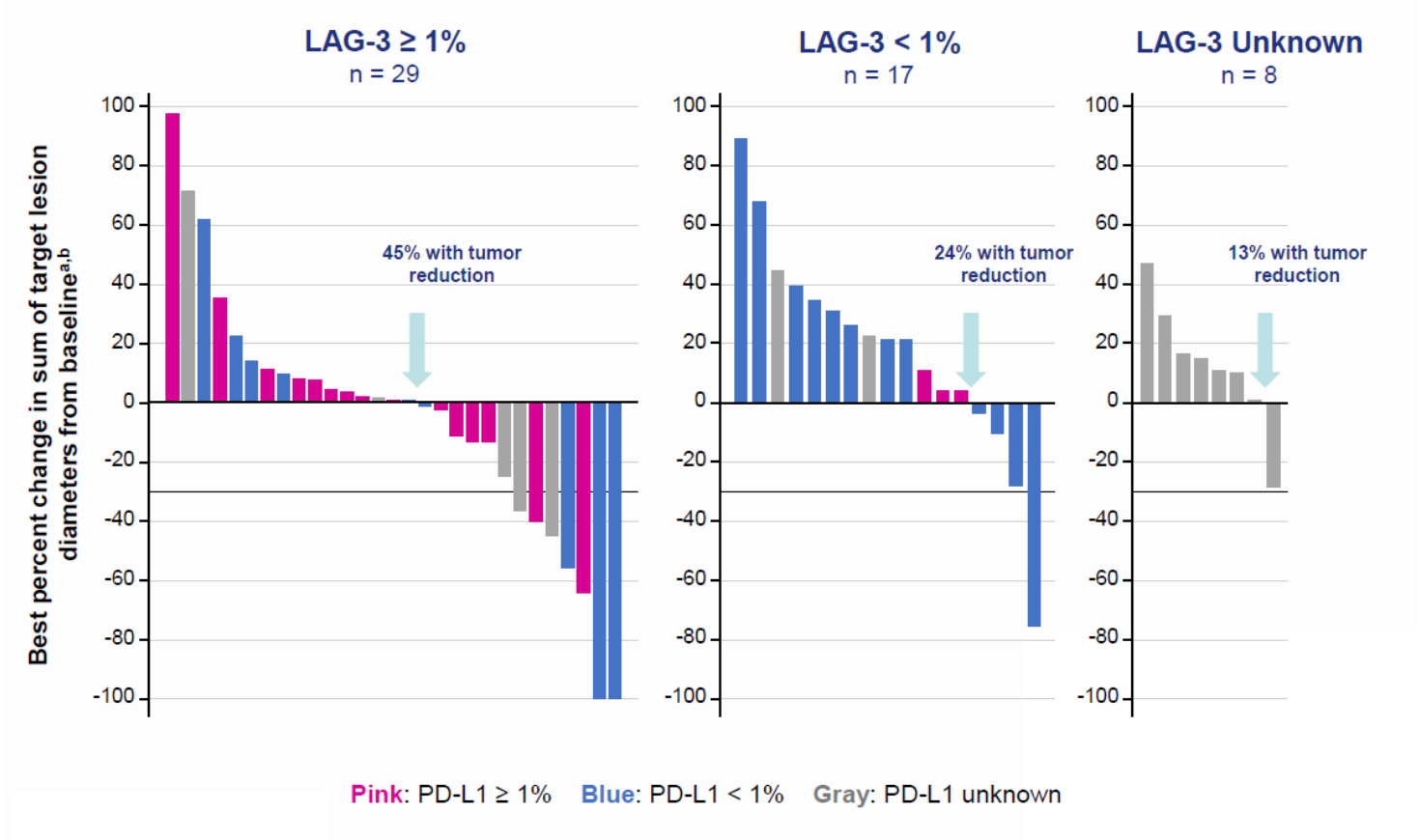
Inhibition of the co-stimulatory receptor, LAG3

- The inhibitory immune checkpoint lymphocyte activation gene-3 (LAG-3) suppresses T cells activation and cytokines secretion
- The interaction of LAG-3 with MHC-II prohibits the binding of the same MHC molecule to a TCR and CD4, thus suppressing the TCR signal.
- LAG-3 has differential inhibitory impacts on various types of lymphocytes and shows a remarkable synergy with PD-1 to inhibit immune responses



Efficacy of BMS-986016 (LAG-3) in combination with nivolumab (PD-1) in pts with melanoma who progressed during prior anti–PD-1/PD-L1 therapy in all-comer and biomarker-enriched populations

- 68 pts were treated; 57% had prior anti–CTLA-4 and 46% had ≥ 3 lines of prior therapy.
- ORR was 11.5% (1 complete, 6 partial responses); DCR was 49%.
- Median DOR was not reached (min [0.1+], max [39.3+]). ORR was ≥ 3.5-fold higher in pts with LAG-3 expression ≥ 1% vs<1%, regardless of PD-L1 expression

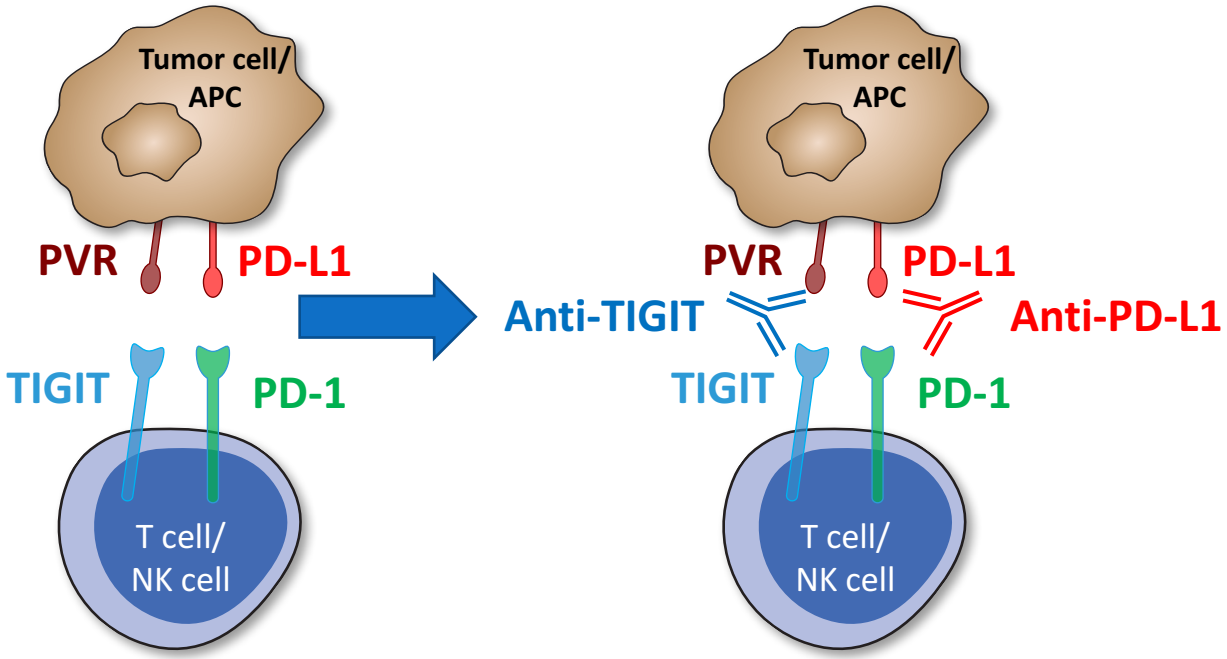


Ascierto P et al 2018, ESMO

Inhibition of the co-stimulatory receptor, TIGIT

- TIGIT is an important inhibitory molecule within the PVR/nectin family, and is associated with human cancers and T cell exhaustion phenotypes.
- TIGIT is an attractive cancer immunotherapy target owing to its role in many of the steps that generate cancer immunity.

TIGIT expression correlates with PD-1, especially in tumour-infiltrating T cells, and is often co-expressed on the same cell



Hypothesis:

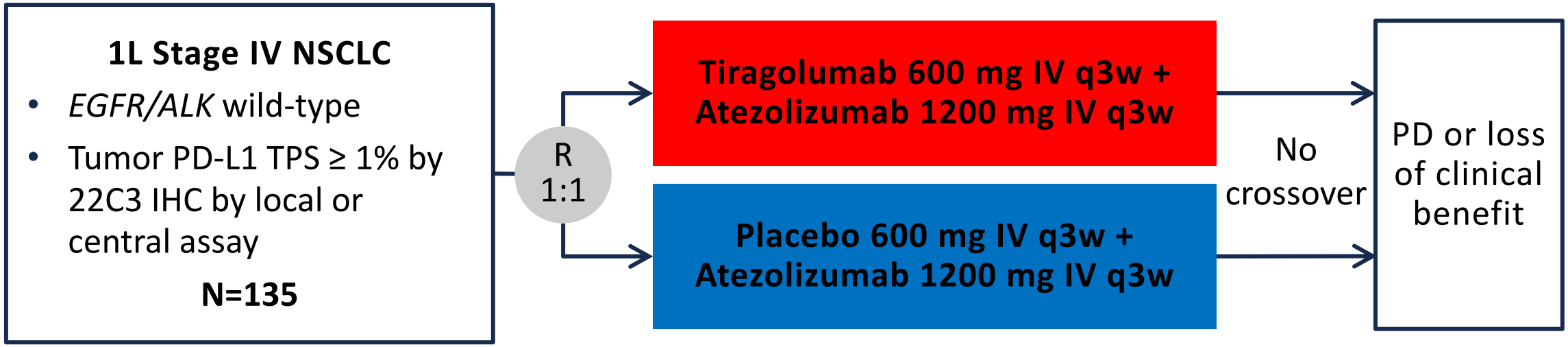
Anti-TIGIT antibodies, which prevent TIGIT from binding, may restore anti-tumour response and enhance anti-PD-L1 antibodies

CITYSCAPE: Primary Analysis of a Randomized, Double-Blind, Phase II Study of the Anti-TIGIT Antibody Tiragolumab plus Atezolizumab versus Placebo plus Atezolizumab as 1L Treatment in Patients with PD-L1-Selected NSCLC

Delvys Rodriguez-Abreu[1], **Melissa L. Johnson[2]**, Maen Hussein[3], Manuel Cobo[4], Anjan J. Patel[5], Nevena Secen[6], Ki Hyeong Lee[7], Bartomeu Massuti[8], Sandrine Hiret[9], James Chih-Hsin Yang[10], Fabrice Barlesi[11], Dae Ho Lee[12], Luis Paz-Ares[13], Robert W. Hsieh[14], Karen Miller[14], Namrata Patil[14], Patrick Twomey[14], Amy V. Kapp[14], Raymond Meng[14], Byoung Chul Cho[15]

[1]Hospital Universitario Insular de Gran Canaria, Las Palmas, Spain; [2]Sarah Cannon Research Institute (SCRI), Nashville, TN, USA; [3] SCRI Florida Cancer Specialists, Leesburg, FL, USA; [4]Medical Oncology, Hospital Regional Universitario de Málaga, Málaga, Spain; [5]SCRI, Florida Cancer Specialists, Sarasota, FL, USA; [6]Institute of Lung Diseases Vojvodina, Sremska Kamenica, Serbia; [7]Chungbuk National University Hospital, Cheongju, South Korea; [8]Hospital Universitario de Alicante, Alicante, Spain; [9]Institute de Cancerologie de l'Ouset, Saint Herblain, France; [10]National Taiwan University Hospital, Taipei, Taiwan; [11]Aix Marseille University, Marseille, France; [12]Asan Medical Center, Seoul, South Korea; [13]Hospital Universitario Doce de Octubre, Madrid, Spain; [14]Genentech, South San Francisco, CA, USA; [15]Yonsei University College of Medicine, Seoul, South Korea

CITYSCAPE Study Design



- **Co-Primary Endpoints: ORR** and **PFS**
- **Key Secondary Endpoints: Safety**, DOR, OS, Patient-reported outcomes (PROs)
- **Exploratory Endpoints:** Efficacy analysis by PD-L1 status

Stratification Factors:

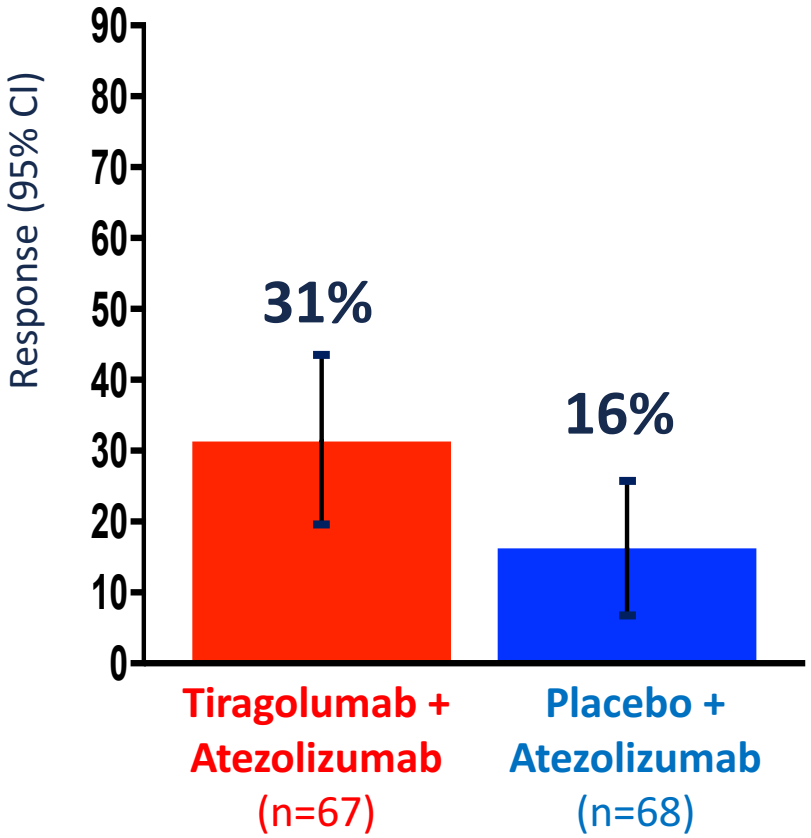
- PD-L1 TPS (1-49% vs ≥ 50%)
- Histology (Non-Squamous vs Squamous)
- Tobacco use (yes vs no)

DOR = duration of response; IHC = immunohistochemistry; ORR = confirmed overall response rate; OS = overall survival; PD = progressive disease; PFS = progression free survival ; q3w = every 3 weeks; R = randomized; TPS = tumor proportion score

Confirmed Overall Response Rate (ORR) and PFS

ITT: ORR

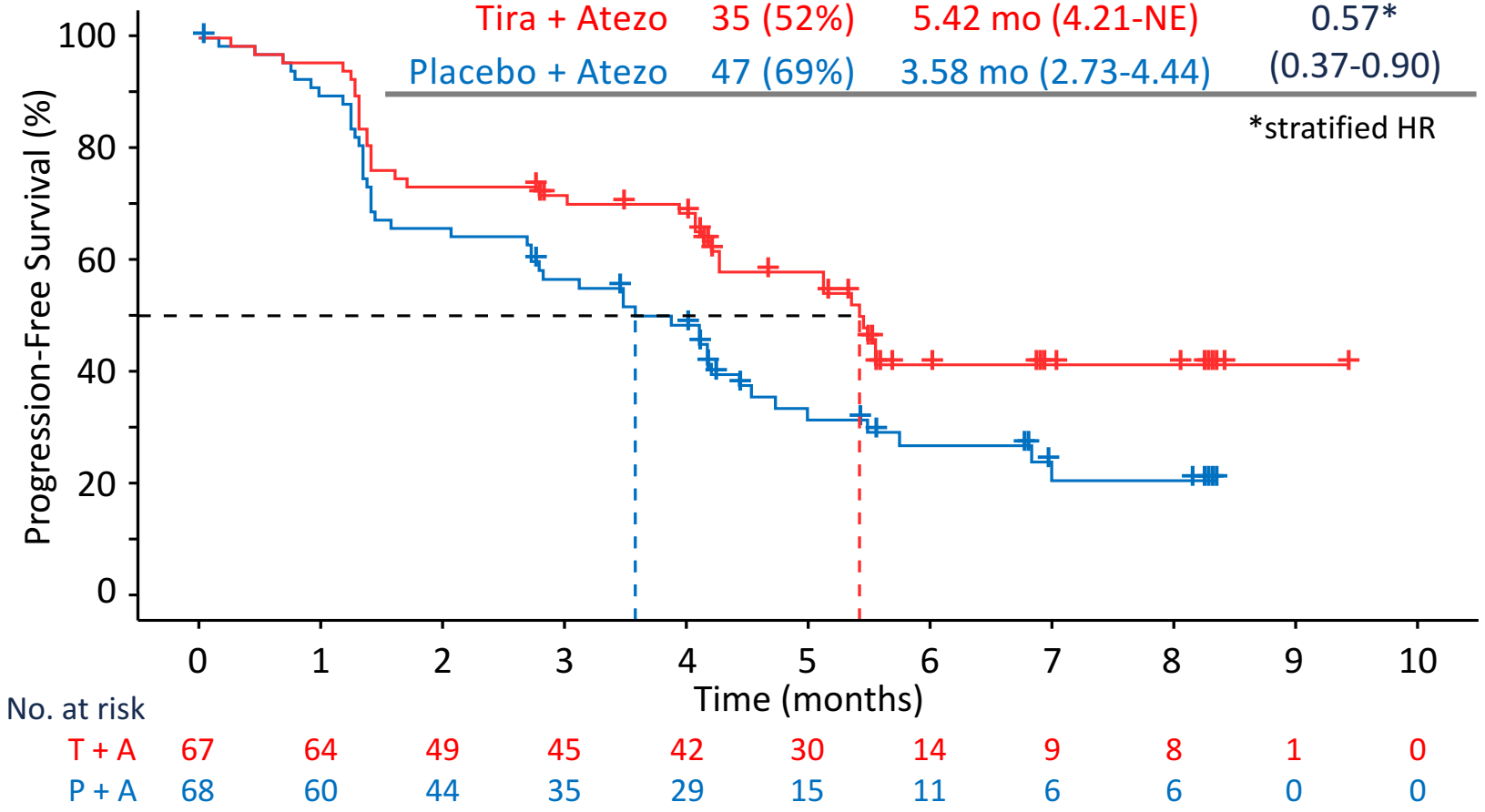
(n=135)



