

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

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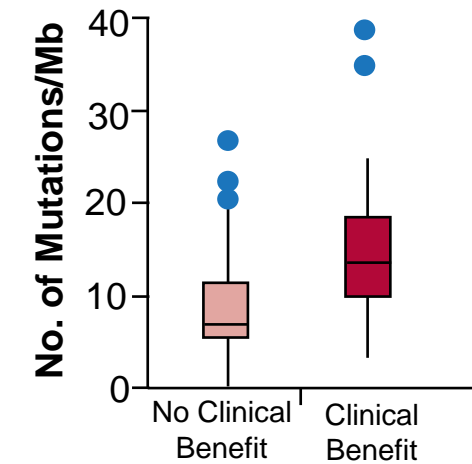
Disclosures

- 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

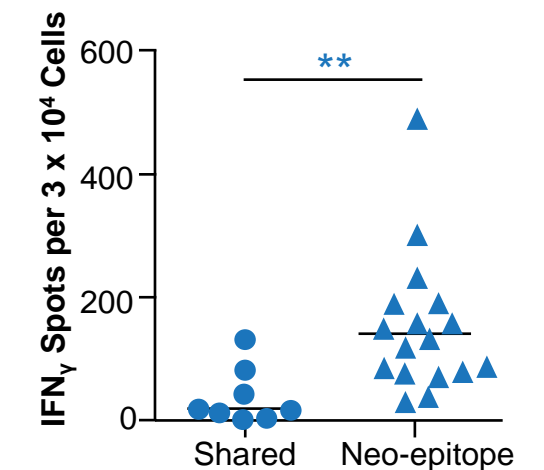
- High tumor mutation burden correlates with clinical response to immune checkpoint blockade
- Mutated neoantigens are recognized as foreign and induce stronger T-cell responses than shared antigens, likely due to the lack of central tolerance
- Most of these mutated neoantigens are not shared between 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



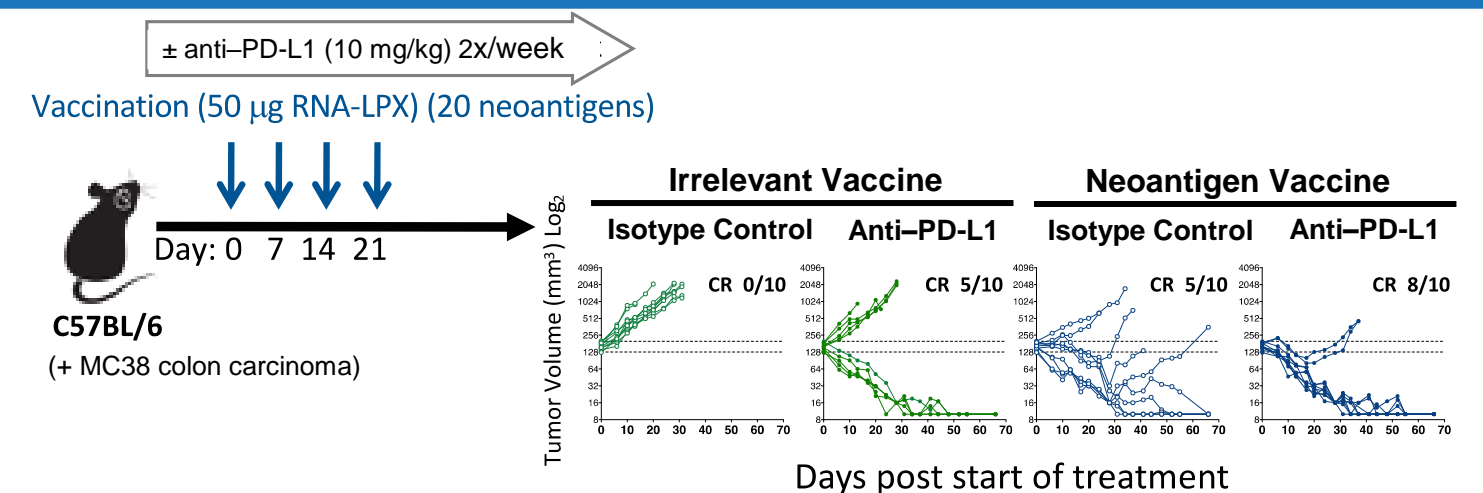
Rosenberg, Lancet 2016

Stronger T-Cell Responses Against Neoantigens



Sahin, Nature 2017

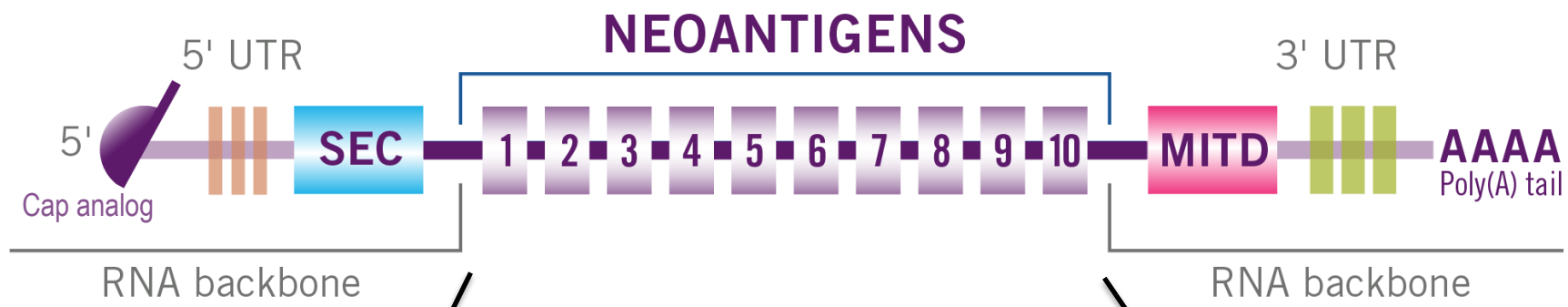
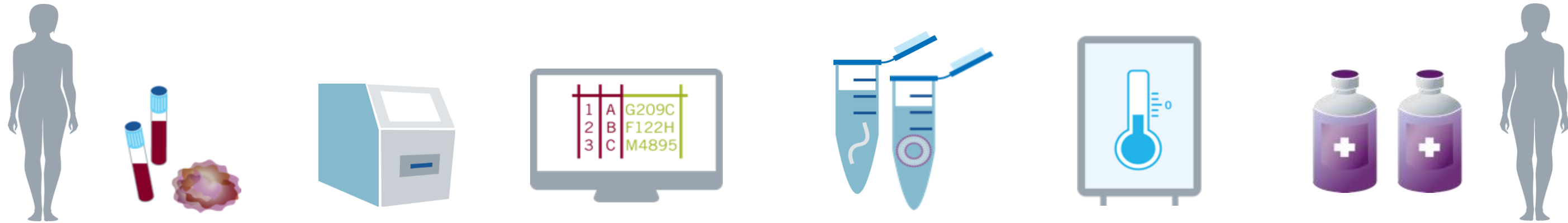
RNA-LPX + Anti-PD-L1 Leads to Enhanced Anti-Tumor Activity



