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#SITC24

Primary analysis of the registration-intended cohort of patients with anti–PD-1–failed melanoma from the IGNYTE trial of RP1 plus nivolumab, including clinical subgroup and initial biomarker data

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Presenter disclosure

- **Michael K Wong** has participated on a Data Safety Monitoring Board or Advisory Board for Bristol Myers Squibb, Castle Biosciences, EMD-Serono, ExiCure, Merck, Pfizer, and Regeneron
- This study is sponsored by Replimune, Inc. (Woburn, MA, USA). Nivolumab was supplied by Bristol Myers Squibb

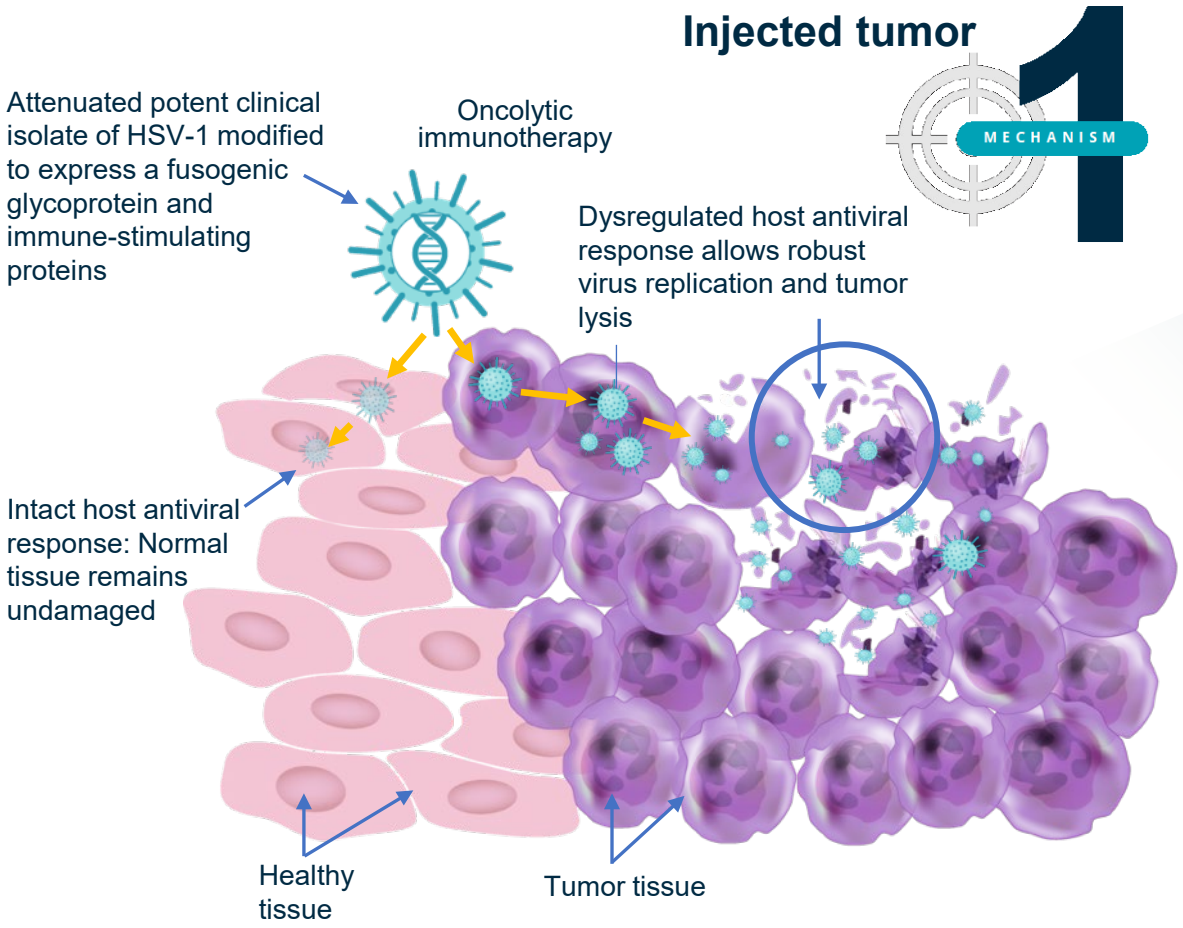
Background

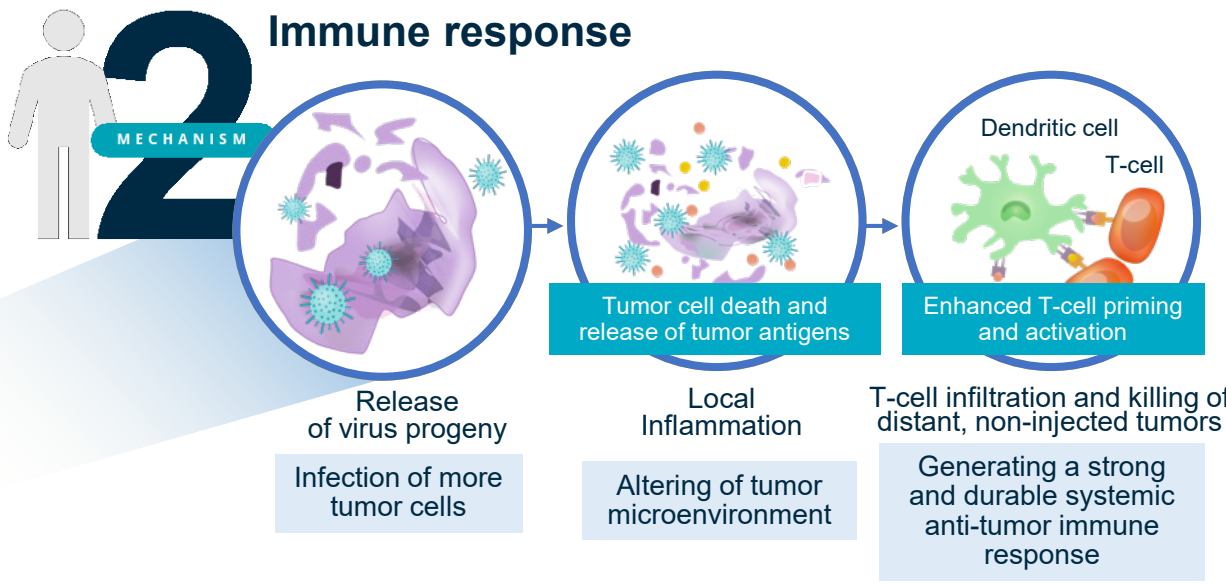
- There are limited treatment options for patients with anti–PD-1–progressed melanoma[1,2]
- Responses to targeted anti–BRAF + MEK for *BRAF*-mutant melanoma are usually not durable[3]
- Single-agent anti–PD-1 after confirmed progressive disease on anti–PD-1 yields a 6%–7% response rate[4,5]
- Nivolumab + ipilimumab is a potential option,[2] but toxicity is high[2,6]
