

Poster #155 NCT03761017

Lorigerlimab, a Bispecific PD-1 x CTLA-4 DART® Molecule in Patients With Metastatic Castration-Resistant Prostate Cancer: A Phase 1 Expansion Cohort

Jason J. Luke, MD,¹ Manish R. Sharma, MD,² Sreenivasa R. Chandana, MD, PhD,² Iwona Lugowska, MD, PhD,³ Cezary A. Szczylik, MD,⁴ Jakub Żolnierak, MD,⁵ Gregory M. Cote, MD, PhD,⁶ Charlene M. Mantia, MD,⁷ Rafal Dziadziuszko, MD, PhD,⁸ Rachel E. Sanborn, MD,⁹ Denise Casey, MD,¹⁰ Lori Long, PhD,¹⁰ Ashley Ward, MD,¹⁰ Angela J. James, PhD,¹⁰ Patrick Kaminker, PhD,¹⁰ Tiziana Di Pucchio, PhD,¹⁰ Jichao Sun, PhD,¹⁰ Bożena Cybulska-Stopa, MD, PhD.¹¹

¹UPMC Hillman Cancer Center and University of Pittsburgh, Pittsburgh, PA, USA; ²START Midwest, Grand Rapids, MI, USA; ³Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland; ⁴European Health Center Otwock, Postgraduate Medical Education Center Warsaw, Poland; ⁵Szarmacka Hospital, LuxMed Oncology, Warsaw, Poland; ⁶Massachusetts General Hospital Cancer Center, Boston, MA, USA; ⁷Dana-Farber Cancer Institute, Boston, MA, USA; ⁸Early Clinical Trials Center, Medical University of Gdańsk, Gdańsk, Poland; ⁹Earles A. Chiles Research Institute, Providence Cancer Institute, Portland, OR, USA; ¹⁰MacroGenics, Inc., Rockville, MD, USA; ¹¹Department of Clinical Oncology, Maria Skłodowska-Curie National Research Institute of Oncology, Cracow Branch, Poland, and Pratia MCM Kraków, Kraków, Poland

INTRODUCTION

- Dual blockade of programmed cell death (PD-1) and cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) enhances antitumor activity in some cancers; however, conventional checkpoint inhibitor antibodies cannot achieve preferential blockade on dual-expressing cells, resulting in increased risk for immune-mediated toxicity.^{1,2}
- Lorigerlimab (MGD019) is an investigational bispecific PD-1 x CTLA-4, Fc-bearing DART molecule (Figure 1) that demonstrates enhanced CTLA-4 blockade on dual PD-1/CTLA-4-expressing tumor-infiltrating lymphocytes and a comparable reduced CTLA-4 blockade on cells expressing CTLA-4 alone. Lorigerlimab maintains maximal PD-1 blockade on PD-1-expressing cells.¹
- CP-MGD019-01 (NCT03761017) is a fully accrued phase 1, first-in-human, dose-escalation and expansion study of lorigerlimab in patients with advanced solid tumors.¹
- Lorigerlimab doses ranging from 0.03 mg/kg to 10 mg/kg were evaluated during dose-escalation. A dose of 6 mg/kg once every 3 weeks (Q3W) was selected for expansion.¹
- Lorigerlimab showed approximate dose proportional PK across 1 to 10 mg/kg dosing Q3W, with sustained PD-1 receptor occupancy evident at doses ≥ 1 mg/kg (Figure 2).¹
- Lorigerlimab yielded dose-dependent upregulation of inducible T-cell costimulator (ICOS) on CD4 T cells, attributable to CTLA-4 blockade, and induced T-cell expansion evidenced by increased fraction of Ki67+ T cells.³
- Lorigerlimab demonstrated acceptable safety among 44 patients. Objective responses were observed at doses ≥ 3 mg/kg (12.5% confirmed objective response rate [ORR]; 3/4[1]).^{1,3}