Javinal, unpublished data

MHC, major histocompatibility complex. ^a Also known as RG6180

Targeting Neoantigens Requires an Individualized Approach

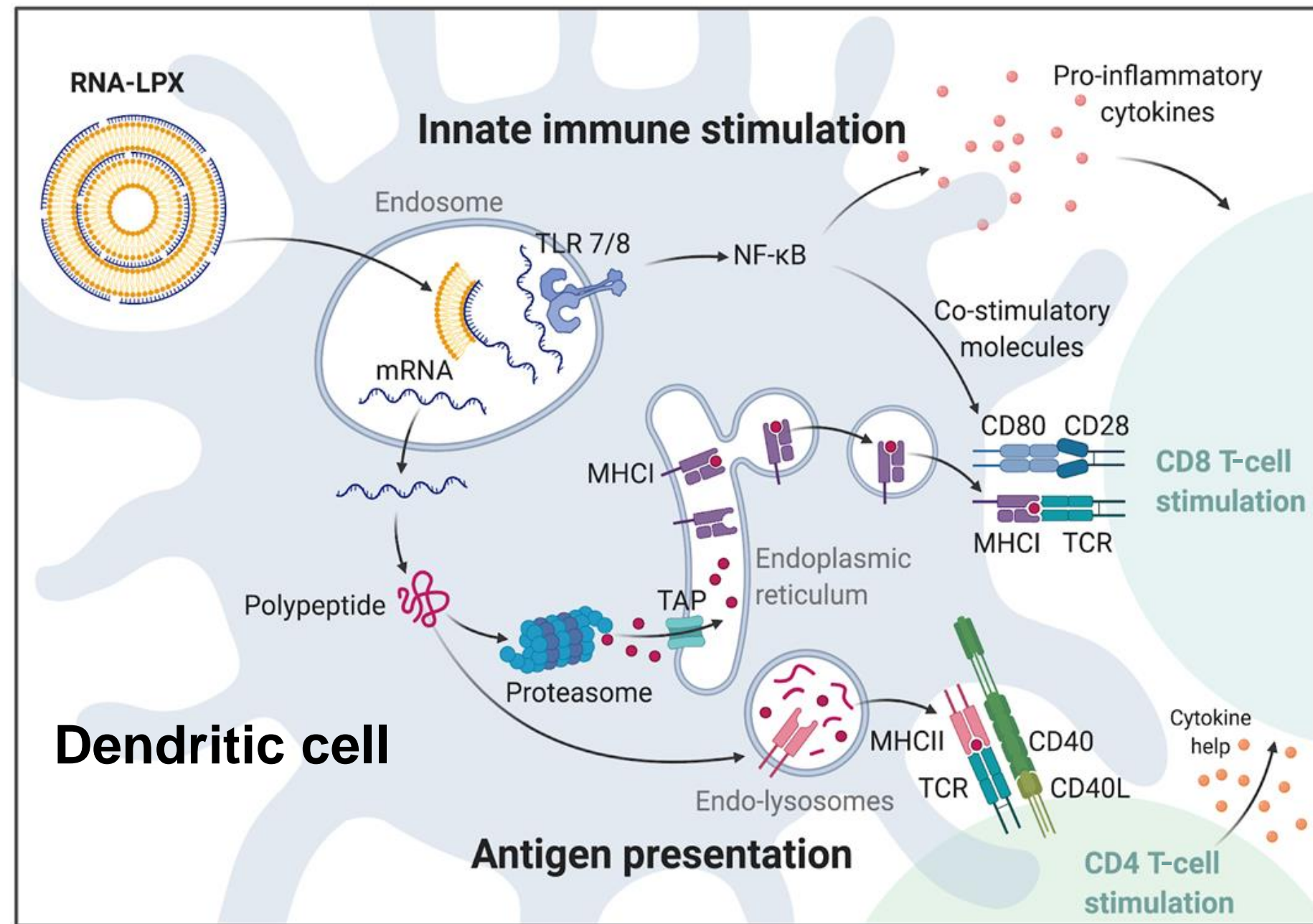
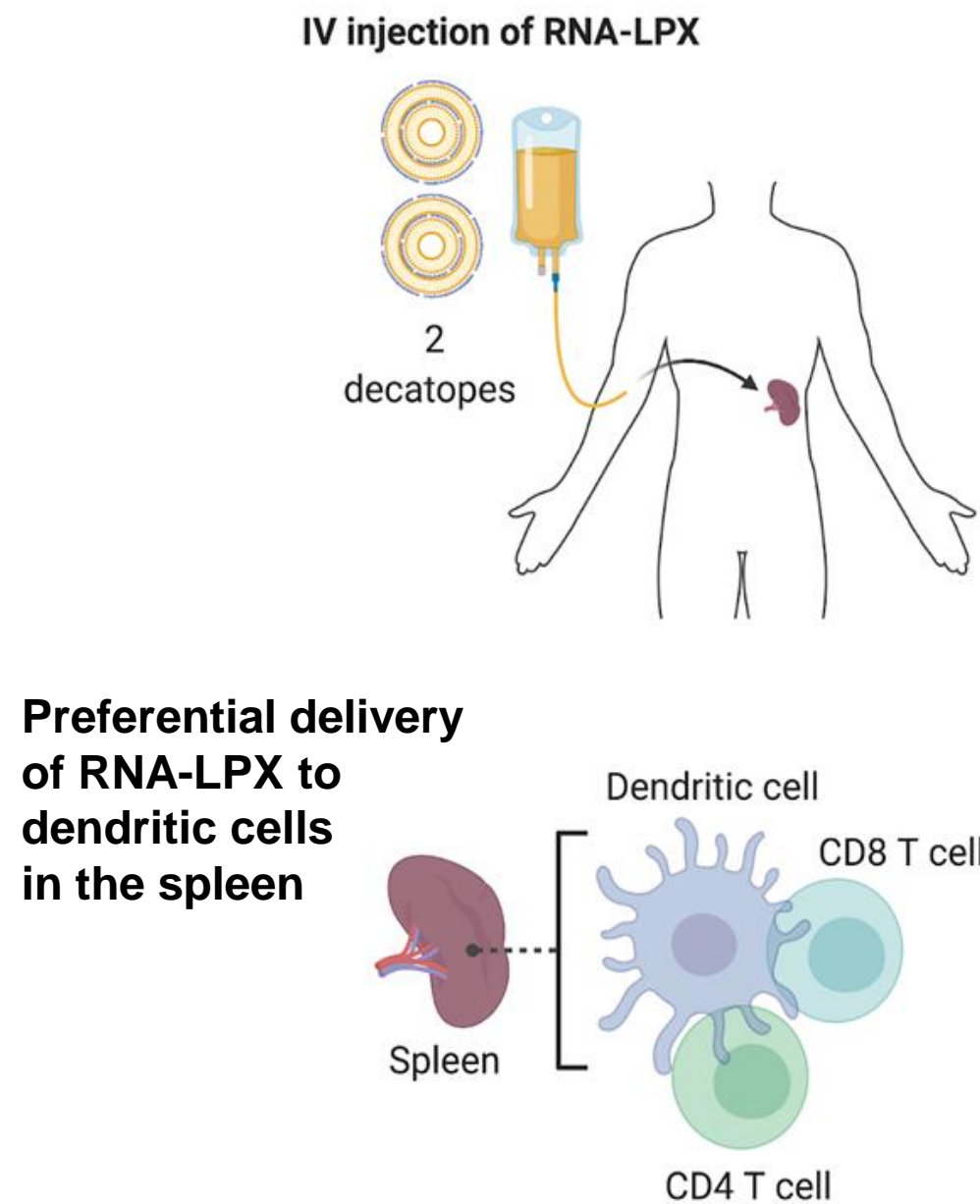


