Merus closing in on cancer

Phase 1 study of MCLA-145, a bispecific antibody targeting CD137 and PD-L1, in solid tumors, as monotherapy or in combination with pembrolizumab

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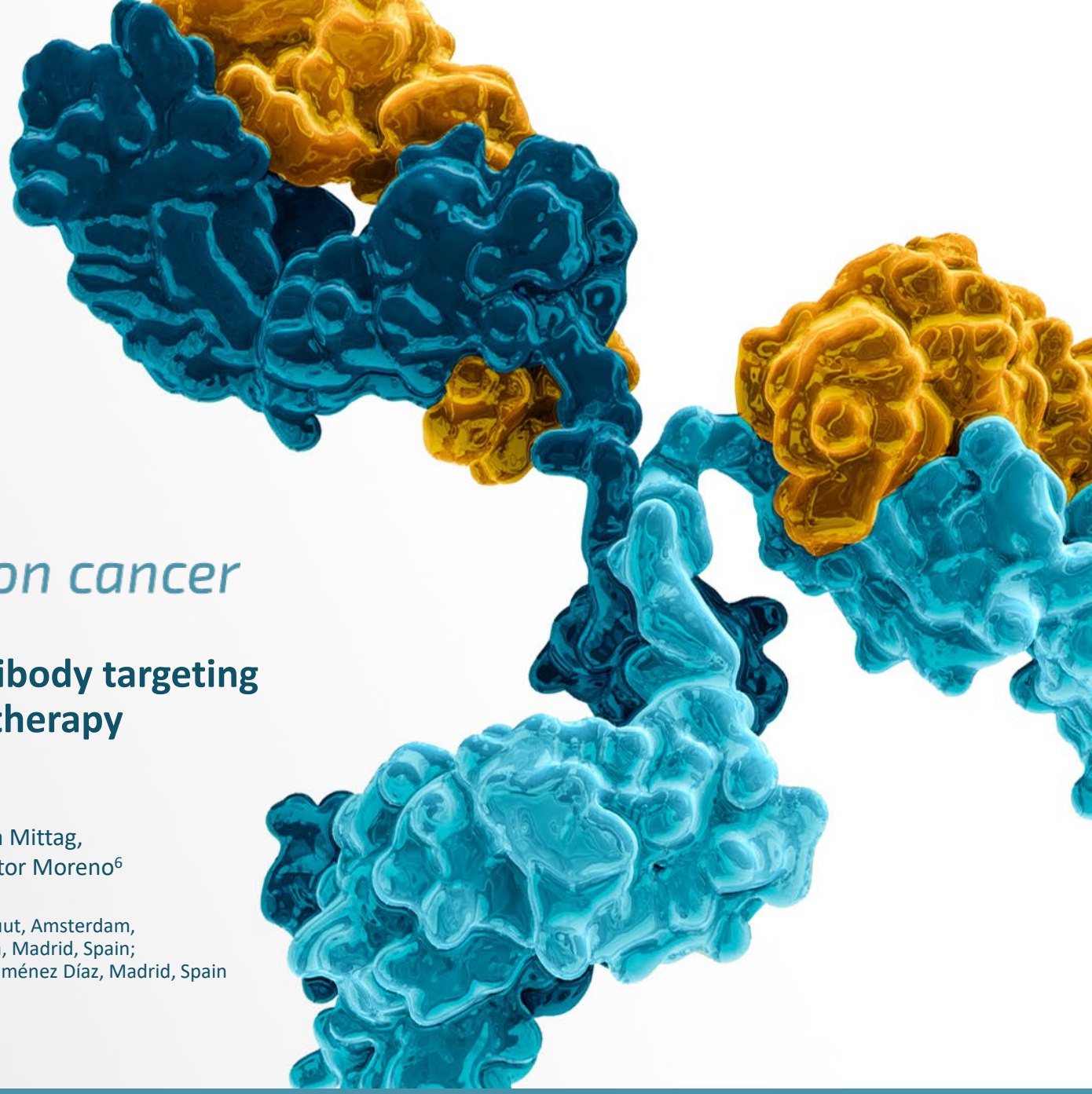

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Key takeaways

- MCLA-145 as monotherapy and in combination with pembrolizumab demonstrated a **manageable safety profile at 40 mg Q3W (RDE)**
- MCLA-145 demonstrated **clinical activity as monotherapy and in combination with pembrolizumab in PD-L1–naïve and –treated patients**
- Pharmacodynamic endpoint and early clinical observations suggested **improved activity at 40 mg Q3W**
- Observation of **improved clinical activity, and persistent CD8+ T-cell proliferation with less frequent dosing** warrants further clinical exploration **particularly in tumors with high CD8+ T-cells at baseline**

PD-L1, programmed cell death ligand 1; Q3W, every 3 weeks; RDE, recommended dose for expansion.