Figure 1. Lorigerlimab Hinge-Stabilized IgG4 DART Molecular Structure

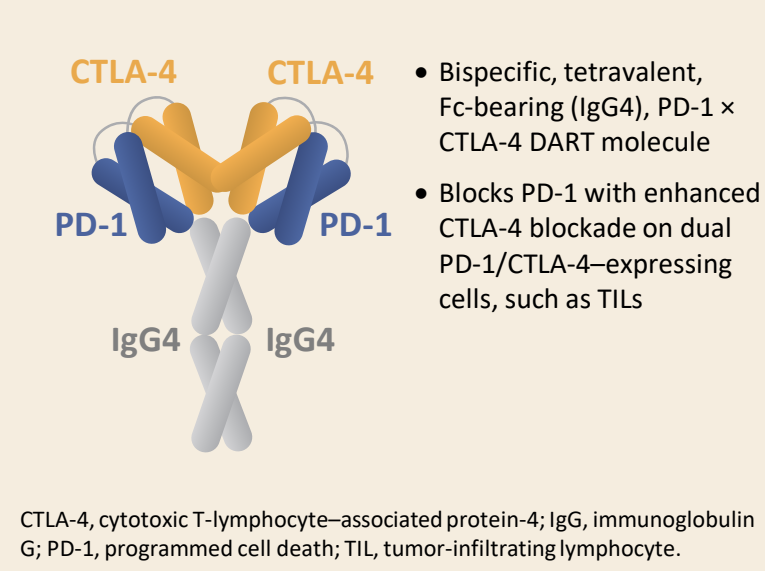
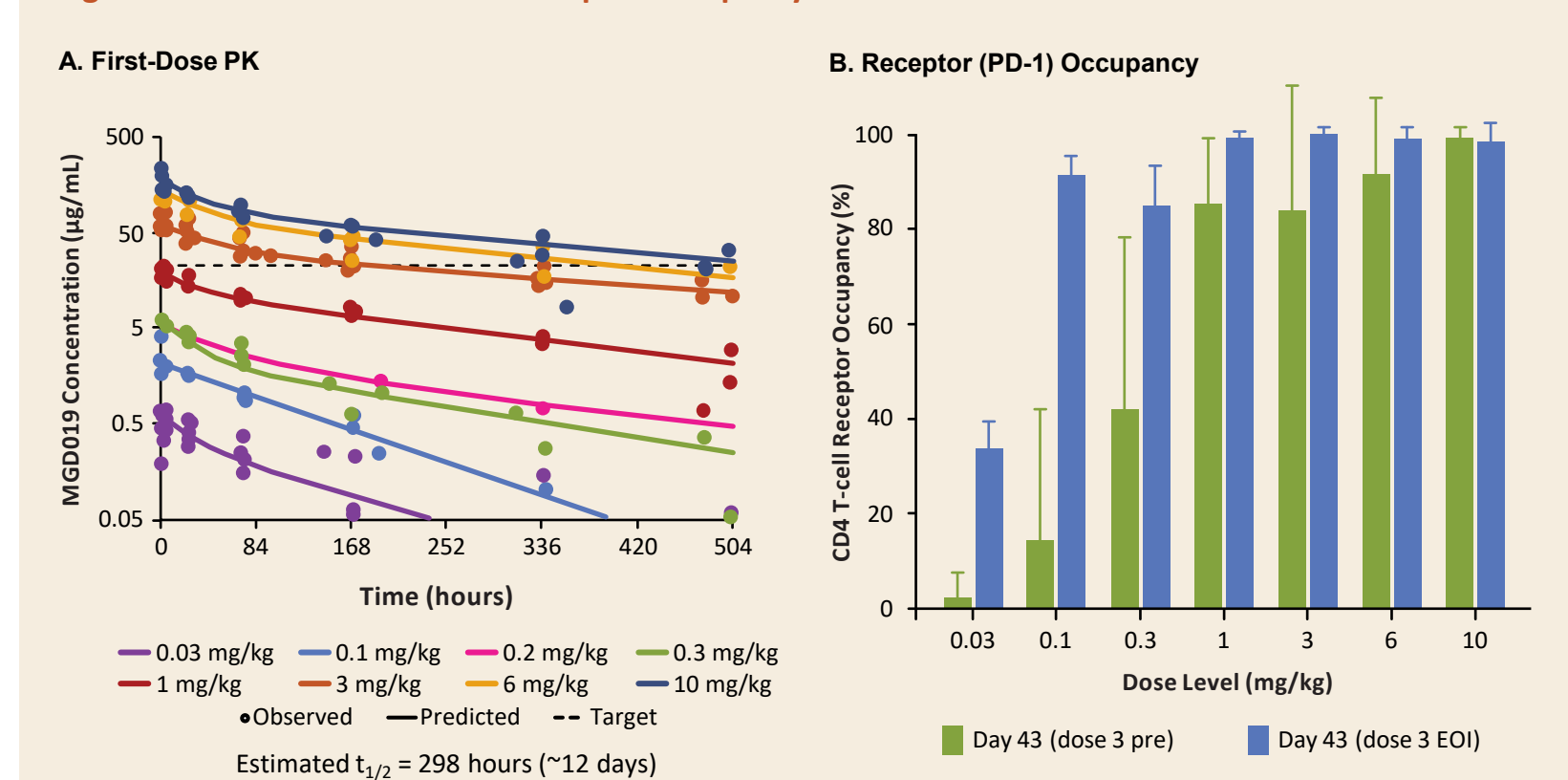


Figure 2. Pharmacokinetics and Receptor Occupancy³



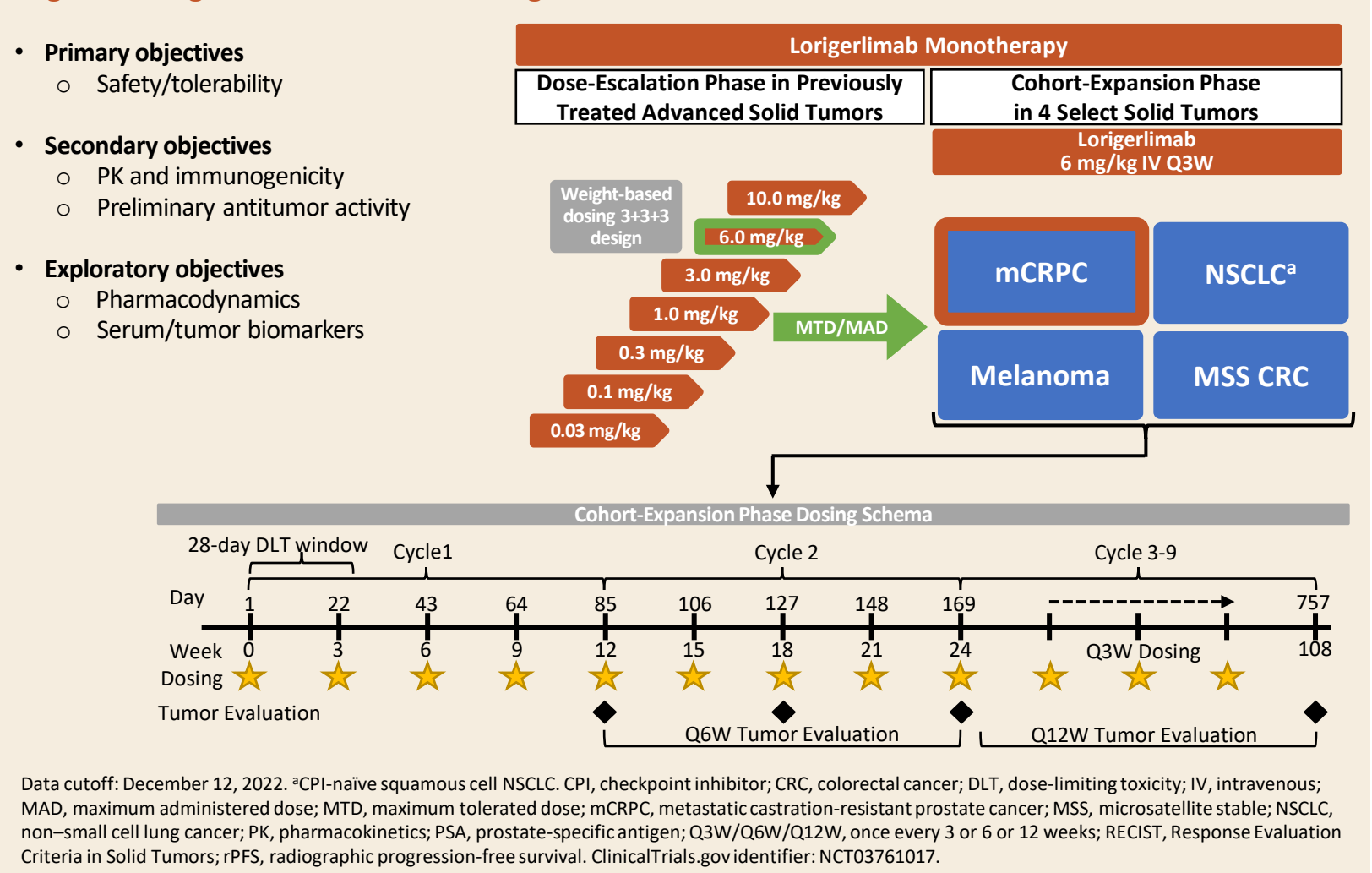
OBJECTIVE

To report updated safety results from 127 patients who received lorigerlimab 6 mg/kg Q3W on Study MGD019-01 and preliminary efficacy results from the mCRPC expansion cohort.

