Bispecific Antibodies in Cancer Care: Actual Reality and Future Projections

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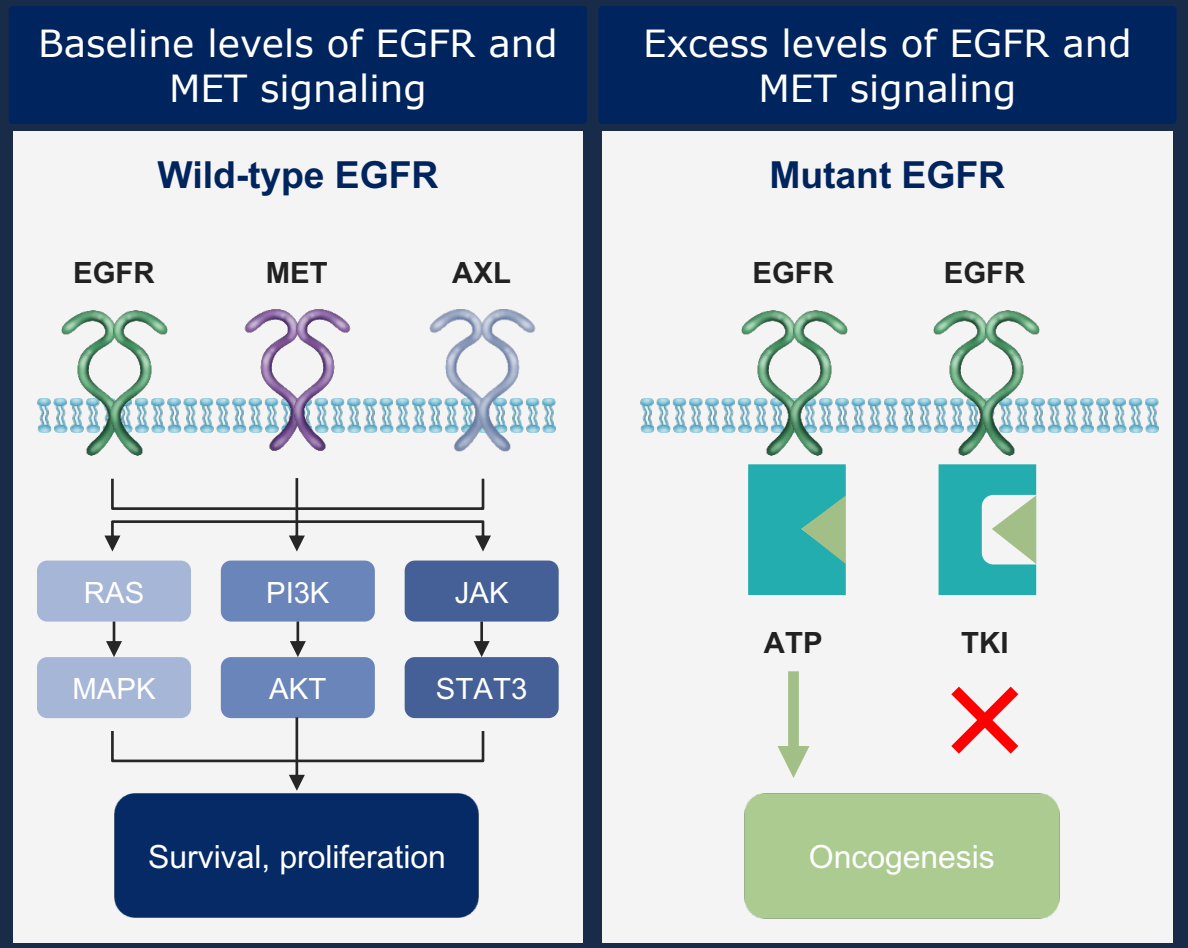
Overview

- Bispecific antibody overview
- Bispecific targeted therapy
- Bispecific immunotherapy

Bispecific Targeted Therapy

Introduction

- NSCLC is the leading cause of cancer-related mortality worldwide[1,2]
- Oncogenic mutations in the EGFR, and less commonly the MET receptor, are observed in patients with NSCLC
- Advancements in the development of targeted therapies for activating *EGFR* and *MET* mutations has accelerated in the last 10 to 20 years



AKT, protein kinase B; ATP, adenosine-triphosphate; AXL, AXL receptor tyrosine kinase; EGFR, epidermal growth factor receptor; JAK, janus kinase; MAPK, mitogen-activated protein kinase; MET, mesenchymal-epithelial transition factor; NSCLC, non-small cell lung cancer; PI3K, phosphatidylinositol-3-kinase; RAS, rat sarcoma virus; STAT3, signal transducer and activator of transcription 3; TKI, tyrosine kinase inhibitor.

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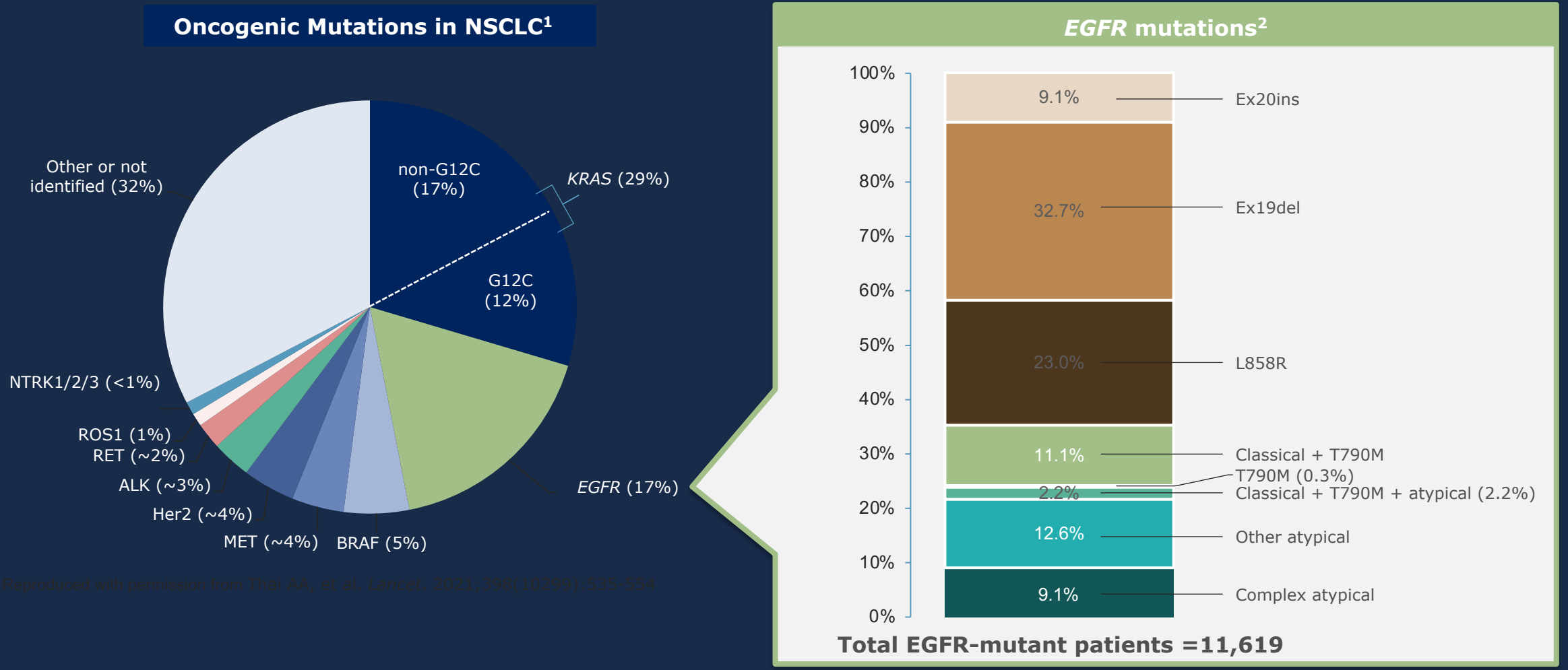
1. Sung H, et al. *CA Cancer J Clin.* 2021;71;209-249. 2. Thai AA, et al. *Lancet.* 2021;398:535-554.

Frequency of Oncogenic Mutations in NSCLC

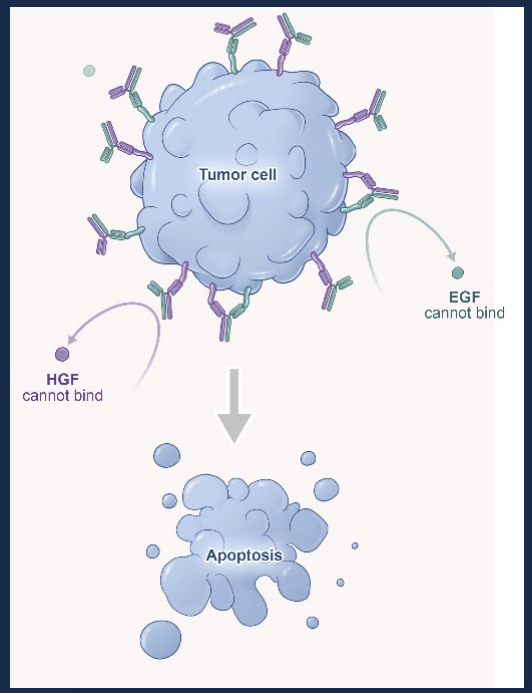


ALK, anaplastic lymphoma kinase; BRAF, B-Raf proto-oncogene; EGFR, epidermal growth factor receptor; ex19del, exon 19 deletion; ex20ins, exon 20 insertion mutation; HER2, human epidermal growth factor receptor 2; KRAS, kirsten rat sarcoma virus; MET, mesenchymal-epithelial transition; NSCLC, non-small cell lung cancer; NTRK, neurotrophic receptor tyrosine kinase; RET, RET proto-oncogene; ROS1, ROS proto-oncogene.