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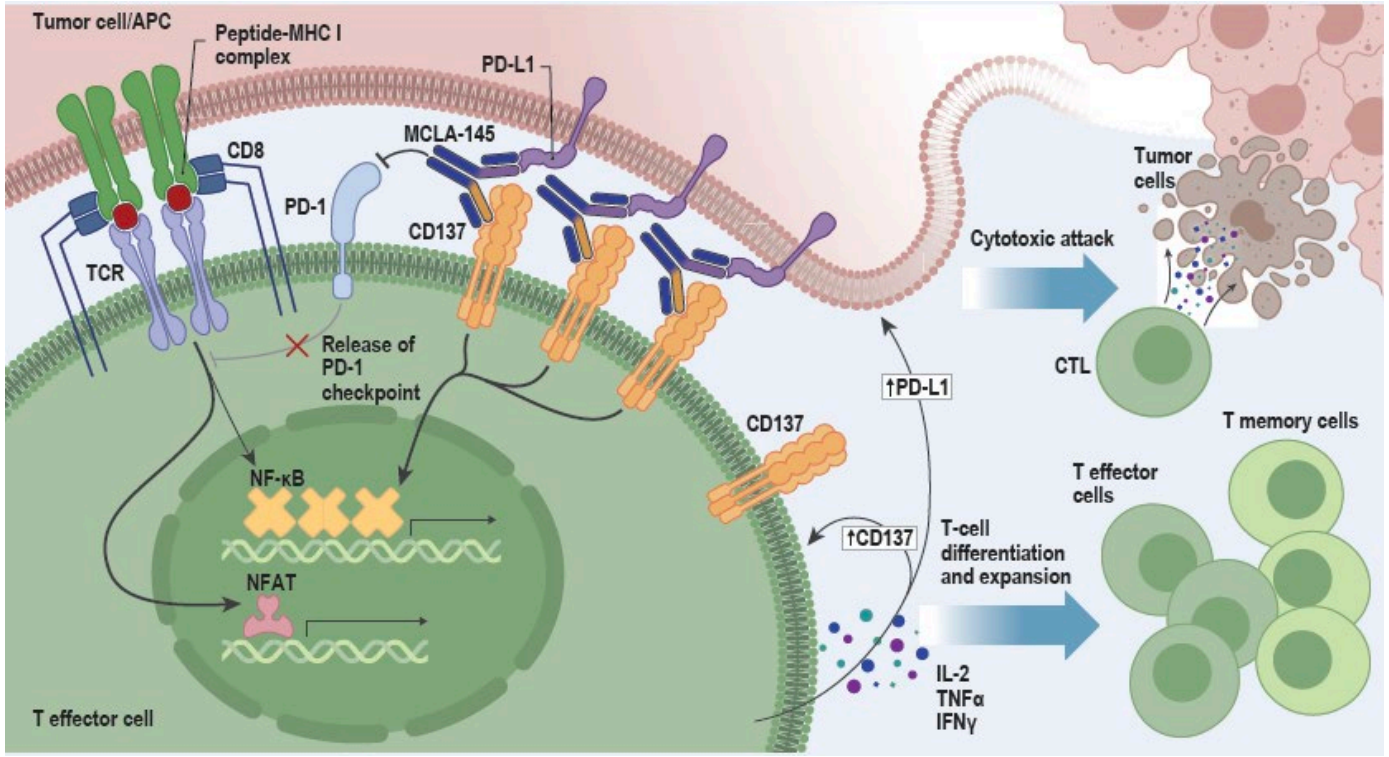
MCLA-145: Fully human bispecific IgG1 antibody targeting PD-L1 and CD137[1,2]

- Enhances antigen-mediated T-cell activation via CD137 co-stimulation and by blocking inhibitory PD-L1[1]
- CD137 activation depends on simultaneous binding to PD-L1 that is expressed on neighboring cells[2]
- Demonstrated antitumor activity in preclinical models, with enrichment of CD8+ T cells in tumors following treatment[2]
- Shown to promote immunological memory in in vitro T-cell priming assays[2] and durable CD8 T-cell responses[3,4]



APC, antigen-presenting cell; CTL, cytotoxic T lymphocyte; IFN, interferon; IgG1, immunoglobulin G1; IL, interleukin; MHC, major histocompatibility complex; NF-κB nuclear factor kappa B; NFAT, nuclear factor of activated T cells; PD-1, programmed cell death protein 1; TCR, T-cell receptor; TNF, tumor necrosis factor. 1. Geng Q, Jiao P. (2024) Molecules 29, 454. 2. Geuijen C, et al. (2021) Nat Commun 12, 4445. 3. Willoughby JE, et al. (2014) J Immunol 193, 244–251. 4. Eskiocak U, et al. (2020) JCI Insight 5, e133647.