Single-stranded mRNA

Innate Immune Stimulation
Intrinsic TLR7/8 agonist

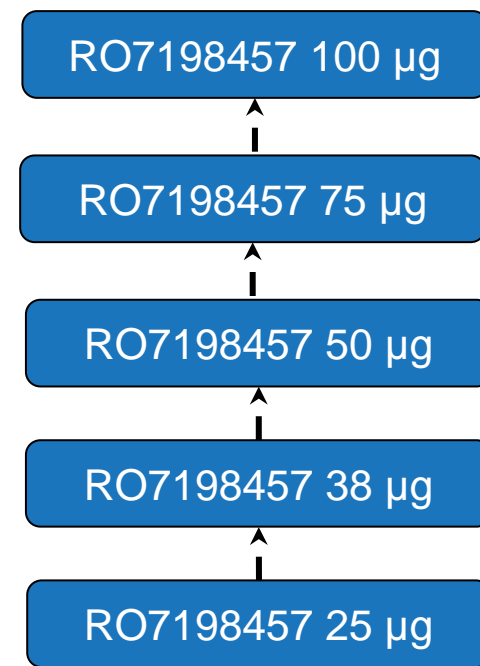
Antigen Expression
Up to 20 neoantigens (2 decatopes)

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



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

Phase Ia Dose Escalation^{a-c}

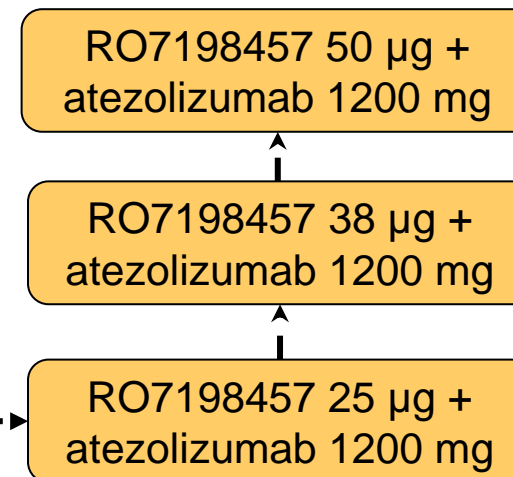


Key Inclusion Criteria

- Age ≥ 18
- Advanced or recurrent solid tumors
- Life expectancy > 12 wk
- ECOG PS ≤ 1