ITT: Investigator-Assessed PFS

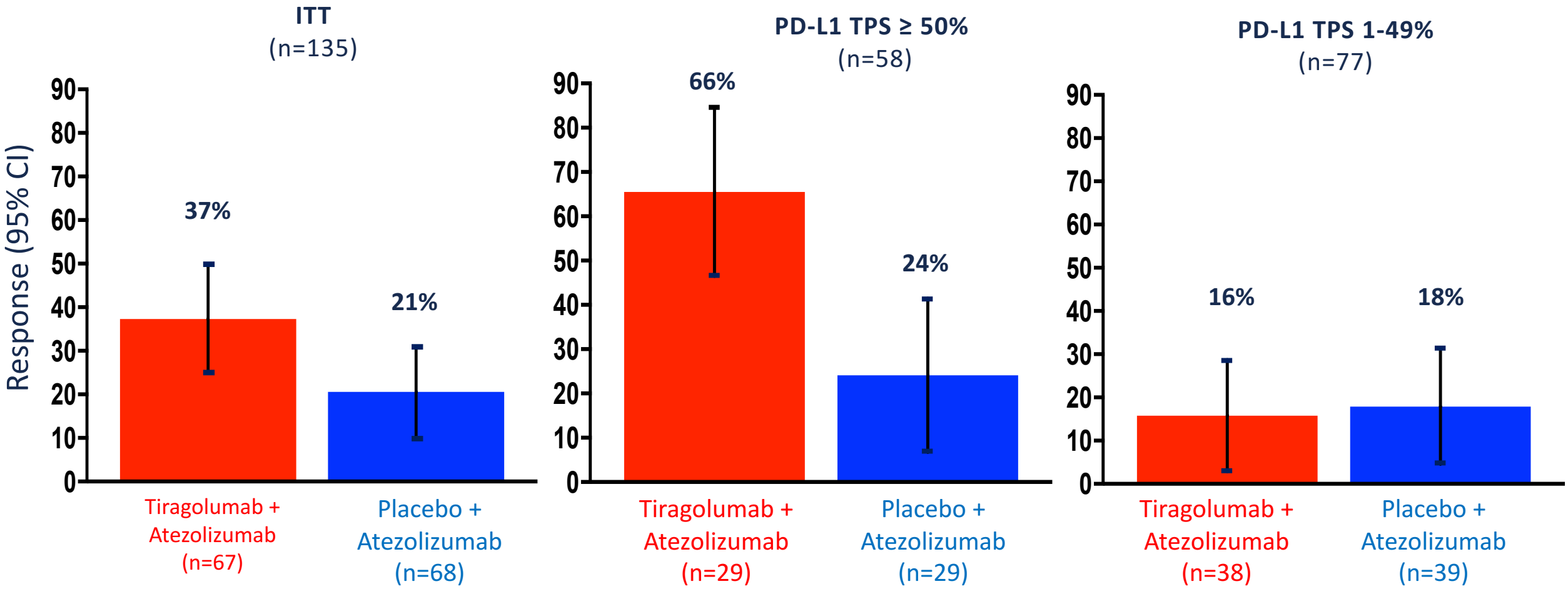
	Events	Median (95% CI)	HR (95% CI)
Tira + Atezo	35 (52%)	5.42 mo (4.21-NE)	0.57* (0.37-0.90)
Placebo + Atezo	47 (69%)	3.58 mo (2.73-4.44)	

*stratified HR



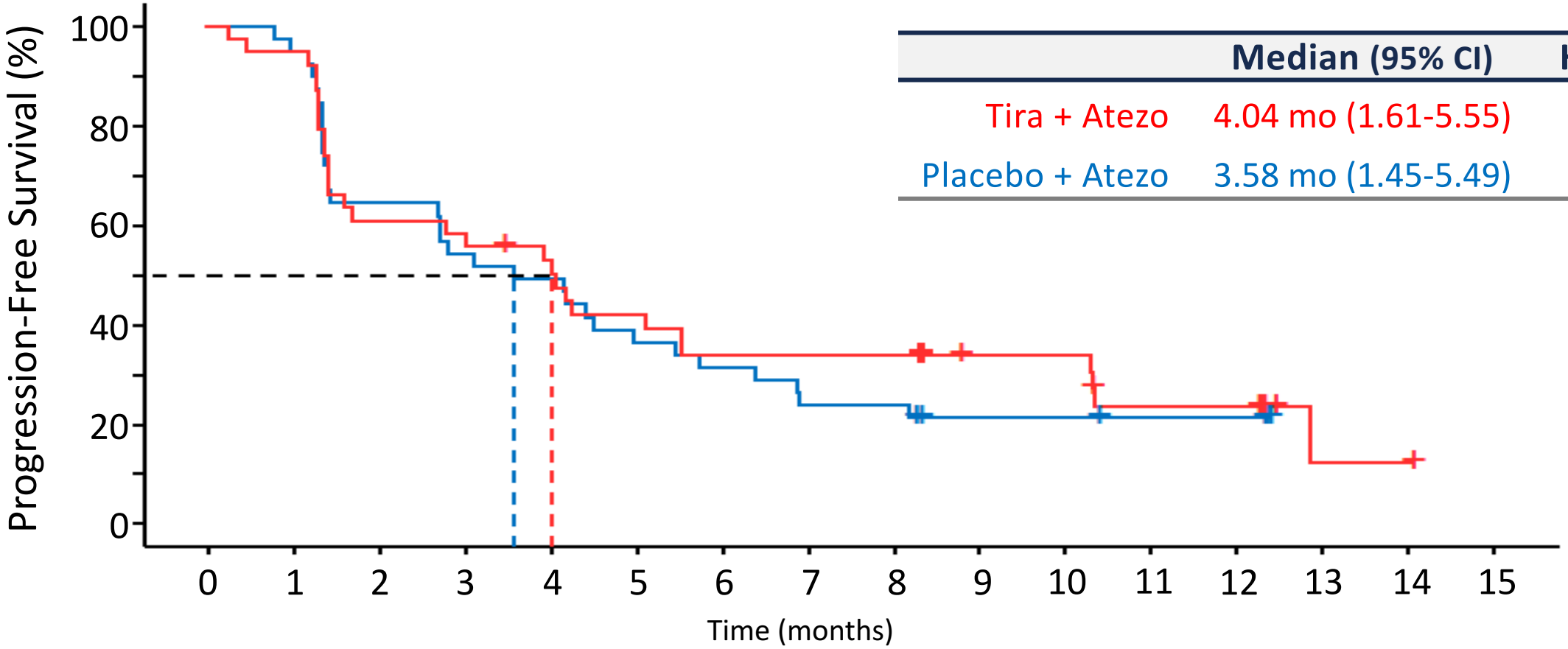
ITT= intention-to-treat; NE = non-evaluable, P+A = placebo + atezolizumab; T+A = tiragolumab + atezolizumab

Confirmed Overall Response Rate (ORR)



ITT = intention-to-treat; TPS = tumor proportion score

Investigator-Assessed PFS: PD-L1 TPS 1-49%

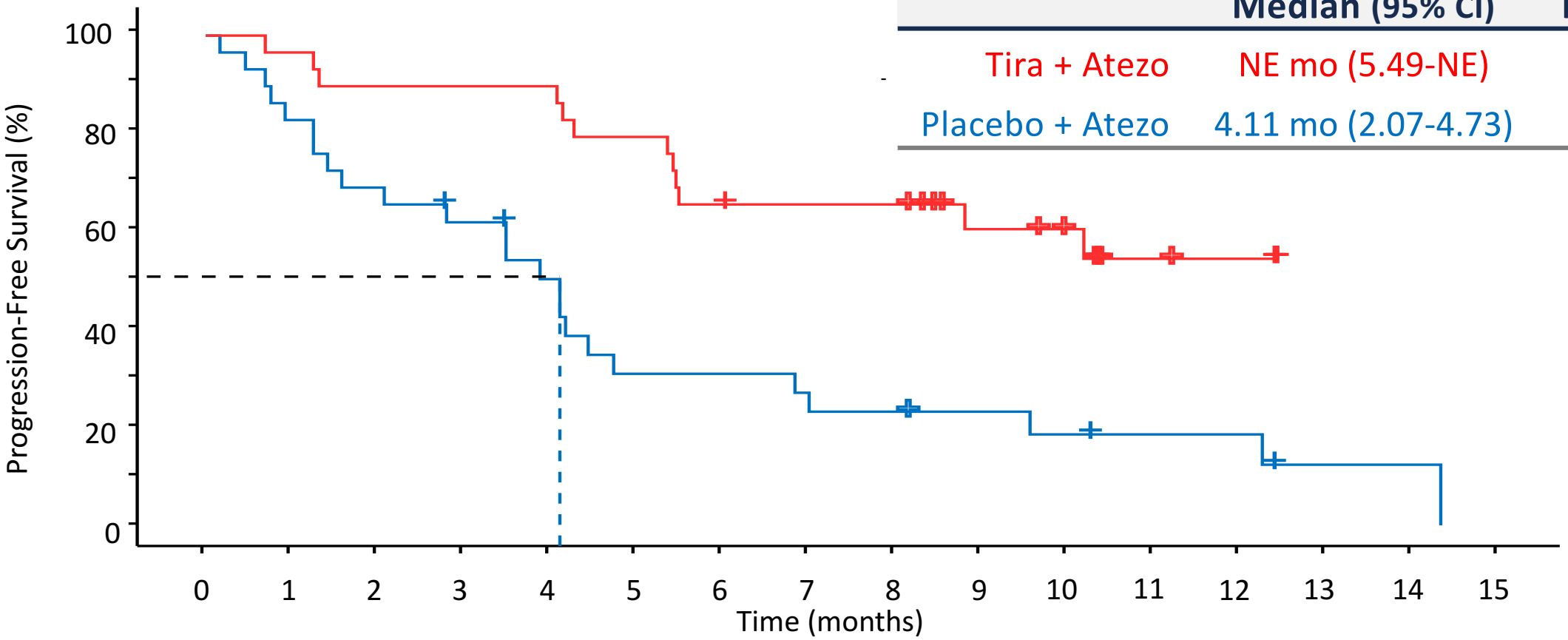


	Median (95% CI)	HR (95% CI)
Tira + Atezo	4.04 mo (1.61-5.55)	0.89* (0.53-1.49)
Placebo + Atezo	3.58 mo (1.45-5.49)	

*unstratified HR

NE = non-evaluable; P+A = placebo + atezolizumab; T+A = tiragolumab + atezolizumab; TPS = tumor proportion score

Investigator-Assessed PFS: PD-L1 TPS ≥ 50%



	Median (95% CI)	HR (95% CI)
Tira + Atezo	NE mo (5.49-NE)	0.30* (0.15-0.61)
Placebo + Atezo	4.11 mo (2.07-4.73)	

*unstratified HR

NE = non-evaluable; P+A = placebo + atezolizumab; T+A = tiragolumab + atezolizumab; TPS = tumor proportion score

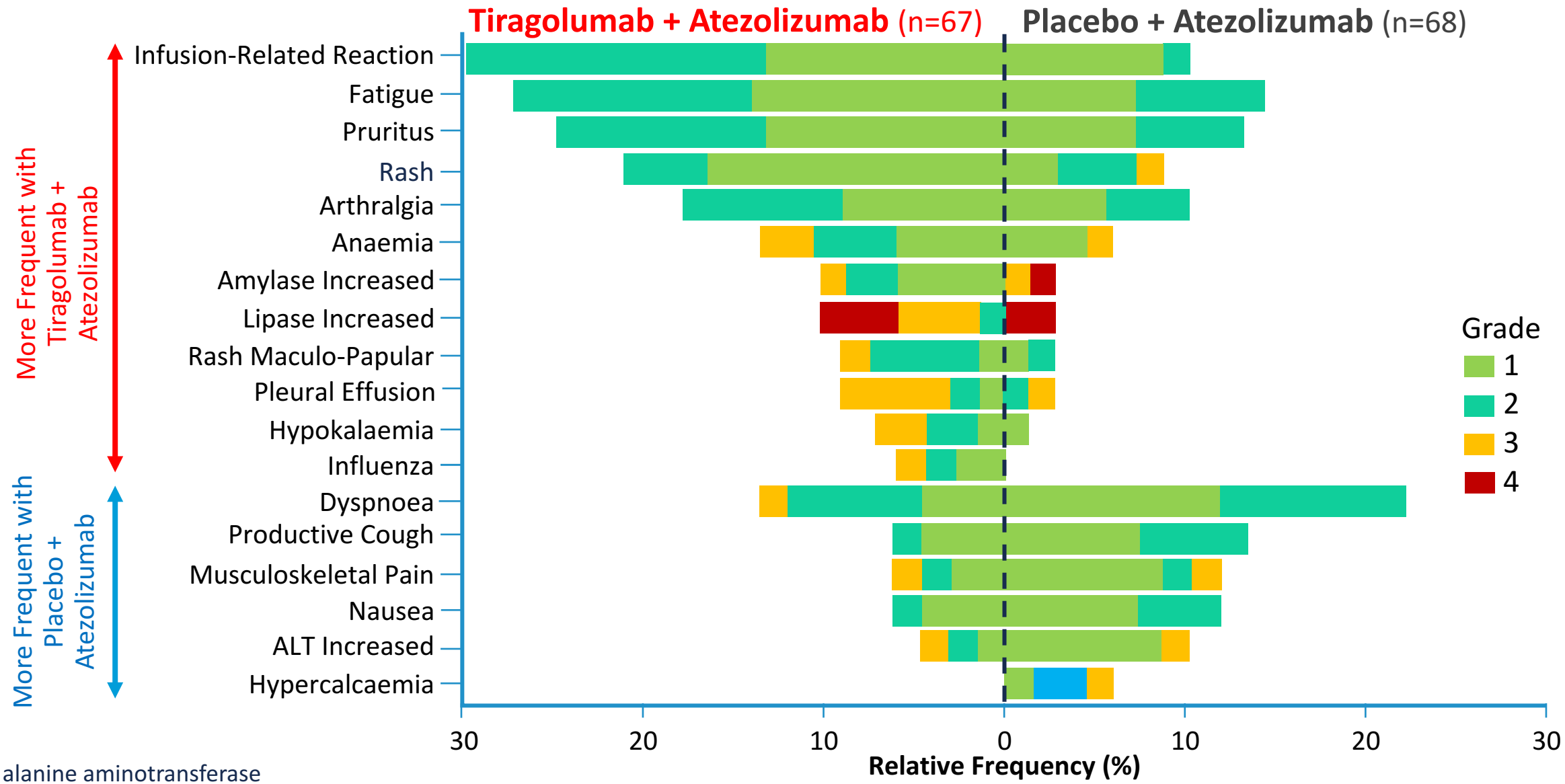
Safety Summary: Exposure and Adverse Events

	Tiragolumab + Atezolizumab (n=67)	Placebo + Atezolizumab (n=68)
Median treatment duration, mo. (min-max)	4.99 (0–15.1)	2.81 (0–14.3)
Any-cause AE, n (%)	66 (99%)	65 (96%)
Grade 3-5 AE	32 (48%)	30 (44%)
Grade 5*	3 (5%)	5 (7%)
Serious AE	25 (37%)	24 (35%)
AE leading to dose modification/interruption	27 (40%)	19 (28%)
AE leading to treatment withdrawal	7 (10%)	6 (9%)

