A Phase Ib Study to Evaluate RO7198457, an Individualized Neoantigen-Specific Immunotherapy (iNeST), in Combination With Atezolizumab in Patients With Locally Advanced or Metastatic Solid Tumors

Lopez J,[1] Camidge DR,[2] Iafolla M,[3] Rottey S,[4] Schuler M,[5] Hellmann MD,[6] Balmanoukian A,[7] Dirix L,[8] Gordon M,[9] Sullivan RJ,[10] Henick BS,[11] Drake C,[11] Wong KM,[12] LoRusso P,[13] Ott PA,[14] Fong L,[15] Schiza A,[16] Yachnin J,[17] Ottensmeier C,[18] Braiteh F,[19] Bendell J,[20] Leidner R,[21] Fisher G,[22] Jerusalem G,[23] Molenaar-Kuijsten L,[24] Schmidt M,[25] Laurie S,[26] Aljumaily R,[27] Rittmeyer A,[28] Gort E,[29] Melero I,[30] Mueller L,[31] Sabado RL,[31] Twomey P,[31] Huang J,[31] Yadav M,[31] Zhang J,[32] Müller F,[33] Derhovanessian E,[33] Türeci Ö,[33] Sahin U,[33] Powles T[34]

[1]Royal Marsden Hospital, Sutton, UK; [2]Division of Medical Oncology, University of Colorado School of Medicine and Developmental Therapeutics Program, University of Colorado Cancer Center, Aurora, CO; [3]Princess Margaret Cancer Centre, Toronto, Canada; [4]Cancer Research Institute Ghent (CRIG Ghent), Ghent, Belgium; [5]Department of Medical Oncology, West German Cancer Center, University Hospital Essen, Essen, Germany; [6]Memorial Sloan Kettering Cancer Center, New York, NY; [7]The Angeles Clinic and Research Institute, Santa Monica, CA; [8]Translational Cancer Research Unit, GZA Hospitals Sint-Augustinus, Antwerp, Belgium; [9]HonorHealth Research Institute, Scottsdale, AZ [10]Massachusetts General Hospital, Boston, MA; [11]Herbert Irving Comprehensive Cancer Center, Columbia University, New York, NY; [12]Seattle Cancer Care Alliance, Seattle, WA; [13]Smilow Cancer Center, Yale University, New Haven, CT; [14]Dana-Farber Cancer Institute, Boston, MA; [15]UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA; [16]Uppsala University, Uppsala, Sweden; [17]Karolinska University Hospital, Stockholm, Sweden; [18]University of Southampton, Southampton, UK; [19]Comprehensive Cancer Center Nevada, Las Vegas, NV; [20]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN; [21]Providence Cancer Center EACRI, Portland, OR; [22]Stanford University School of Medicine, Stanford, CA; [23]CHU Liege and Liege University, Liege, Belgium; [24]Netherlands Cancer Institute, Amsterdam, Netherlands; [25]Johannes Gutenberg-Universitat Mainz, Mainz, Germany; [26]Ottawa Hospital Cancer Centre, Ontario, Canada; [27]Stephenson Cancer Center, The University of Oklahoma, Oklahoma City, OK; [28]Lungenfachklinik Immenhausen, Immenhausen, Germany; [29]UMC Utrecht, Utrecht, Netherlands; [30]University Clinic of Navarra, Centre of Applied Medical Research, Navarra, Spain; [31]Genentech, Inc, South San Francisco, CA; [32]F. Hoffmann-La Roche, Ltd, Basel, Switzerland; [33]BioNTech SE, Mainz, Germany; [34]Barts Cancer Institute, London, UK.

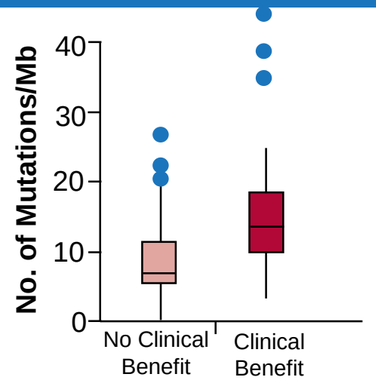
Disclosures

- Dr Lopez has the following relationships to disclose:
  - Research grant funding: Roche/Genentech, Basilea, Genmab
  - Ad board: Basilea

Cancer Mutations Are Drivers of Protective Immunity

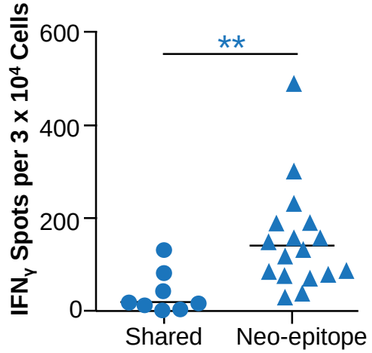
- High tumor mutation burden correlates with clinical response to immune checkpoint blockade
- Mutated neoantigens are recognized as foreign and induce stronger T-cell responses than shared antigens, likely due to the lack of central tolerance
- Most of these mutated neoantigens are not shared between patients; therefore, targeted neoantigen-specific therapy requires an individualized approach
- RO7198457[a] is a systemically administered RNA-Lipoplex Neoantigen Specific immunoTherapy (iNeST), designed to stimulate T-cell responses against neoantigens
- RO7198457 has the potential to increase anti-tumor activity of atezolizumab (anti–PD-L1) by expanding the number of neoantigen-specific T cells