RO7198457 + Atezolizumab 1200 mg IV q3w

Dose Escalation

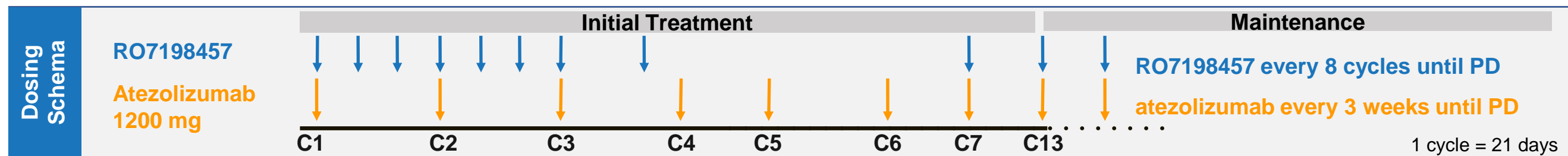
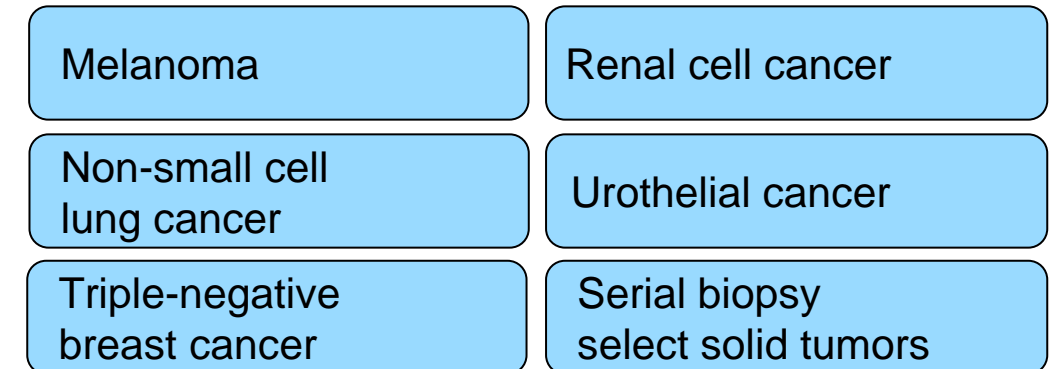


Indication-Specific Expansion Cohorts

Checkpoint inhibitor experienced



Checkpoint inhibitor naive



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 Braithe F, et al. AACR II 2020. Poster CT169. NCT03289962.

Data cutoff: January 10, 2020.

Patient Demographics and Disease Characteristics

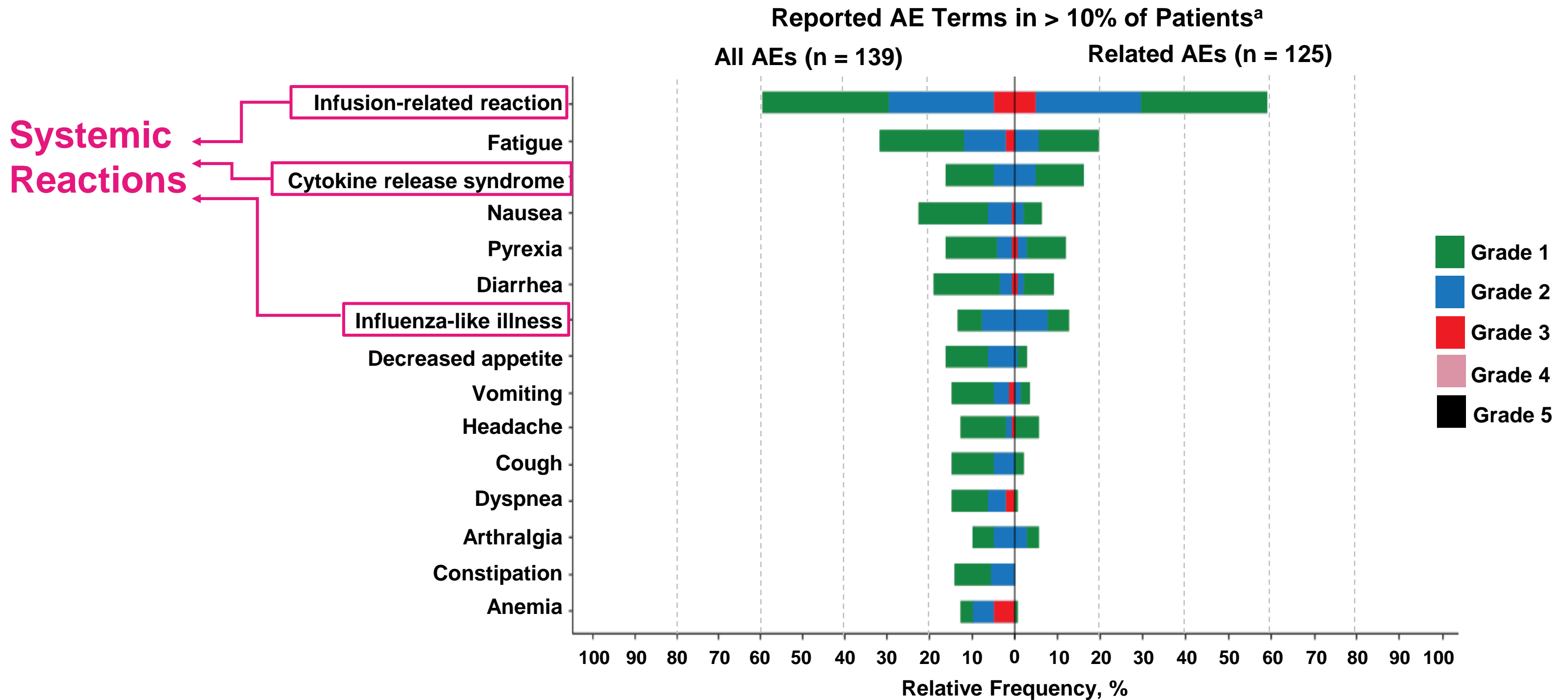
	Dose Escalation	Expansion	
	Total (n = 30)	CPI Experienced (n = 42)	CPI Naive (n = 72)
Median age (range), years	57.5 (35-77)	61.5 (36-82)	57.5 (29-79)
Male, n (%)	17 (56.6)	25 (59.5)	31 (43.1)
ECOG PS, n (%)			
0	15 (50.0)	19 (45.2)	38 (52.8)
1	15 (50.0)	23 (54.8)	34 (47.2)
Most common tumor types, 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)

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.