AE = adverse event

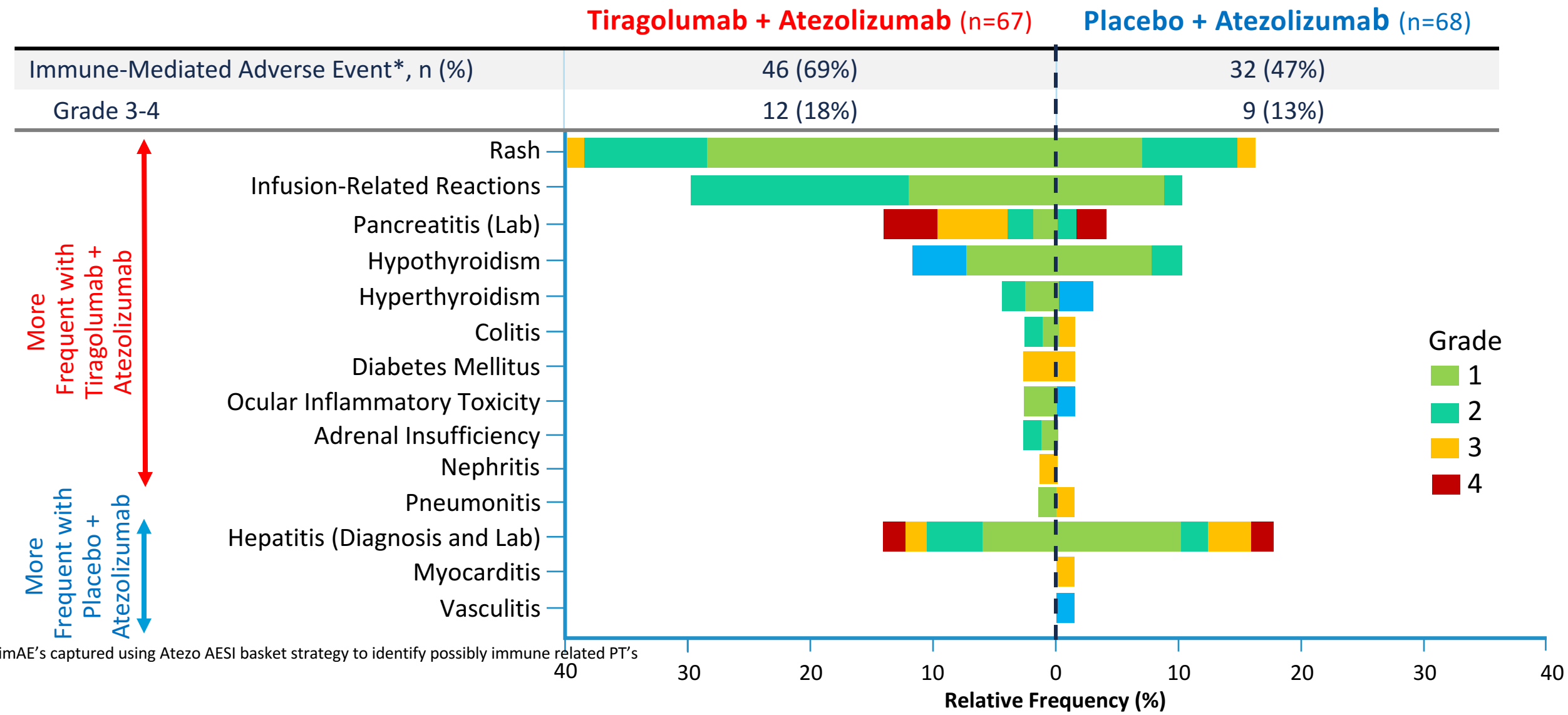
* Grade 5 AEs for tiragolumab + atezolizumab: Epstein-Barr virus infection, pyrexia, and pneumonia
Grade 5 AEs for placebo + atezolizumab: cardiorespiratory arrest, cerebrovascular accident, multiple organ dysfunction, pneumonia, and pulmonary embolism

All-Cause Adverse Events *(>5% difference between arms)*



ALT, alanine aminotransferase

Immune-Mediated Adverse Events



*imAE's captured using Atezo AESI basket strategy to identify possibly immune related PT's

Conclusions

- Tiragolumab + atezolizumab showed clinically meaningful improvement in ORR and PFS in the ITT population compared to placebo + atezolizumab

- the treatment benefit of tiragolumab + atezolizumab showed a greater magnitude of improvement seen in the PD-L1 TPS ≥ 50% subgroup

- Immune-mediated adverse events (imAEs) were more frequent with tiragolumab + atezolizumab but were primarily Grade 1-2 imAEs (mostly IRR and rash) and were manageable

- The observed activity and safety of tiragolumab + atezolizumab is to be confirmed in an ongoing Phase III study (SKYSCRAPER-01) in first-line PD-L1 TPS ≥ 50% NSCLC (NCT04294810)

IO-IO Checkpoint Inhibitor Combinations

- Apart from the discovery of new biomarkers and novel therapeutic targets, optimizing combination therapy regimens will require consideration of the timing and sequence of the drugs' administration.

- Must introduce a strong and long-lasting T-cell response

- Consider overlapping adverse event profiles and avoid super-added toxicities

- New trial designs considering longitudinal effect of immune-escape mechanisms

Bispecific antibodies – An old strategy revisited

- Concept of Bispecific antibodies around for > 50 years - target to epitopes with one molecule
- 290 anti-cancer Bispecific Abs in development - so far three drugs approved by various agencies
- The majority can be classified as

    - Bispecific immune cell engager

    - Bispecific ABs targeting two tumour associated antigens

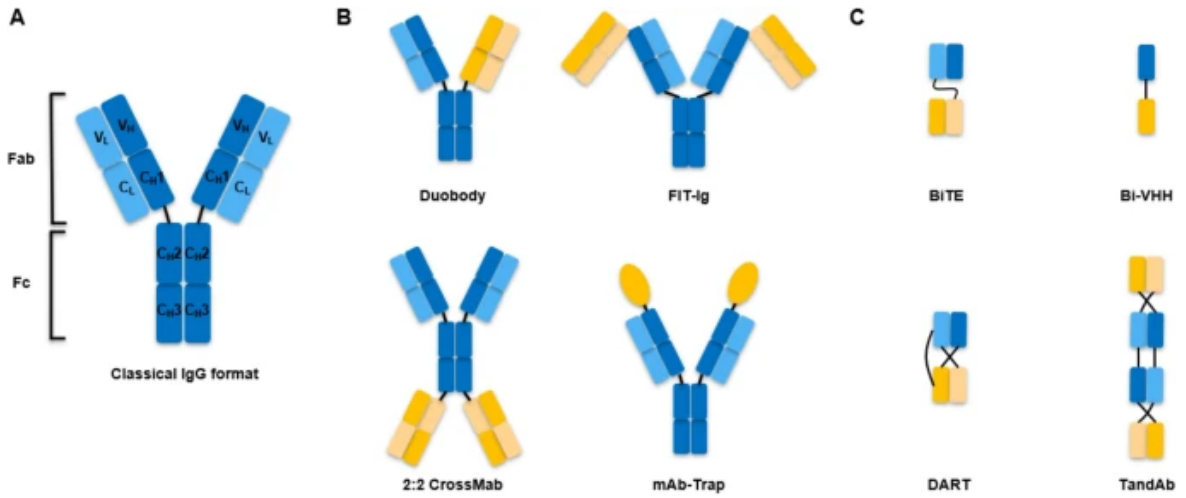
Bispecific antibodies – Aiming for the optimal Bispecific format

a) Classical IgG structure

b) Representative Fc-containing Bispecific Ab formats

c) Representative Fc-less Bispecific Ab formats:

FIT-Ig (Fab-in-tandem immunoglobulin)
scFv (Single-chain variable fragment)
BiTE (Bispecific T cell engager)
VHH (variable domain of heavy chain)
DART (dual-affinity retargeting molecule)
TandAb (tandem diabody)



Types of Bispecific antibodies

	Fc containing	Fc less
Representative platform	Duobody, CrossMab, FIT-Ig	BiTE, DART, TandAb
Representative drug	Catumaxomab (CD-3/EPCAM)	Blinatumumab (CD-3/CD19)
Advantages	Good solubility and stability Effect: Induce secondary immune functions (ADCC, ADCP and CDC) long in vivo half-life	Small size, high yield, easy to produce Effect: Low immunogenicity; Fewer side-effects; Better tissue-penetrating capacity; For CD3×antigen format, T cell mediated tumour cell killing is better than which Fc mediated
Disadvantages	Mis-pairing and purification problems; relatively poor permeability of tumour tissue	Requires specific purification technology; require half-life extension or frequent dosing

antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC), Antibody-dependent cellular phagocytosis (ADCP)

Bispecific ABs in Oncology – Targeting Hallmarks of Cancer

- Target cell depletion

Target CD3 (Catumaxomab (CD3/EPCAM); blinatumomab (CD3/CD19)

CD16 NK-cells

CD47 Macrophages

MOA: increase cell-mediated cytotoxicity, reduce CRS

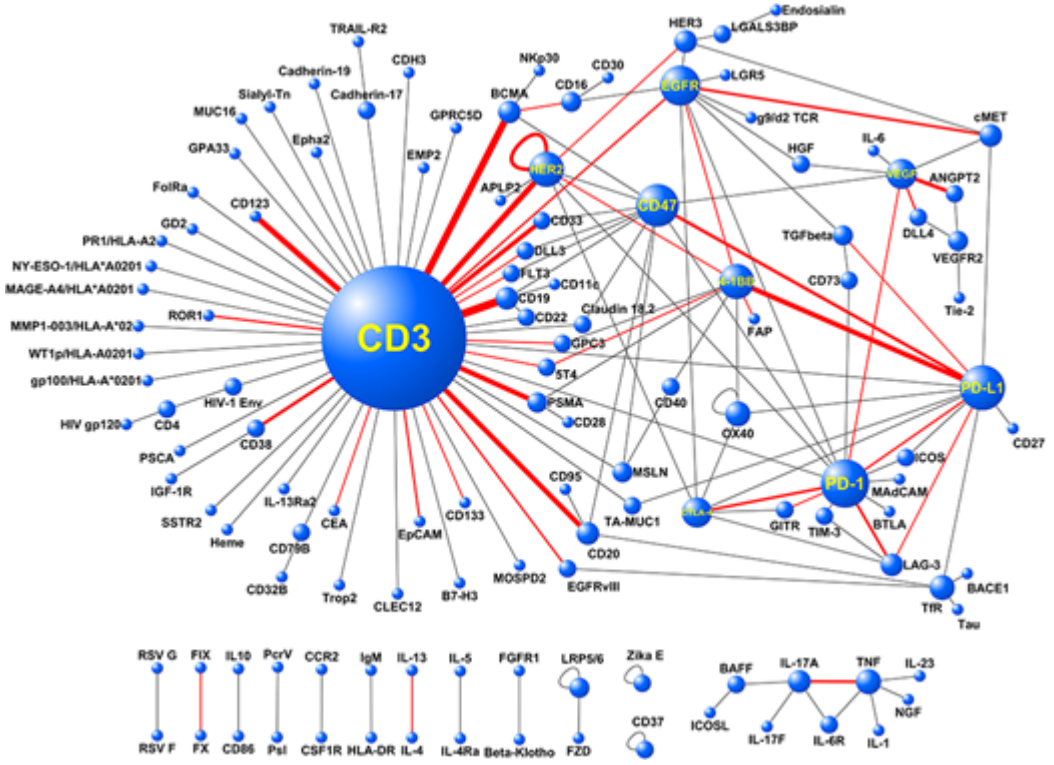
Target TRAILR; CD95

MOA: induce apoptosis

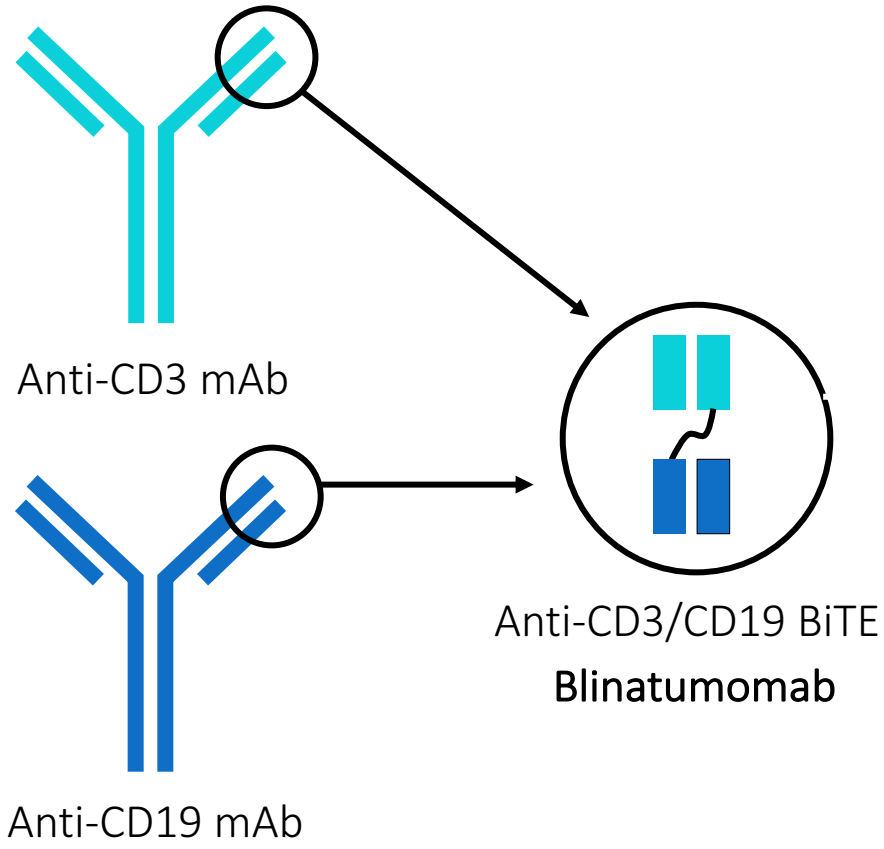
Target HER-2/APLP2

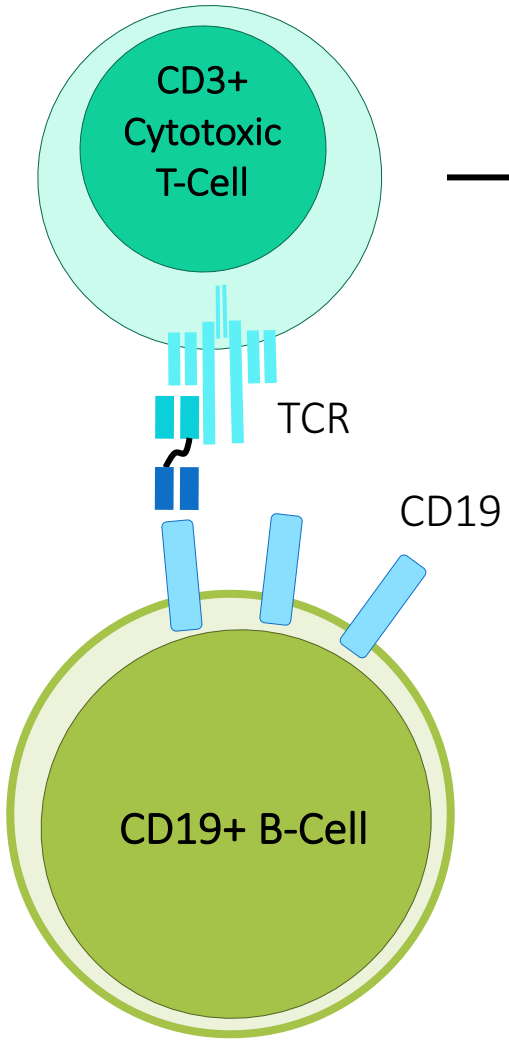
MOA: bispecific ADC

- **Enhance anti-tumour immunity** (i.e. CTLA4/PD-1; 4-1BB/Her-2)
- **Anti-angiogenesis** (i.e. DLL4/VEGF; VEGF/cMET)
- **Anti-tumourigenesis** (i.e. Her-2/Her-3; EGFR/c-Met; LRP5/LRP6))
- **Modulate TME** (i.e. PD-1/TGFb; CD73/TGFb)



Blinatumomab: Anti-CD19 Bispecific Antibody (BITE)





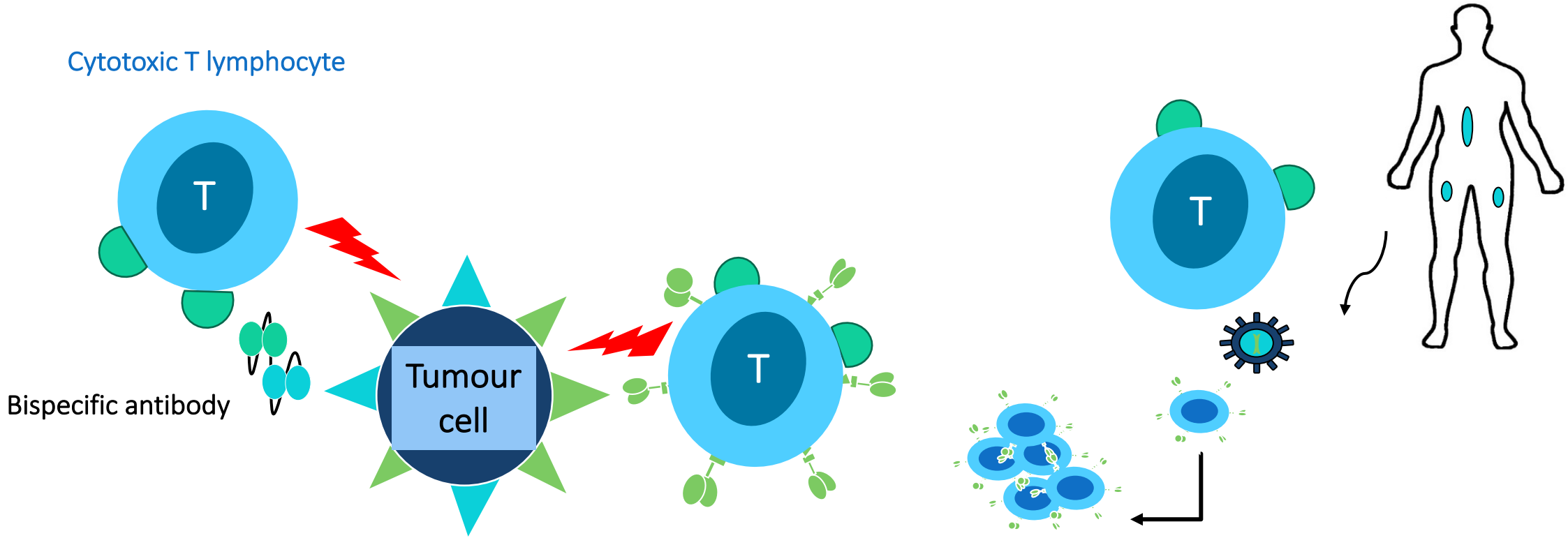
Contact with CD19+ B-cells leads to CTC activation/ proliferation

Through serial lysis, individual CTCs can induce apoptosis of multiple CD19+ B-cells

CD19: highly specific B-cell marker expressed throughout B-cell development and in > 90% of B-cell lineage cancers

Blinatumomab PI. Hoffmann. Int J Cancer. 2005;115:98. Raponi. Leuk Lymphoma. 2011:52;1098.