METHODS

- The study design is shown in Figure 3
- Safety Analysis:
 - The safety population included 127 patients with advanced solid tumors who received ≥ 1 dose of lorigerlimab 6 mg/kg
 - Adverse events (AEs) from initiation of lorigerlimab through 30 days after last dose or until start of subsequent anticancer therapy were assessed
- Key Eligibility Criteria, mCRPC expansion cohort:
 - Histologically confirmed metastatic prostate carcinoma and castration testosterone levels
 - Prior therapy:
 - ≤ 2 prior lines of an androgen receptor antagonist or androgen synthesis inhibitor
 - Patients may have received prior chemotherapy
 - Patients with known homologous recombination repair gene alterations should have received available therapy
 - No prior checkpoint inhibitor therapy
 - Progressive mCRPC with a PSA value ≥ 2 ng/mL and at least 1 of the following:
 - Progression in measurable disease per RECIST v1.1
 - ≥ 2 new bone lesions per PCWG-2⁵
 - PSA progression per PCWG-2⁵
 - ECOG performance status of 0-1
 - No systemic therapy within 4 weeks, radiation within 2 weeks or radioligand (e.g., radium-223) within 6 months prior to study entry
- Efficacy assessment, mCRPC expansion cohort:
 - Target/nontarget lesions evaluated at baseline; weeks 12, 18, and 24; then every 12 weeks until study discontinuation
 - ORR was measured in patients with measurable disease per RECIST v1.1⁶ at study entry
 - Objective response assessments required confirmation 24 weeks after initial observation
 - Bone lesions assessed by bone scan at baseline and each tumor evaluation time point
 - PSA response was measured in patients with baseline PSA ≥ 2 ng/mL and ≥ 1 postbaseline PSA evaluation
 - Confirmed PSA50 response defined as $\geq 50\%$ decline in PSA from baseline with confirmation ≥ 3 weeks later
- Statistical analyses:
 - Objective data were summarized by the number and percent of patients. Continuous variables were summarized by descriptive statistics
 - The 2-sided 95% exact binomial CI of both RECIST and PSA response rate was calculated
 - The Kaplan-Meier method was used to estimate RECIST duration of response
- Pharmacodynamics and biomarker assessment:
 - Expression of proliferation marker, Ki67, and inducible costimulator (ICOS) on peripheral T cells assessed by flow cytometry
 - Two-sided Wilcoxon matched-pairs signed-rank test was used to compare biomarker expression before and after infusion

Figure 3. Lorigerlimab Phase 1 Trial Design



RESULTS

Table 1. Demographics and Baseline Characteristics, Safety Population (N=127)

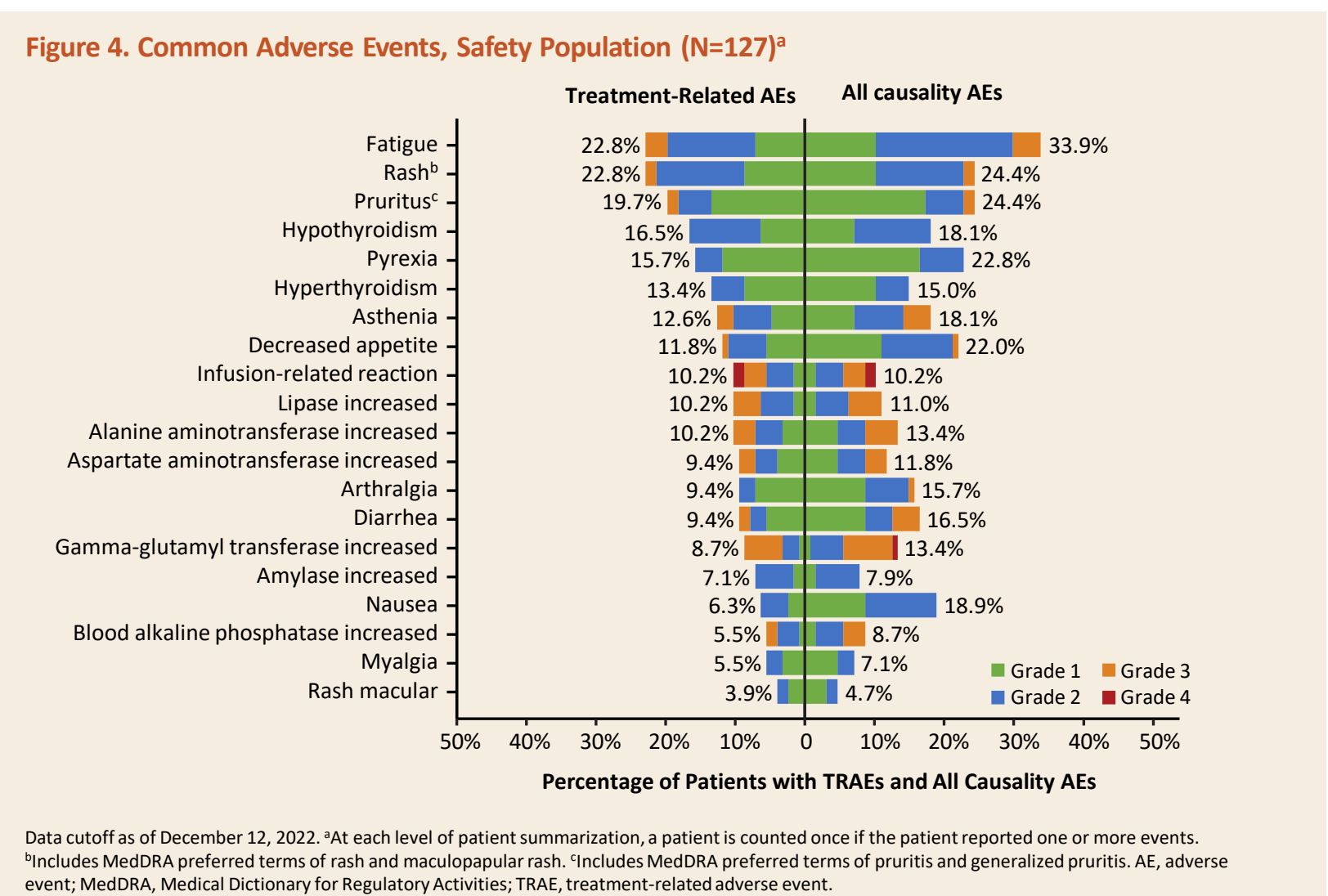
Parameter	Safety Population (N=127)
Dose-escalation phase	9
Cohort-expansion phase	118
Median (range) age, years	65 (21-84)
Gender, n (%)	
Male	92 (72.4)
Female	35 (27.6)
ECOG performance status, n (%)	
0	40 (31.5)
1	87 (68.5)
Prior checkpoint inhibitor, n (%)	
Yes	42 (33.1)
No	57 (44.9)
Unknown	28 (22.0)