AEs Occurring in Patients Treated With RO7198457 + Atezolizumab



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

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

Systemic Reactions Were Transient and Generally Manageable in the Outpatient Setting

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

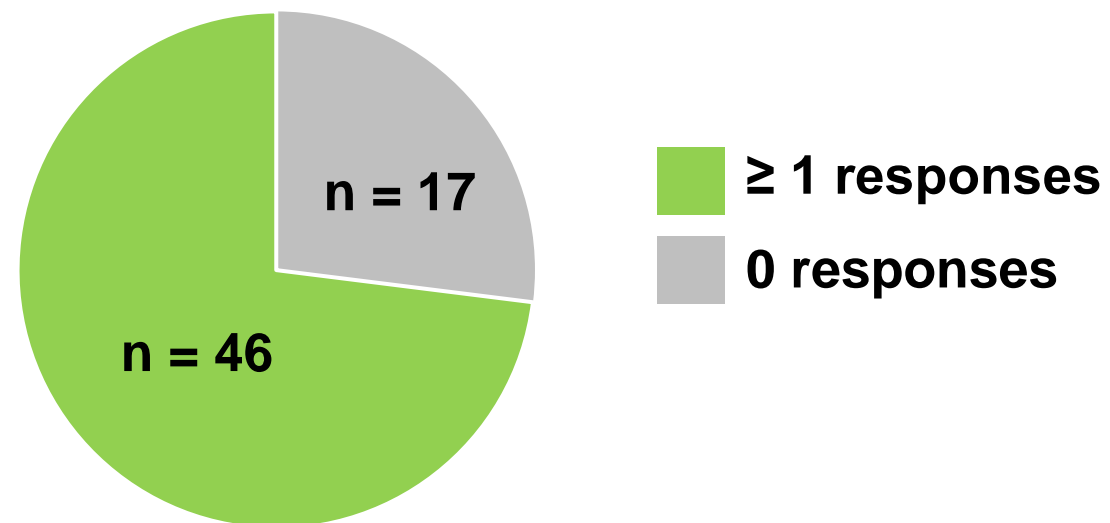
n (%)	RO7198457 IV Dose + Atezolizumab 1200 mg IV q3w				
	15 µg (n = 27)	25 µg (n = 95)	38 µg (n = 11)	50 µg (n = 9)	All Patients (N = 142)
Pyrexia	10 (37.0)	60 (63.2)	10 (90.9)	6 (66.7)	86 (60.6)
Chills	11 (40.7)	58 (61.1)	8 (72.7)	7 (77.8)	84 (59.2)
Nausea	2 (7.4)	14 (14.7)	2 (18.2)	2 (22.2)	20 (14.1)
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)

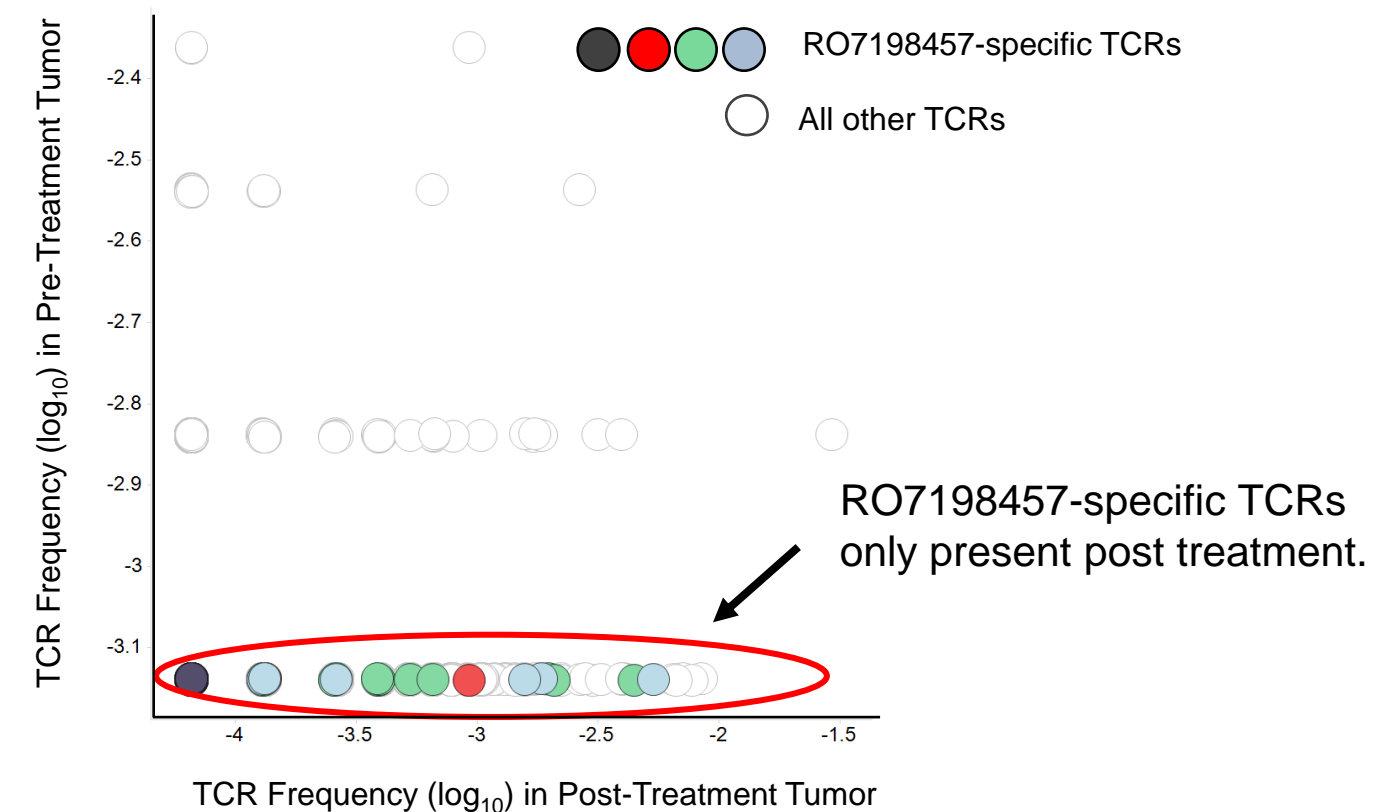
RO7198457 + Atezolizumab Induced Neoantigen-Specific T-Cell Responses in the Majority of Patients