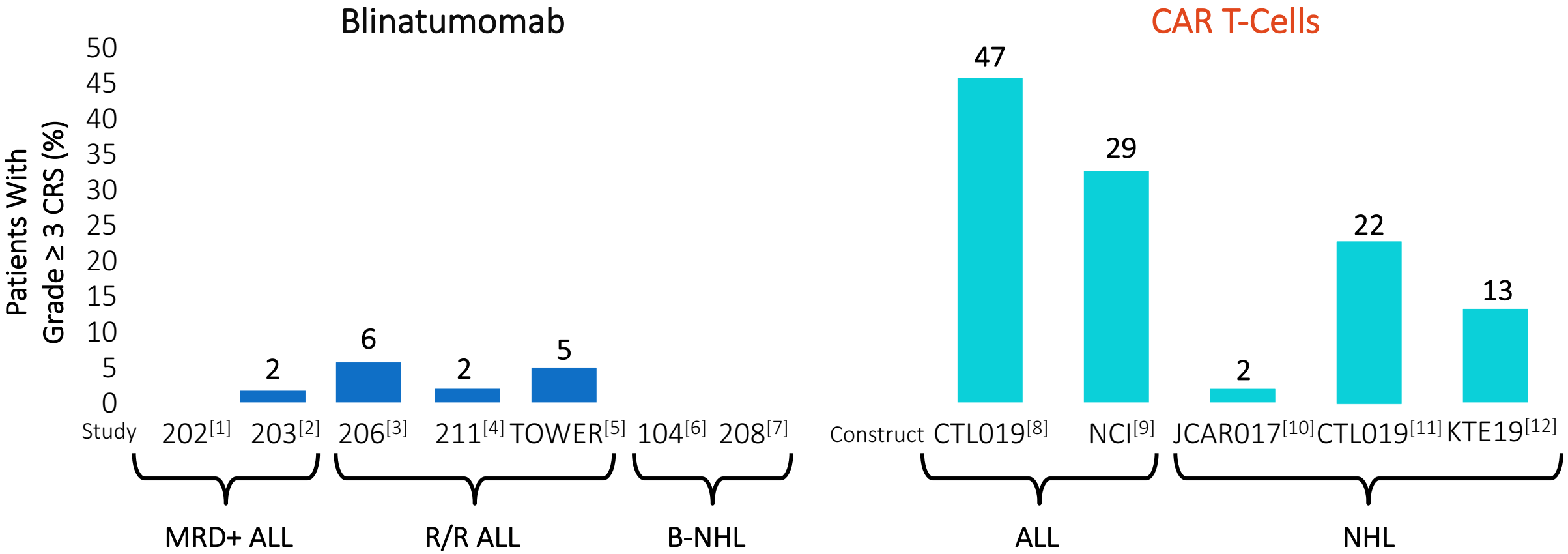
Bispecific Antibodies vs CAR T-Cell Therapy



Characteristic	Bispecific Antibodies	CAR T-Cell Therapy
Preparation	"Off the shelf"	In vitro manufacturing (3-4 wks)
Dosing	Repetitive	Single (following lymphodepleting CT)
CRS incidence	Less	Greater

Slaney. Cancer Discov. 2018;8:924. Blinatumomab PI. Tisagenlecleucel PI.

Grade ≥ 3 CRS in Trials of Blinatumomab and CAR T-Cell Therapy



1. Topp. JCO. 2011;29:2493. 2. Gökbuget. Blood. 2018;131:1522. 3. Topp. JCO. 2014;32:4134. 4. Topp. Lancet Oncol. 2015;16:57. 5. Kantarjian. NEJM. 2017;376:836. 6. Goebeler. JCO. 2016;34:1104. 7. Viardot. Blood. 2016;127:1410. 8. Maude. NEJM. 2018;378:439. 9. Lee. Lancet. 2015;385:517. 10. Abramson. ASH 2019. Abstr 241. 11. Schuster. NEJM. 2019;380:45. 12. Neelapu. NEJM. 2017;377:2531.

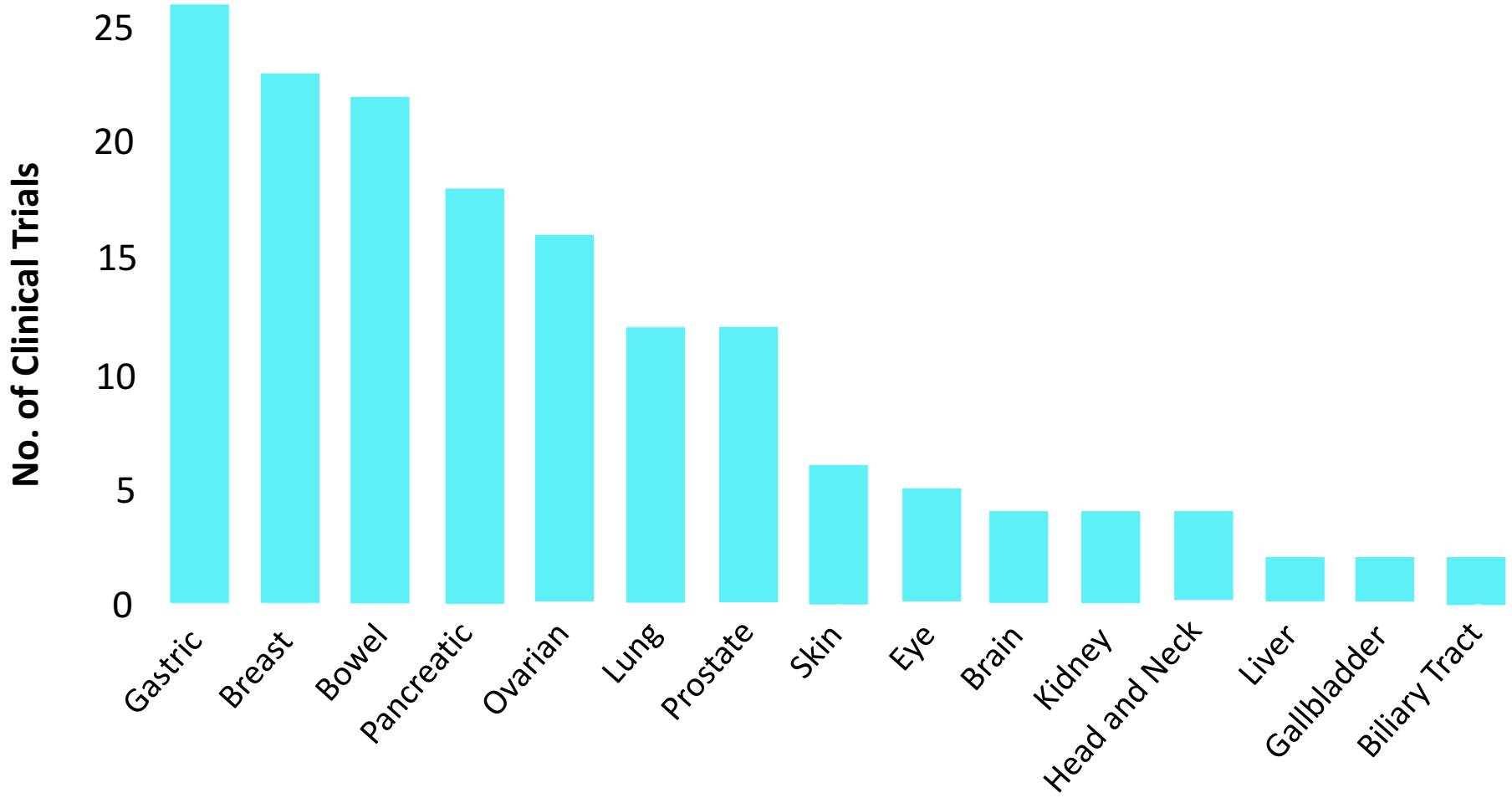
Anti-CD20 Bispecific Antibodies in Lymphoma: Safety

AE, %	CRS		Neurotoxic Events	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Bispecific antibodies				
Mosunetuzumab[1]	28.9*	1.1*	43.7	3.7
REGN1979[2]	59.1	6.4	NR	NR
CD20-TCB (RG6026)[3]	51*	4*	NR	NR
CAR T-cell therapy				
Tisagenlecleucel[4]	58†	22†	21‡	12‡
Axicabtagene ciloleucel[5]	93*	13*	64	28

*Lee 2014 criteria. †Penn scale. ‡Occurring within 8 wks of receiving tisagenlecleucel.

1. Schuster. ASH 2019. Abstr 6. 2. Bannerji. ASH 2019. Abstr 762. 3. Dickinson. ICML 2019. Abstr 053.
4. Schuster. NEJM. 2019;380:45. 5. Neelapu. NEJM. 2017;377:2531.

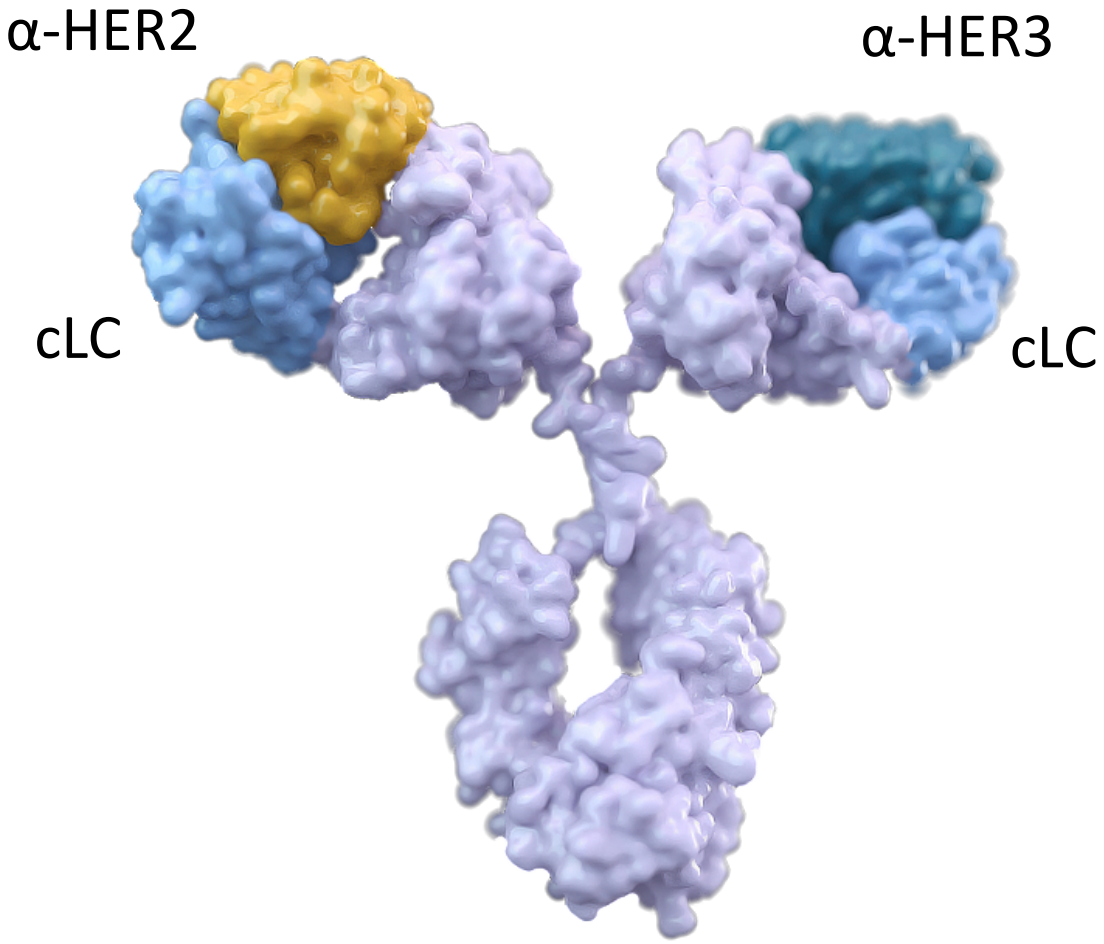
CD3 Bispecific Antibody Trials in Solid Tumours



As of February 2020

ClinicalTrials.gov. Adapted from figure created by Hanson Wade.

MCLA-128 – HER2/HER3 Bispecific antibody (Zenocutuzumab)



Cancer Cell

CellPress

Volume 33, Issue 5, 14 May 2018, Pages 922-936.e10

Article

Unbiased Combinatorial Screening Identifies a Bispecific IgG1 that Potently Inhibits HER3 Signaling via HER2-Guided Ligand Blockade

Cecile A.W. Geuijen [1], Camilla De Nardis [2], David Maussang [1], Eric Rovers [1], Tristan Gallenne [1], Linda J.A. Hendriks

Highlights

- Unbiased phenotypic screening identifies bispecific antibody with unique properties
- Therapeutic agent that potently and specifically blocks the HRG/HER3 pathway
- Dock and block mechanism of action dependent on bispecific format

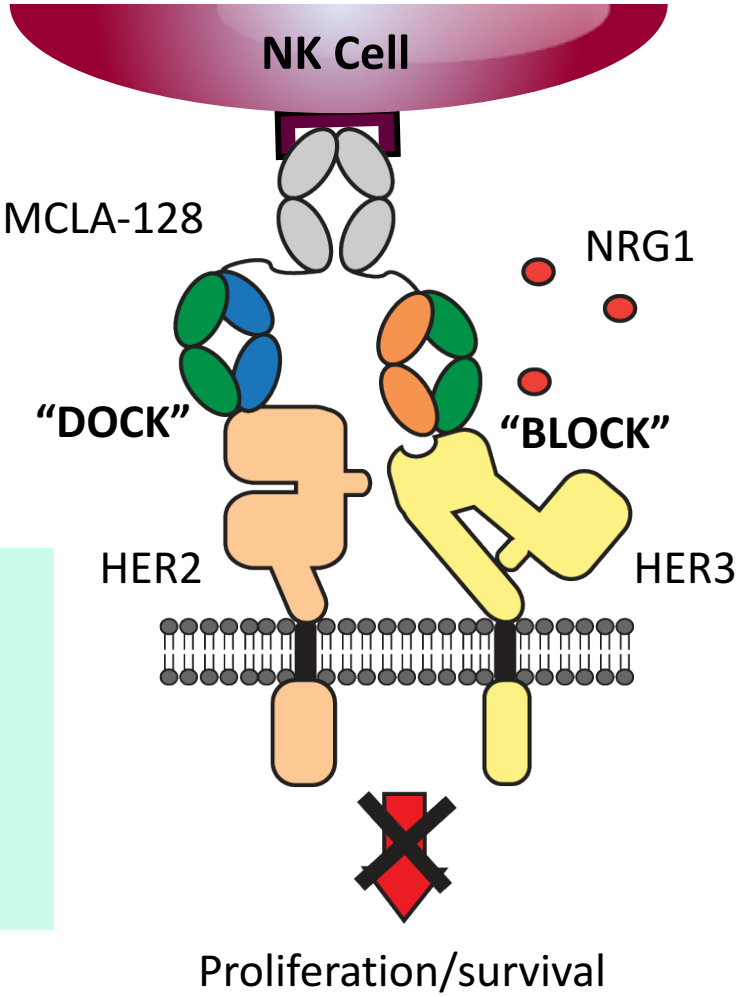
MCLA-128 – HER2/HER3 Bispecific antibody (Zenocutuzumab)

Dock on HER2, abundantly expressed on tumour cells

Block HER3 signaling, even under high Neuregulin stress environments

Enhanced ADCC - recruitment of immune killer cells

Specific for HER2/HER3 (does NOT block e.g. HER2/EGFR dimerization)



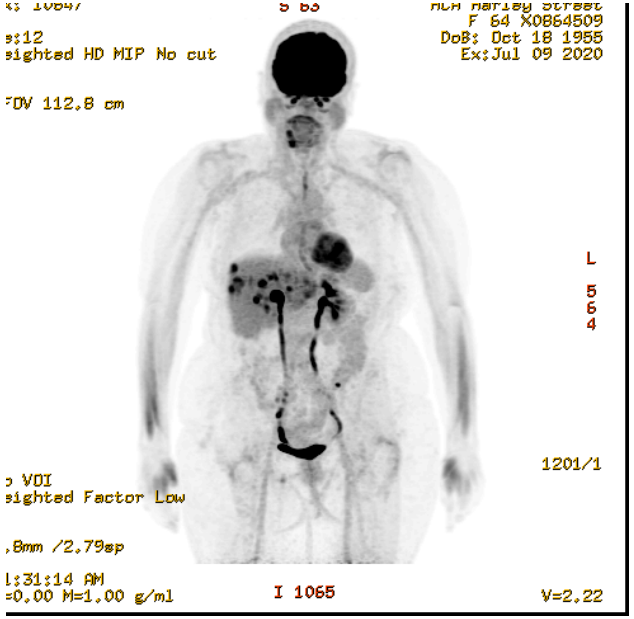
Neuregulin 1 (NRG1) is a ligand that binds HER3, promoting HER2/HER3 heterodimerization and activation of PI3K/AKT/mTOR signalling

