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# Phase I Dose Escalation Study of MCLA-145, a Bispecific Antibody Targeting CD137 and PD-L1 in Solid Tumors


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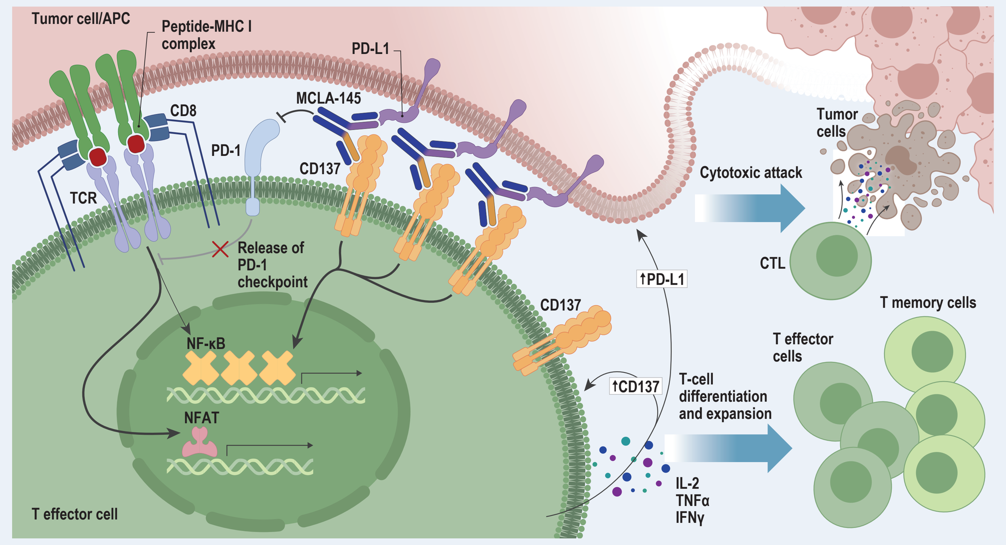
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## Introduction

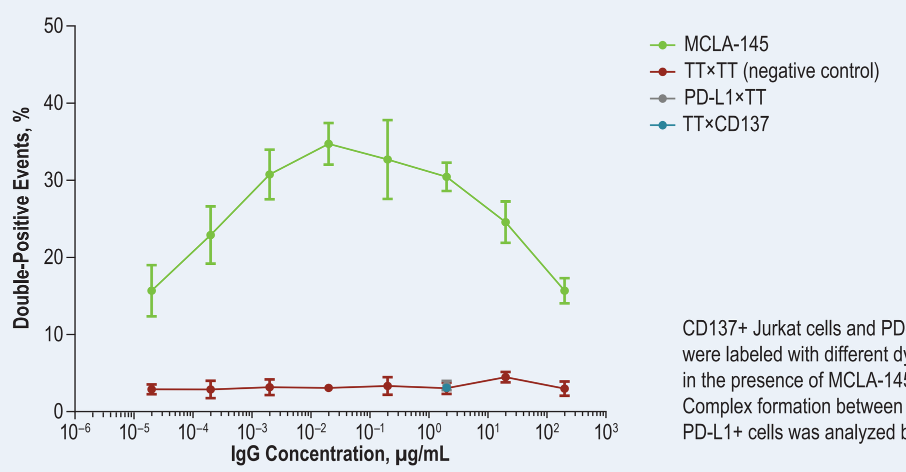
- MCLA-145 is a fully human common light chain IgG1-based bispecific antibody that binds CD137 and PD-L1[1]
  - MCLA-145 was Fc silenced to block nonspecific Fcγ receptor-mediated effects
- Preclinically, MCLA-145 induces CD137 signaling in the presence of PD-L1 and correlates with PD-L1 expression levels[1,2]
- Targeting CD137 and the PD-1/PD-L1 axis with MCLA-145 enhances antigen-mediated T-cell activation via CD137 costimulation and blocking inhibitory PD-L1 (**Figure 1**)[1]
- A bell-shaped dose-response curve was observed for MCLA-145 *in vitro* (**Figure 2**)
- MCLA-145 was shown to promote immunologic memory in *in vitro* T-cell priming assays,[1] consistent with literature demonstrating that CD137 costimulation promotes durable CD8 T-cell responses[3,4]
- In preclinical xenograft models, MCLA-145 demonstrated antitumor activity, with enrichment of CD8+ T cells in tumors following treatment[1]
- MCLA-145-CL01/MCLA-145-101 is a phase I multicenter trial investigating MCLA-145 in different solid tumors considered not amenable to surgery or other curative treatments or procedures
  - The trial includes dose escalation and expansion parts