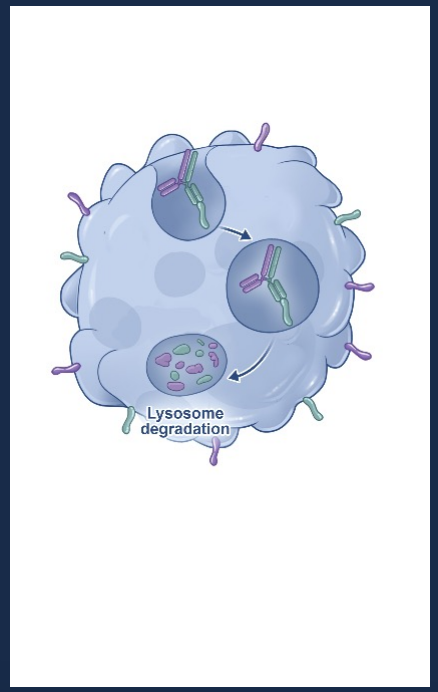
1. Thai AA, et al. *Lancet*. 2021;398(10299):535-554. 2. Robichaux JP, et al. *Nature*. 2022;597:732-737. The Creative Commons license may be viewed at https://creativecommons.org/licenses/by/4.0/.

Amivantamab has Three Distinct MOAs

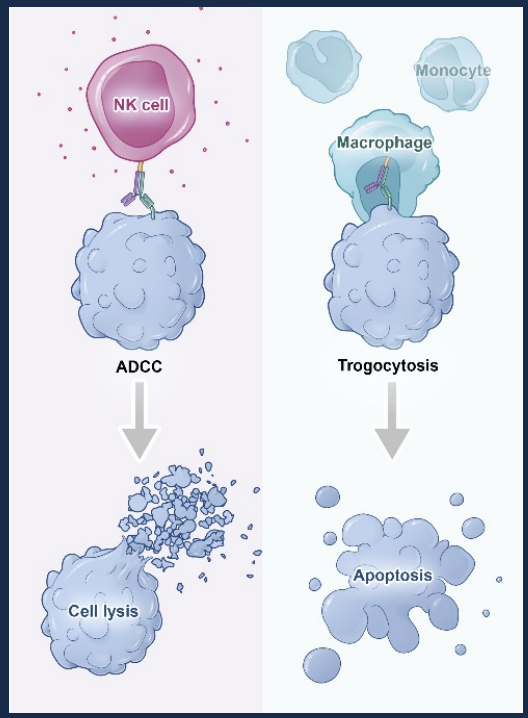
1 **Inhibition of ligand binding**



2 **Receptor degradation**



3 **Antibody-dependant cellular cytotoxicity (ADCC) and trogocytosis**



Not all MOAs occur concomitantly, nor are all required to occur for clinical activity[1-3]

ADCC, antibody-dependent cellular cytotoxicity, EGF, epidermal growth factor; HGF, hepatocyte growth factor; MOA, mechanism of action; NK, natural killer.

1. Grugan KD, et al. *MAbs.* 2017;9:114–126. 2. Moores SL, et al. *Cancer Res.* 2016;76:3942–3953. 3. Vijayaraghavan S, et al. *Mol Cancer Ther.* 2020;19:2044–2056.

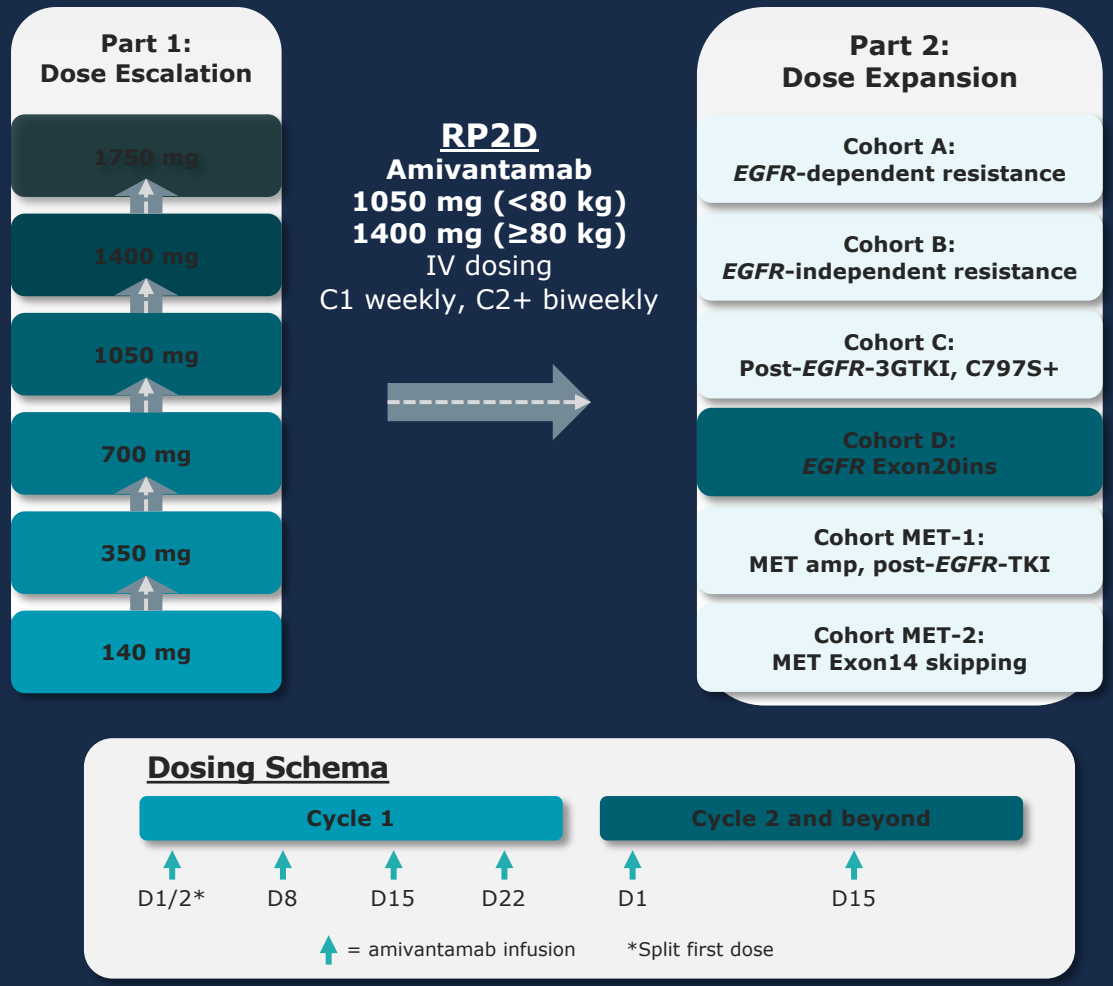
CHRYSALIS Study Design

Key Objectives
- Part 1: Establish RP2D
- Part 2: Safety and efficacy at RP2D

Key Eligibility Criteria
- Metastatic/unresectable NSCLC
- Failed/ineligible for SOC therapy
- Advanced NSCLC (Part 1)
- Measurable disease (Part 2)
- Activating/resistance *EGFR* or *MET* mutations/amplifications (Part 2)

Primary Endpoints
- Part 1: Dose-limiting toxicity (DLT)
- Part 2: Overall response rate (ORR)

Key Secondary Endpoints
- Duration of response (DOR)
- Clinical benefit rate (CBR)
- Progression-free survival (PFS)
- Overall survival (OS)



C, cycle; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; Exon20ins, exon 20 insertion; IV, intravenous; MET, receptor tyrosine kinase MET; NSCLC, non-small cell lung cancer; RP2D, recommended phase 2 dose; SOC, standard of care; TKI, tyrosine kinase inhibitor.

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Park K, et al. J Clin Oncol. 2021. http://ascopubs.org/doi/full/10.1200/JCO.21.00662

Response as Assessed by Blinded Independent Central Review (BICR)

Response per RECIST	Efficacy Population (n=81)
Overall response rate*	40% (95% CI, 29–51)
Clinical benefit rate†	74% (95% CI, 63–83)
Best response, n (%)	
Complete response	3 (4)
Partial response	29 (36)
Stable disease	39 (48)
Progressive disease	8 (10)
Not evaluable	2 (2)

*Proportion of total patients in the efficacy population who had partial and complete responses.
†Proportion of total patients in the efficacy population who had partial and complete responses or stable disease for at least 11 weeks (corresponding to two disease assessments).

CI, confidence interval; RECIST, Response Evaluation Criteria in Solid Tumors.

Park K, et al. J Clin Oncol. 2021. http://ascopubs.org/doi/full/10.1200/JCO.21.00662

Amivantamab Safety is Consistent With EGFR/MET Receptor Inhibition

AE, n (%)[a]	TEAE[1] (n=114)		TRAE[2] (n=114)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
AE associated with EGFR inhibition				
Rash	98 (86)	4 (4)	98 (86)	4 (4)
Paronychia	51 (45)	1 (1)	48 (42)	1 (1)
Stomatitis	24 (21)	0	21 (18)	0
Pruritis	19 (17)	0	19 (17)	0
Diarrhea	14 (12)	4 (4)		
AE associated with MET receptor inhibition				
Hypoalbuminemia	31 (27)	3 (3)	17 (15)	2 (2)
Peripheral edema	21 (18)	0	11 (10)	0

[a]Median follow-up: 5.1 months.