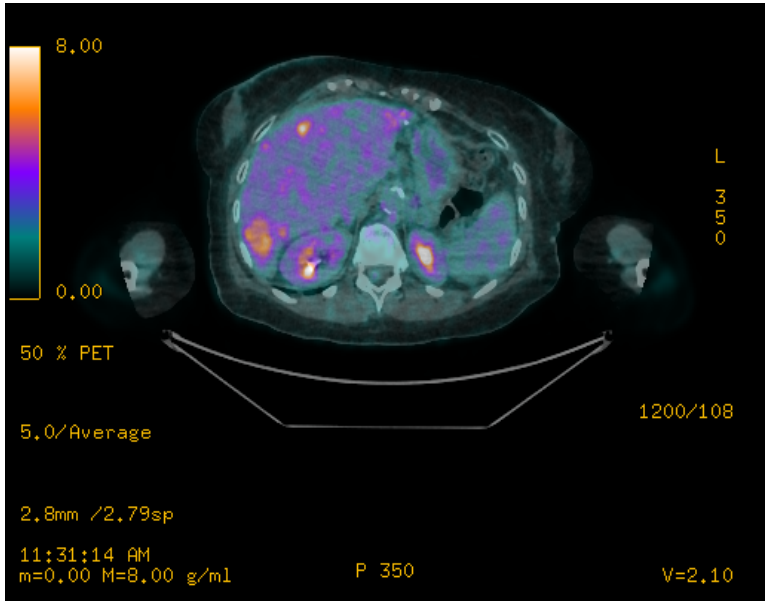
NRG1 fusions are oncogenic drivers found across numerous solid tumour types

- Low overall incidence <1%
- Enriched in RASwt pancreas and lung invasive mucinous adenocarcinoma (IMA)

Zenocutuzumab (HER-2/HER-3 Bispecific) for NRG1-fusion

- 58 year old patient with a bifocal carcinoma of the right breast in 2013, (ER/PR 8/8, Her-2 neg)
- Tx: reduction mammoplasty and sentinel node biopsy, followed by adjuvant radiotherapy and tamoxifen.
- Relapse 05/2014 with multifocal liver and bone disease (ER/PR 8/8); commenced on taxane/bevacizumab with metabolic CR after 3#, continued with letrozole/denosumab, remission lasting for 24 months.
- 03/2018, PD in liver and bone (ER/PR 8/8, Her-2neg); commenced on fulvestrant/palbociclib, denosumab.
- 03/2019 PD liver, commenced on capecitabine, with metabolic response. NGS: NRG1-SLC3A2 gene fusion
- After slow progression on capecitabine, patient commenced on Zenocutuzumab 750 mg IV (day 1 and 15, in a 28-day cycle)

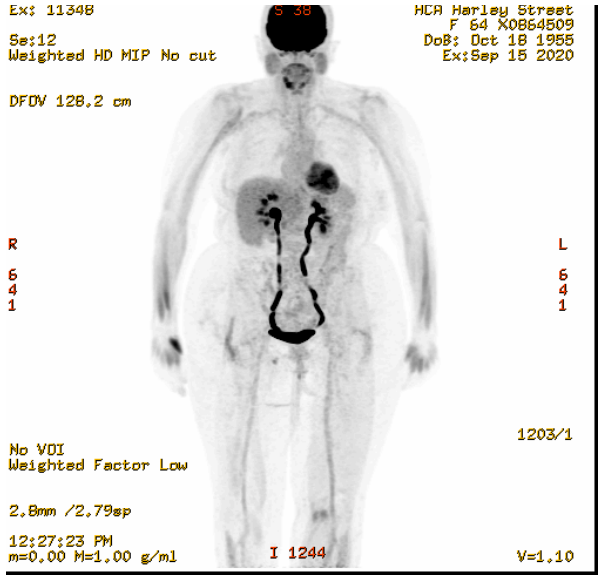


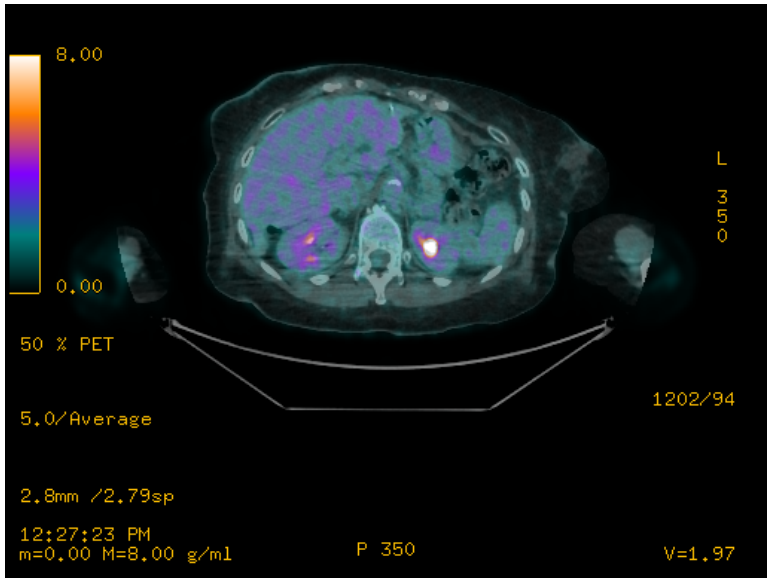


Zenocutuzumab (HER-2/HER-3 Bispecific) for NRG1-fusion

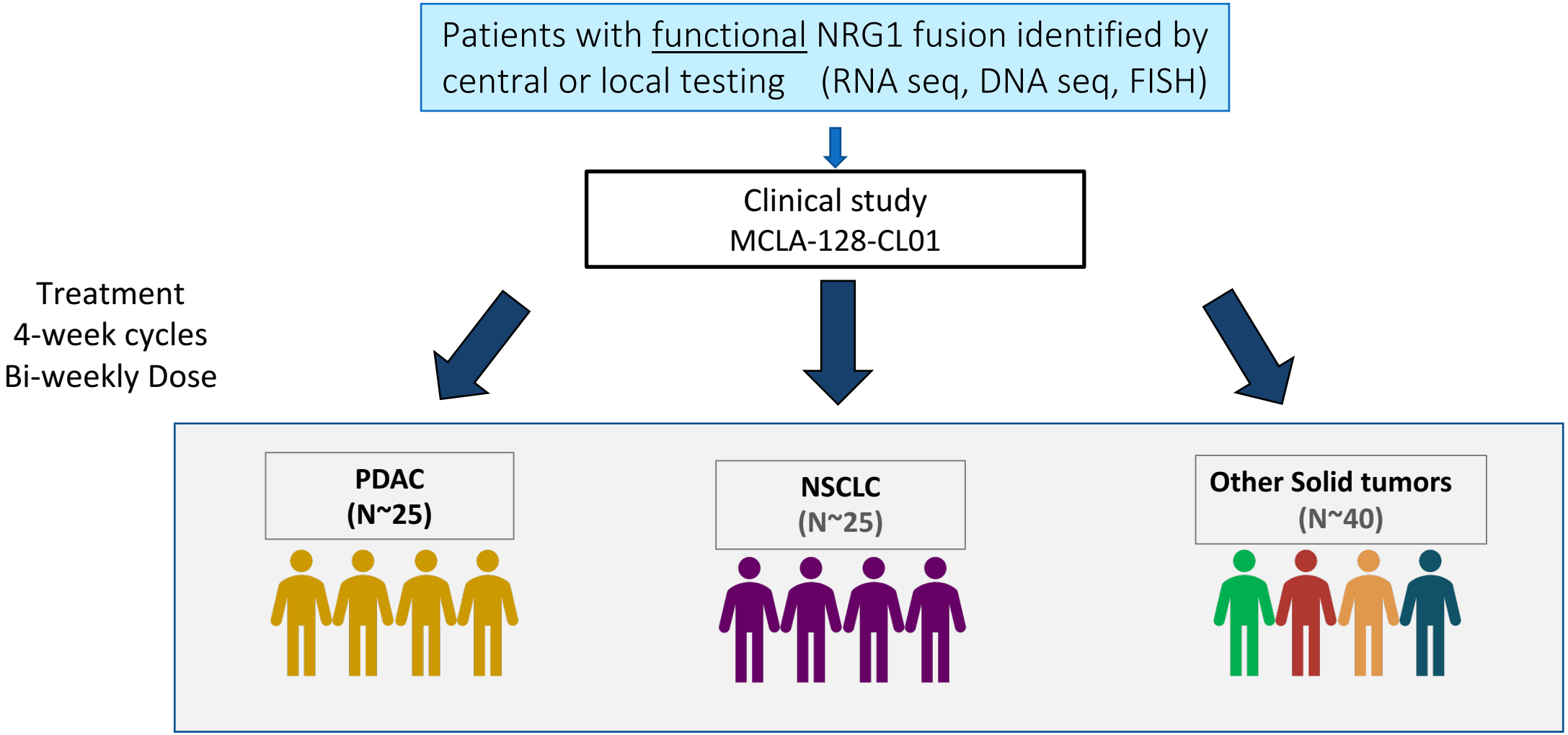
Treatment is well tolerated - G1 nausea is managed with metoclopramide and G1 diarrhoea controlled with loperamide.

After 2 cycles, a PET/CT demonstrated complete metabolic response of the four liver lesions with 35% RECIST reduction of the two target lesions, and partial response of bone lesions. Disease response is maintained (03/2021)





eNRGy Trial


Patients with functional NRG1 fusion identified by central or local testing (RNA seq, DNA seq, FISH)
Clinical study
MCLA-128-CL01
Treatment
4-week cycles
Bi-weekly Dose
PDAC
(N~25)
NSCLC
(N~25)
Other Solid tumors
(N~40)

MGD019 (PD-1/CTLA4, DART)

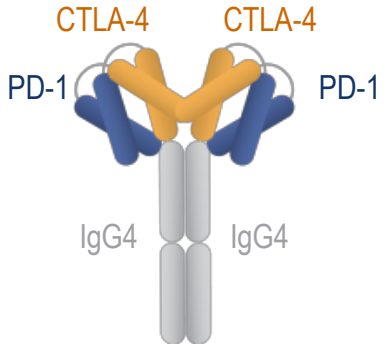
PD-1 and CTLA-4 are checkpoint molecules with complementary mechanisms of action

Dual blockade has yielded enhanced efficacy with approved agents, albeit with increased toxicity

MGD019, an investigational DART molecule:

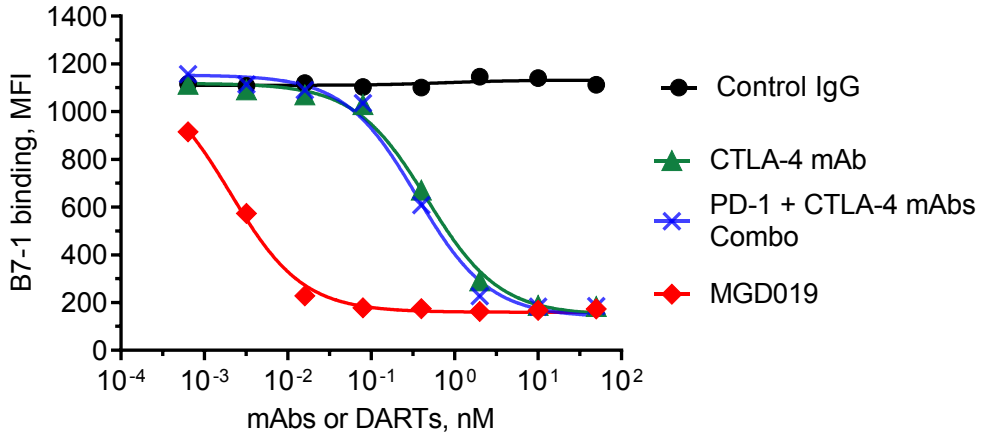
- Maintains uncompromised PD-1 blockade versus benchmark mAbs
- Blocks **both** PD-1 and CTLA-4 pathways with potentially **enhanced CTLA-4 blockade** on dual-expressing cells prevalent in TME

MGD019



PD-1 × CTLA-4
Tetravalent Bispecific
DART Molecule

CTLA-4 blockade on PD-1(+)/CTLA-4(+) cells



10-100 fold enhanced activity by MGD019 relative to PD-1/CTLA-4 mAb combination

DART bispecific platform:

- Diabody based structure
- Flexible design supports various configurations (e.g. bivalent or tetravalent)

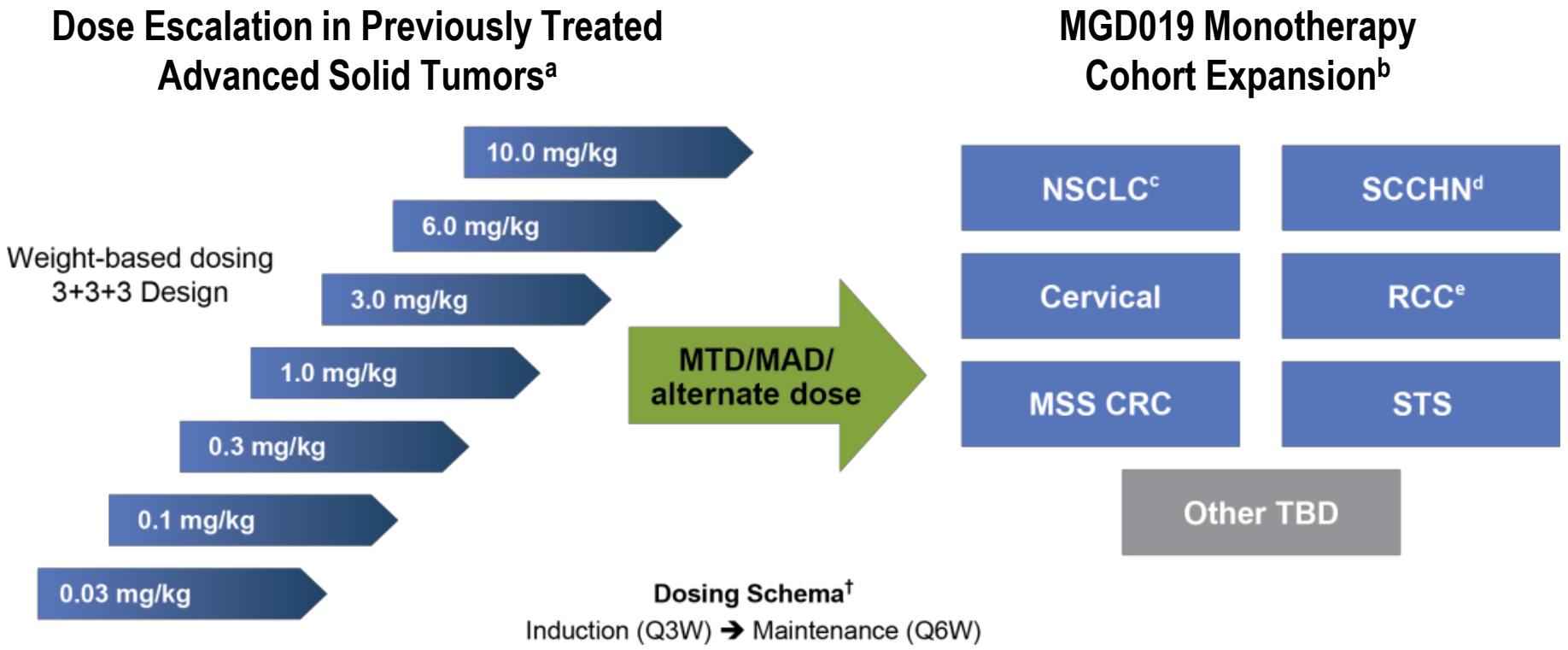
Sharma et al ESMO 2020

MGD019 (PD-1/CTLA4 DART molecule)

Primary objectives:
- Safety, tolerability
- DLTs, MTD, MAD
- Alternate dose

Secondary objectives:
- Pharmacokinetics
- Immunogenicity
- Preliminary activity

Exploratory PD objectives:
- Receptor/ligand expression
- Serum biomarkers
- Gene expression profiling