**Figure 1. MCLA-145 Mechanism of Action**



Tumor cell/APC
Peptide-MHC I complex
PD-L1
CD8
MCLA-145
PD-1
CD137
TCR
Release of PD-1 checkpoint
Cytotoxic attack
Tumor cells
CTL
↑PD-L1
CD137
T memory cells
T effector cells
NF-κB
NFAT
↑CD137
T-cell differentiation and expansion
IL-2
TNFα
IFNγ
T effector cell


**Figure 2. Complex Formation by Flow Cytometry Demonstrated a Bell-Shaped Dose Response**



Double-Positive Events, %
IgG Concentration, µg/mL
MCLA-145
TT×TT (negative control)
PD-L1×TT
TT×CD137


CD137+ Jurkat cells and PD-L1+ CHO cells were labeled with different dyes and co-cultured in the presence of MCLA-145 or controls. Complex formation between CD137+ and PD-L1+ cells was analyzed by flow cytometry.

## Purpose

- Evaluation of the safety and preliminary efficacy of MCLA-145 in advanced or metastatic solid tumors

## Methods

### *Patients and Study Design*

- This open-label phase I study (NCT03922204) is currently enrolling patients in the dose escalation part
- Adult patients (age ≥18 years) with histologically or cytologically confirmed advanced or recurrent/metastatic solid tumors known to respond to immunotherapy (limit of 1 prior anti–PD-1 immunotherapy regimen allowed), Eastern Cooperative Oncology Group (ECOG) status of 0–1, ≤4 prior systemic treatment regimens are eligible
- Key exclusion criteria are prior therapy with a CD137 (4-1BB) agonist, prior chimeric antigen receptor (CAR) T-cell therapy, prior grade ≥3 immune-mediated adverse events (AEs) with anti–PD-1 therapy, or prior anti–PD-1 therapy-associated liver toxicity of grade >1
- MCLA-145 is being administered intravenously (range, 0.4–75 mg) every 14 days (Q2W) in 28-day cycles; the study includes dose escalation and confirmation/safety expansion

### *Objectives*

- The primary objective is to evaluate the safety, tolerability, and dose-limiting toxicity (DLT) of MCLA-145 and to determine maximum tolerated dose (MTD) and/or recommended dose for expansion (RDE)
- Secondary objectives include the following:
  - Evaluation of pharmacokinetics
  - Exploration of preliminary antitumor activity through assessment of objective response rate (ORR; complete response [CR] + partial response [PR]), disease control rate (DCR; CR + PR + stable disease [SD]), progression-free survival (PFS), and duration of response (DOR) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
- Exploratory objectives include evaluating the effect of MCLA-145 on tumor and immune cell infiltrate biomarkers as predictive markers of MCLA-145 activity