High Tumor Mutation Burden Correlates With Clinical Response



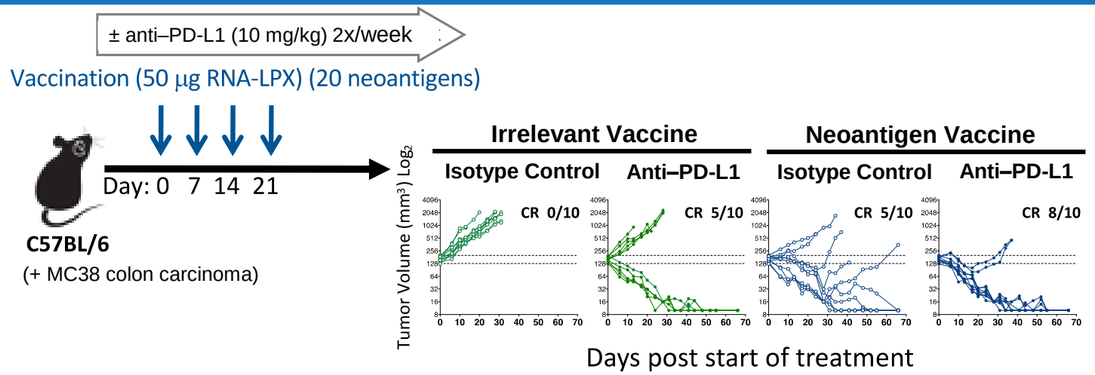
Rosenberg, Lancet 2016

Stronger T-Cell Responses Against Neoantigens



Sahin, Nature 2017

RNA-LPX + Anti–PD-L1 Leads to Enhanced Anti-Tumor Activity

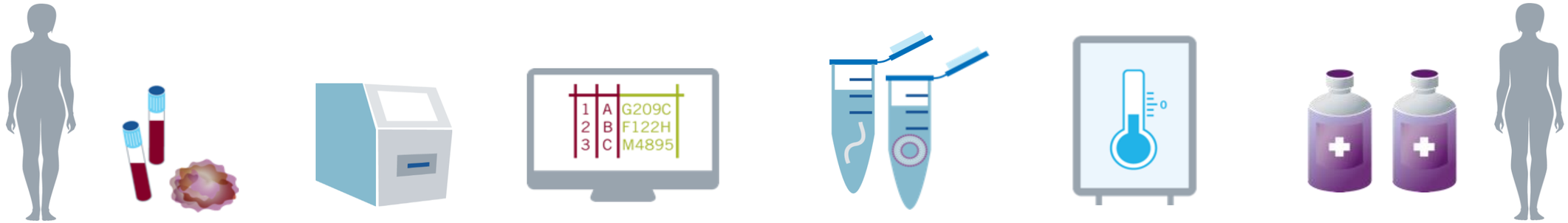


Javinal, unpublished data

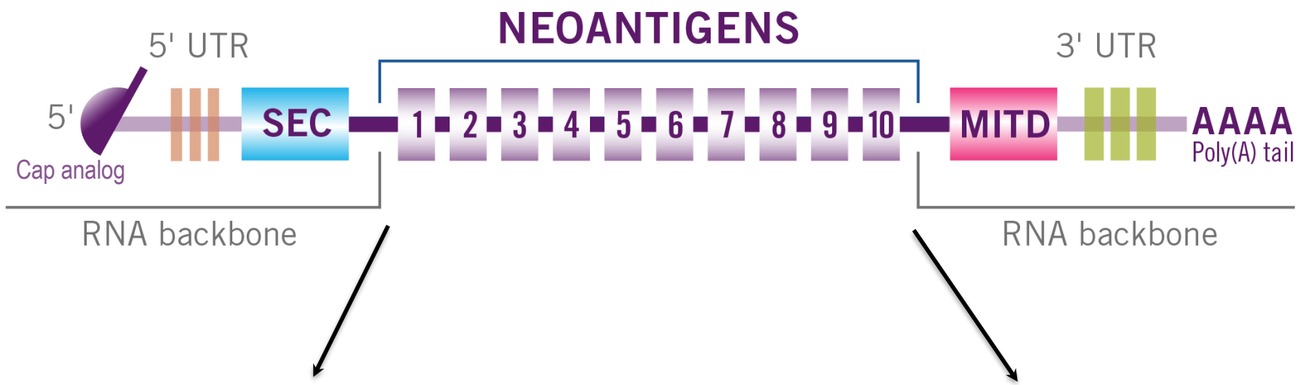
LPX, lipoplex; MHC, major histocompatibility complex.
[a] Also known as RG6180.

Lopez J, et al. Phase Ib of RO7198457 https://bit.ly/3gJdHA2

Targeting Neoantigens Requires an Individualized Approach



Blood and tumor biopsy collection › Sequencing › Bioinformatics Neoantigen Prediction › RNA-LPX manufacturing › Cold storage and distribution › Intravenous administration



Single-stranded mRNA

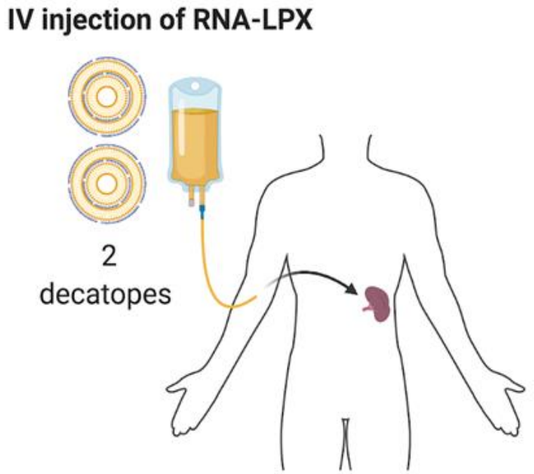
Innate Immune Stimulation
Intrinsic TLR7/8 agonist

Antigen Expression
Up to 20 neoantigens (2 decatopes)

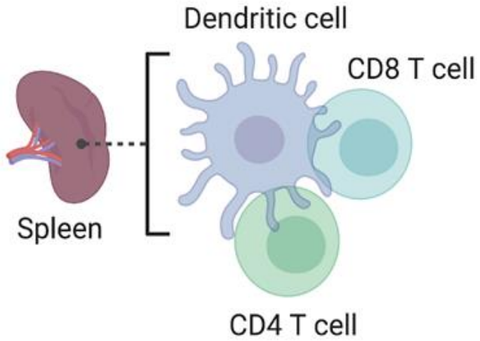
Türeci et al. *Clin Canc Res*. 2016; Vormehr et al. *Annu Rev Med*. 2019; Sahin et al. *Science*. 2018.