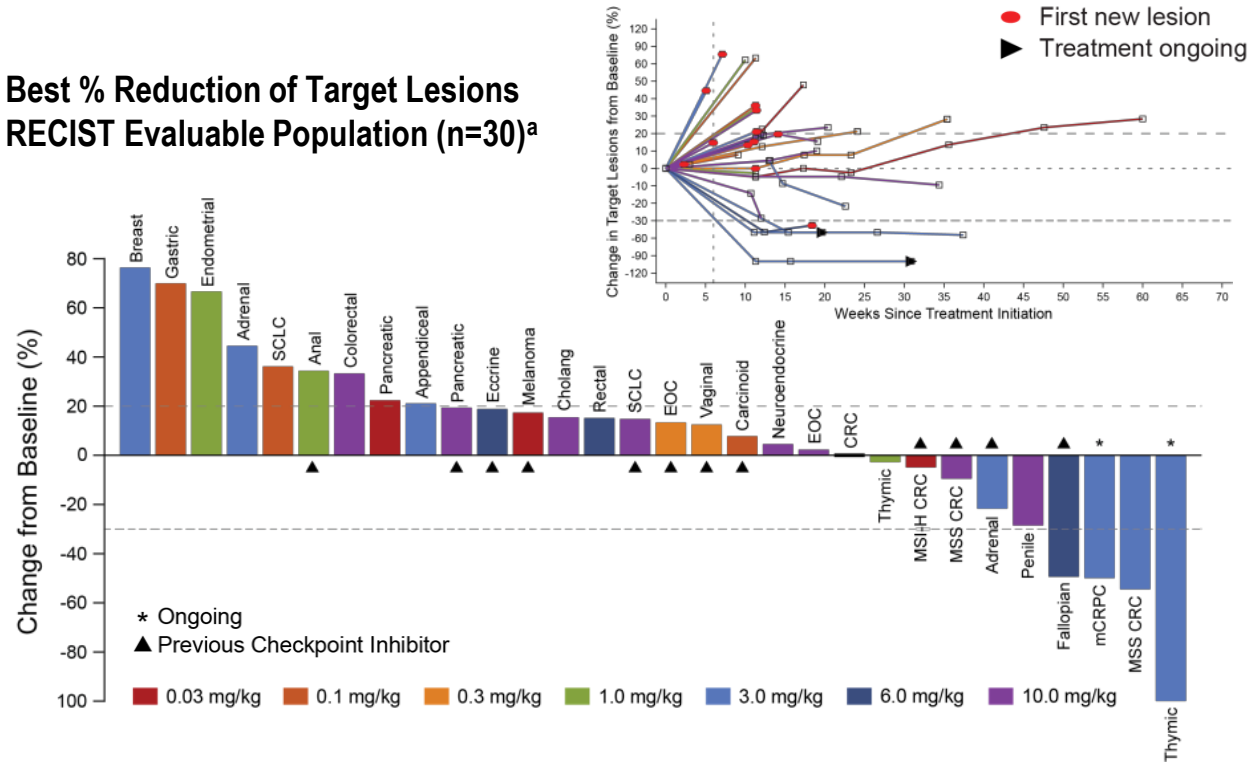
Sharma et al ESMO 2020

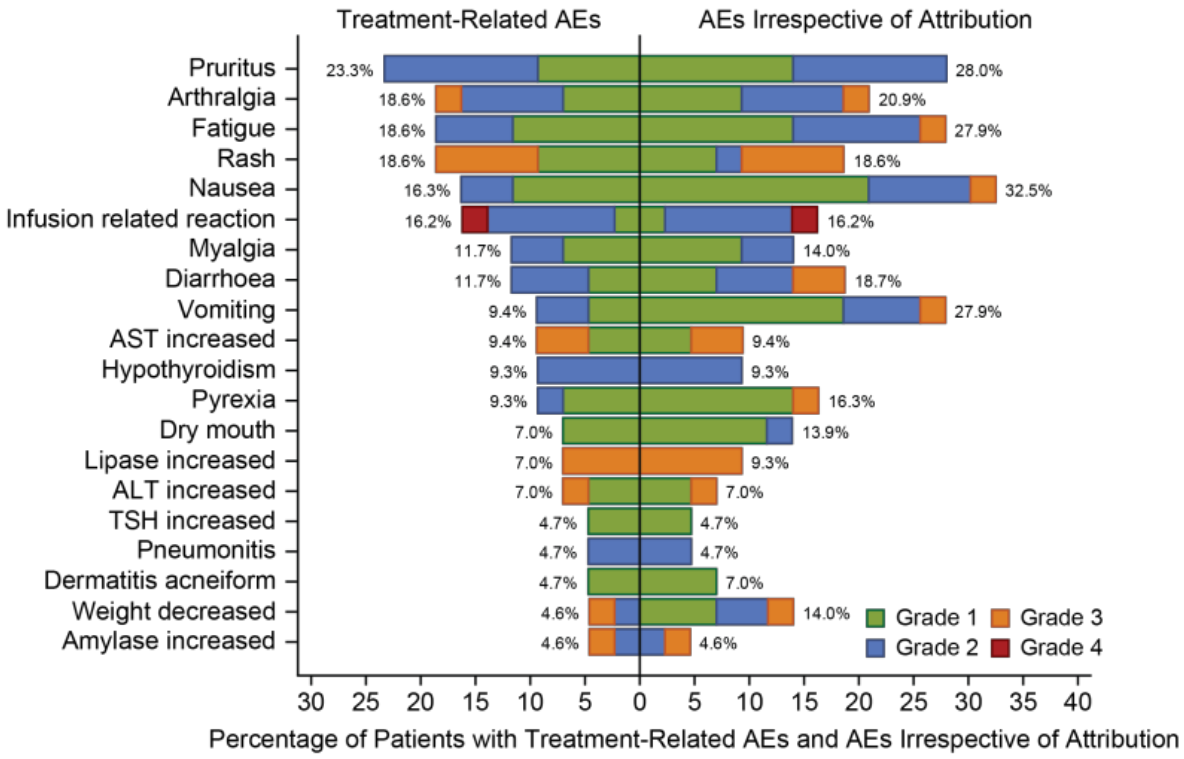
MGD019 (PD-1/CTLA4 DART molecule)

Dose of >3mg/kg: ORR 22% and DCR >50%

Generally well tolerated at dose levels <10mg/kg

Increased grade 3 irAEs





Sharma et al ESMO 2020

MGD019 (PD-1/CTLA4 DART molecule)

Purpose-designed bispecific checkpoint inhibitor

- Effects independent or coordinate blockade of PD-1 and CTLA-4
  - Enhanced CTLA-4 blockade on dual-expressing TILs vs. PD-1/CTLA-4 mAb combination
  - Maintains uncompromised PD-1 blockade vs. anti-PD1 mAb benchmarks
- GLP toxicology results compare favorably to that of ipilimumab + nivolumab preclinical profile

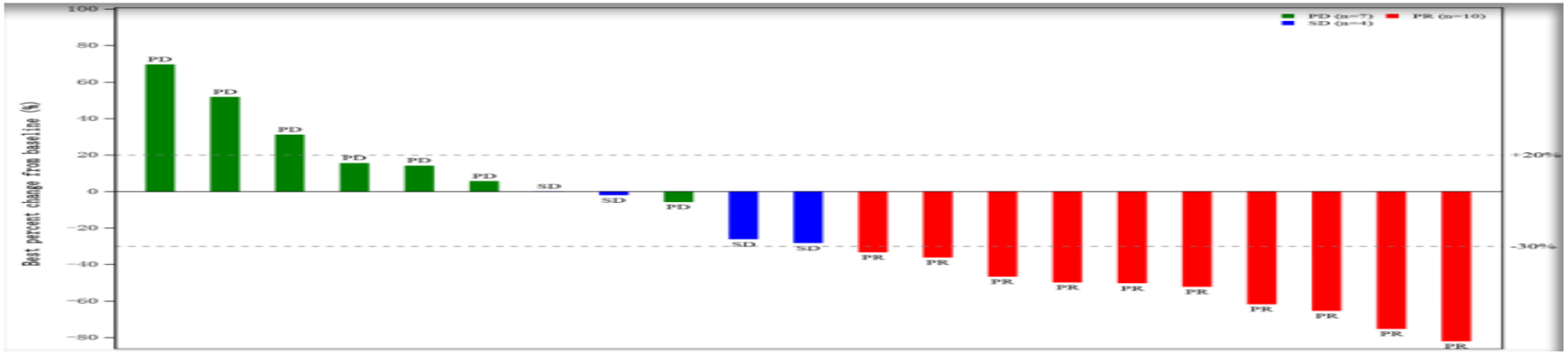
Encouraging activity in tumors traditionally unresponsive to checkpoint blockade

- Generally well tolerated at doses < 10 mg/kg
- Full peripheral PD-1 blockade evident at doses ≥ 1 mg/kg
- Dose-dependent ICOS upregulation evident in responding patients
- Responding patients with low PD-L1 expression at baseline

Enrollment in select monotherapy expansion cohorts at RP2D of 6.0 mg/kg forthcoming

Sharma et al ESMO 2020

Cadonilimab (AK104) - PD-1/CTLA4 Bispecific AB

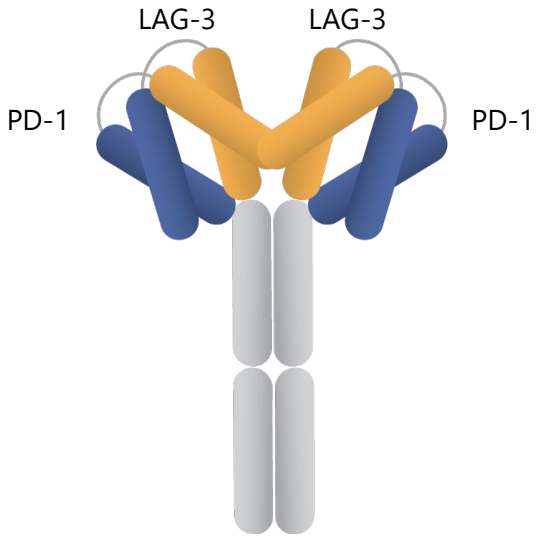


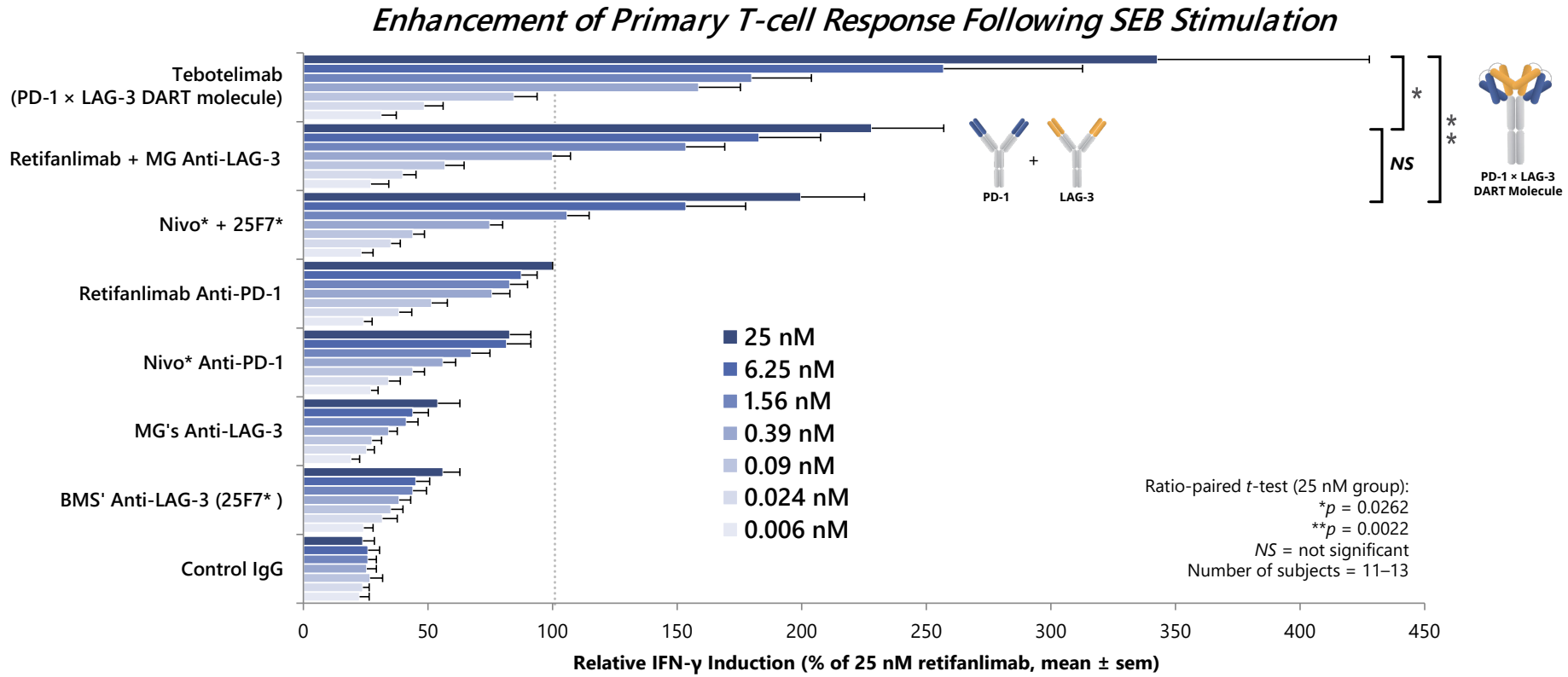
2L/3L Cervical Cancer ORR = 47.6%, DCR = 66.7%

Categories	AK104 All dose levels (N = 228)	AK104 6mg/kg (N = 141)	AK104 15mg/kg (N = 12)	Checkmate-214 RCC (Nivo 3mg/kg +Ipi 1 mg/kg)	Checkmate-067 Melanoma (Nivo 1mg/kg +Ipi 3 mg/kg)	Checkmate-2273 (Nivo 3mg/kg +Ipi 1 mg/kg Q6W)
Drug-related TRAE	147 (64.5%)	86 (61.0%)	9 (75.0%)	93%	96%	77%
≥ Grade 3 TRAE	29 (12.7%)	11 (7.8%)	1 (8.3%)	46%	59%	33%
TRAEs leading to discontinuation	15 (6.6%)	8 (5.7%)	2 (16.7%)	22%	39%	18%

Fast-track designation approval by FDA and break-through designation by China NMPA for 2L/3L cervical cancer

MGD013 (PD-1/LAG3 Bispecific), Tebotelimab

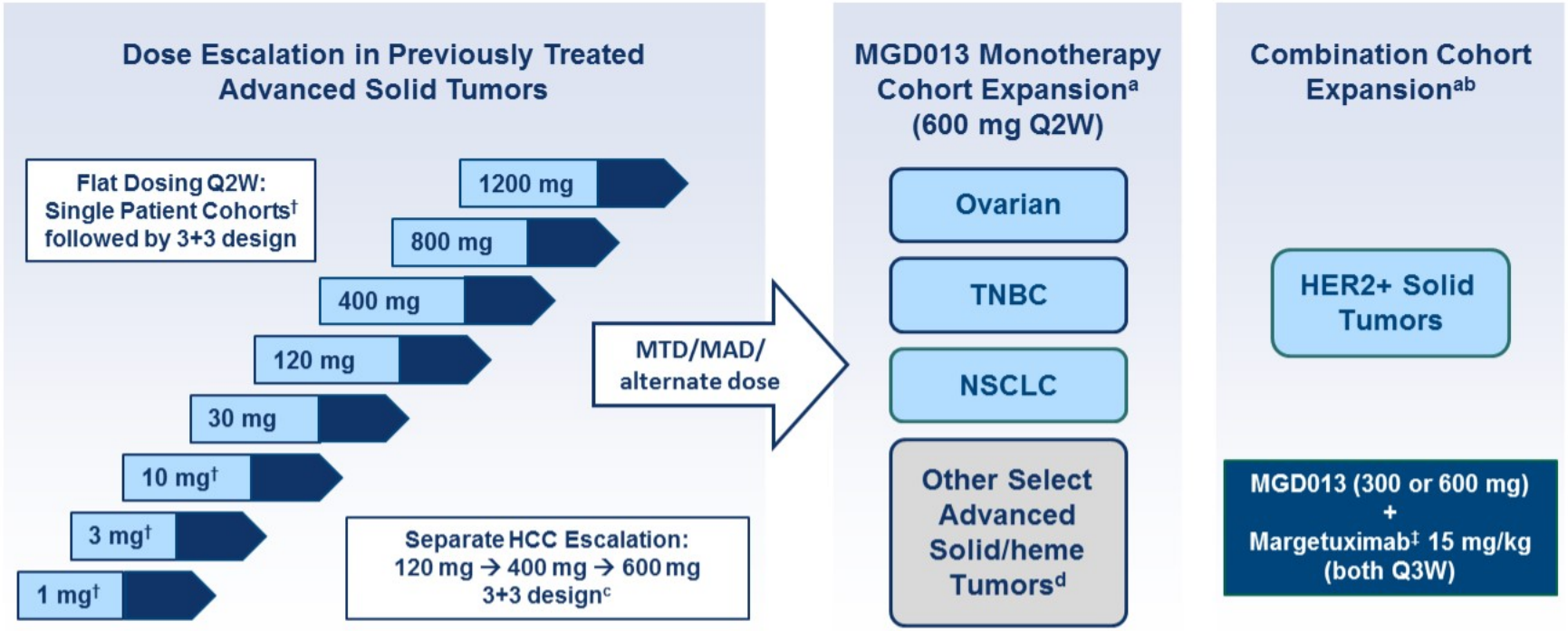




MGD013 (PD-1/LAG3 Bispecific), Tebotelimab

MGD013 Phase 1 Trial Design

- **Primary objectives:**
  - Safety, tolerability
  - DLTs, MTD, MAD
  - Alternate dose
- **Secondary objectives:**
  - Pharmacokinetics
  - Immunogenicity
  - Preliminary activity
- **Exploratory PD objectives:**
  - Receptor/ligand expression
  - Serum biomarkers
  - Gene expression profiling