### *Statistical Analyses*

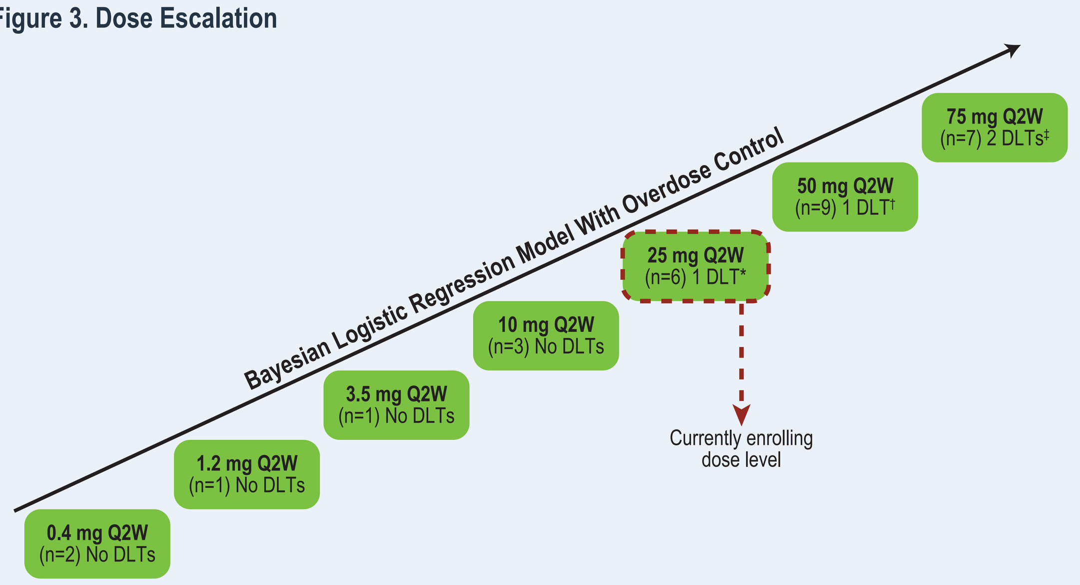
- Dose escalation was guided by an adaptive Bayesian logistic regression model (BLRM) with overdose control
- Data are analyzed using descriptive statistics

## Results

### *Dosing and Baseline Patient Characteristics*

- As of 14 July 2021, 34 patients were enrolled and treated (**Figure 3**); median (range) age was 60.5 (27–81) years, and 55.9% were male (**Table 1**)

**Figure 3. Dose Escalation**



Bayesian Logistic Regression Model With Overdose Control
0.4 mg Q2W (n=2) No DLTs
1.2 mg Q2W (n=1) No DLTs
3.5 mg Q2W (n=1) No DLTs
10 mg Q2W (n=3) No DLTs
25 mg Q2W (n=6) 1 DLT*
50 mg Q2W (n=9) 1 DLT†
75 mg Q2W (n=7) 2 DLTs‡
Currently enrolling dose level


ALT, alanine aminotransferase; AST, aspartate aminotransferase; DLT, dose-limiting toxicity (DLT period is defined as 28 days from the first infusion); Q2W, every 14 days.
Intermediate dose levels from 25 to 75 mg have been explored in 5 additional patients not included in the figure above.
* Febrile neutropenia. † Myositis. ‡ ALT/AST increased, febrile neutropenia.

**Table 1. Baseline Patient Demographics and Clinical Characteristics (Full Analysis Set)**

| Characteristic | Total (N=34) |
|---|---|
| Age, median (range), y | 60.5 (27–81) |
| Male, n (%) | 19 (55.9) |
| White, n (%) | 30 (88.2) |
| ECOG status, n (%) | |
| 0 | 16 (47.1) |
| 1 | 18 (52.9) |
| Time since initial diagnosis, median (range), y | 2.2 (0.2–10.1) |
| Most common tumor types,*† n (%) | |
| Colorectal cancer | 5 (14.7) |
| Lung cancer | 4 (11.8) |
| Renal cancer | 4 (11.8) |
| Glioblastoma | 4 (11.8) |
| Pancreatic cancer | 3 (8.8) |
| Previous lines of therapy, n (%) | |
| 0 | 0 |
| 1 | 5 (14.7) |
| 2 | 10 (29.4) |
| ≥3 | 19 (55.9) |
| Previous immunotherapy, n (%) | 17 (50.0) |
| PD-L1 expression on tumor cells, n (%) | |
| 0% | 11 (32.4) |
| ≥1% | 7 (20.6) |
| Unknown / not evaluable | 16 (47.1) |
| PD-L1 expression on tumor-associated immune cells, n (%) | |
| 0% | 4 (11.8) |
| ≥1% | 14 (41.2) |
| Unknown / not evaluable | 16 (47.1) |

ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed cell death ligand 1.
* Occurring in >2 patients.
† Tumor type in n=2 patients was head and neck cancer.