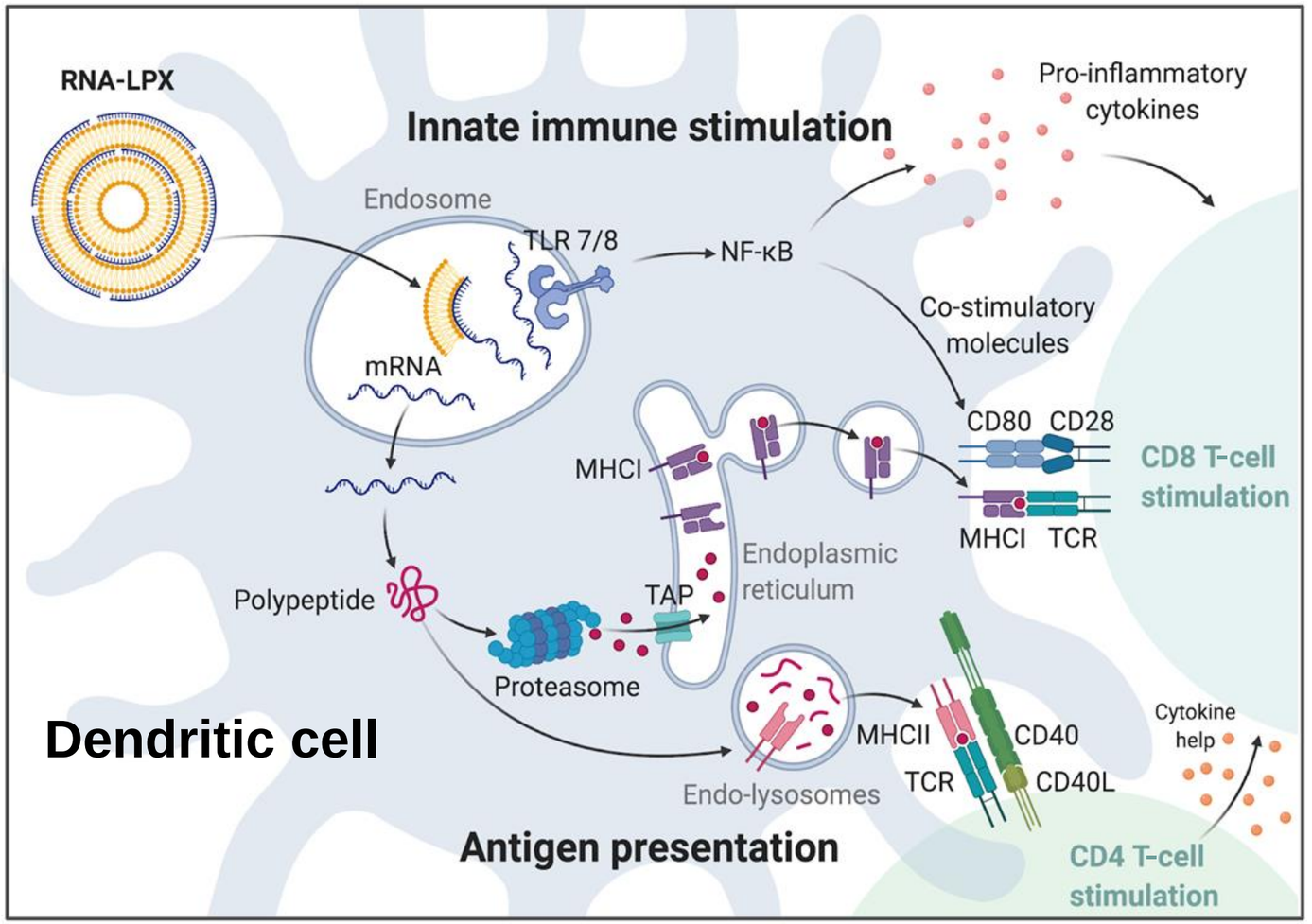
Lopez J, et al. Phase Ib of RO7198457 https://bit.ly/3gJdHA2

Proposed Dual MOA of RO7198457: Innate Immune Stimulation and Neoantigen Presentation



Preferential delivery of RNA-LPX to dendritic cells in the spleen

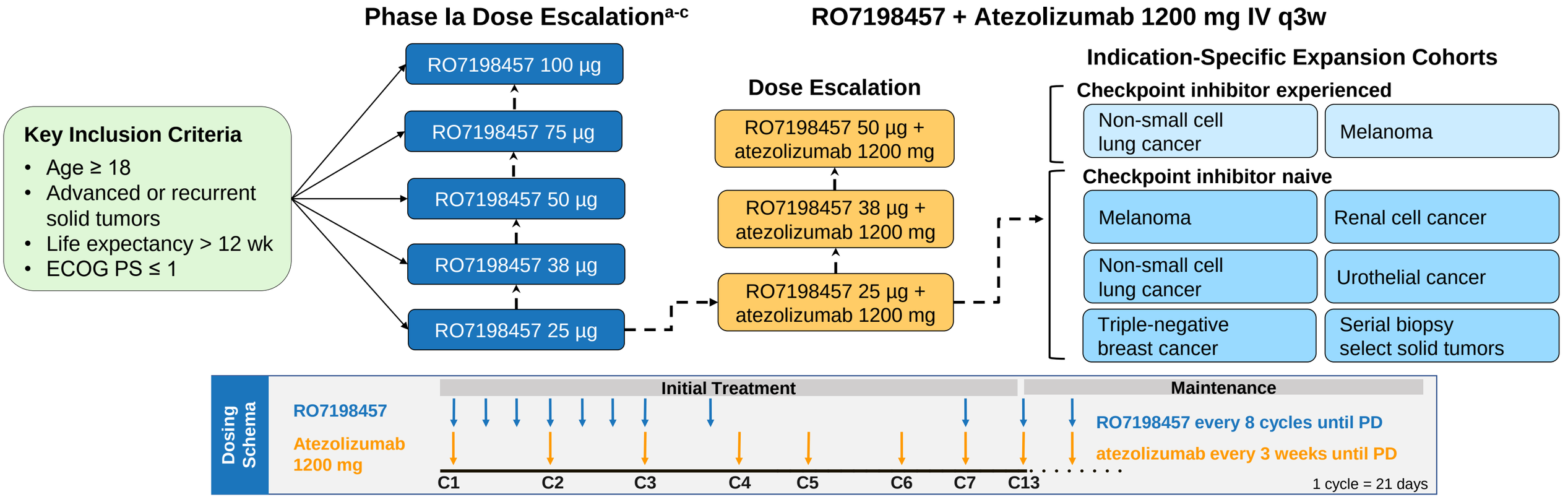




TCR, T-cell receptor. Kranz et al. Nature. 2016.

Lopez J, et al. Phase Ib of RO7198457 https://bit.ly/3gJdHA2

Phase Ib Study of RO7198457 in Combination With Atezolizumab in Advanced Solid Malignancies



1 Primary objective

- Safety and tolerability

2 Secondary objectives

- MTD, RP2D, pharmacodynamic activity, preliminary anti-tumor activity

C, cycle; DLT, dose-limiting toxicity; MTD, maximum tolerated dose; PD, progressive disease; q3w, every 3 weeks; RP2D, recommended Phase 2 dose.
[a] 3 + 3 dose escalation: 21-day DLT window; backfill enrollment at cleared dose levels; [b] Phase Ia patients with disease progression or loss of clinical benefit may cross over to combination therapy in Phase Ib. [c] Braiteh F, et al. AACR II 2020. Poster CT169. NCT03289962.
Data cutoff: January 10, 2020.