AE, adverse event; EGFR, epidermal growth factor receptor; MET, mesenchymal epithelial transition factor; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

1. Park K, et al. *J Clin Oncol*. 2021;39:3391–402. 2. Sabari JK, et al. WCLC 2021: abstract 3031 (oral presentation).

Amivantamab is being investigated in combination with lazertinib

Efficacy		
Study	**ORR (%)**	**CBR (%)**
CHRYSALIS-2 (NCT04077463)[1] amivantamab + Lazertinib	33	57
CHRYSALIS-2(NCT04077463)[2] amivantamab + lazertinib + carboplatin/pemetrexed	50	80
CHRYSALIS (NCT02609776)[3] amivantamab + lazertinib	100	n/a
CNS Progression		
Study	**amivantamab + lazertinib**	**amivantamab monotherapy**
CHRYSALIS (NCT02609776)[4] amivantamab + lazertinib	7%	17%

Amivantamab and lazertinib combinations are also being investigated in phase 3 **MARIPOSA** (NCT04487080)[5] and **MARIPOSA-2** (NCTNCT04988295)[6] studies.

1. Shu CA, et al. *J Clin Oncol.* 2022;40:9006. 2. Marmarelis ME, et al. *J Thorac Oncol.* 2022;17:S68. 3. Cho BC, et al. ESMO 2020. Abstract 12580.
4. Leighl NB, et al. ESMO 2021: abstract 1192MO. 5. NCT04988295. ClinicalTrials.gov. Accessed November 1, 2022. 6. NCT04487080. ClinicalTrials.gov. Accessed November 1, 2022.

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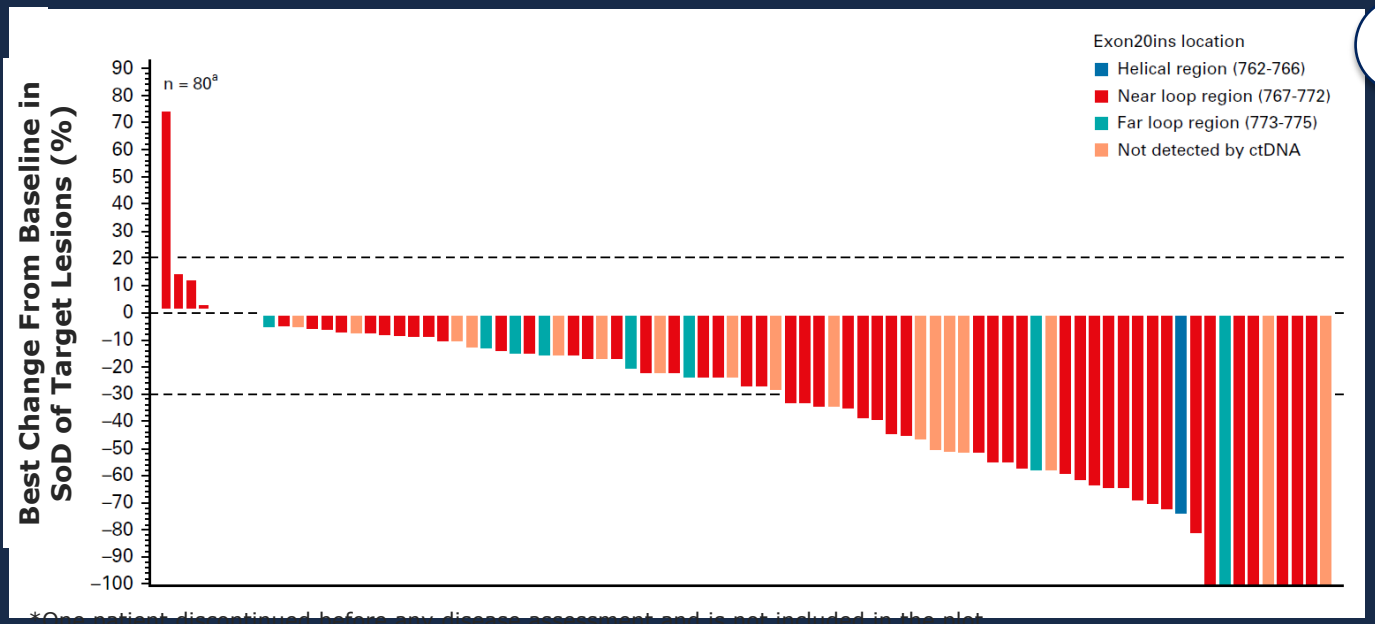
Antitumor Response by Insertion Region



*One patient discontinued before any disease assessment and is not included in the plot.

762 E (n = 0)	763 A (n = 1)	764 Y (n = 0)	765 V (n = 0)	766 M (n = 0)	767 A (n = 19)	768 S (n = 13)	769 V (n = 1)	770 D (n = 9)	771 N (n = 9)	772 P (n = 3)	773 H (n = 8)	774 V (n = 0)	775 C (n = 0)
Helical region (n = 1) ORR = 100% CBR = 100%					Near loop (n = 54) ORR = 41% CBR = 70%						Far loop (n = 8) ORR = 25% CBR = 75%		
Not detected by ctDNA (n = 18) ORR = 39% CBR = 83%													

- All 81 patients in the efficacy population had ctDNA or tumor samples submitted for central testing, of which 63 had detectable ctDNA, identifying **25 distinct Exon20ins variants**
- Antitumor responses were observed in patients who harbored insertions within the helical, near-loop, and far-loop regions of ex20

ctDNA, circulating tumor DNA; ex20, exon 20; SoD, sum of lesion diameters.

Park K, et al. J Clin Oncol. 2021. http://ascopubs.org/doi/full/10.1200/JCO.21.00662

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Amivantamab in NSCLC patients with MET exon 14 skipping mutation: Updated results from the CHRYSALIS study

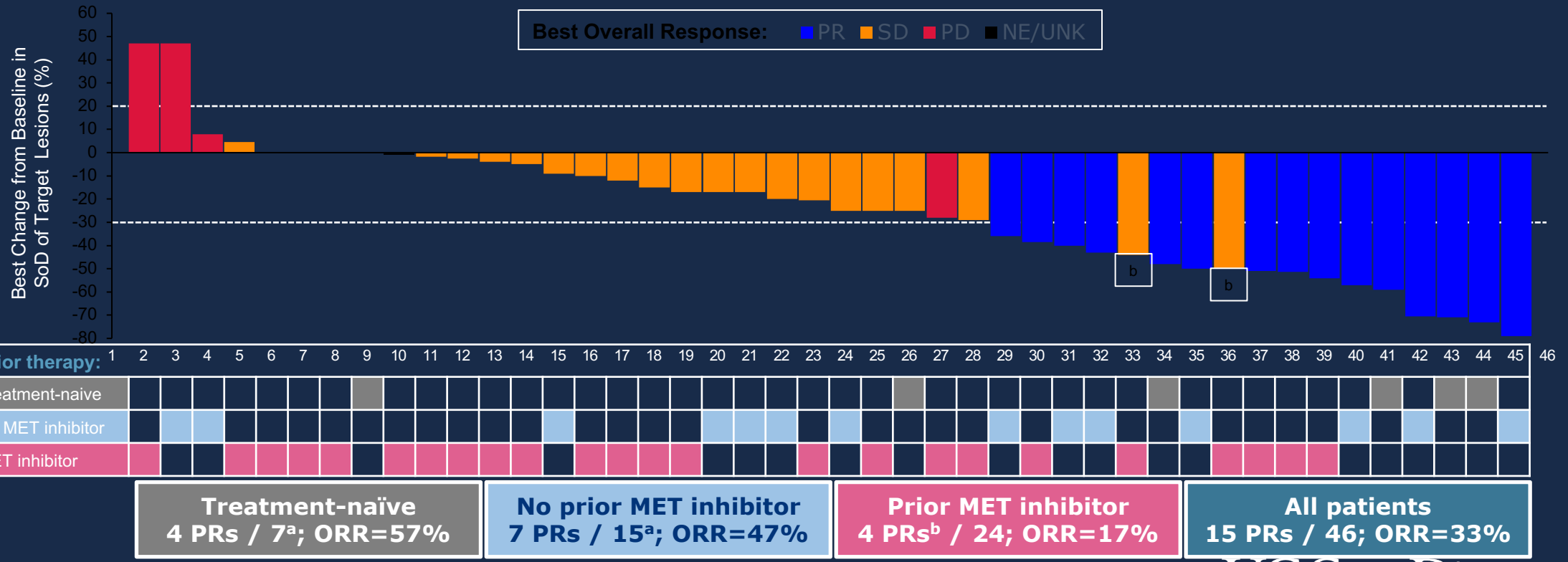
Matthew G. Krebs[1], Alexander I. Spira[2], Byoung Chul Cho[3], Benjamin Besse[4], Jonathan W. Goldman[5], Pasi A. Jänne[6], Zhiyong Ma[7], Aaron S. Mansfield[8], Anna Minchom[9], Sai-Hong Ignatius Ou[10], Ravi Salgia[11], Zhijie Wang[12], Casilda Llacer Perez[13], Grace Gao[14], Joshua C. Curtin[14], Amy Roshak[14], Robert W. Schnepp[14], Meena Thayu[14], Roland E. Knoblauch[14], Chee Khoon Lee[15]

[1]Division of Cancer Sciences, The University of Manchester and The Christie NHS Foundation Trust, Manchester, UK; [2]Virginia Cancer Specialists Research Institute, US Oncology Research, Fairfax VA; [3]Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea; [4]Institut Gustave Roussy, Villejuif, France; [5]David Geffen School of Medicine at UCLA, Los Angeles, CA; [6]Dana Farber Cancer Institute, Boston, MA; [7]Henan Cancer Hospital, Zhengzhou, China; [8]Mayo Clinic, Rochester, MN; [9]Drug Development Unit, Royal Marsden/Institute of Cancer Research, Sutton, UK; [10]University of California Irvine, Orange, CA; [11]City of Hope, Duarte, CA; [12]Cancer Hospital Chinese Academy of Medical Sciences, Beijing, China; [13]Medical Oncology Intercenter Unit. Regional and Virgen de la Victoria University Hospitals. IBIMA. Málaga, Spain; [14]Janssen R&D, Spring House, PA; [15]St George Hospital, Kogarah, Australia

Presented at ASCO 2022 Annual Meeting; June 3-7, 2022; Chicago, IL, USA.