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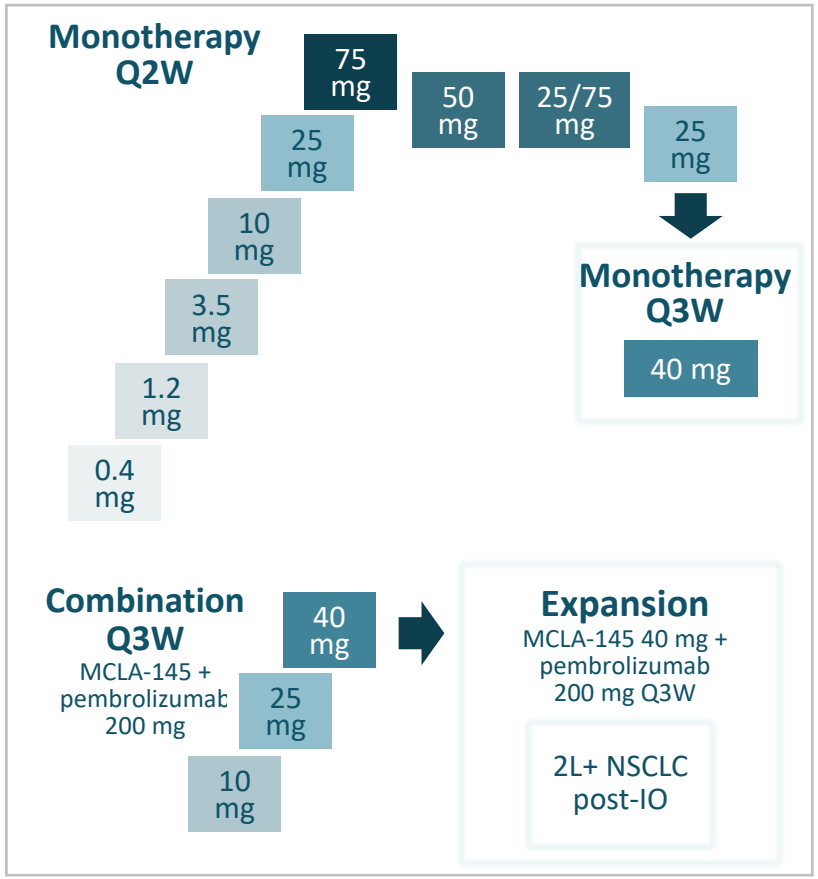
MCLA-145-CL01 Phase 1 trial (NCT03922204)

Open-label, dose-escalation trial with expansion cohorts



Demographics, disease features, and treatment exposure	Monotherapy Q2W/Q3W (N=53)	Combination Q3W (N=19)
Age, years, median (range)	60 (27–81)	61 (50–80)
Male / female, n (%)	26 (49) / 27 (51)	9 (47) / 10 (53)
White, n (%)	45 (85)	18 (95)
ECOG status 0 / 1, n (%)	23 (43) / 30 (57)	6 (32) / 13 (68)
Number of prior lines of therapy, median (range)	3 (1–8)	3 (2–5)
Prior PD-(L)1 therapy, n (%)	26 (49)	19 (100)
Most common solid tumor cancer type, n (%)		
Lung	5 (9)	13 (68)
Colorectal	5 (9)	1 (5)
Gastric	5 (9)	1 (5)
Pancreatic	5 (9)	0
Metastatic / locally advanced disease, n (%)	46 (87) / 7 (13)	19 (100) / 0
Number of cycles initiated, median (range)	2 (1–39)	5 (1–18)
Relative dose intensity, %, median (range)	100 (29–100)	100 (80–100)

**Prior to a protocol amendment, some patients who did not have PD-L1 expression ≥1% were included. †The RDE will be considered a dose that achieves a functional target engagement of PD-L1 and CD137. 2L+, second-line or later-line; ECOG, Eastern Cooperative Oncology Group; IO, immunotherapy; NSCLC, non-small cell lung cancer; ORR, overall response rate; Q2W, every 2 weeks.*