### *Safety*

- Median (range) duration of treatment with MCLA-145 was 6 (1–74) weeks
- Treatment-emergent AEs (TEAEs) occurred in 33 patients (97.1%); treatment-related TEAEs occurred in 23 patients (67.6%), most commonly fatigue (n=6, 17.6%) and decreased neutrophil count (n=6, 17.6%; **Table 2**)
- DLTs occurred in 4 patients (11.8%) and were managed as follows:
  - 25 mg: grade 3 febrile neutropenia (responsive to filgrastim)
  - 50 mg: grade 2 myositis (responsive to steroid treatment)
  - 75 mg: grade 3 febrile neutropenia (resolved without growth factor support)
  - 75 mg: grade 3 alanine aminotransferase (ALT) and aspartate aminotransferase (AST) increase (responsive to steroid treatment)

**Table 2. Summary of Overall and Most Common* TEAEs**

| | Any TEAE (N=34) | | Treatment-Related TEAE (N=34) | |
|---|---|---|---|---|
| Characteristic, n (%) | Any Grade | Grade ≥3 | Any Grade | Grade ≥3 |
| Any TEAE | 33 (97.1) | 22 (64.7) | 23 (67.6) | 10 (29.4) |
| Serious TEAE | 16 (47.1) | 14 (41.2) | 4 (11.8) | 4 (11.8) |
| Fatal TEAE | 3 (8.8) | 3 (8.8) | 0 | 0 |
| Most common TEAEs* | | | | |
| Fatigue | 14 (41.2) | 0 | 6 (17.6) | 0 |
| Decreased appetite | 11 (32.4) | 1 (2.9) | 2 (5.9) | 0 |
| Dyspnea | 9 (26.5) | 0 | 2 (5.9) | 0 |
| Nausea | 7 (20.6) | 1 (2.9) | 1 (2.9) | 0 |
| Decreased neutrophil count | 7 (20.6) | 6 (17.6) | 6 (17.6) | 5 (14.7) |
| Diarrhea | 6 (17.6) | 0 | 1 (2.9) | 0 |
| Productive cough | 6 (17.6) | 0 | 0 | 0 |
| Vomiting | 6 (17.6) | 2 (5.9) | 2 (5.9) | 0 |
| Decreased lymphocyte count | 5 (14.7) | 5 (14.7) | 4 (11.8) | 4 (11.8) |
| Myalgia | 5 (14.7) | 0 | 3 (8.8) | 0 |
| Pyrexia | 5 (14.7) | 0 | 2 (5.9) | 0 |
| ALT increased | 4 (11.8) | 3 (8.8) | 3 (8.8) | 2 (5.9) |
| Arthralgia | 4 (11.8) | 0 | 0 | 0 |
| Headache | 4 (11.8) | 1 (2.9) | 1 (2.9) | 0 |
| Non-cardiac chest pain | 4 (11.8) | 1 (2.9) | 0 | 0 |
| Pruritus | 4 (11.8) | 0 | 3 (8.8) | 0 |
| Maculopapular rash | 4 (11.8) | 0 | 4 (11.8) | 0 |
| Decreased white blood cell count | 4 (11.8) | 4 (11.8) | 4 (11.8) | 4 (11.8) |