Antitumor Activity of Amivantamab Monotherapy

- A total of 46 patients were efficacy evaluable



[a]Two additional patients had a best timepoint response of PR but did not confirm.

NE/UNK, not evaluable/unknown; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; SoD, sum of diameters; TKI, tyrosine kinase inhibitor.

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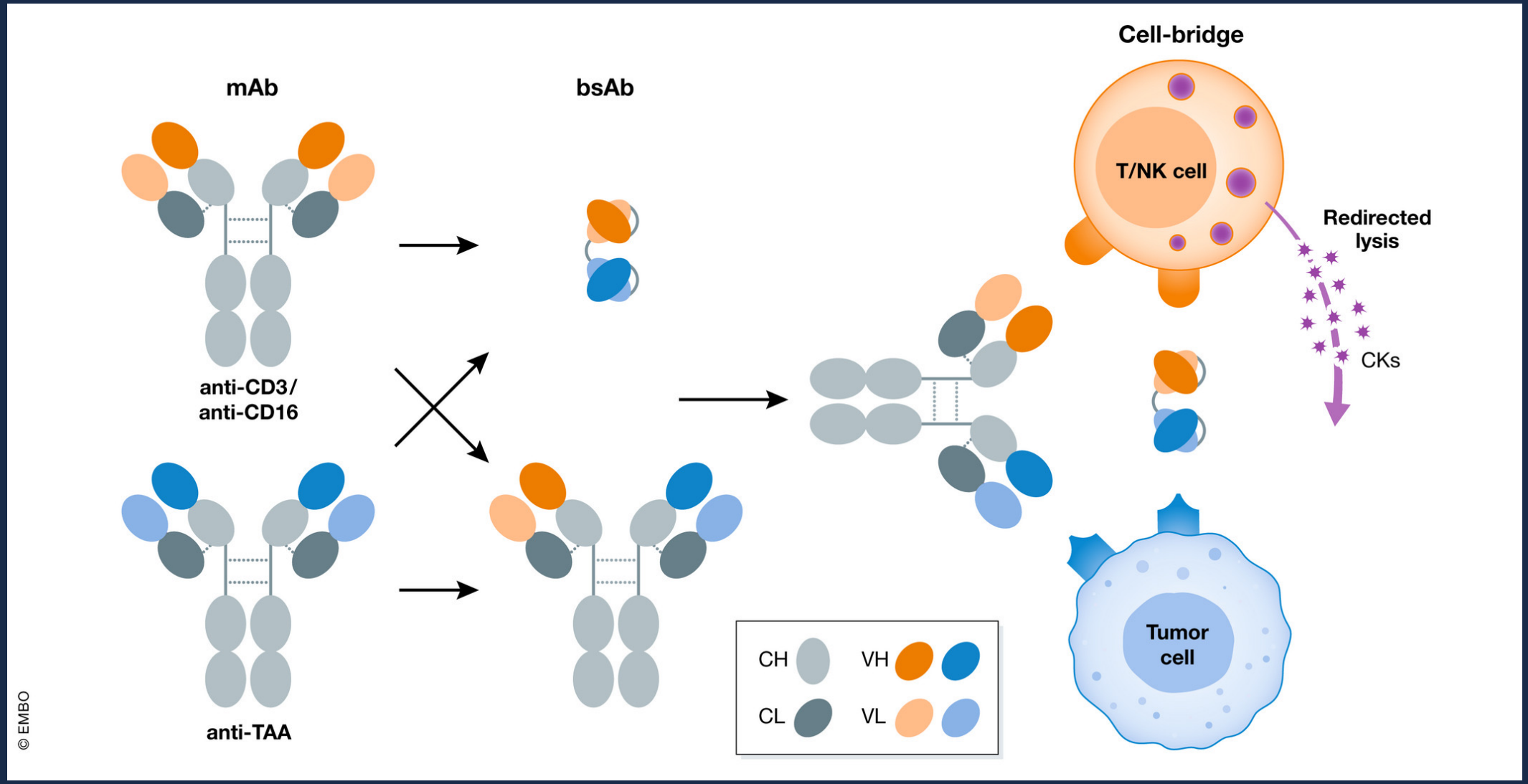
Bispecific Immunotherapy

The state of the art of bispecific antibodies for treating human malignancies



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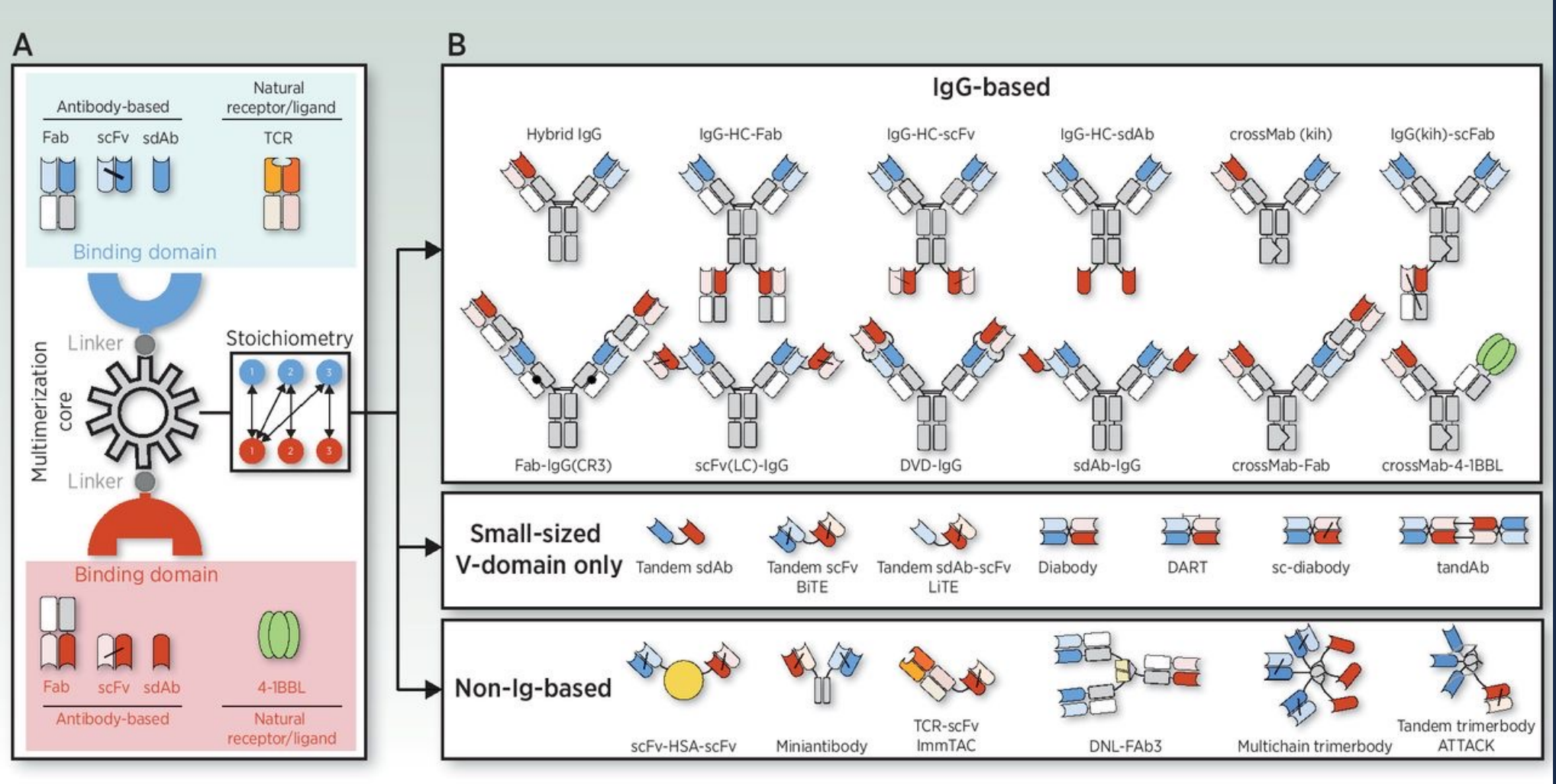
EMBO Mol Med, Volume: 13, Issue: 9, First published: 24 August 2021, DOI: (10.15252/emmm.202114291)