Data cutoff as of December 12, 2022. ECOG, Eastern Cooperative Oncology Group.

Table 2. Summary of AEs, Safety Population (N=127)

AE	Safety Population (N=127)	
	All Grade, n (%)	Grade ≥ 3 , n (%)
Any AE (all causality)	125 (98.4)	79 (62.2)
Treatment-related AEs	110 (86.6)	45 (35.4)
Serious AEs (all causality)	50 (39.4)	44 (34.6)
Treatment-related SAEs	22 (17.3)	18 (14.2)
AEs leading to lorigerlimab discontinuation	32 (25.2)	27 (21.3)
Adverse event of special interest	40 (31.5)	16 (12.6)
Immune-related AEs	31 (24.4)	10 (7.9)

Data cutoff as of December 12, 2022. Adverse events of special interest included infusion reactions and immune-related AEs. AE, adverse event; SAE, serious adverse event.



Metastatic Castration-Resistant Prostate Cancer Expansion Cohort Results

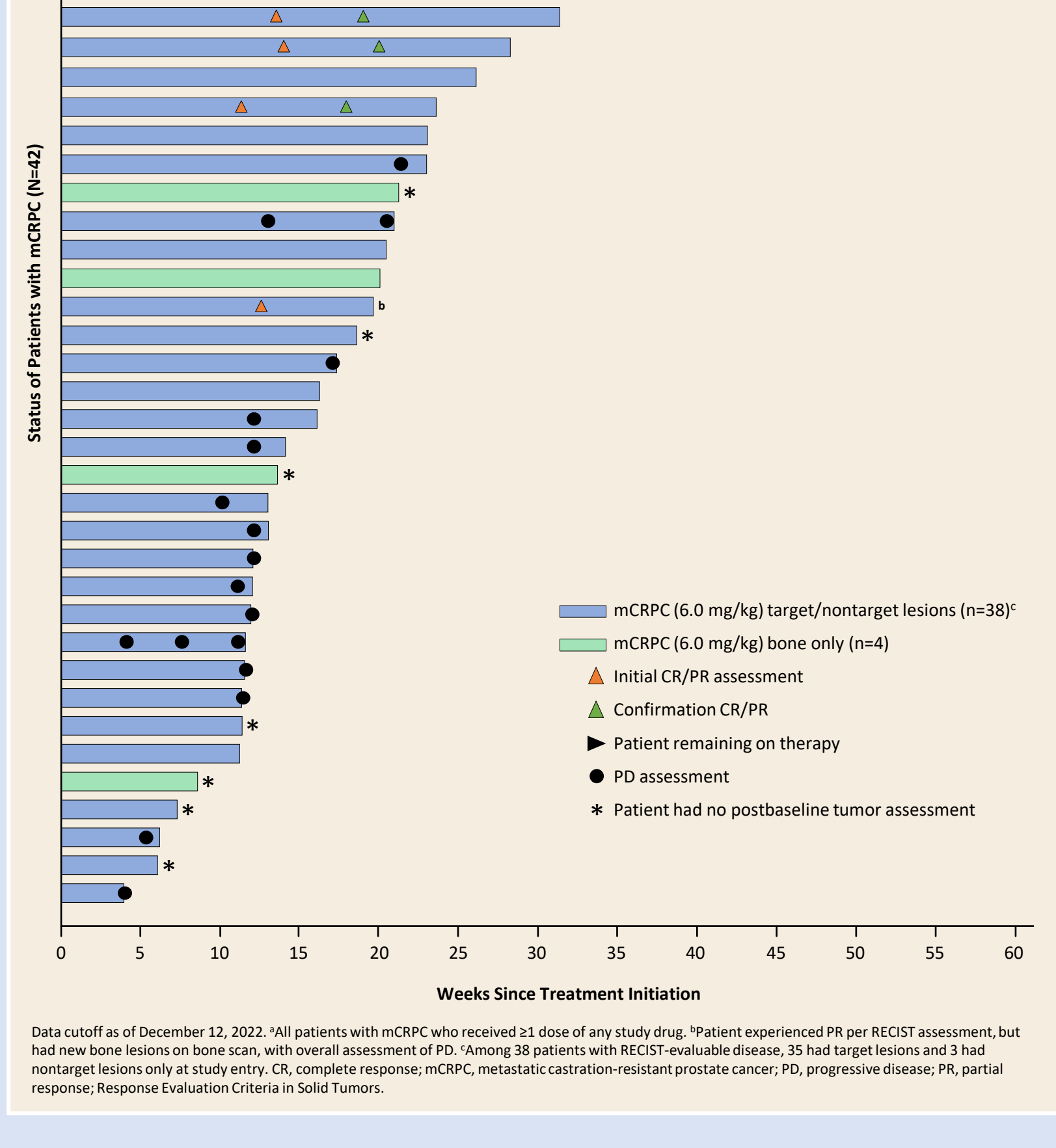
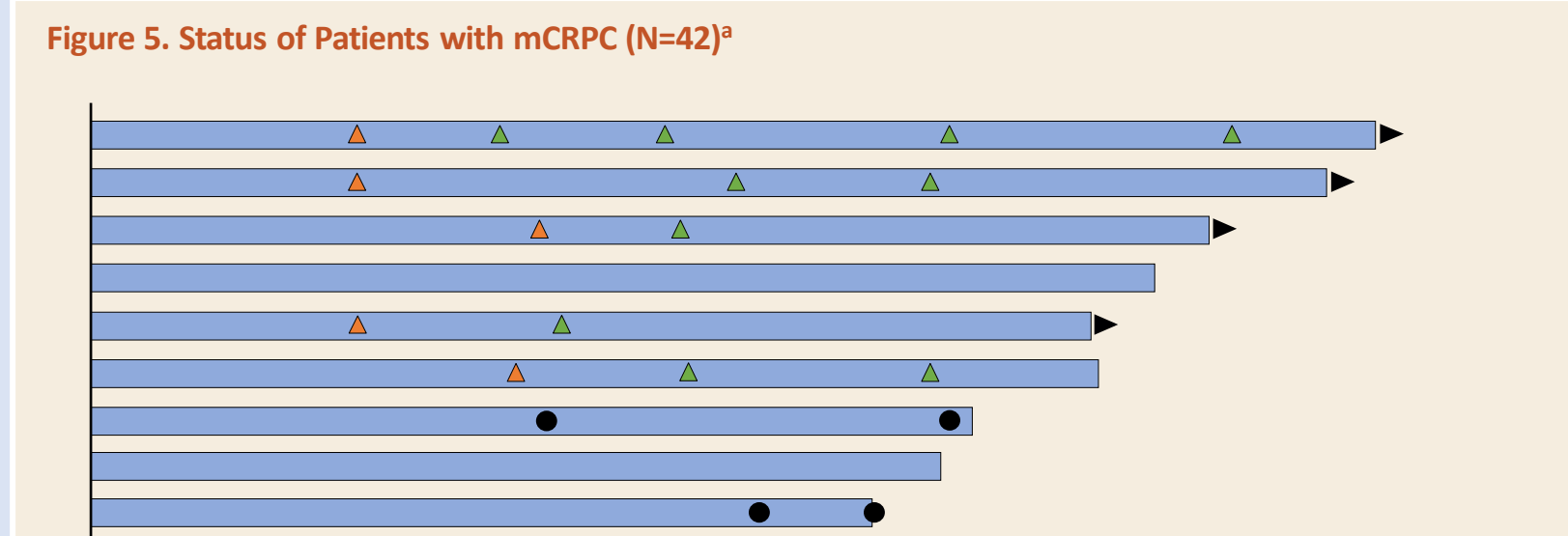
Table 3. Demographics and Baseline Characteristics, mCRPC Cohort (N=42)