Patient Demographics and Disease Characteristics

	Dose Escalation	Expansion	
	Total (n = 30)	**CPI Experienced (n = 42)**	**CPI Naive (n = 72)**
Median age (range), years	57.5 (35-77)	61.5 (36-82)	57.5 (29-79)
Male, n (%)	17 (56.6)	25 (59.5)	31 (43.1)
ECOG PS, n (%)			
0	15 (50.0)	19 (45.2)	38 (52.8)
1	15 (50.0)	23 (54.8)	34 (47.2)
Most common tumor types, n (%)			
Colon cancer	9 (30.0)	–	–
NSCLC	–	30 (71.4)	10 (13.9)
Melanoma	5 (16.7)	8 (19.0)	9 (12.5)
Rectal cancer	3 (10.0)	–	–
RCC	3 (10.0)	–	9 (12.5)
TNBC	–	–	24 (33.3)
UC		–	10 (13.9)
Median number (range) of prior systemic therapies for metastatic disease, n	4 (1 - 9)	3 (1-10)	2 (1-11)
Prior checkpoint inhibitor, n (%)	13 (43.3)	42 (100)	0
PD-L1 (Ventana SP142), n (%)			
< 5% IC and TC	24 (80.0)	21 (50.0)	54 (75.0)
≥ 5% IC or TC	5 (16.7)	12 (28.6)	10 (13.9)
Missing	1 (3.3)	9 (21.4)	8 (11.1)

CPI, checkpoint inhibitor; IC, tumor-infiltrating immune cell; NSCLC, non-small cell lung cancer; RCC, renal cell cancer; TC, tumor cell; TNBC, triple-negative breast cancer; UC, urothelial cancer. Data cutoff: January 10, 2020.

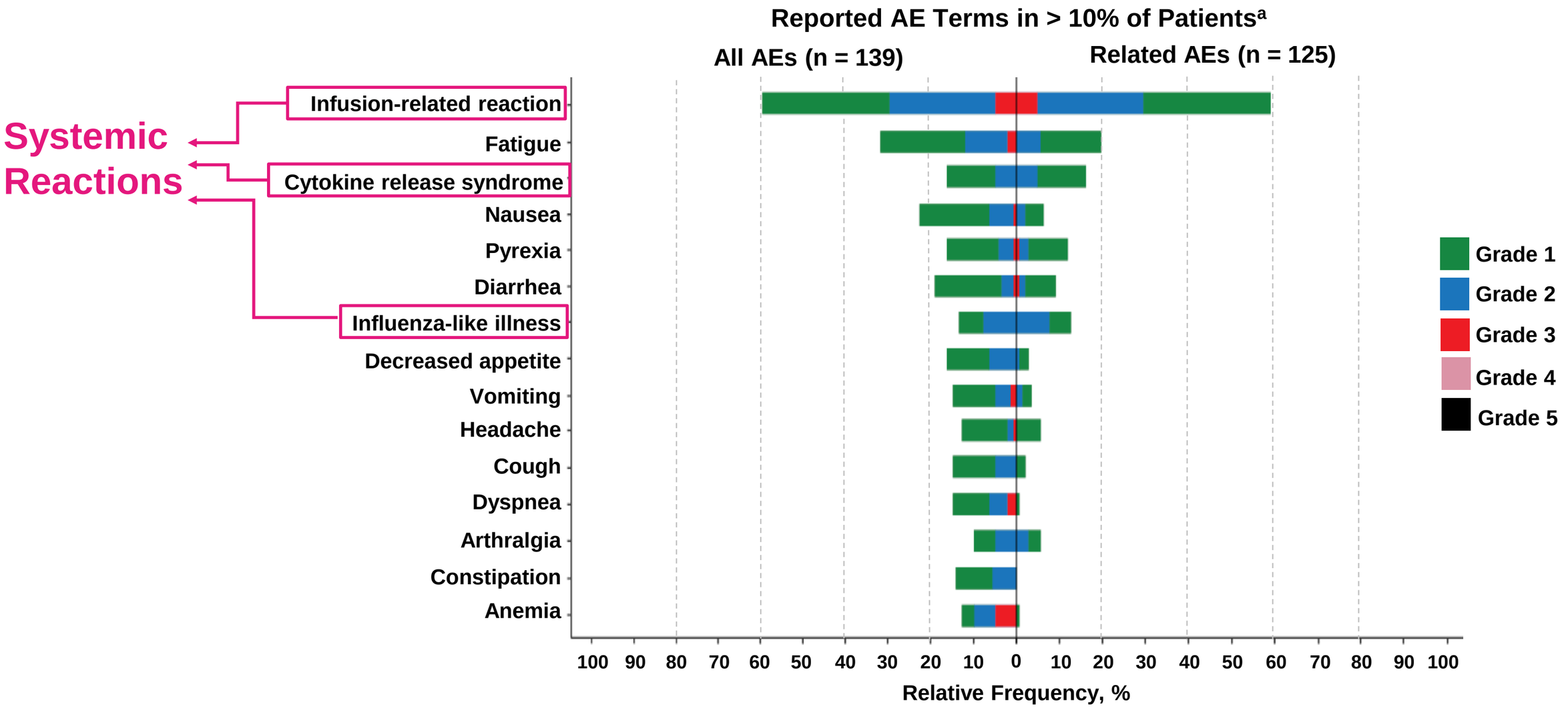
Patient Exposure and Disposition

	RO7198457 IV Dose + Atezolizumab 1200 mg IV q3w				
	15 µg (n = 27)	**25 µg (n = 95)**	**38 µg (n = 11)**	**50 µg (n = 9)**	**Total (N = 142)**
DLT, n (%)	0	0	0	0	0
RO7198457 dose reduction, n (%)	1 (3.7)	2 (2.1)	1 (9.1)	2 (22.2)	6 (4.2)
Median (range) treatment duration with RO7198457, days	65 (8-253)	57 (1-400)	64 (35-441)	36 (1-253)	57 (1-441)
Median (range) treatment duration with atezolizumab, days	104 (1-316)	64 (1-462)	106 (21-504)	22 (1-296)	66 (1-504)
Continuing treatment, n (%)	9 (33.3)	22 (23.2)	2 (18.3)	0	33 (23.2)
Discontinued RO7198457 only, n (%)	0	1 (1.1)[a]	0	0	1 (0.7)
Discontinued both study treatments, n (%)	18 (66.7)	72 (75.8)	9 (81.8)	9 (100)	109 (76.8)
Reasons for RO7198457 discontinuation, n (%)					
Disease progression	15 (55.6)	61 (64.2)	8 (72.7)	6 (66.7)	90 (63.4)
Death[b]	1 (3.7)	4 (4.2)	0	0	5 (3.5)
AE	0	5 (5.3)	1 (9.1)	2 (22.2)	8 (5.6)
Withdrawal by patient	1 (3.7)	1 (1.1)	0	0	2 (1.4)
Other	1 (3.7)	2 (2.1)	0	1 (11.1)	4 (2.8)
Discontinued treatment due to disease progression prior to completing 6 weeks of therapy, n (%)	2 (7.4)	19 (20.0)	1 (9.1)	2 (22.2)	24 (16.9)

AE, adverse event. [a] Patient discontinued atezolizumab at the same time as RO7198457. However, atezolizumab discontinuation information was not completed until after data cut. [b] Four deaths were due to malignant neoplasm progression. One death was due to malignant pericardial effusion. No deaths were related to study drugs. Data cutoff: January 10, 2020.