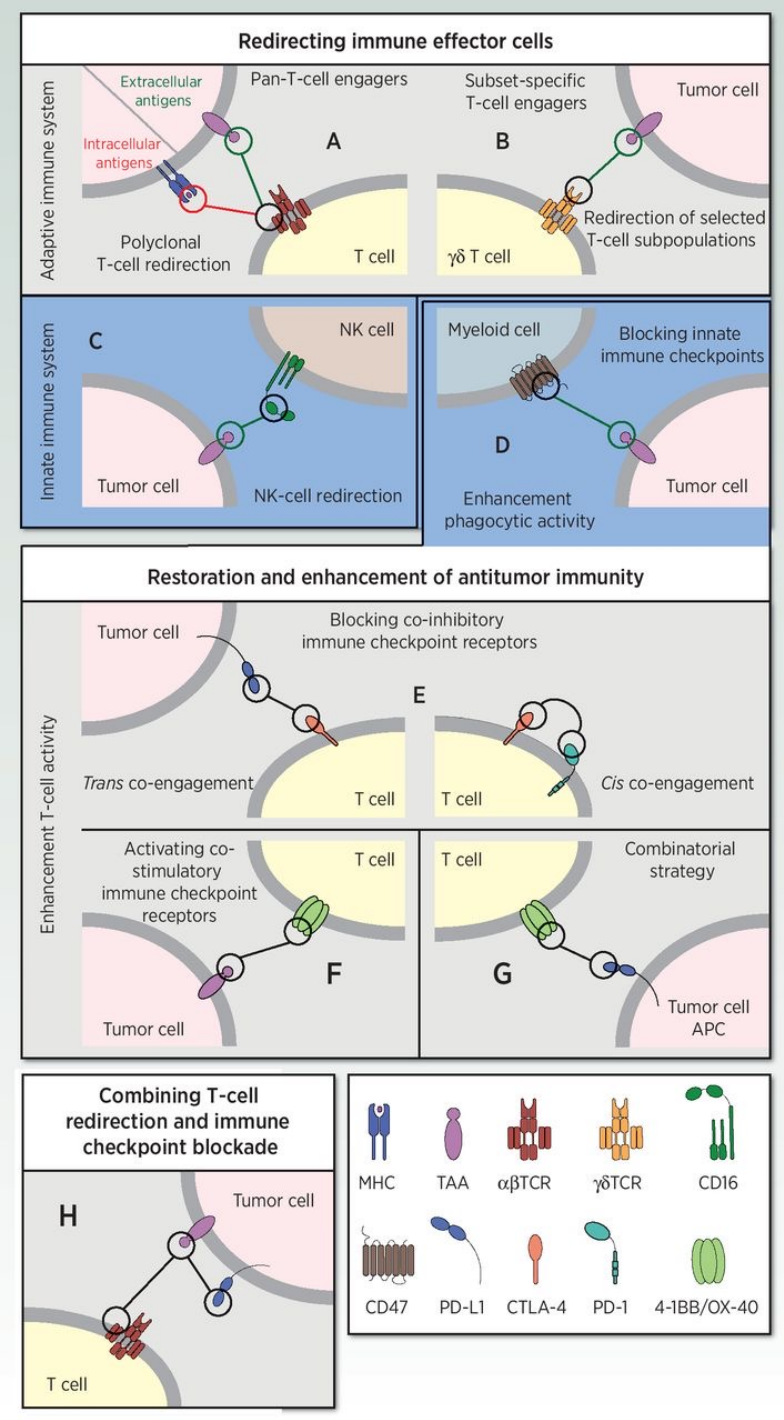
Multitude of bispecific “lego” pieces that determine efficacy, toxicity



Clin Cancer Res. 2021;27(20):5457-5464. doi:10.1158/1078-0432.CCR-20-3770

Two is better than one?

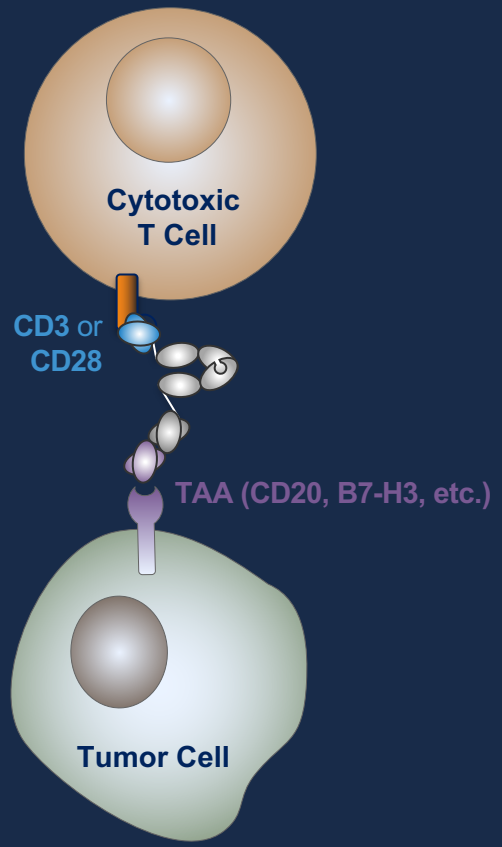
Redirecting combinatorial immune responses



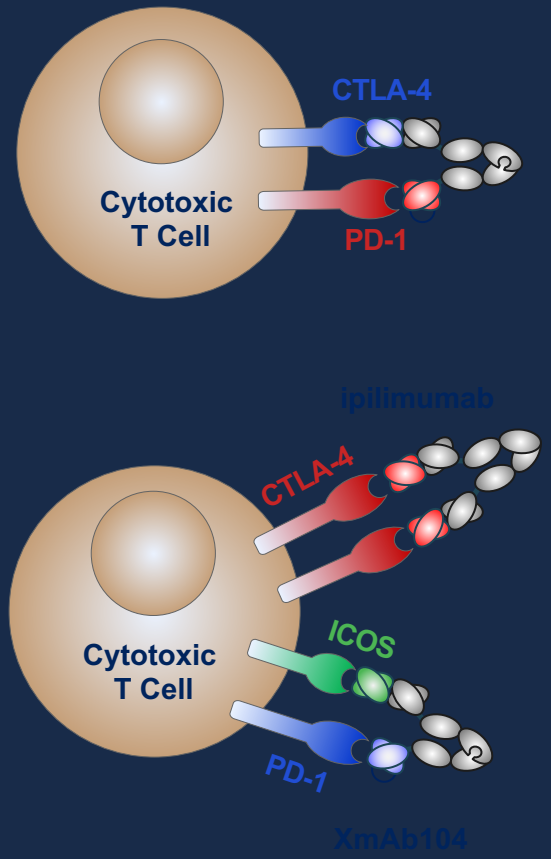
Clin Cancer Res. 2021;27(20):5457-5464. doi:10.1158/1078-0432.CCR-20-3770

Multiple mechanisms of action in vivo

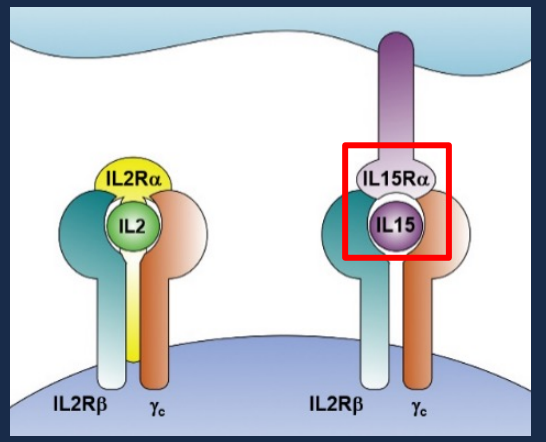
T Cell Engager

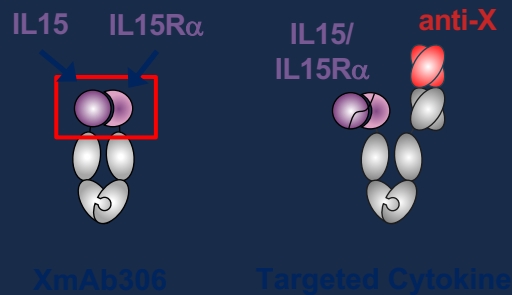


Dual Checkpoint/Co-stim



Cytokine-Fc





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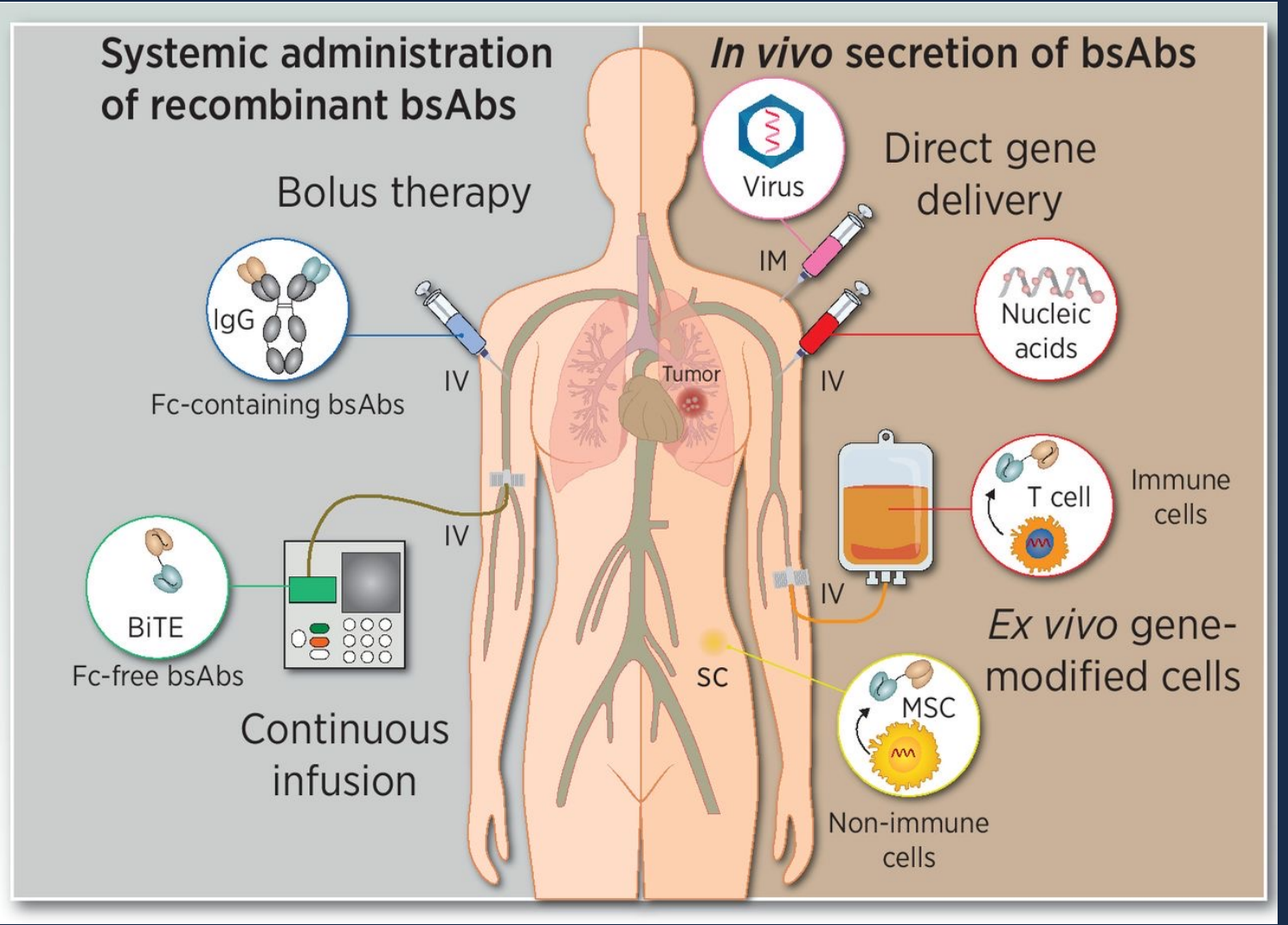
Courtesy: Xencor