- 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

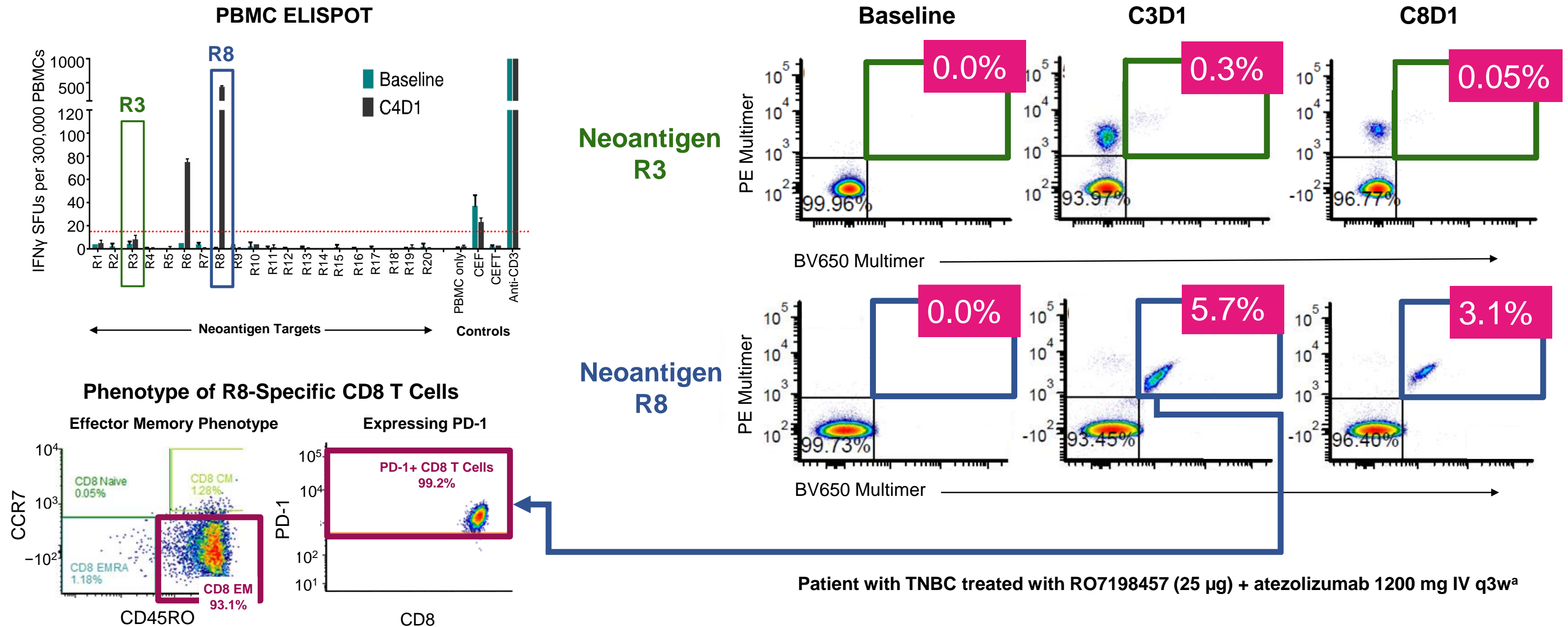
- Preliminary evidence suggests infiltration of RO7198457 stimulated T cells in the tumor (patient with rectal cancer treated with RO7198457 38 μg + atezolizumab 1200 mg IV q3w)^b



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

Ex Vivo T-Cell Responses Induced by RO7198457 + Atezolizumab

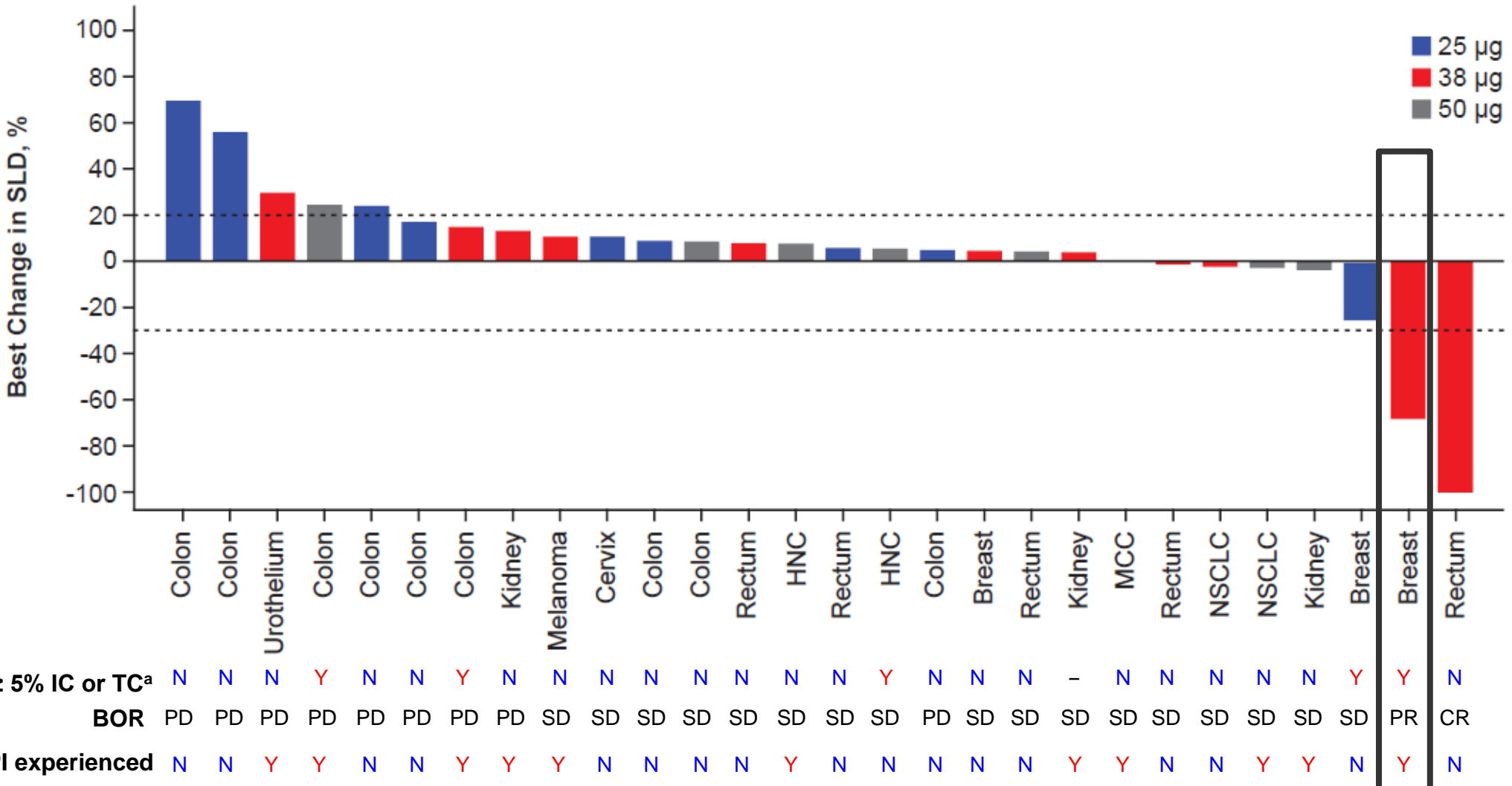
- The magnitude of CD8 T cells induced by RO7198457 can reach > 5% in peripheral blood, with primarily effector memory phenotype and high expression of PD-1