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Safety profile – Q3W compared with Q2W dosing

n (%)	Monotherapy, n (%)				Combination, n (%)	
	Q2W 0.4–75 mg (N=47)		Q3W 40 mg (N=6)		Q3W 10–40 mg (N=19)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
TEAEs	46 (98)	31 (66)	6 (100)	2 (33)	18 (95)	6 (32)
Serious TEAEs	24 (51)	19 (40)	2 (33)	1 (17)	4 (21)	3 (16)
AEs leading to discontinuation	6 (13)	5 (11)	1 (17)	1 (17)	3 (16)	2 (11)
AEs leading to infusion interruption	20 (43)	14 (30)	2 (33)	1 (17)	6 (32)	2 (11)
TEAEs in ≥25% of patients*						
Fatigue	24 (51)	2 (4)	3 (50)	0	12 (63)	2 (11)
Cough	3 (6)	0	2 (33)	0	8 (42)	0
Nausea	10 (21)	1 (2)	1 (17)	0	6 (32)	0
Constipation	5 (11)	0	0	0	6 (32)	0
Decreased appetite	15 (32)	1 (2)	2 (33)	0	5 (26)	0
Pyrexia	10 (21)	0	3 (50)	0	5 (26)	0
ALT/AST increased†	11 (23)	4 (9)	2 (33)	1 (17)	4 (21)	2 (11)
Dyspnea	15 (32)	0	1 (17)	0	4 (21)	1 (5)
Anemia	14 (30)	4 (9)	1 (17)	0	2 (11)	1 (5)
Neutropenia‡	13 (28)	10 (21)	1 (17)	1 (17)	0	0

- Dose-limiting toxicities:
  - Monotherapy, observed in 6 patients at doses: 25mg, 50mg, 75mg Q2W; 40mg Q3W
  - Combination: None observed
- RDE:
  - Monotherapy: 40mg Q3W
  - Combination: 40mg Q3W + pembrolizumab 200mg Q3W
- Grade ≥3 TEAEs observed to be less frequent with Q3W dosing
- No Grade 4 liver toxicities were observed with Q3W dosing

Data cutoff date: January 3, 2024.

**≥25% in any group. †Number of patients experiencing ALT and AST increase were the same. ‡Composite term including neutrophil count decreased, white blood cell count decreased, febrile neutropenia, leukopenia.AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event.*

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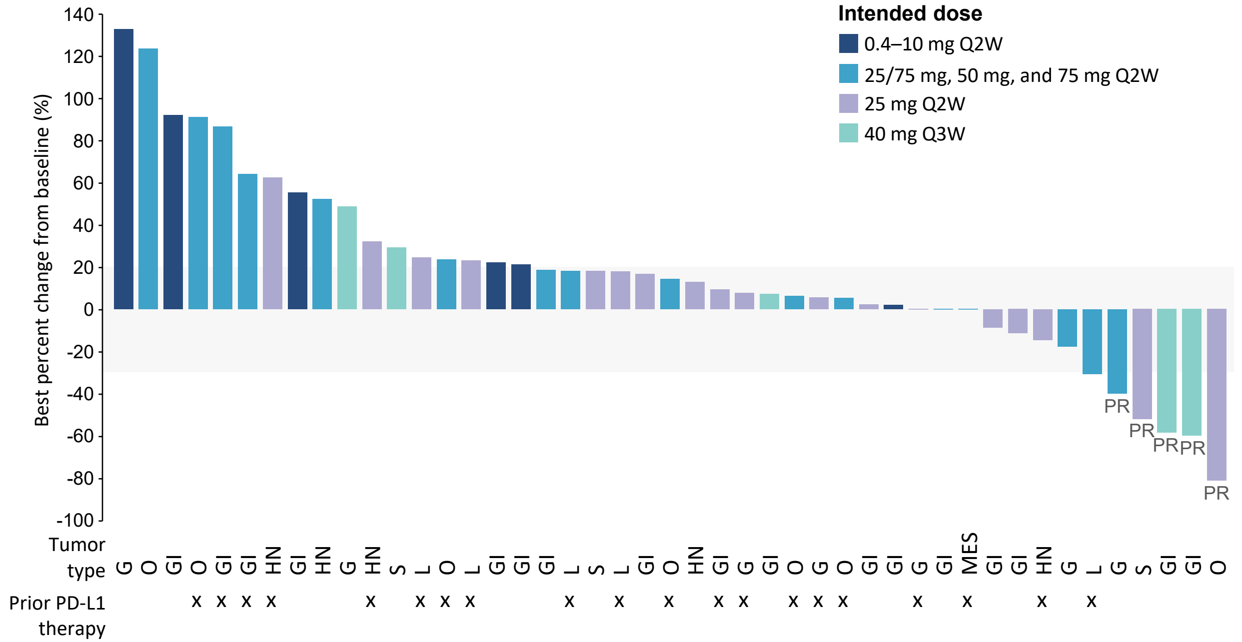
Clinical activity as monotherapy and in combination