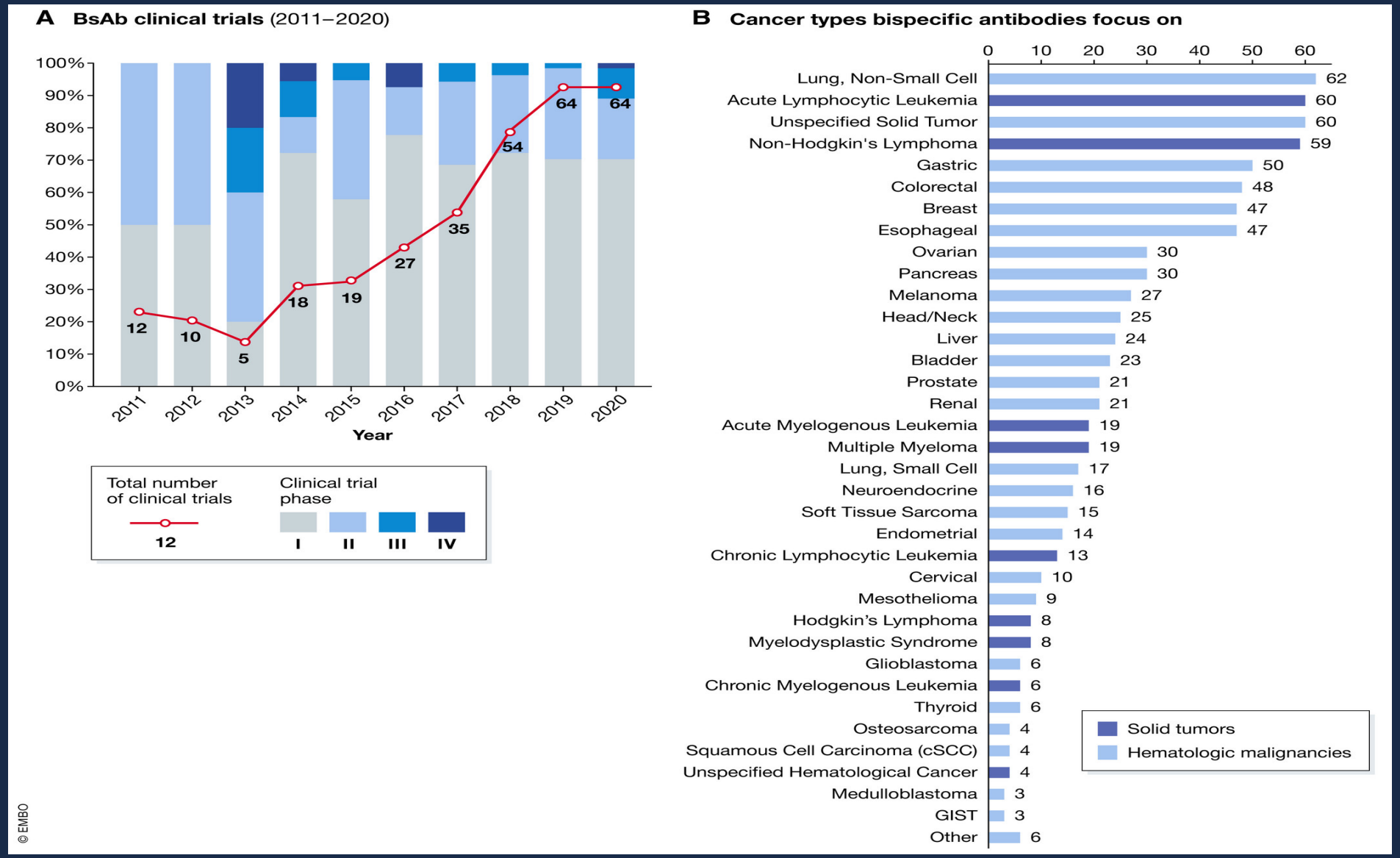
18

Advantages to bispecific antibodies recruiting immune cells at one terminus



Clin Cancer Res. 2021;27(20):5457-5464. doi:10.1158/1078-0432.CCR-20-3770

Landscape of bispecific immunomodulatory clinical trials



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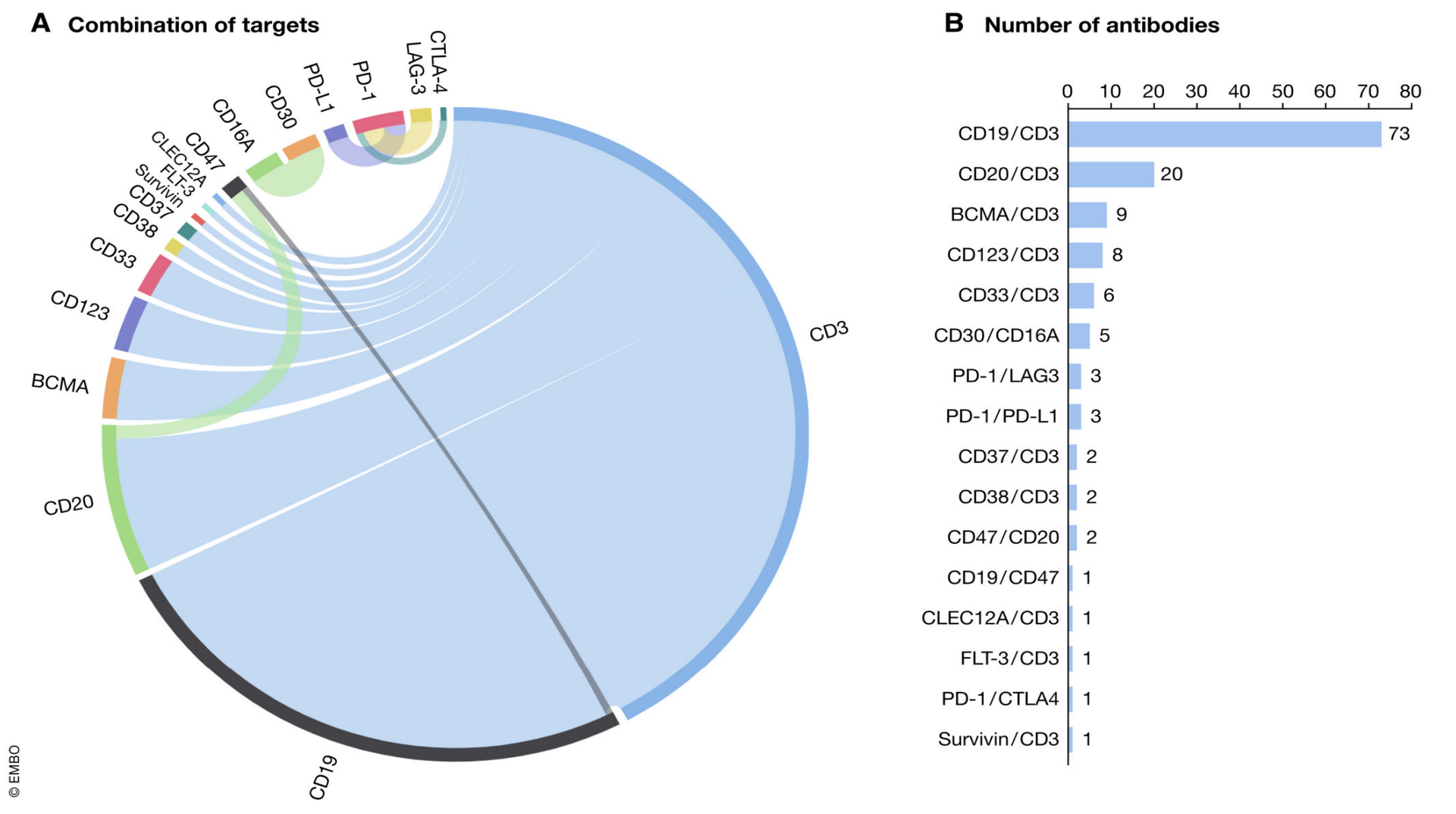
EMBO Mol Med, Volume: 13, Issue: 9, First published: 24 August 2021, DOI: (10.15252/emmm.202114291)