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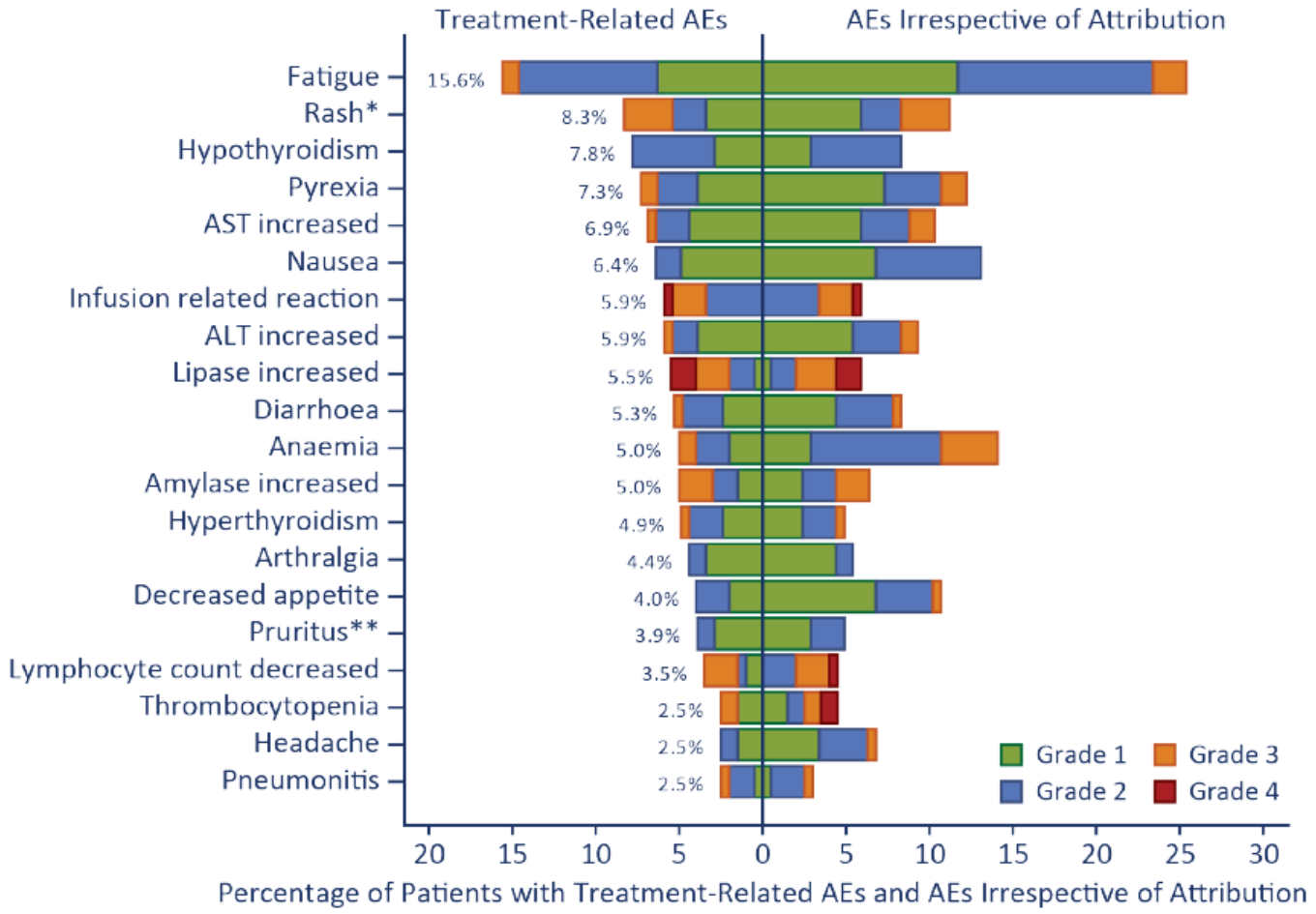
MGD013 (PD-1/LAG3 Bispecific), Tebotelimab

Overall AE Totals	No. (%) of Patients	
	All Grades (N=205)	≥ Grade 3 (N=205)
AE (irrespective of causality)	178 (86.8)	86 (42.0)
Treatment-related AE	118 (57.6)	37 (18.0)[a]
SAE (irrespective of causality)	63 (30.7)	47 (22.9)
Treatment-related SAE	18 (8.8)	11 (5.4)
AE leading to discontinuation	18 (8.8)	16 (7.8)
AESIs in ≥ 2 Patients		
Rash	17 (8.3)	6 (2.9)
Hypothyroidism	16 (7.8)	0 (0.0)
IRR or CRS	13 (6.3)	5 (2.4)
Diarrhea	11 (5.4)	1 (0.5)
Lipase increased	11 (5.4)	7 (3.4)
Hyperthyroidism	10 (4.9)	1 (0.5)
Arthralgia	9 (4.4)	0 (0.0)
Pneumonitis	4 (2.0)	1 (0.5)
Myalgia	4 (2.0)	0 (0.0)
Peripheral neuropathy	3 (1.5)	1 (0.5)
Hepatitis	3 (1.5)	2 (1.0)
Adrenal insufficiency	2 (1.0)	0 (0.0)



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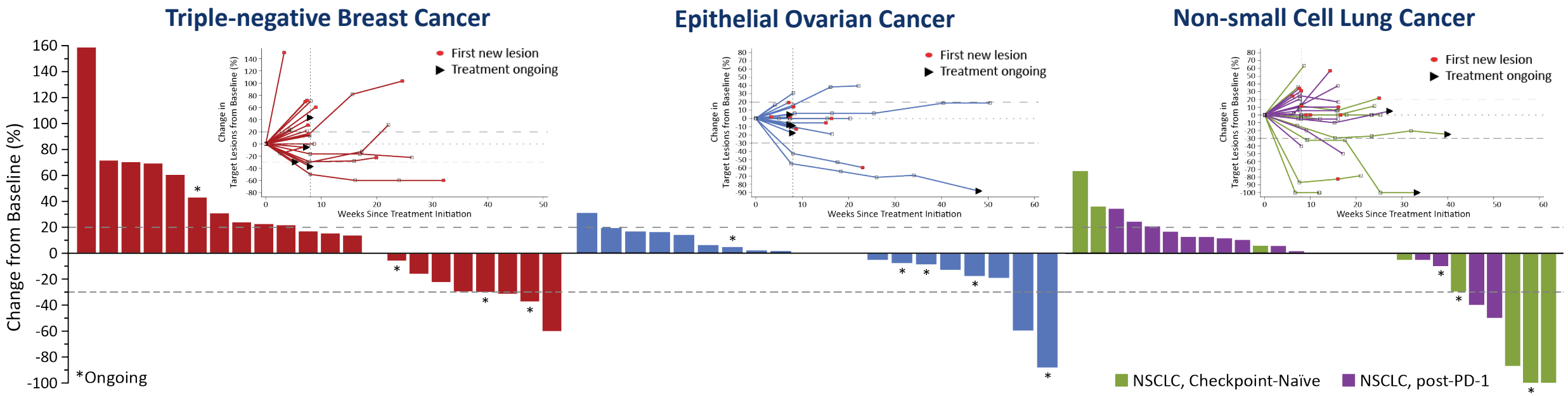
MGD013 (PD-1/LAG3 Bispecific), Tebotelimab - Monotherapy



	TNBC	EOC	NSCLC, CPI-Naïve	NSCLC, post-PD-1
Evaluable Patients	23	23	14	15
ORR (Confirmed)	4.3% (1/23)	8.7% (2/23)	14.3% (2/14)	0% (0/15)
ORR (Confirmed + Unconfirmed)	17.4% (4/23)	8.7% (2/23)	21.4% (3/14)	13.3% (2/15)
SD	34.8% (8/23)	43.5% (10/23)	50.0% (7/14)	53.3% (8/15)
DCR	39.1% (9/23)	52.2% (12/23)	64.3% (9/14)	53.3% (8/15)

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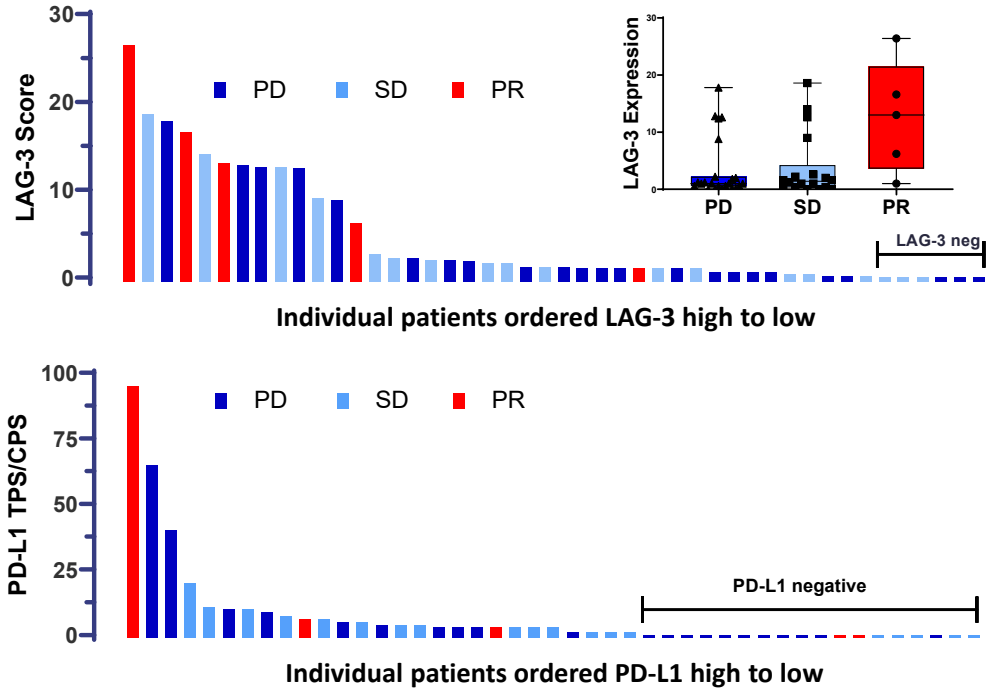
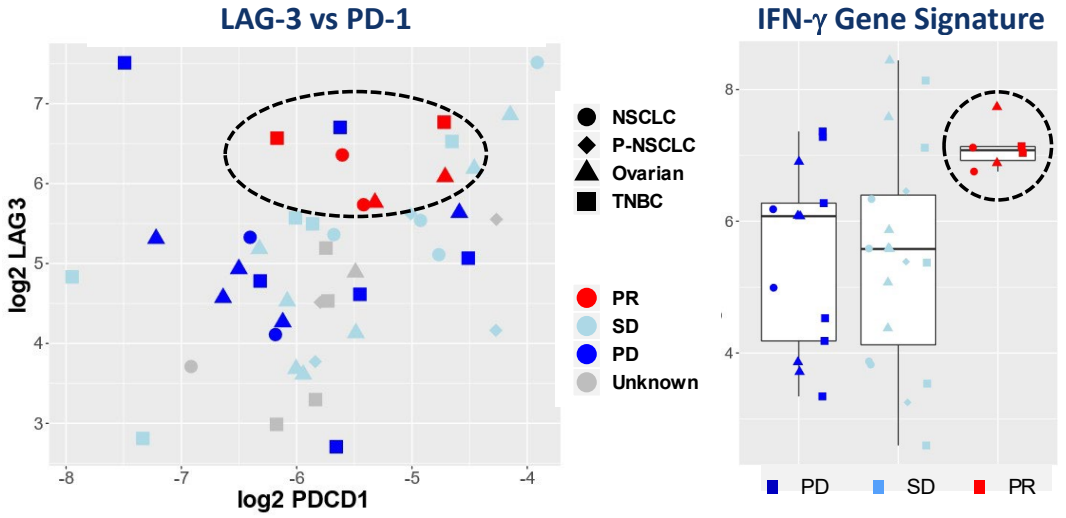
MGD013 (PD-1/LAG3 Bispecific), Tebotelimab – LAG-3 Expression

Inflammatory interferon-γ signature elevated in patients with clinical response

Retrospective IHC Analyses



Transcript Profiling (Baseline Tumor Biopsy)



Objective responses associated with high baseline LAG-3/PD-1 expression and IFN-g gene signature (CXCL9, CXCL10, CXC11, STAT1)

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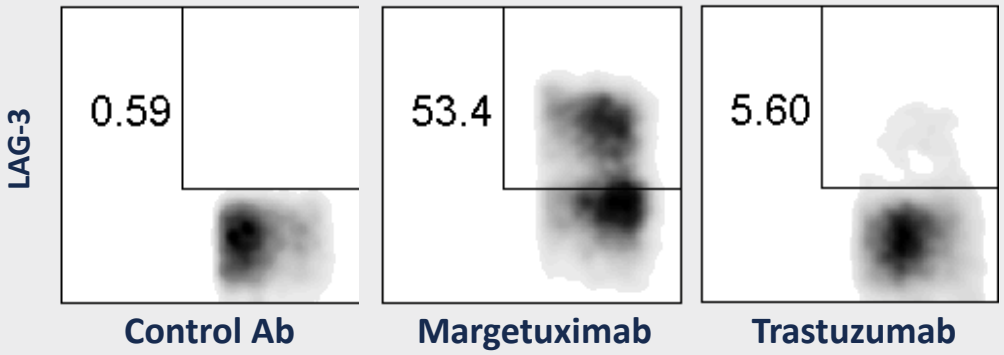
Can tumours be made responsive to PD-1/LAG3 intervention?

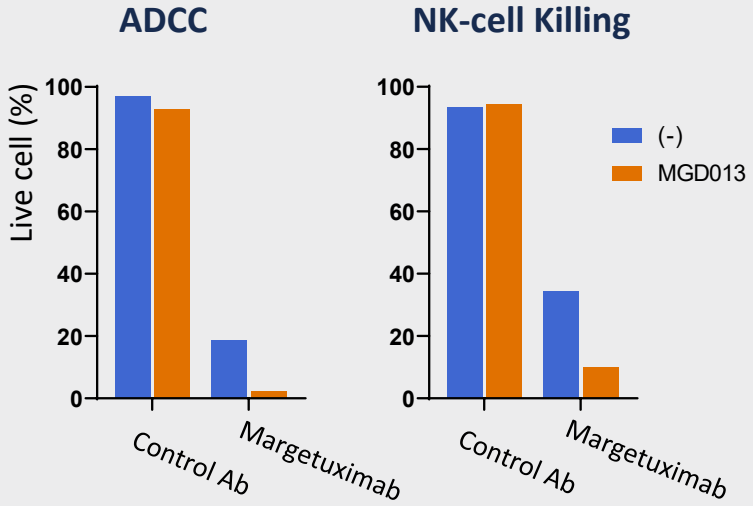
Fc-engineered margetuximab up-regulates LAG-3 and PD-L1 on NK, monocytes and T cells

Margetuximab Enhances LAG-3 Expression by NK Cells



Human PBMC + N87 (HER2+) gastric cancer cells; E:T=10:1; (IL-2, 20 U/mL) Control Ab 50ng/mL, margetuximab/trastuzumab, 5ng/mL; FACS analyses (72h) on $CD3^{-}CD56^{+}$-gated NK cells.

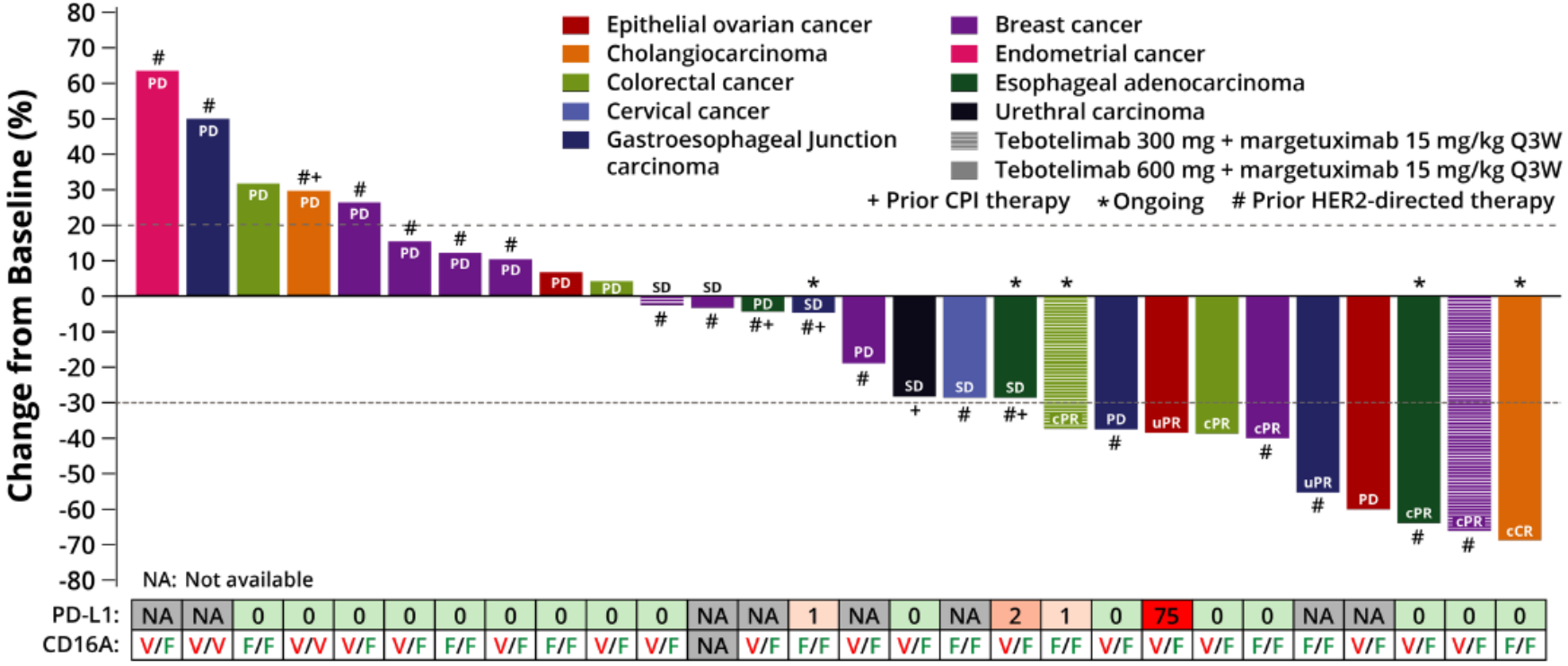
Tebotelimab enhances lytic activity of immune cells primed by Fc-engineered mAb (margetuximab)



ADCC (target: margetuximab opsonized N87, E:T=10) and NK-cell killing (target: K562, E:T=10) mediated by immune cells activated for 6 days by margetuximab +/- tebotelimab in the presence of N87 tumor cells.