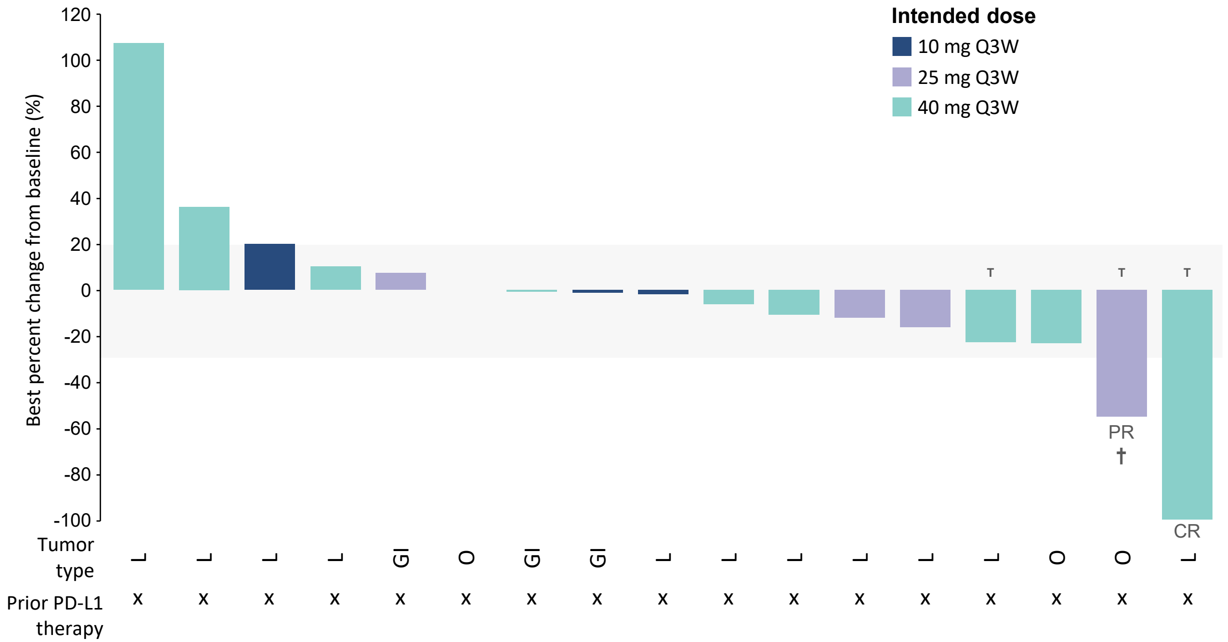
Monotherapy ORR* 5/52 (10%, 95% CI: 3–21)

ORR at RDE (40 mg Q3W) 2/6 (33%)



Combination ORR* 2/19 (11%, 95% CI: 1–33)

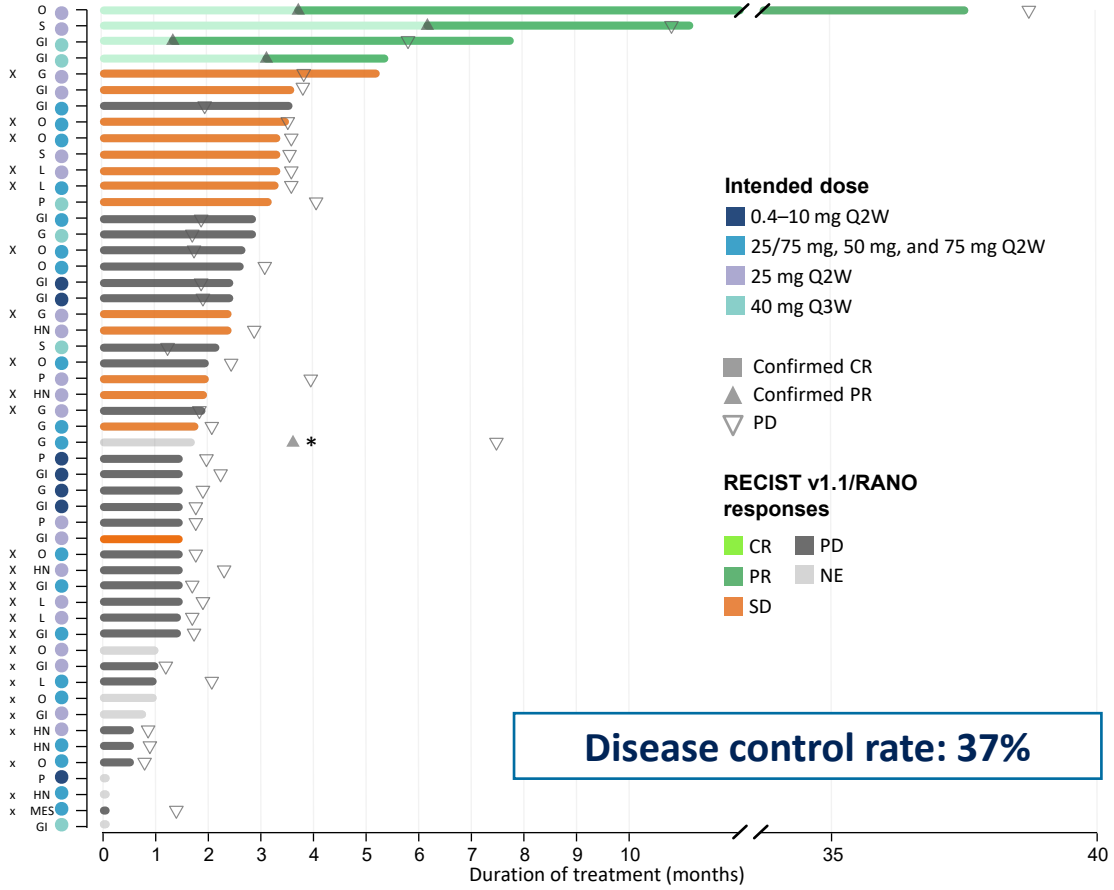
ORR in NSCLC at RDE (40 mg Q3W) 1/9 (11%)