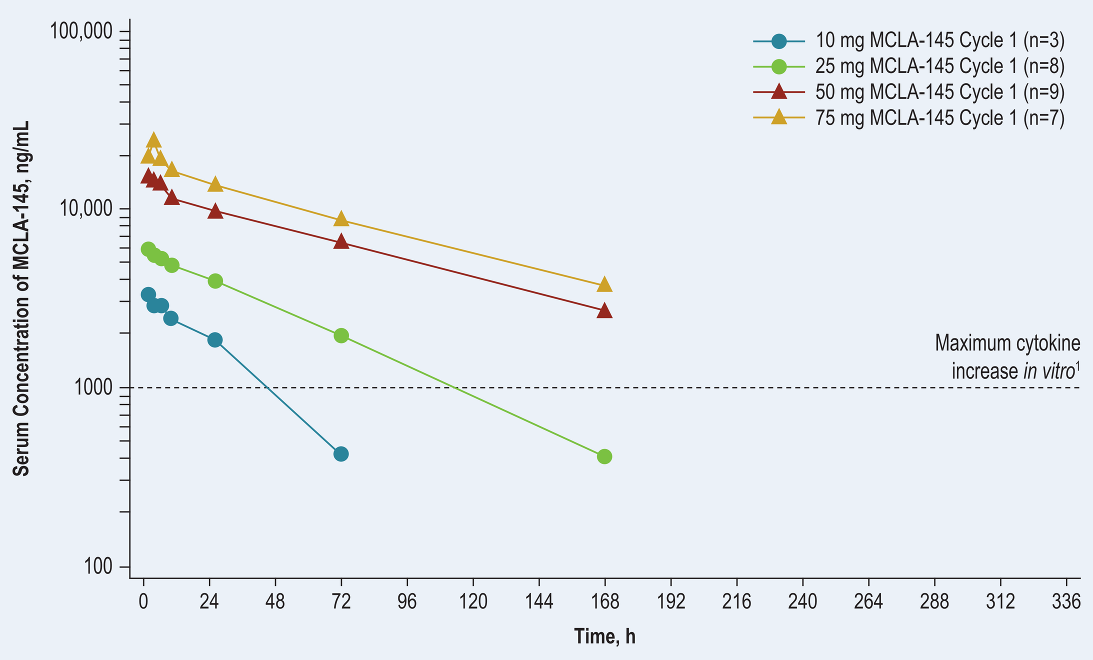
ALT, alanine aminotransferase; TEAE, treatment-emergent adverse event.
* Occurring in ≥10% of patients.

- Laboratory ALT/AST elevations of any grade were observed in 15 unique patients (44.1%), with grade ≥3 ALT/AST elevations in 6 patients (17.6%), mainly seen at doses 50 to 75 mg
  - Laboratory grade ≥3 elevations included ALT elevations in 5 patients (14.7%) and AST elevations in 4 patients (11.8%)
  - No fatalities were observed, and all patients recovered

### *Pharmacokinetics/Pharmacodynamics*

- Exposure was dose dependent, with mean terminal half-life increasing from 28 to 69 hours in the 10-mg to 75-mg dose range; MCLA-145 followed target-mediated drug disposition (**Figure 4**, **Table 3**)
- At doses of 10 mg and above, peripheral T-cell activation, including cytotoxic CD8+ T cells, was observed (**Figure 5**)
- Pharmacodynamic effects reached a plateau across 10 to 75 mg dose levels, which is consistent with signs of a bell-shaped dose-response curve observed *in vitro* (**Figure 2**)[1]
  - *In vitro*, maximum IL-2, IFNγ, and TNFα was released by activated T cells after 3 days of incubation with MCLA-145 at concentrations below 1 µg/mL
- This is in line with a predicted plateau for simultaneous binding of MCLA-145 to its targets PD-L1 and CD137 in tumors (trimers) by an integrated semi-mechanistic pharmacokinetic/pharmacodynamic model