Lopez J, et al. Phase Ib of RO7198457 https://bit.ly/3gJdHA2

AEs Occurring in Patients Treated With RO7198457 + Atezolizumab



- No increase in immune-mediated AEs compared with atezolizumab single-agent experience (data not shown)

[a] A serious AE of malignant neoplasm progression was reported in 14% of patients (data not shown). Data cutoff: January 10, 2020.

Lopez J, et al. Phase Ib of RO7198457 https://bit.ly/3gJdHA2

Systemic Reactions Were Transient and Generally Manageable in the Outpatient Setting

Individual Signs and Symptoms of Systemic Reactions (CRS/IRR/ILI) in ≥ 5 Patients

	RO7198457 IV Dose + Atezolizumab 1200 mg IV q3w				
n (%)	15 µg (n = 27)	25 µg (n = 95)	38 µg (n = 11)	50 µg (n = 9)	All Patients (N = 142)
Pyrexia	10 (37.0)	60 (63.2)	10 (90.9)	6 (66.7)	86 (60.6)
Chills	11 (40.7)	58 (61.1)	8 (72.7)	7 (77.8)	84 (59.2)
Nausea	2 (7.4)	14 (14.7)	2 (18.2)	2 (22.2)	20 (14.1)
Tachycardia	1 (3.7)	8 (8.4)	2 (18.2)	3 (33.3)	14 (9.9)
Headache	3 (11.1)	7 (7.4)	2 (18.2)	0	12 (8.5)
Vomiting	1 (3.7)	9 (9.5)	2 (18.2)	0	12 (8.5)
Hypertension	1 (3.7)	5 (5.3)	0	2 (22.2)	8 (5.6)
Hypotension	3 (11.1)	3 (3.2)	1 (9.1)	0	7 (4.9)
Myalgia	2 (7.4)	4 (4.2)	1 (9.1)	0	7 (4.9)
Back pain	0	4 (4.2)	1 (9.1)	1 (11.1)	6 (4.2)
Fatigue	1 (3.7)	4 (4.2)	0	0	5 (3.5)
Hypoxia	0	3 (3.2)	1 (9.1)	1 (11.1)	5 (3.5)

Median Time to Onset and Resolution of Systemic Reactions

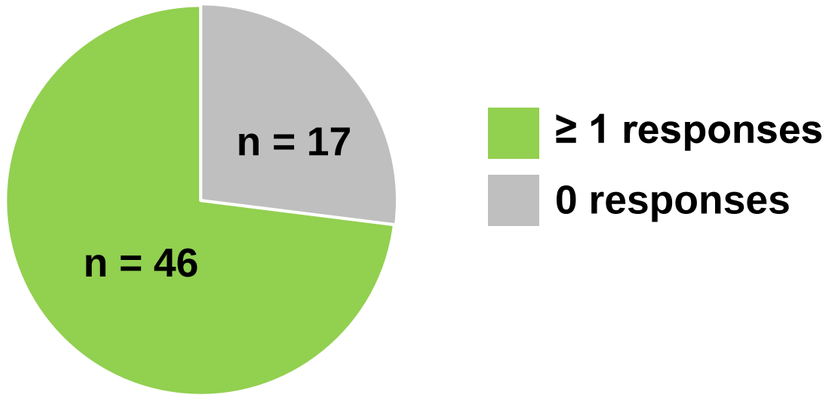
RO7198457 IV Dose + Atezolizumab 1200 mg IV q3w	Median (range) Onset Time, hours (n = 70)	Median (range) Resolution Time, hours (n = 57)
15 µg	5.7 (1.1-11.8)	1.8 (0.3-5.1)
25 µg	4.0 (0.7-9.7)	1.8 (0.1-20.1)
38 µg	4.1 (2.1-6.1)	1.5 (0.4-3.3)
50 µg	3.2 (2.4-5.9)	1.4 (0.4-1.7)

CRS, cytokine release syndrome (CTCAE v.5.0); IRR, infusion-related reaction; ILI, influenza-like illness. Data cutoff: January 10, 2020.

Lopez J, et al. Phase Ib of RO7198457 https://bit.ly/3gJdHA2

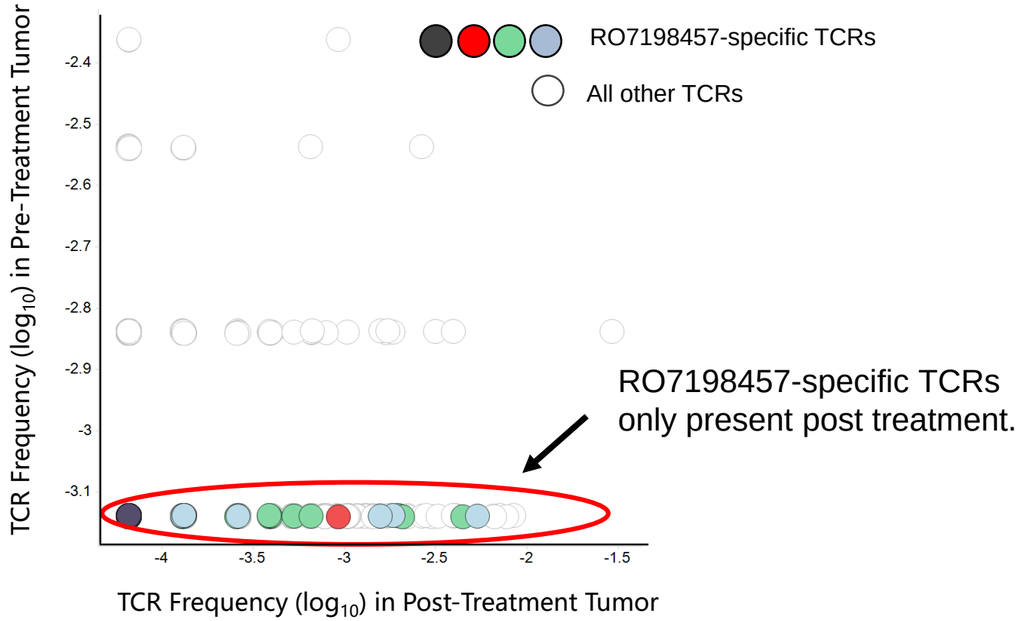
RO7198457 + Atezolizumab Induced Neoantigen-Specific T-Cell Responses in the Majority of Patients

- Induction of pro-inflammatory cytokines with each dose was observed, similar to findings in the Phase Ia[a]
- Ex vivo T-cell responses were detected (ELISPOT and MHC multimers) in nearly 73% of patients evaluated (n = 63)