Parameters	Values
Age	Median (range) 67 (55-79)
ECOG performance status, n (%)	0: 12 (28.6), 1: 30 (71.4)
Location of metastatic disease, n (%)	Bone: 40 (95.2), Liver: 11 (26.2), Lung: 8 (19.0)
Baseline SLD, mm n=35 with target lesion measures	Median (range) 48 (10-207)
Baseline PSA, ng/mL	Median (range) 94 (11-2523)
Prior lines of systemic therapy, n (%)	Median (range) prior lines: 2 (1-9), 1: 7 (16.7), 2: 15 (35.7), 3: 9 (21.4), 4+: 11 (26.2)
Prior systemic therapy, n (%)	Docetaxel: 35 (83.3), AR inhibitor: 34 (81), PARP inhibitor: 5 (11.9), Cabazitaxel: 6 (14.3)
Microsatellite instability status, n (%)	n=20 ^a , Stable: 20 (100)

Data cutoff as of December 12, 2022. ^aNumber of specimens qualified for microsatellite instability analysis. AR, androgen receptor; mCRPC, metastatic castration-resistant prostate cancer; PARP, poly (adenosine diphosphate-ribose) polymerase; PSA, prostate-specific antigen; SLD, sum of longest diameters.

Exposure/Disposition, mCRPC cohort

- Median (range) exposure was 19.2 weeks (3.3-55.1) with a median of 5 infusions administered per patient
- 24 patients remain on lorigerlimab; 103 discontinued for progressive disease (PD; n=66), AEs (n=31), patient/physician decision (n=5), or death due to PD (n=1)



ORR of 25.7% among 35 patients with measurable disease per RECIST v1.1 at study entry