Luke ASCO 2020

Margetuximab + Tebotelimab in patients with relapsed HER-2+ tumours



Conclusions

- Duration of response (n=6 confirmed responders): 4.21–8.97 months (3 pts. ongoing)
- Majority of responding patients with baseline PD-L1 expression ≤1
- All responding patients carry less favorable CD16A-158F allotype (i.e., V/F or F/F)
- Baseline LAG-3 and PD-1 mRNA expression associated w/clinical response
- Analyses ongoing to define patient enrichment biomarker

RR: 28.6%; 8/28 patients

Patel M SITC 2020

Margetuximab + Tebotelimab in patients with relapsed HER-2+ tumours

MGD013 (PD-1 × LAG-3 DART Molecule): Conclusions

First-in-class bispecific checkpoint inhibitor

- Designed to independently or coordinately block PD-1 and LAG-3
- Well tolerated at doses up to 1200 mg Q2W
- RP2D: 600 mg Q2W or Q3W
- Safety profile consistent with anti-PD-1 monotherapy

Encouraging monotherapy activity in multiple tumor types

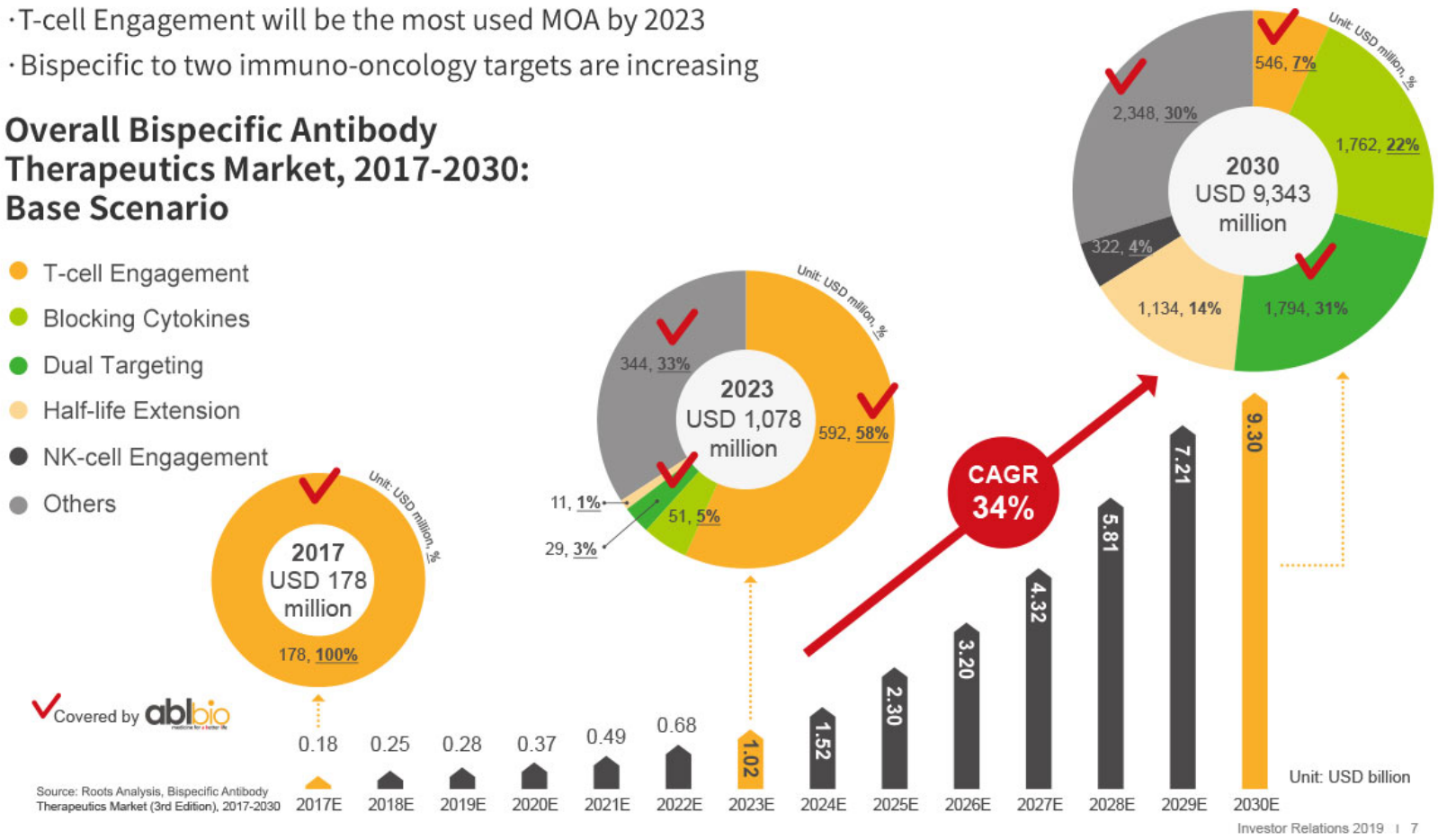
- Baseline LAG-3 expression & IFN-γ signature associated with objective response

Compelling preliminary combinatorial activity with margetuximab (Fc-engineered mAb)

- >40% ORR observed in low PD-L1-expressing, relapsed/refractory $HER2^{+}$ tumors
  - Compares favorably to low historical response rates to anti-HER2 ± CPI

Future and challenges in the Development of Bispecific ABs

- In 2030, overall bispecific antibody therapeutics market is expected to grow by over USD 9.3 billion
- T-cell Engagement will be the most used MOA by 2023
- Bispecific to two immuno-oncology targets are increasing



Challenges:

- Cost of manufacturing
- Purity and stability of drugs
- Target selection and clinical development guidelines (New FDA guidelines)
- **Tumour/TME:** Tumour heterogeneity, intractable tumour microenvironment
- **Immune System:** co-stimulatory signals to activate T-cells and others immune cells (NK, macrophages)

Thank you!

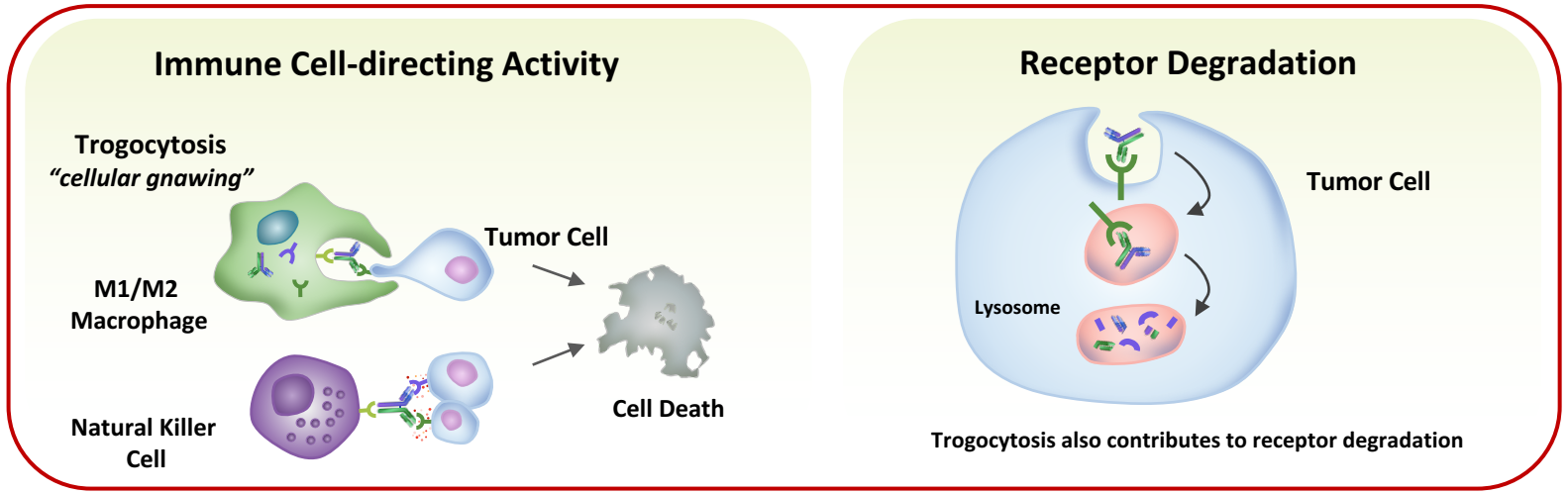
26th March 2021

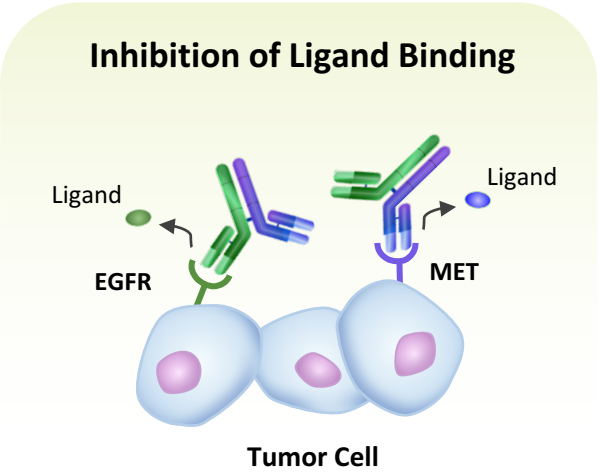
SARAH CANNON

Amivantamab: EGFR-MET Bispecific Antibody

- Fully human EGFR-MET bispecific antibody with immune cell-directing activity
- Targets activating and resistance EGFR mutations and MET mutations and amplifications
- Demonstrated monotherapy activity in patients with diverse EGFRm disease including EGFR Exon19del, L858R, T790M, C797S, Exon20ins, and MET amplification[3-4]

MOA Relevant to EGFR Exon20ins-mutated NSCLC





Vijayaraghavan *Mol Cancer Ther* 19(10):2044. Yun *Cancer Discov* 10(8):1194. Haura *JCO* 37(15_suppl):9009. Park *JCO* 38(15_suppl):9512

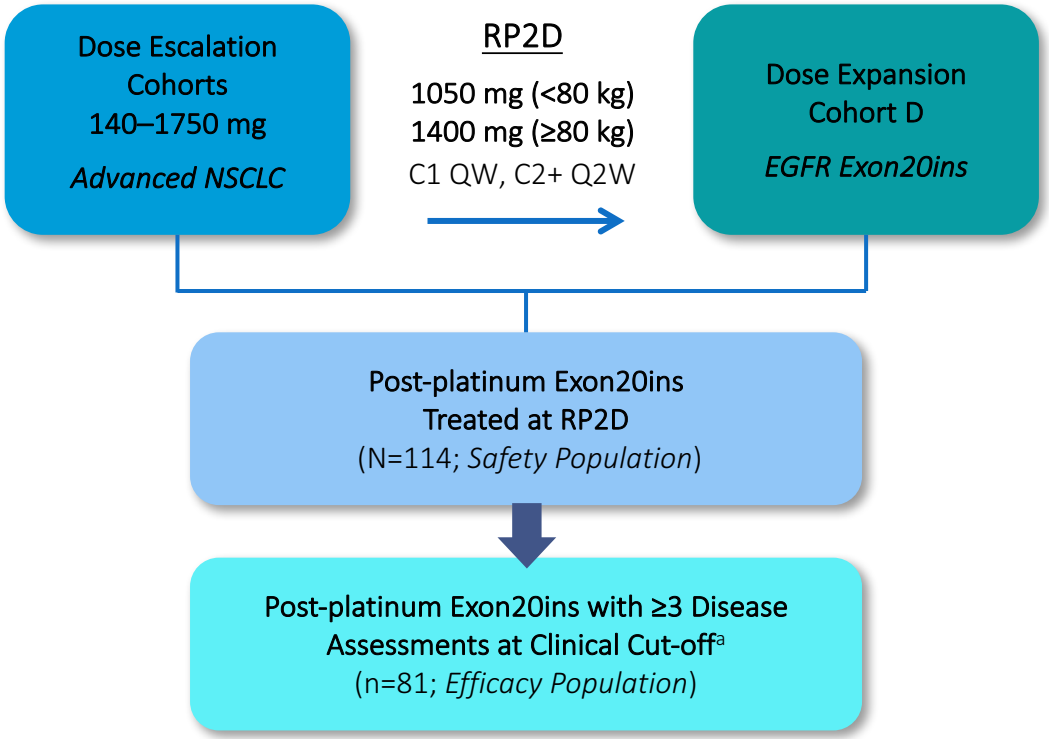
CHRYSALIS Study Design: Post-platinum Exon20ins Population

Key Objectives

- Dose escalation: Establish RP2D
- Dose expansion: Assess safety and efficacy at RP2D

Key Eligibility Criteria for Post-platinum Population

- Metastatic/unresectable NSCLC
- EGFR Exon20ins mutation
- Progressed on platinum-based chemotherapy



Efficacy End Points

Primary

- Overall response rate per RECIST v1.1

Key Secondary

- Clinical benefit rate
- Duration of response
- Progression-free survival
- Overall survival

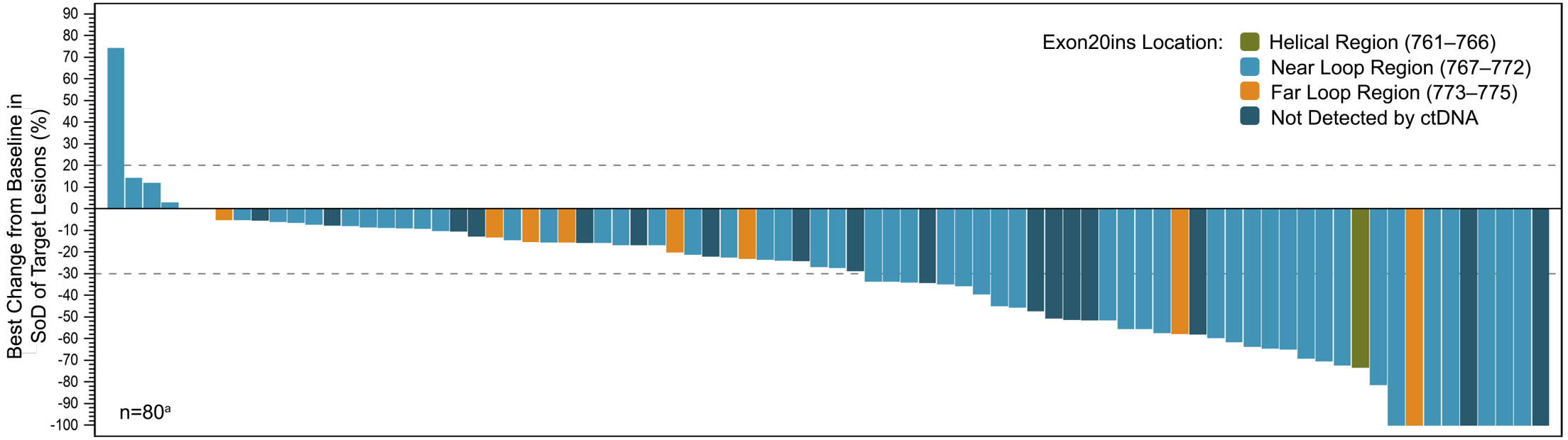
Amivantamab: Adverse Events

AE (≥15% of Treatment-emergent AEs), n (%)	Safety Population (N=114)			
	Treatment-emergent AE		Treatment-related AE	
	Total	Grade ≥3	Total	Grade ≥3
EGFR-related				
Rash[a]	98 (86)	4 (4)	98 (86)	4 (4)
Paronychia	51 (45)	1 (1)	48 (42)	1 (1)
Stomatitis	24 (21)	0	21 (18)	0
Pruritus	19 (17)	0	19 (17)	0
MET-related				
Hypoalbuminemia	31 (27)	3 (3)	17 (15)	2 (2)
Peripheral edema	21 (18)	0	11 (10)	0
Other				
Infusion related reaction	75 (66)	3 (3)	75 (66)	3 (3)
Constipation	27 (24)	0	7 (6)	0
Nausea	22 (19)	0	13 (11)	0
Dyspnea	22 (19)	2 (2)	6 (5)	0
Fatigue	21 (18)	2 (2)	14 (12)	1 (1)
Increased ALT	17 (15)	1 (1)	14 (12)	1 (1)

- Safety profile consistent with inhibition of EGFR and MET pathways
- 2% discontinued due to rash
- 12% had diarrhea (10% treatment-related)
  - 8.5% grade 1–2
  - 3.5% grade 3
- 94% of IRRs occurred with the first infusion and rarely impacted ability to continue with subsequent treatments

Best ORR by Insertion Region of Exon 20 (detected by ctDNA)

Helical Region (n=1)	**Near Loop** (n=54)	**Far Loop** (n=8)	**Not Detected by ctDNA** (n=18)
ORR=100%; CBR=100%	ORR=41%; CBR=70%	ORR=25%; CBR=75%	ORR=39%; CBR=83%



25 distinct Exon20ins variants identified by NGS of ctDNA (Guardant360®) from 63 evaluable patient samples

Amivantamab: EGFR-MET Bispecific Antibody

- Amivantamab has a tolerable safety profile consistent with inhibition of EGFR and MET pathways
  - ✓ Treatment-related AEs were primarily grade 1–2 (16% grade ≥3)
  - ✓ Amivantamab shows robust efficacy with ORR of 40% and median duration of response of 11.1 months
  - ✓ CBR of 74% and mPFS of 8.3 months
  - ✓ Antitumor activity was observed in all patient subgroups and across insertion regions of EGFR Exon 20

- Amivantamab activity compares favorably to currently available treatment options for Exon20ins NSCLC

- Combination approaches being pursued:

  - PAPILLON: Randomized Phase 3 Study of Amivantamab Plus Chemotherapy vs Chemotherapy Alone in EGFR Exon20ins NSCLC (NCT04538664[a])

  - MARIPOSA: Randomized Phase 3 Study of First-line Amivantamab + Lazertinib vs Osimertinib vs Lazertinib in EGFR-mutant NSCLC (NCT04487080)