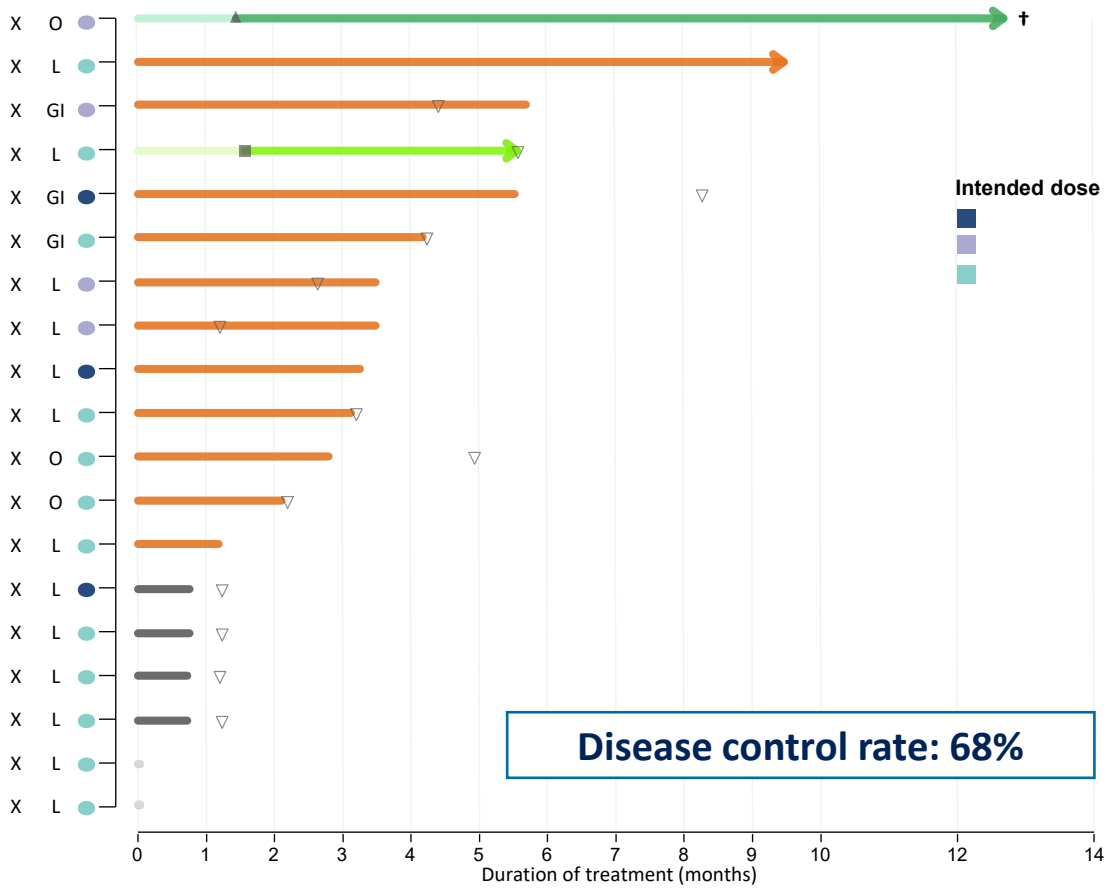
*ORR per RECIST v1.1 per investigator assessment: percentage of patients having a confirmed CR or PR as the best on-study response. 7 patients in monotherapy and 2 in combination included in the efficacy analysis did not have a post-baseline scan. †Patient will be further explored in patient spotlight. CI, confidence interval; CR, complete response; G, gynecological cancer; GI, gastrointestinal cancer; HN, head and neck cancer; L, non-small cell lung cancer; MES, mesothelioma; O, other cancer type; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; S, sarcoma; T, treatment ongoing; X, prior PD-L1 therapy.