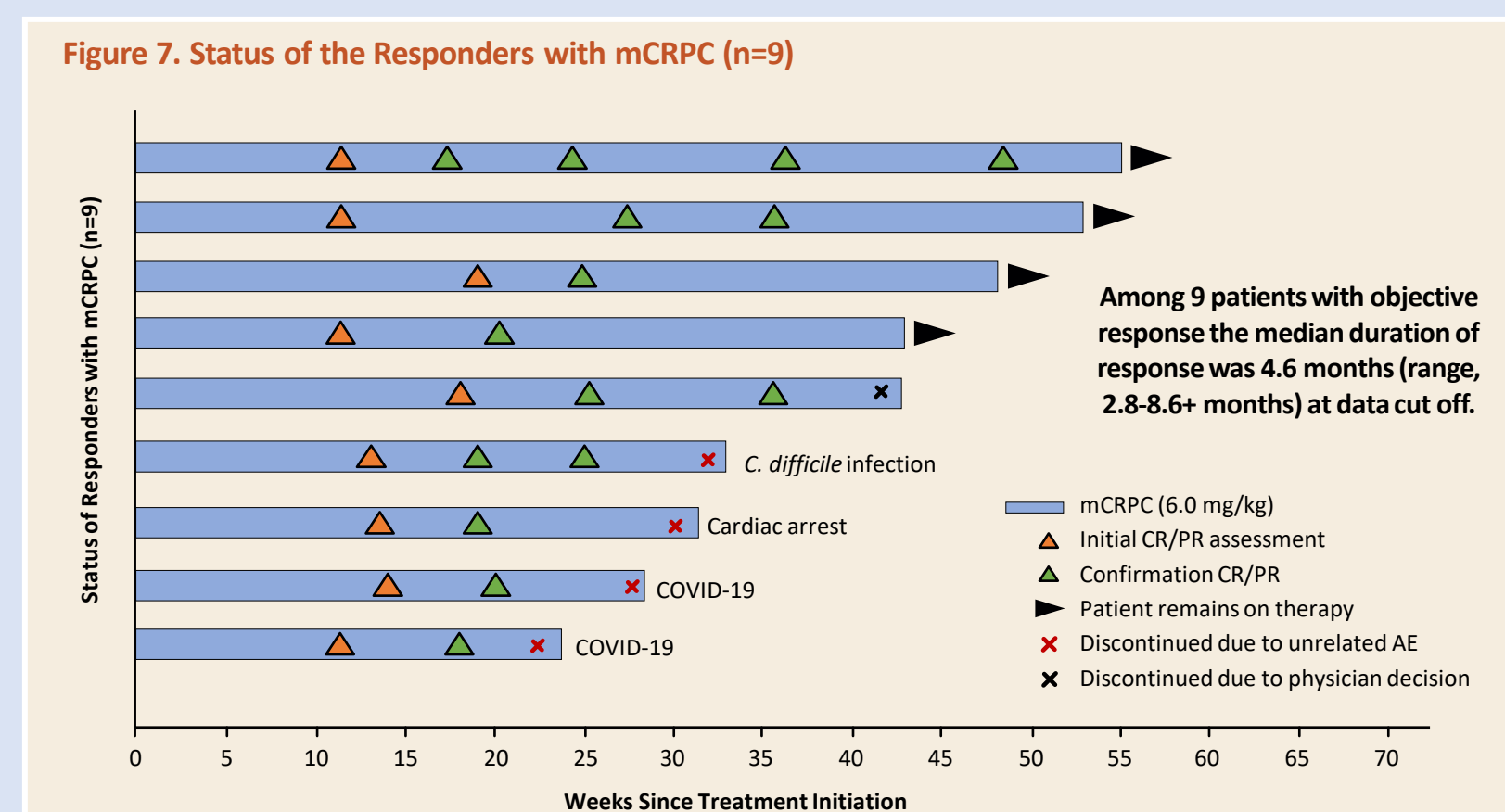
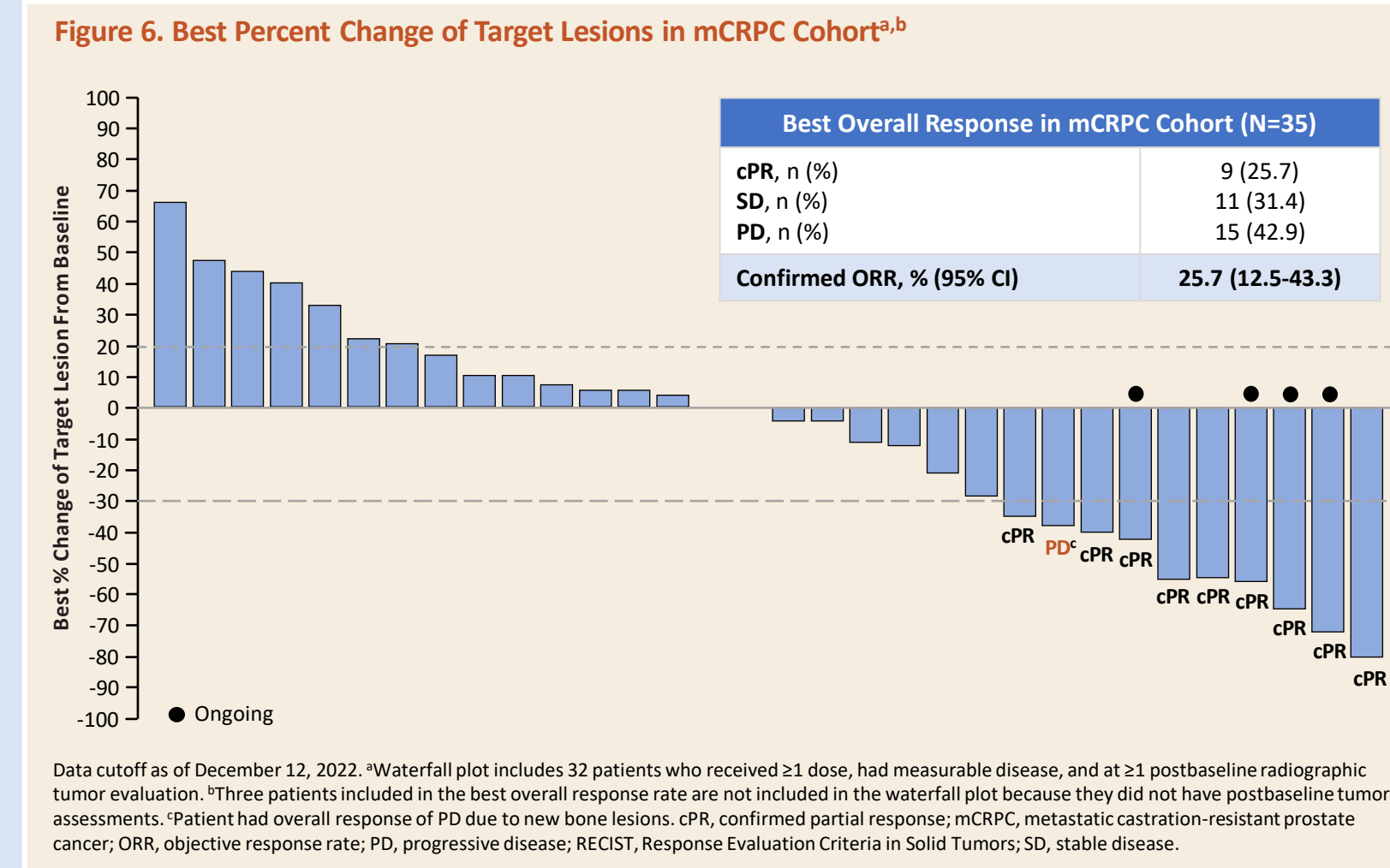


Table 4. Treatment History of the mCRPC Responders (n=9)