D, day; IFN, interferon; PBMC, peripheral blood mononuclear cell; PD-1, programmed death-1; SD, stable disease; SFU, spot forming units.

^a Best response of SD; PD-L1 \geq 5% IC or TC.

Dose Escalation: RO7198457 + Atezolizumab Clinical Activity



	Colon	Colon	Urothelium	Colon	Colon	Colon	Colon	Kidney	Melanoma	Cervix	Colon	Colon	Rectum	HNC	Rectum	HNC	Colon	Breast	Rectum	Kidney	MCC	Rectum	NSCLC	NSCLC	Kidney	Breast	Breast	Rectum
PD-L1 ≥ 5% IC or TC ^a	N	N	N	Y	N	N	Y	N	N	N	N	N	N	N	Y	N	N	N	-	N	N	N	N	N	N	Y	Y	N
BOR	PD	PD	PD	PD	PD	PD	PD	PD	SD	SD	SD	SD	SD	SD	SD	SD	PD	SD	SD	SD	SD	SD	SD	SD	SD	SD	PR	CR
CPI experienced	N	N	Y	Y	N	N	Y	Y	Y	N	N	N	N	Y	N	N	N	N	Y	Y	N	Y	Y	N	Y	Y	N	

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

Screening **Cycle 4**

Baseline **Post Treatment**

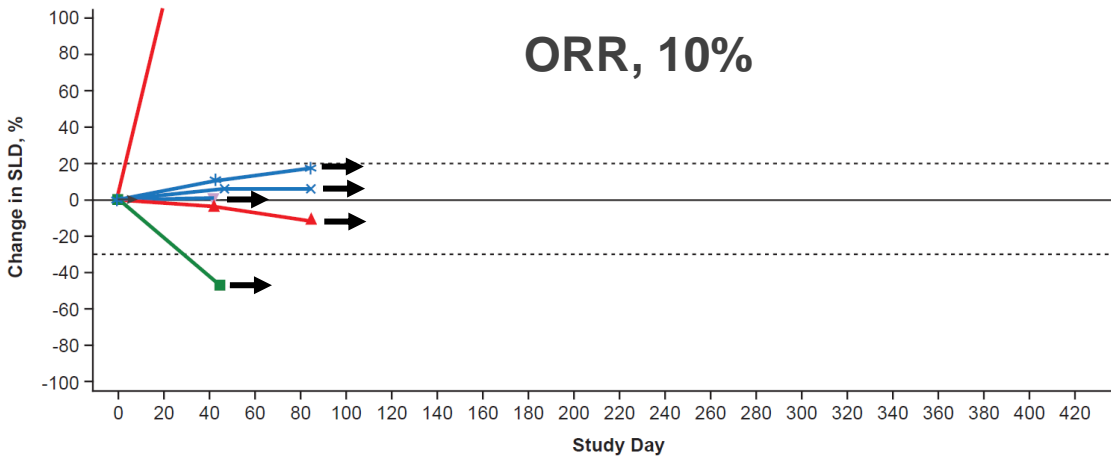
BV421 Multimer

BV605 Multimer

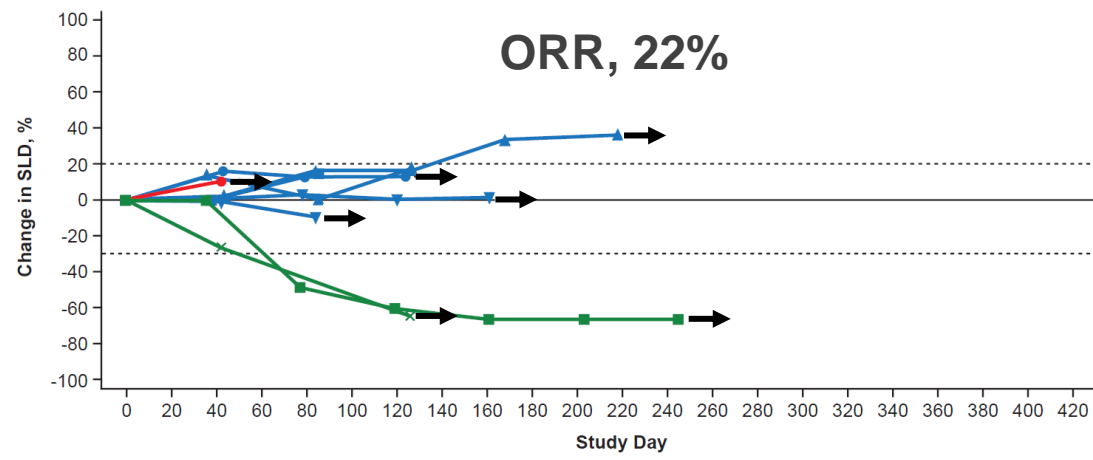
BOR, best overall response; CR, complete response; HNC, head and neck cancer; MCC, Merkel cell carcinoma; N, no; PR, partial response; Y, yes.
^a PD-L1 expression on IC/TC analyzed by the Ventana SP142 assay. Data cutoff: January 10, 2020.