- Median number of 2.6 neoantigen-specific responses (range, 1-9). Ex vivo data are not available for all vaccine targets due to limited material availability and T-cell fitness
- Both CD4 and CD8 T-cell responses were detected in patients where it was possible to delineate them (n = 14)
- In vitro stimulation with ELISPOT as a more sensitive measure of immune response to RO7198457 is ongoing

- Preliminary evidence suggests infiltration of RO7198457 stimulated T cells in the tumor (patient with rectal cancer treated with RO7198457 38 µg + atezolizumab 1200 mg IV q3w)[b]

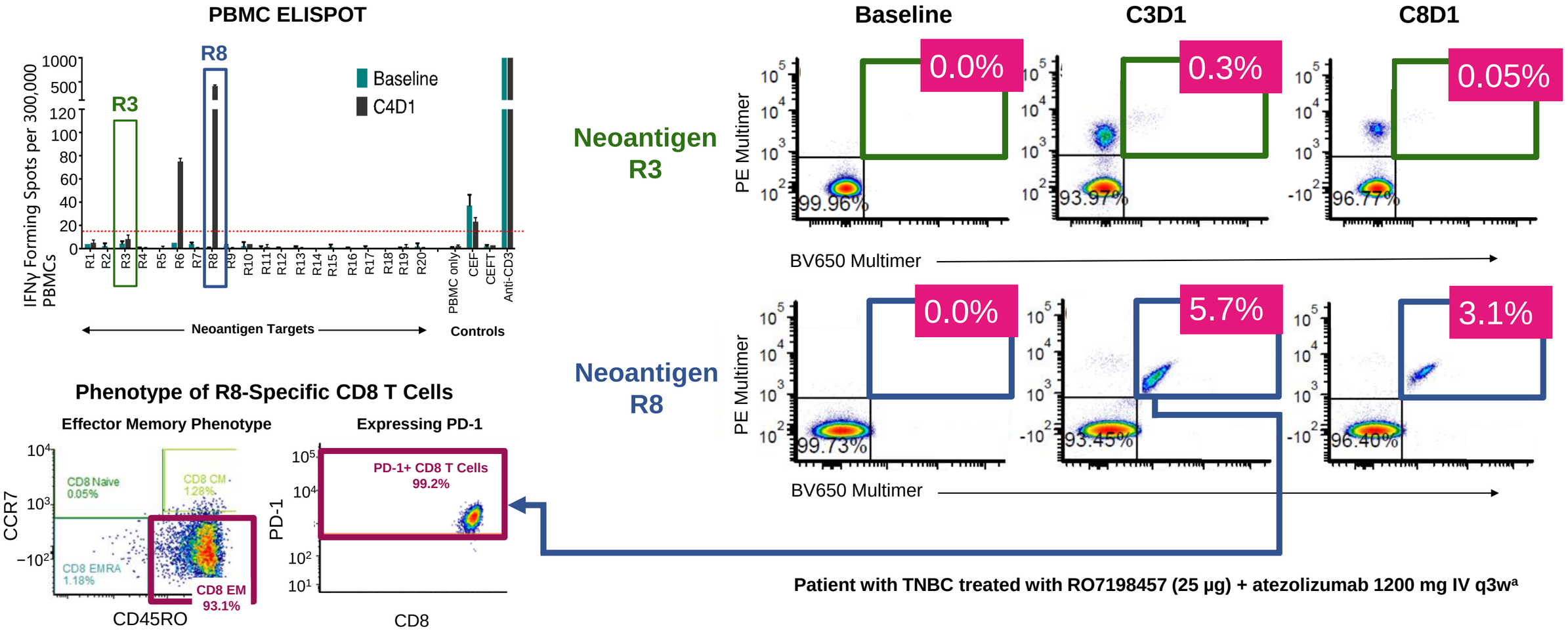


[a] See Braiteh et al. AACR II 2020. Poster CT169. [b] In collaboration with Adaptive Biotechnologies. Data cutoff: January 10, 2020.

Lopez J, et al. Phase Ib of RO7198457 https://bit.ly/3gJdHA2

Ex Vivo T-Cell Responses Induced by RO7198457 + Atezolizumab

- The magnitude of CD8 T cells induced by RO7198457 can reach > 5% in peripheral blood, with primarily effector memory phenotype and high expression of PD-1