Landscape of bispecific antibody immunomodulatory targets in oncology



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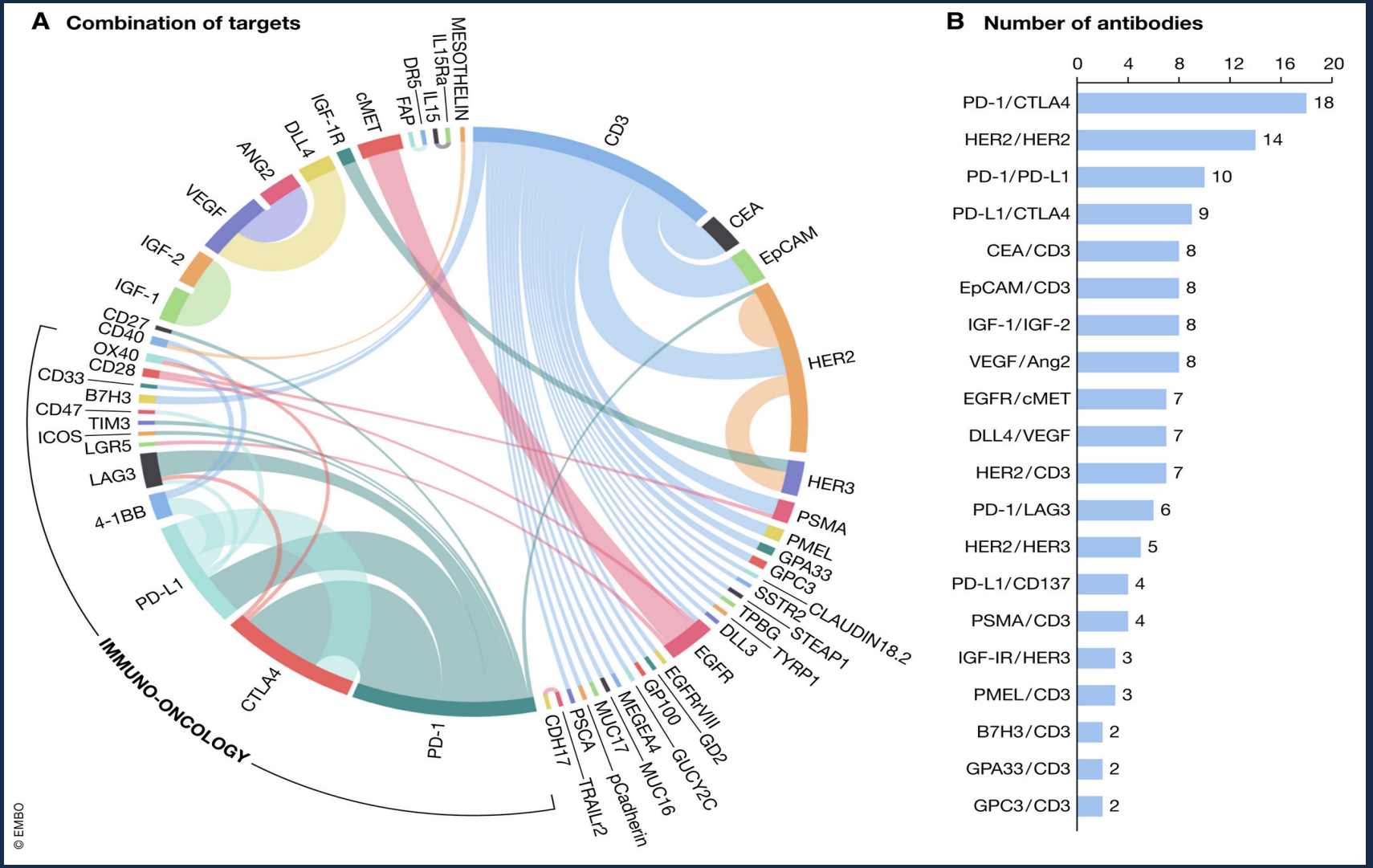
Landscape of bispecific antibodies in solid tumor oncology



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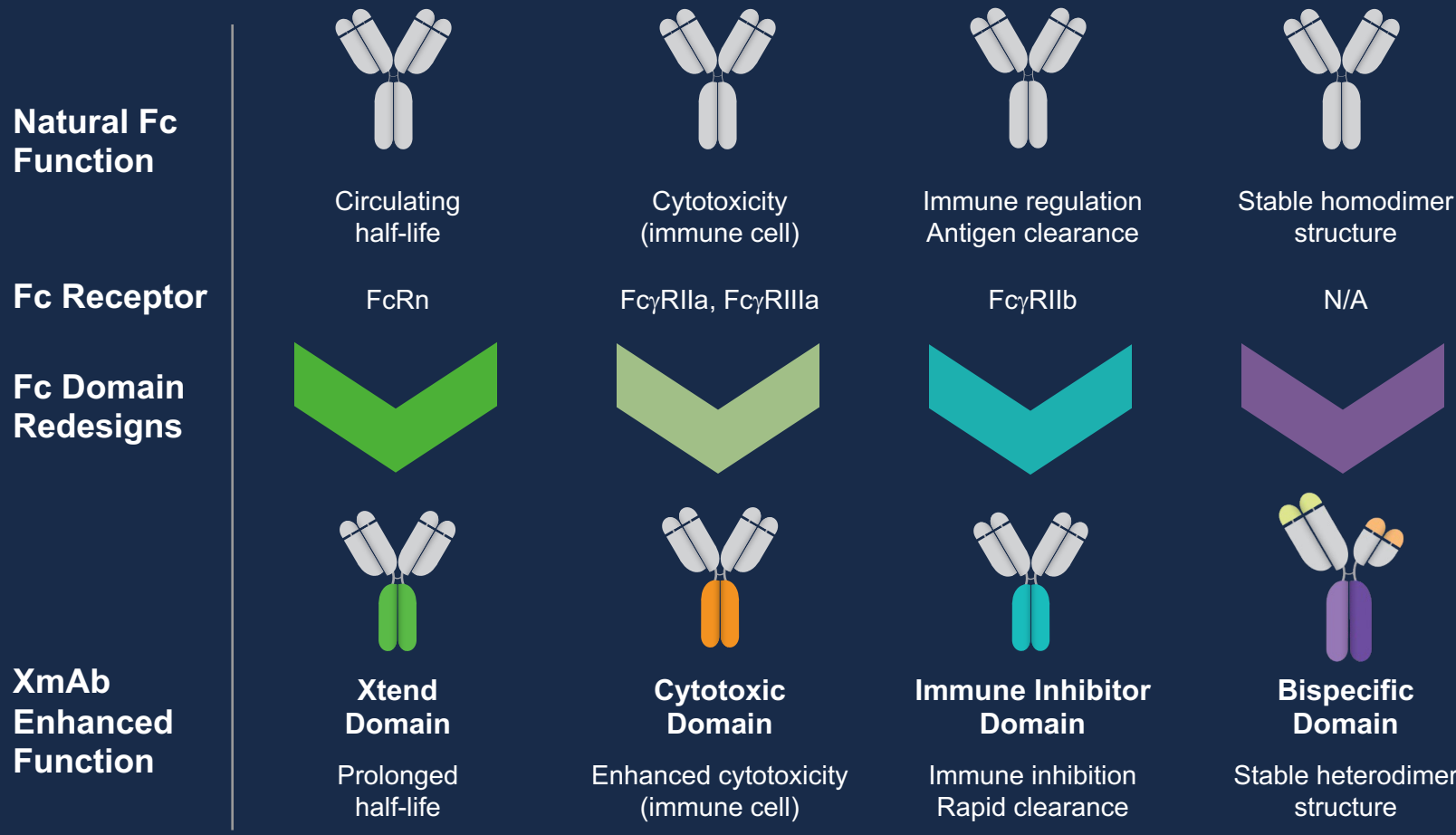
One example of bispecific engineering



Additional Fc domains: stability, complement activation

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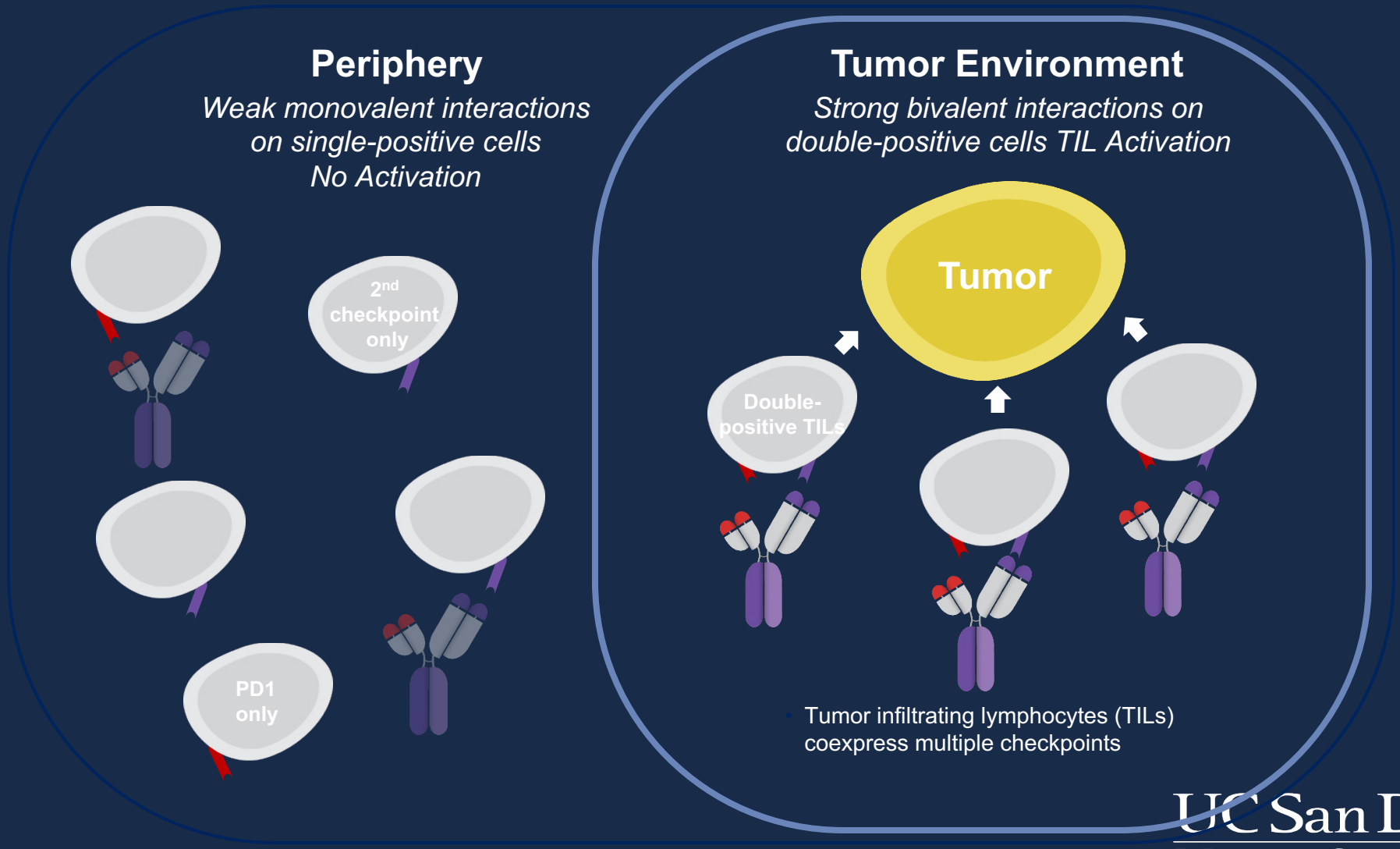
Potential stimulation of more activated “double positive” TIL