Metastatic Disease	Prior Lines of Therapy	Treatment	Lorigerlimab Best Response/Status
Bone Lymph nodes	1	Docetaxel	cPR, PSA reduction ~99.9%
	2	Enzalutamide	20 infusions
	3	Cabazitaxel	Treatment ongoing
	4	Niraparib	Treatment ongoing
Bone Liver Lymph nodes	1	Docetaxel	cPR, PSA reduction ~99.9%
	2	Abiraterone	16 infusions
	3	Abiraterone	Treatment ongoing
	4	Abiraterone + niraparib	Treatment ongoing
Bone Lymph nodes	1	Docetaxel	cPR, PSA reduction ~99.8%
	2	Onvansertib/abiraterone	12 infusions
	3	Enzalutamide	Treatment ongoing
	4	Enzalutamide	Treatment ongoing
Bone Soft tissue Lymph nodes	1	Bicalutamide	cPR, PSA reduction ~99.8%
	2	Docetaxel	11 infusions
	3	Enzalutamide	11 infusions
	4	Abiraterone	Discontinued for cardiac arrest
	5	Docetaxel	Discontinued for cardiac arrest
	6	Cyclophosphamide + encorton Carboplatin	Discontinued for cardiac arrest
Bone Liver Soft tissue Lymph nodes	1	Docetaxel	cPR, PSA reduction ~95.6%
	2	Enzalutamide	7 infusions
	3	Enzalutamide	Discontinued for COVID-19
	4	Docetaxel	5 infusions
	5	Carboplatin/cabazitaxel	Discontinued for COVID-19

cPR, confirmed partial response; mCRPC, metastatic castration-resistant prostate cancer; PSA, prostate-specific antigen.

Figure 8. Best Percent Change of PSA in mCRPC Cohort (PSA Response-Evaluable Population, N=42)³

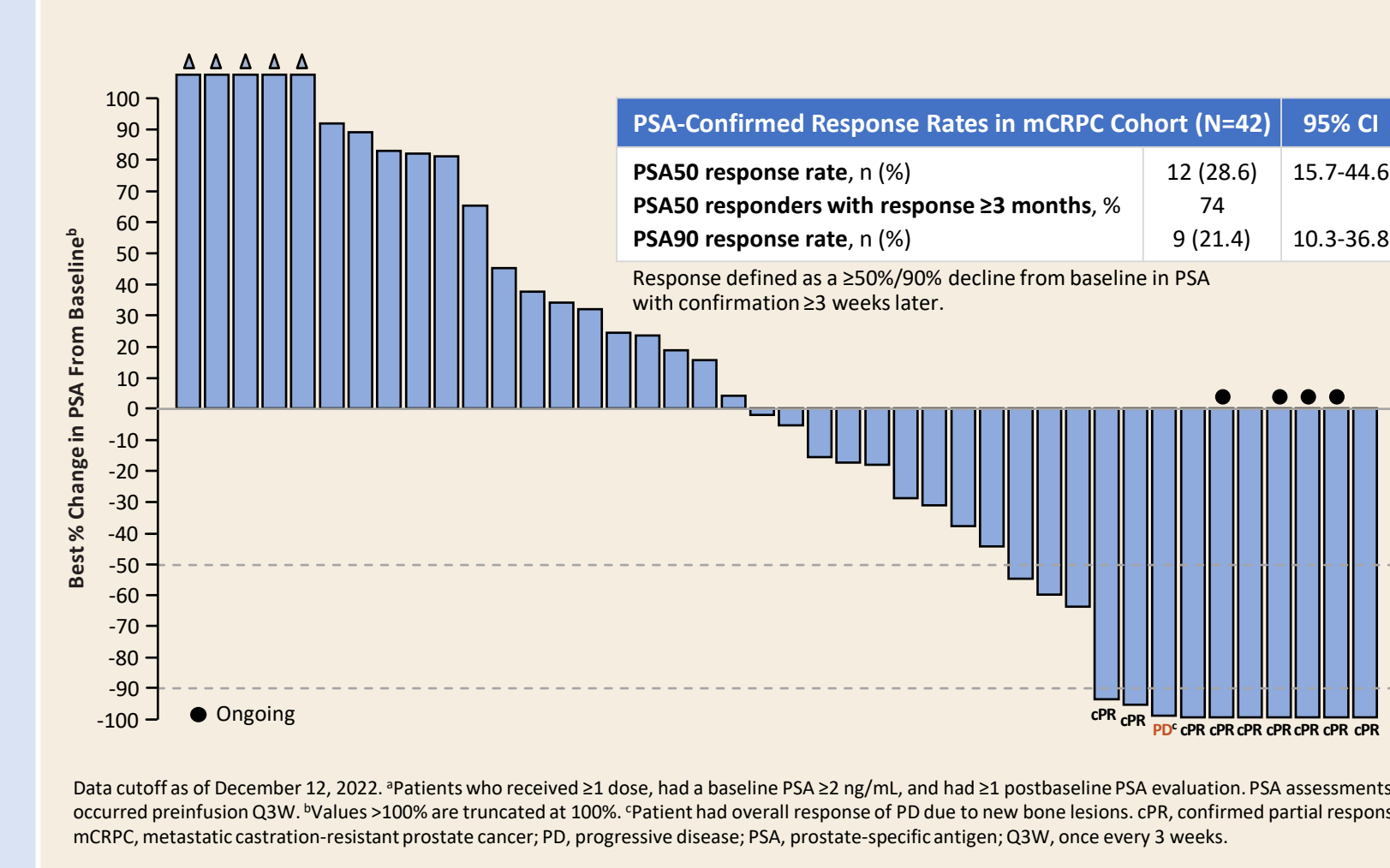
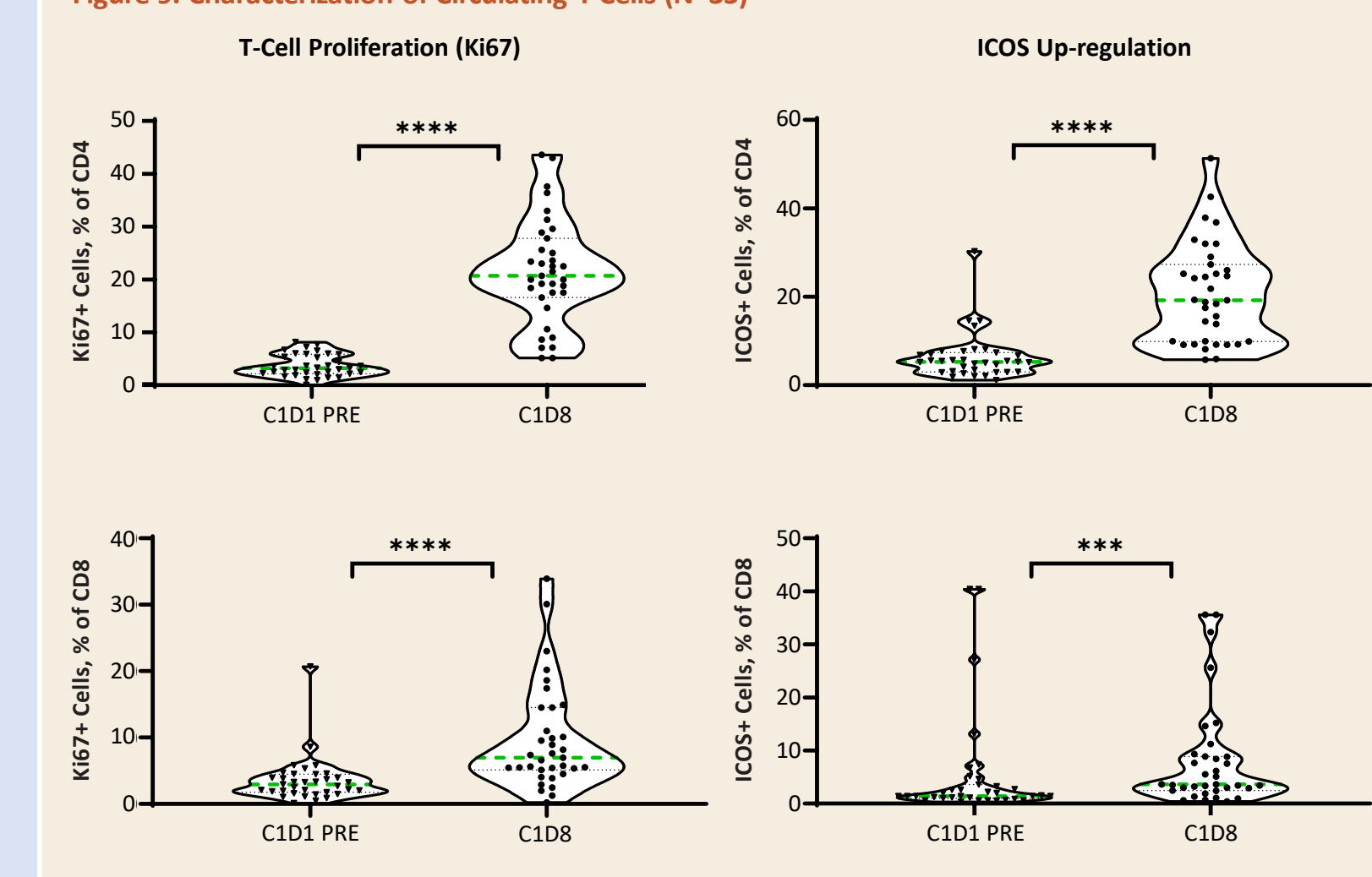