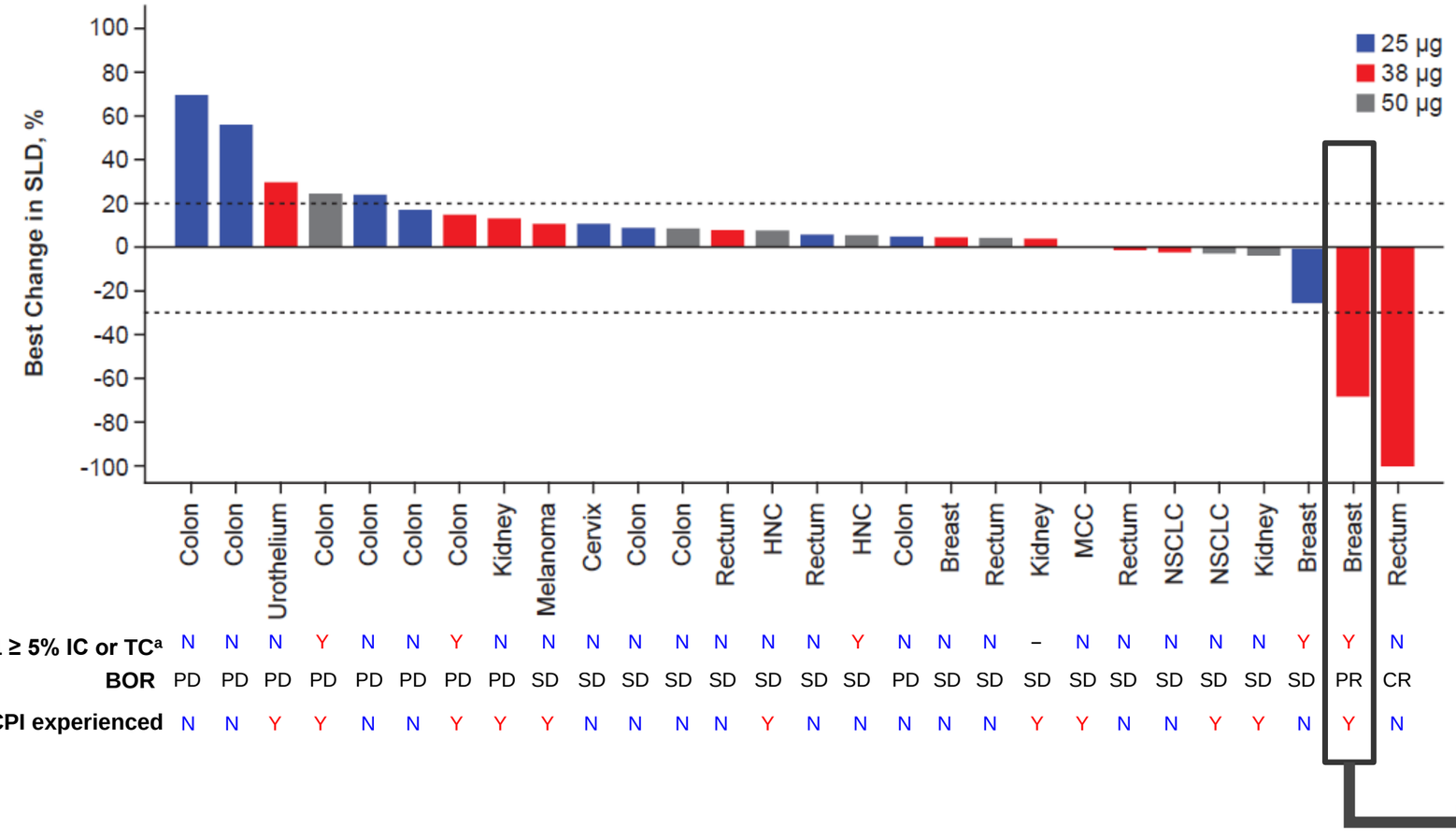


Patient with TNBC treated with RO7198457 (25 µg) + atezolizumab 1200 mg IV q3w[a]

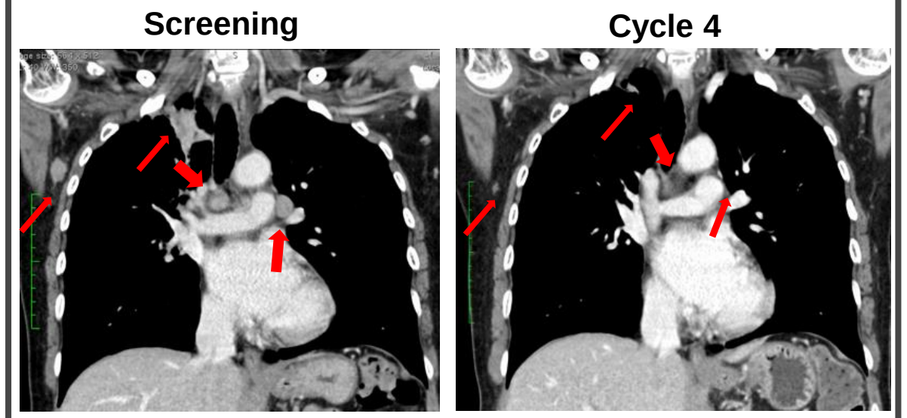
D, day; IFN, interferon; PBMC, peripheral blood mononuclear cell; PD-1, programmed death-1; SD, stable disease.
[a] Best response of SD; PD-L1 ≥ 5% IC or TC.

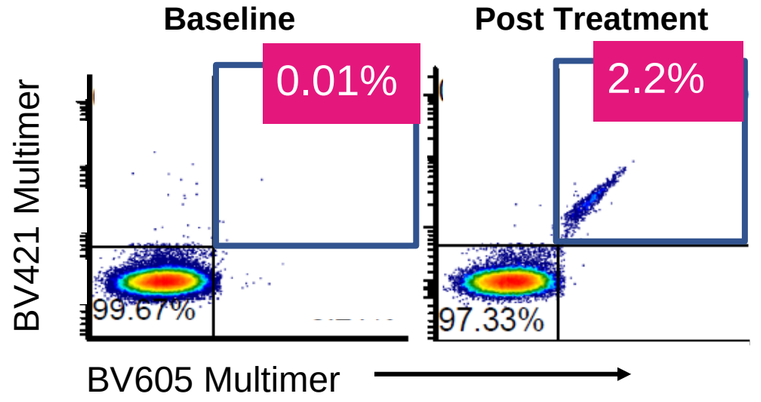
Lopez J, et al. Phase Ib of RO7198457 https://bit.ly/3gJdHA2

Dose Escalation: RO7198457 + Atezolizumab Clinical Activity



Patient With TNBC (CPI experienced) Treated With RO7198457 (38 µg) + Atezolizumab 1200 mg IV q3w





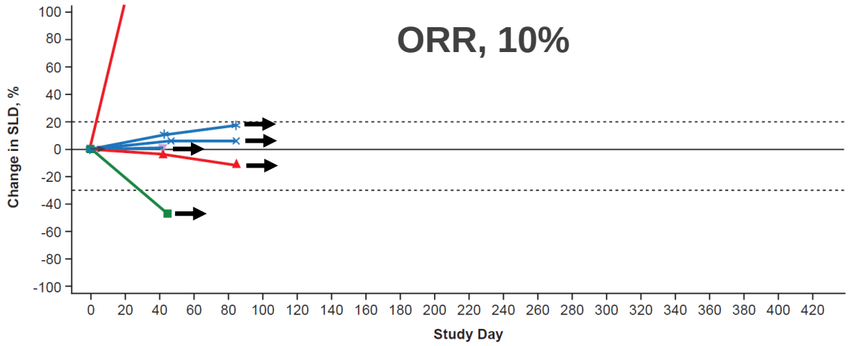
BOR, best overall response; CR, complete response; HNC, head and neck cancer; MCC, Merkel cell carcinoma; N, no; PR, partial response; Y, yes.
[a] PD-L1 expression on IC/TC analyzed by the Ventana SP142 assay. Data cutoff: January 10, 2020.