- Tumor infiltrating lymphocytes (TILs) coexpress multiple checkpoints

- (Matsuzaki 2010, Fourcade 2012, Gros 2014)

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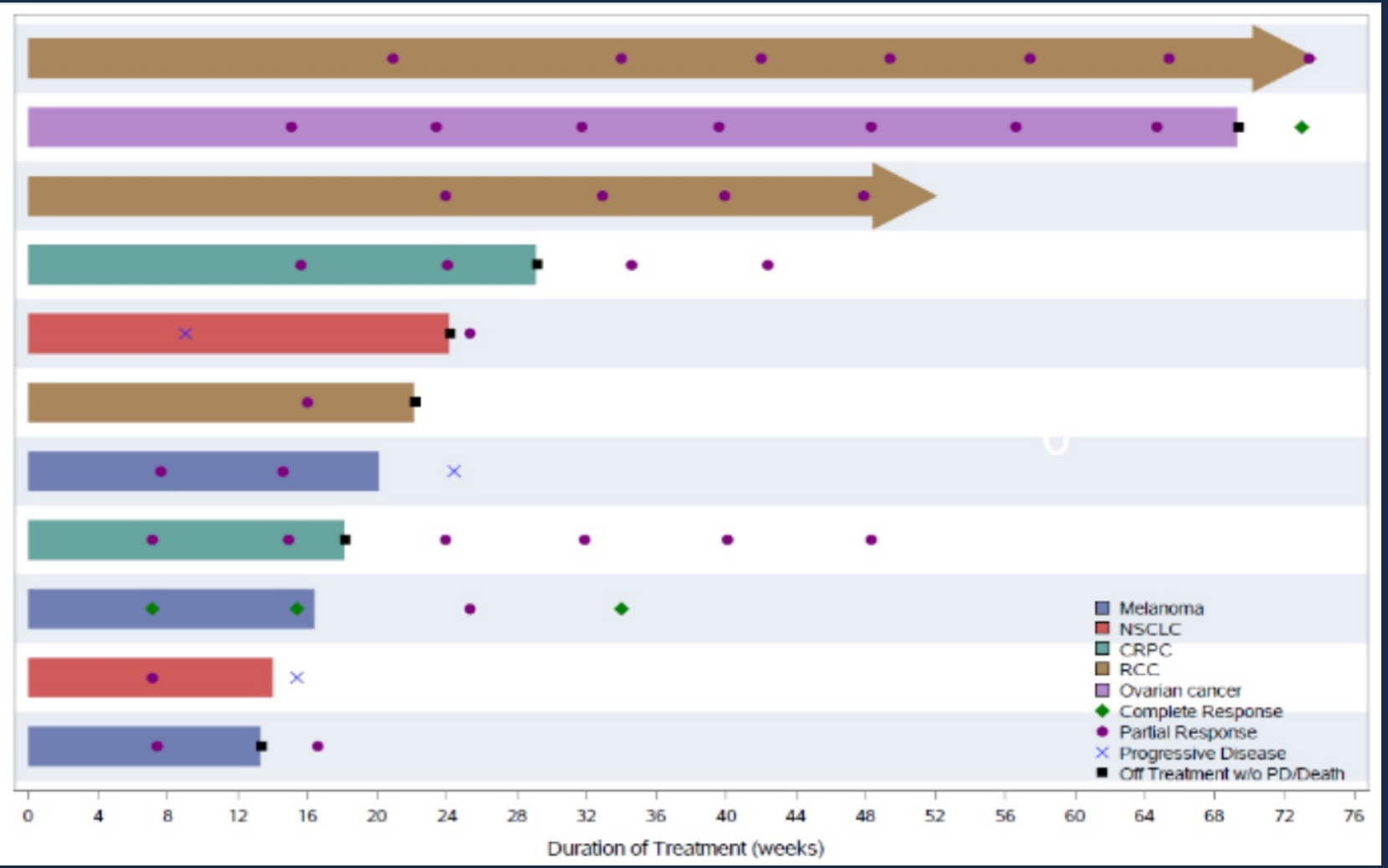
Vudalimab: Selective PD-1 x CTLA-4 Inhibition Bispecific



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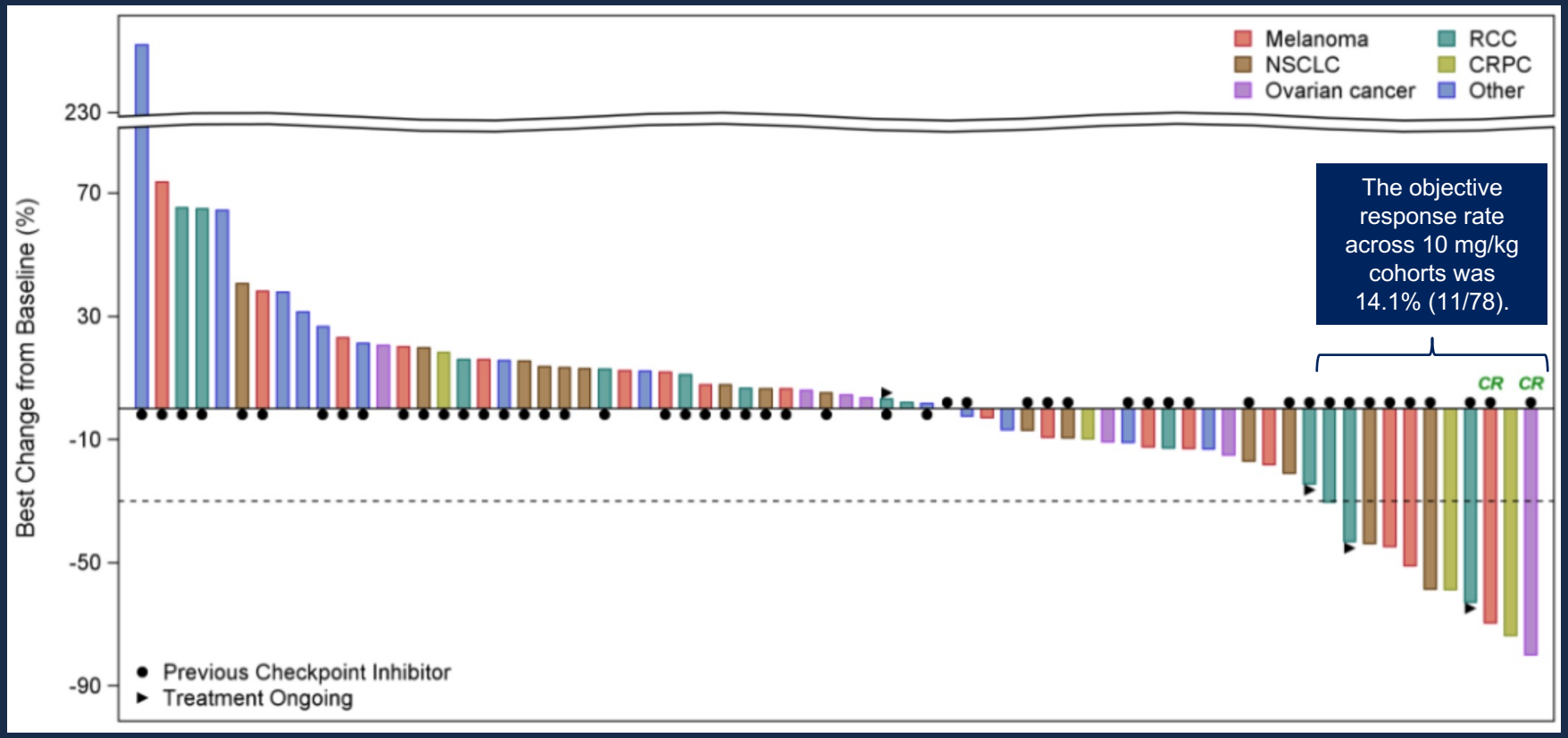
Efficacy in Prior ICI treated Cancers



The median duration of response for all responders was 18.3 weeks (unadjusted).
The median duration of response for patients with RCC was 24.1 weeks (unadjusted), and two RCC patients remained on treatment.

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Summary

- Bispecific monoclonal antibody technology allows for dual targeting within a single molecule
  - Targeted therapy opportunities (EGFR/MET i.e. amivantamab)
  - Recruiting T cells to target opportunities (CD19/CD3 i.e. blinatumomab)
- Activating dual synergistic immunologic pathways or recruiting dual cell populations may be an attractive approach in solid tumor immuno-oncology
- Question of synergy vs additive effect (one bispecific antibody vs two monovalent antibodies) is under investigation
- Biomarker-directed strategies needed in order to optimize therapeutic benefit relative to toxicity

Questions?

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