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

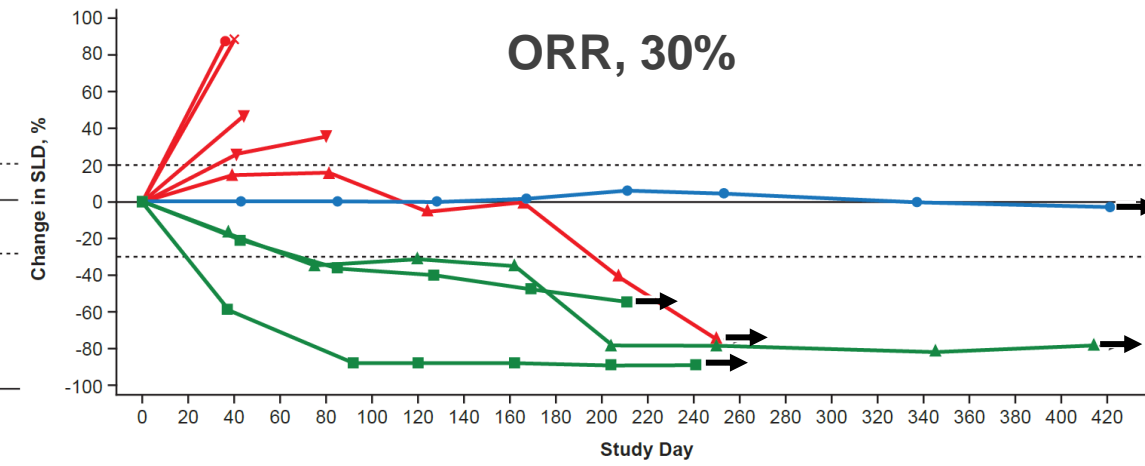
UC
ORR, 10%



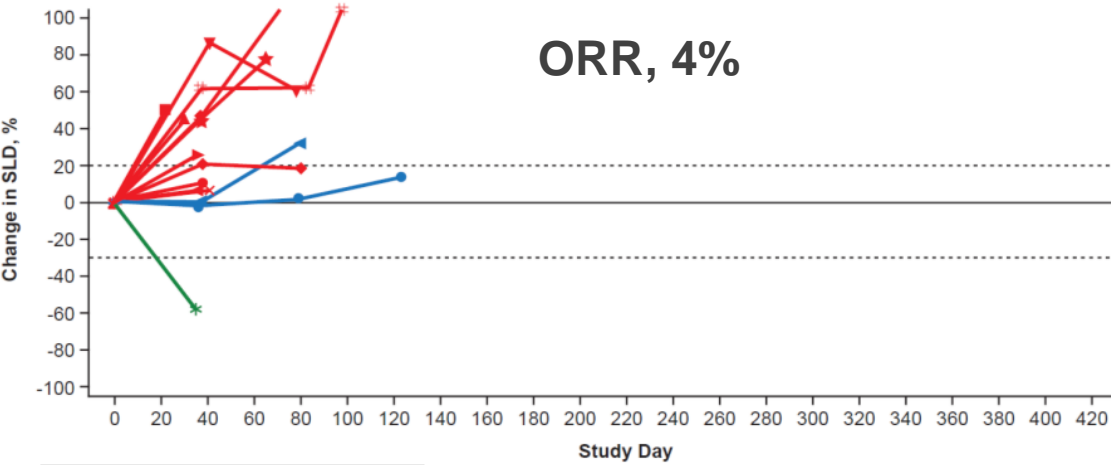
RCC
ORR, 22%



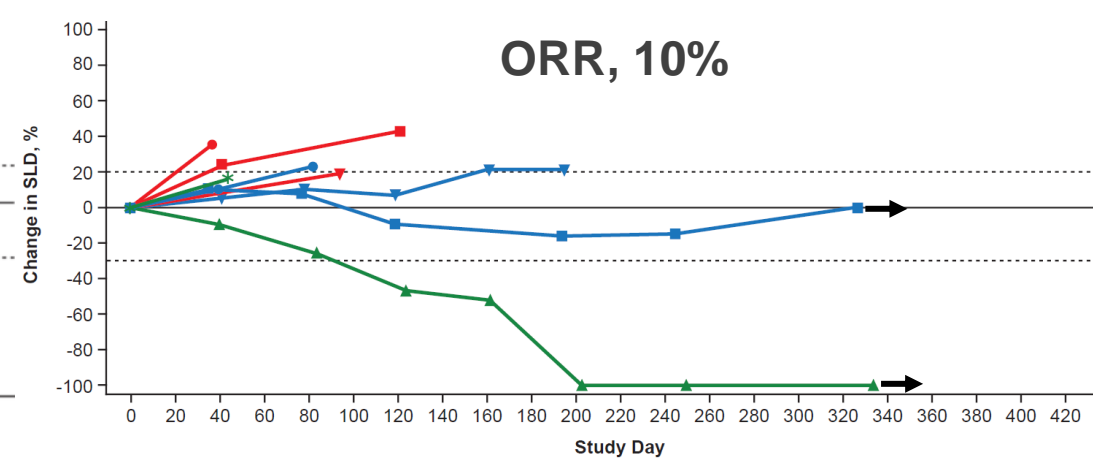
Melanoma
ORR, 30%



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)

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 - 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-Universität 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
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