Duration of treatment as monotherapy and in combination

Monotherapy: Median 2 months (range <0.1–38, N=53)



Combination: Median 3 months (range <0.1–13, N=19)



**Confirmed PR observed after treatment discontinuation. †Patient will be further explored in patient spotlight.*
NE, not estimable; P, pancreatic cancer; PD, progressive disease; RANO, Response Assessment in Neuro-Oncology; SD, stable disease.

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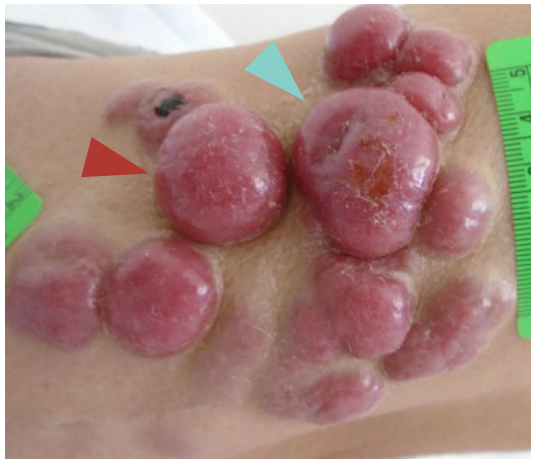
Patient spotlight: PR in a patient with Merkel cell carcinoma treated with combination therapy

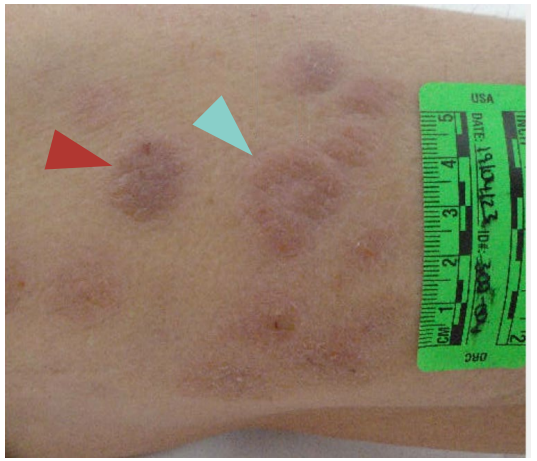
Patient characteristics

- **Age:** 80-year-old male
- **Diagnosis:** Merkel cell carcinoma on thigh with local extension
- **Pretreated with:**
  - Avelumab, best response: PD
  - Carboplatin/etoposide, best response: PR
- **PD-L1 expression:** 1–10%
- **Treatment:** 18 cycles of MCLA-145 25 mg Q3W and pembrolizumab 200 mg Q3W
- **Response:** PR at 1.5 months
  - Duration of response: 11 months from initial PR to data cutoff
  - 55% decrease in target lesions
  - Post data cutoff, patient died due to AE unrelated to treatment