- Nivolumab + anti–LAG-3 offers sub-optimal efficacy[7]
- TIL therapy gives response rates of ~30%,[8] but nearly all patients have grade 4 toxicity[9,10]

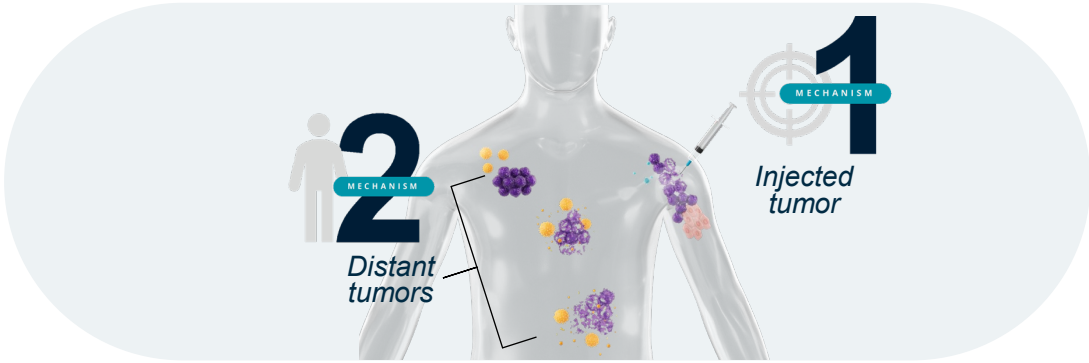
LAG-3, lymphocyte activation gene 3; PD-1, programmed cell death protein 1; TIL, tumor-infiltrating lymphocyte.

1. Mooradian MJ, et al. *Oncology*. 2019;33(4):141-8. 2. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Melanoma: Cutaneous. Version 2. 2024. 3. Dixon-Douglas JR, et al. *Curr Oncol Rep*. 2022;24(8):1071-9. 4. Beaver JA, et al. *Lancet Oncol*. 2018;19(2):229-39. 5. Ribas A, et al. *Lancet Oncol*. 2018;19(5):e219. 6. Pires da Silva I, et al. *Lancet Oncol*. 2021;22(6):836-47. 7. Ascierto PA, et al. *J Clin Oncol*. 2023;41(15)2724-35. 8. Chesney J, et al. *J Immunother Cancer*. 2022;10(12):e005755. 9. US Food and Drug Administration. BLA clinical review and evaluation - AMTAGVI. BLA 125773. Updated February 6, 2024. Accessed May 31, 2024. https://www.fda.gov/media/176951/download. 10. Sarnaik AA, et al. *J Clin Oncol*. 2021;39(24):2656-66.