Lopez J, et al. Phase Ib of RO7198457 https://bit.ly/3gJdHA2

CPI–Naive Dose Expansion Activity: RO7198457 25 µg + Atezolizumab

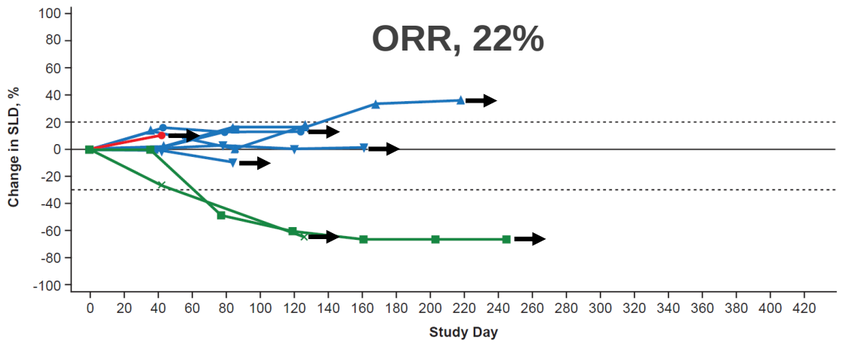
UC

ORR, 10%



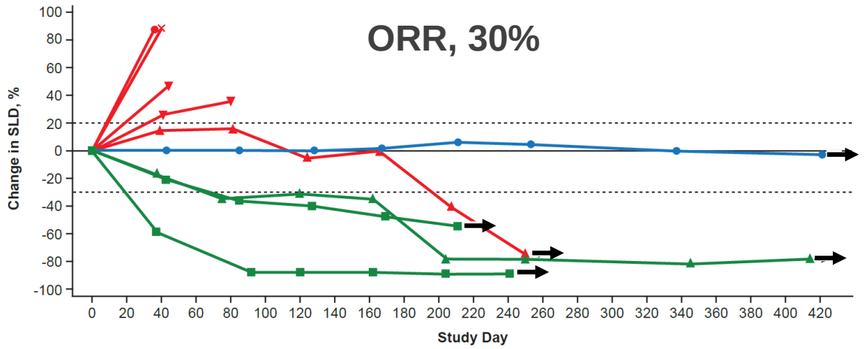
RCC

ORR, 22%



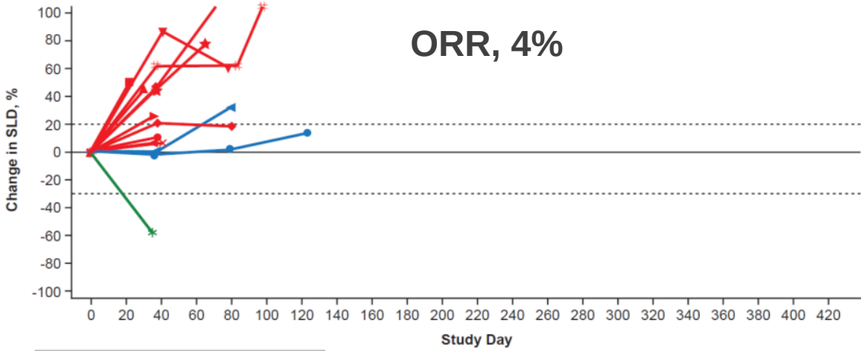
Melanoma

ORR, 30%



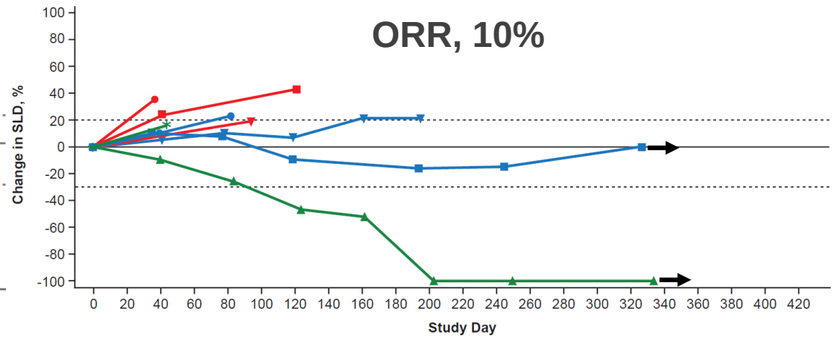
TNBC

ORR, 4%



NSCLC

ORR, 10%



Cohort	Median (range) Prior Therapies, n	PD-L1 Expression, n (%)[a]		
		< 5%	≥ 5%	Missing
UC (n = 10)	1 (1-3)	7 (70.0)	3 (30.0)	0
NSCLC (n = 10)	1.5 (1-5)	8 (100)	0	2
TNBC (n = 22)	3.5 (1-11)	16 (80.0)	4 (20.0)	2
RCC (n = 9)	1 (1-1)	7 (77.7)	2 (22.2)	0
Melanoma (n = 10)	1 (1-2)	9 (90.0)	0	1

ORR, objective response rate.
[a] PD-L1 expression on IC/TC analyzed by the Ventana SP142 assay.
Data cutoff: January 10, 2020.

Summary and Conclusions

- RO7198457 combined with atezolizumab was generally well tolerated
  - MTD was not reached and no DLTs were observed
  - Treatment-related AEs were primarily systemic reactions, manifesting as low-grade CRS, IRR or ILI symptoms that were transient, reversible and manageable in the outpatient setting
- RO7198457 in combination with atezolizumab induced the release of pro-inflammatory cytokines and peripheral T-cell responses in the majority of patients
  - Preliminary evidence suggests infiltration of RO7198457–stimulated T cells in the tumor; a more detailed analysis of intra-tumoral immune responses is being evaluated in a dedicated biomarker cohort
- Delineation of the efficacy of combination treatment and correlation with immune responses are under investigation in 2 ongoing randomized Phase II studies of RO7198457:
  - RO7198457 + pembrolizumab for the first-line treatment of patients with melanoma (NCT03815058)
  - RO7198457 + atezolizumab as adjuvant treatment in patients with NSCLC (NCT04267237)

Acknowledgments

- We thank all of the patients who participated in this study and their families
- We also thank the investigators and clinical research staff at the following clinical sites:

Royal Marsden Hospital
Princess Margaret Cancer Centre
University Hospital Essen
The Angeles Clinic and Research Institute
HonorHealth Research Institute
Herbert Irving Comprehensive Cancer Center, Columbia University
Smilow Cancer Center, Yale University
UCSF Helen Diller Family Comprehensive Cancer Center
Karolinska University Hospital
Comprehensive Cancer Center Nevada
Providence Cancer Center EACRI
CHU Liege and Liege University
Johannes Gutenberg-Universitat Mainz
Stephenson Cancer Center, The University of Oklahoma
UMC Utrecht
Barts Cancer Institute
University of Colorado Cancer Center
Cancer Research Institute Ghent (CRIG Ghent)
Memorial Sloan Kettering Cancer Center
Translational Cancer Research Unit, Sint-Augustinus
Massachusetts General Hospital
Seattle Cancer Care Alliance
Dana-Farber Cancer Institute
Uppsala University
University of Southampton
Sarah Cannon Research Institute/Tennessee Oncology
Stanford University School of Medicine
Netherlands Cancer Institute
Ottawa Hospital Cancer Centre
Lungenfachklinik Immenhausen
University Clinic of Navarra, Centre of Applied Medical Research

- We thank the Genentech multimer group: Alberto Robert, Leesun Kim, Oliver Zill, Martine Darwish and Craig Blanchette
- Editorial assistance for this presentation was provided by Charli Dominguez, PhD, of Health Interactions and funded by F. Hoffmann-La Roche, Ltd