**Figure 4. Serum Concentrations of MCLA-145 After First Dose**



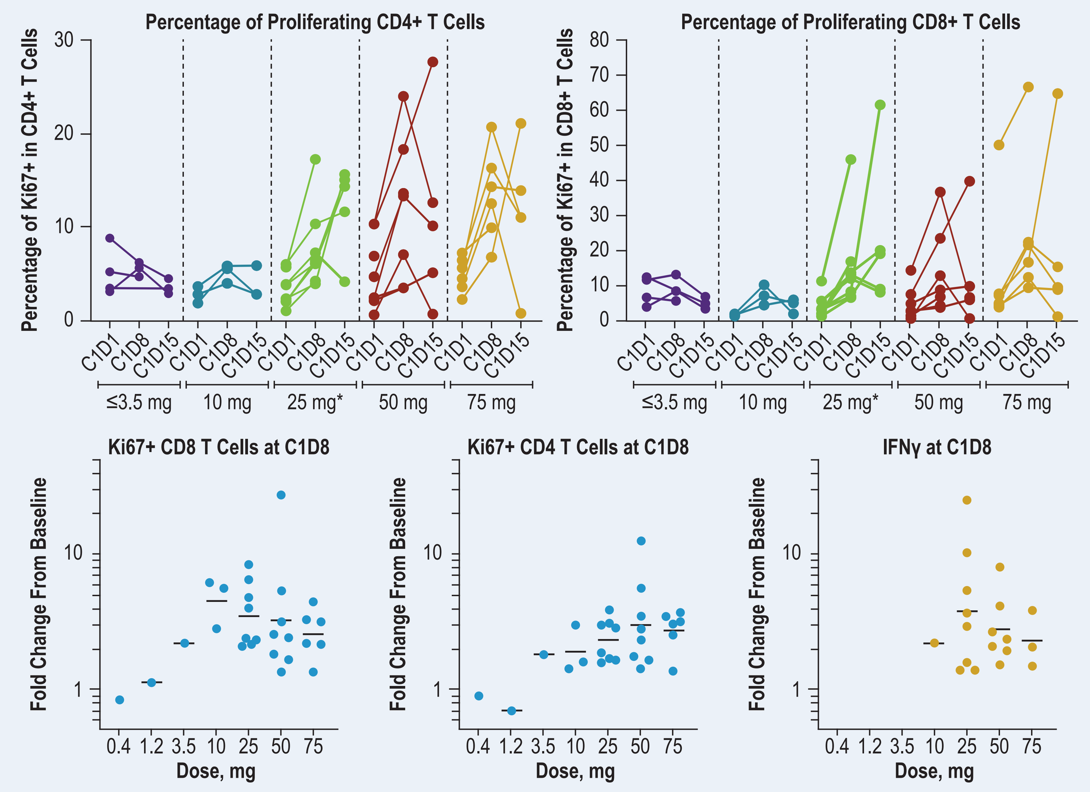
10 mg MCLA-145 Cycle 1 (n=3)
25 mg MCLA-145 Cycle 1 (n=8)
50 mg MCLA-145 Cycle 1 (n=9)
75 mg MCLA-145 Cycle 1 (n=7)
Serum Concentration of MCLA-145, ng/mL
Maximum cytokine increase *in vitro*[1]
Time, h


**Table 3. Pharmacokinetic Parameters After First Dose**

| Dose, mg | n | $C_{max}$, µg/mL | $AUC_{inf}$, mg·h/mL | $t_{1/2}$, h |
|---|---|---|---|---|
| 10 | 3 | 3.3 | 135 | 28 |
| 25* | 8 | 6.3 | 388 | 40 |
| 50 | 9 | 15.7 | 1511 | 64 |
| 75 | 7 | 26.7 | 1998 | 69 |

$AUC_{inf}$, area under the curve from 0 to infinity; $C_{max}$, maximum concentration; $t_{1/2}$, half-life.
* 25 mg data includes patients from the intermediate dosing cohort.

**Figure 5. Peripheral Blood T-Cell Proliferation**



Percentage of Proliferating CD4+ T Cells
Percentage of Ki67+ in CD4+ T Cells
Percentage of Proliferating CD8+ T Cells
Percentage of Ki67+ in CD8+ T Cells
C1D1 C1D8 C1D15
≤3.5 mg
10 mg
25 mg*
50 mg
75 mg
Ki67+ CD8 T Cells at C1D8
Ki67+ CD4 T Cells at C1D8
IFNγ at C1D8
Fold Change From Baseline
Dose, mg


C, cycle; D, day.
* 25 mg data includes patients from the intermediate dosing cohort.
Horizontal lines=Geometric mean per dose level.
Limited data for IFNγ fold change due to levels below detection limit for 13/33 patients.