Figure 9. Characterization of Circulating T Cells (N=35)



Whole blood was stained for CD45, CD3, CD4, CD8, and ICOS by fluorescence-labeled antibodies followed by intracellular staining for Ki67 (all antibodies from Becton Dickinson) and analyzed on a FACScan flow cytometer. T-cell subpopulations were gated on CD45+ and CD3+, and subgated on CD4+ or CD8+ cells. Percentage of CD4 and CD8 cells that stained for Ki67 (left panels) or ICOS (right panels) were calculated at baseline (C1D1 PRE) and at cycle 1 day 8 (C1D8) after lorigerlimab infusion. Data shown are from matched-pairs samples from 35 patients. Horizontal lines in the violin plots show median in green and quartiles in black. ****p<0.0004 and ****p<0.0003 by 2-tailed Wilcoxon matched-pairs signed-rank test. ICOS, inducible T-cell costimulator.

Biomarkers

- Flow cytometry analyses performed on peripheral blood of patients with mCRPC before (C1D1 PRE) and after (C1D8) first cycle of lorigerlimab infusion
- Increased frequencies of peripheral Ki67+ and ICOS+ circulating T cells were observed on day 8 posttreatment (Figure 9)

SUMMARY AND CONCLUSIONS

- Lorigerlimab has a manageable safety profile in an advanced solid tumor population
- Lorigerlimab shows preliminary evidence of durable antitumor activity in a mCRPC population refractory to chemotherapy and androgen receptor targeted therapy
 - Confirmed ORR of 25.7% and confirmed PSA50 response rate of 28.6%
- Biomarker analyses indicate that lorigerlimab induces T-cell activation as evidenced by an increase of circulating Ki67+ and ICOS+ T cells
- Further evaluation of lorigerlimab in mCRPC is warranted

REFERENCES

- Bereznyy A, et al. Cell Rep Med. 2020;1(9):100163.
- Larkin J, et al. N Engl J Med. 2015;373(1):23-34.
- Sharma M, et al. Ann Oncol. 2020;31(suppl 4):S64S-S67L.
- Center for Drug Evaluation and Research. KEYTRUDA (pembrolizumab) clinical pharmacology and biopharmaceutics review(s). 2014. Accessed January 26, 2023. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/125514Orig1s000ClinPharmR.pdf.
- Scher HI, et al. J Clin Oncol. 2008;26(7):1148-1159.
- Eisenhauer EA, et al. Eur J Cancer. 2009;45(2):228-247.

ACKNOWLEDGMENTS

Funding for the CP-MGD019-01 study, this analysis, and medical writing support were provided by MacroGenics, Inc., Rockville, MD, USA. Medical writing and/or editorial assistance was provided by Emily Cullinan, PhD, CMPA, and Francesca Balorini, PhD, CMPA, of The Lockwood Group (Stamford, CT, USA), in accordance with Good Publication Practice (GPP 2022) guidelines.

Presented at the American Society of Clinical Oncology Genitourinary (ASCO-GU) Cancers Symposium February 16-18, 2023, San Francisco, CA, USA. lukejj@upmc.edu

©2023 MacroGenics, Inc. All rights reserved.