Screening



Cycle 7



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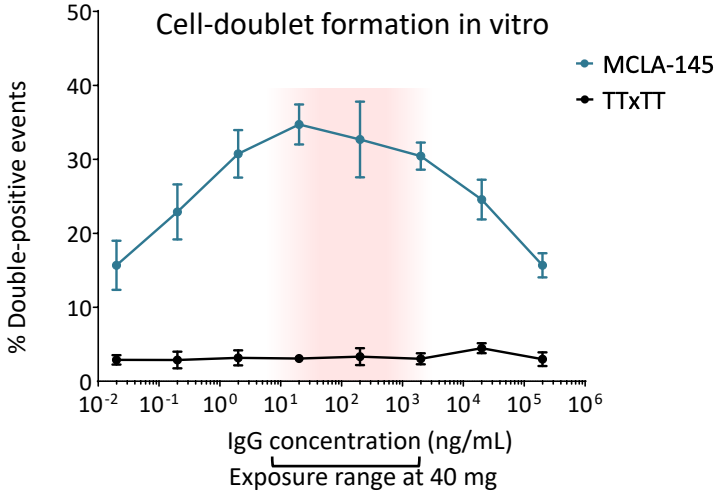
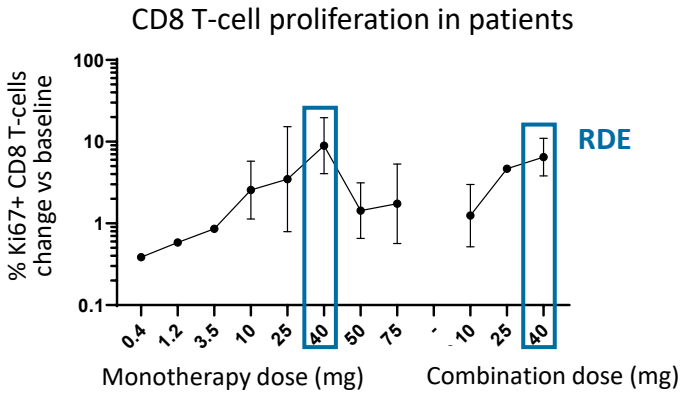
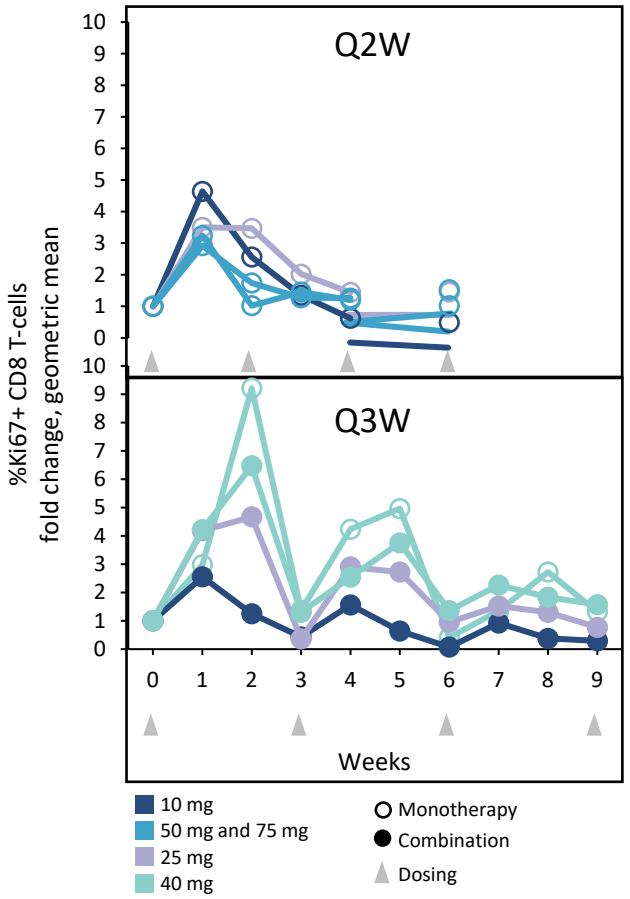
Pharmacodynamic data suggest improved activity at 40 mg Q3W

Dose: Bell-shaped dose response observed in vitro was confirmed in patients with maximum T-cell proliferation at 40 mg dose

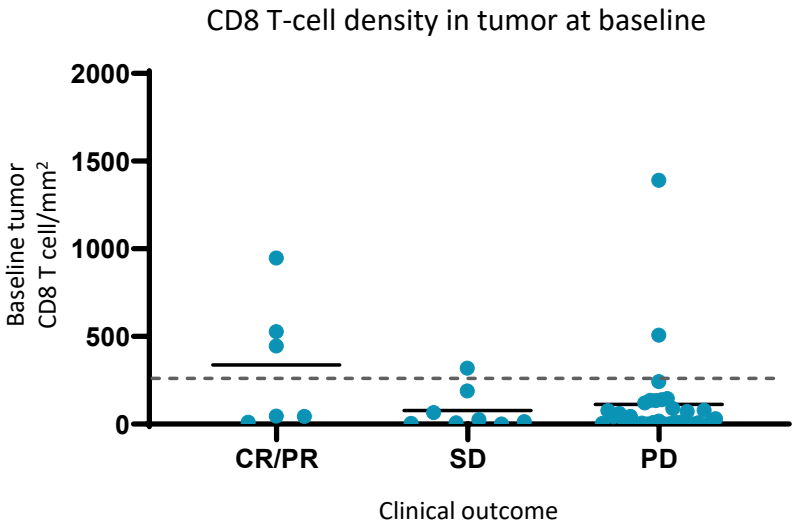




Schedule: More sustained T-cell stimulation observed with less frequent dosing



Response: 3 of 6 (50%) evaluable patients with baseline tumor CD8 T-cell density of ≥250 cells/mm^2 were responders



Data cutoff date: January 3, 2024.
TT, tetanus toxic.

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Conclusions

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Acknowledgments

Thanks to:

- Patients and their families
- Investigators and their teams, research nurses, study coordinators, and site staff
- Merus colleagues
  - Steven Harrison
  - Arianna Fumagalli
  - Stefan Hagedoorn
  - Meli Ajradini
- CRO and vendors
- Emmaline Tregembo at LiNK Health Group

CRO, contract research organization.