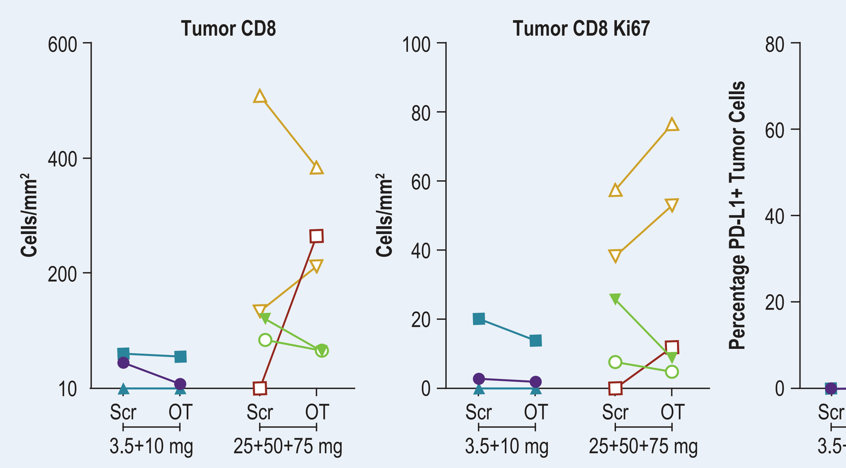
### *Signs of Antitumor Activity*

- Among patients treated at doses between 25 and 75 mg (n=27), 5 of 12 patients with available data had documented PD-L1 tumor expression ≥1%, including the cervical cancer patient with a PR (Patient 1)
- Preliminary evidence of antitumor activity has been observed at doses ≥25 mg
  - **Patient 1 (MCLA-145, 50 mg, PD-L1+)** with papillary cervical cancer diagnosed in 2014 who enrolled in the study following surgery, radiation therapy, and chemotherapy
    - Achieved a partial response (35% decrease) per RECIST v1.1 as determined by the investigator after discontinuation from MCLA-145 therapy due to elevated ALT/AST
  - **Patient 2 (MCLA-145, 25 mg, PD-L1 status unknown)** with glioblastoma diagnosed in 2010, who received prior surgery, radiation therapy, and treatment with temozolomide
    - Showed shrinkage of brain lesion present at screening; latest response assessment continues to show stable brain lesion and is fluid-attenuated inversion recovery (FLAIR) stable
    - Treatment ongoing, >21 months

### *Tumor Biomarkers*

- Paired biopsies were available for 8 patients; changes in tumor CD8 and PD-L1 levels pre- and post-dose are shown in **Figure 6**

**Figure 6. Tumor Biomarkers in 8 Patients With Available Paired Biopsies**



Tumor CD8
Tumor CD8 Ki67
Tumor PD-L1
Cells/mm²
Percentage PD-L1+ Tumor Cells
Scr OT
3.5+10 mg
25+50+75 mg


3.5 mg, purple; 10 mg, blue; 25 mg, green; 50 mg, red; 75 mg, orange.
Scr, screening; OT, on treatment.

## Conclusions

- **Thirty-four patients have been treated with MCLA-145 at dose levels ranging from 0.4 to 75 mg Q2W**
- **Reported AEs are consistent with the mechanism of action and can be managed with drug interruption and/or administration of steroids in some patients**
- **Preliminary evidence of antitumor activity has been observed at doses ≥25 mg**
- **Peripheral blood shows robust T-cell activation following treatment with MCLA-145, including activation of cytotoxic CD8+ cells and IFNγ, and reached a plateau across the MCLA-145 10 to 75 mg Q2W dosing range**
- **Increase in tumor CD8+ T cells and PD-L1 expression has been observed in some patients**
- **Patients continue to be enrolled at 25 mg Q2W. Further evaluation of optimal dose and efficacy in PD-L1+ tumors is planned. Full blockade of PD-L1 may be required**

## Disclosures

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## References


**1.** Geuijen C, et al. *Nat Commun*. 2021;12(1):4445. **2.** Plyte S, et al. *J Immunother Cancer*. 2019;7(Suppl 1):282 (abstract P489). **3.** Willoughby JE, et al. *J Immunol*. 2014;193(1):244. **4.** Eskiocak U, et al. *JCI Insight*. 2020;5(5):e133647.


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