Oncolytic immunotherapy is intended to activate a systemic anti-tumor response[1]



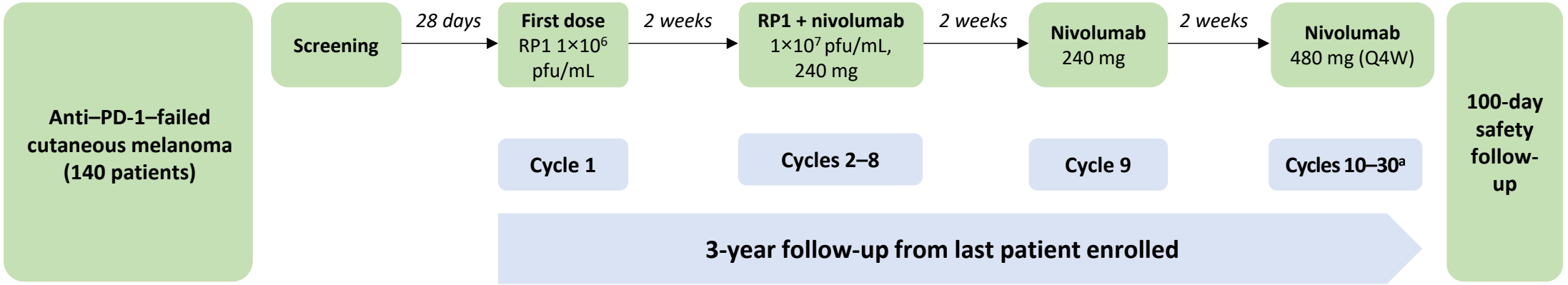




HSV-1, herpes simplex virus type 1.

1. Bommareddy PK, et al. *Am J Clin Dermatol*. 2017;18(1):1-15.

Study design



***Tumor response assessment**: Radiographic imaging at baseline and every 8 weeks from first dose and every 12 weeks after confirmation of response*

Primary objective

- Safety and efficacy using mRECIST* v1.1 by independent central review (sensitivity analysis by RECIST v1.1)

Secondary objectives

- ORR by investigator assessment (mRECIST* v1.1)
- DOR, CR rate, DCR, and PFS by central and investigator assessment, 1-year and 2-year OS

** For mRECIST, PD must be confirmed by further progression at least 4 weeks after initial PD; intended to better allow for pseudoprogression than RECIST v1.1*

Key eligibility

Anti–PD-1–failed advanced melanoma; measurable disease; adequate organ function; no prior oncolytic therapy; ECOG performance status 0–1

Criteria for prior anti–PD-1–failure

Confirmed progression while being treated with at least 8 weeks of anti–PD-1 therapy, alone or in combination; anti–PD-1 must be the last prior therapy. Patients on prior adjuvant therapy must have confirmed progression while being treated with adjuvant treatment (PD can be confirmed by biopsy)

***Primary analysis conducted when all patients had* ≥12 months follow-up**

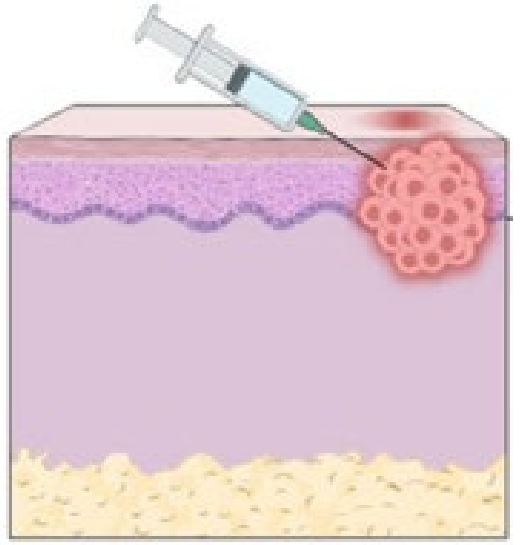
[a]RP1 can be reinitiated beyond 8 cycles if protocol-specified criteria are met.

CR, complete response; DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; mRECIST, modified RECIST; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-1, programmed cell death protein 1; PFS, progression-free survival; pfu, plaque-forming unit; Q4W, every 4 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.

RP1 administration

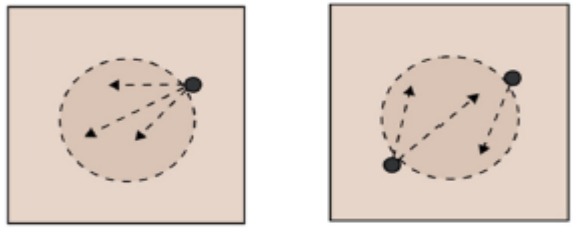
- RP1 is injected into superficial and/or deep/visceral tumors
- Both superficial and deep/visceral tumors may be injected in the same injection day
- Deep/visceral injections are done by ultrasound or CT
- The volume of RP1 is dependent on the lesion size
- Multiple tumors may be injected with up to 10 mL of RP1
- Generally, injections should be made from largest to smallest lesions

Injection administration for superficial tumors

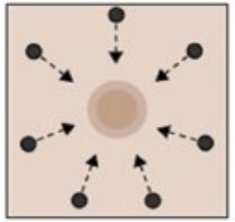


For nonulcerated superficial tumor

Top-down view of skin



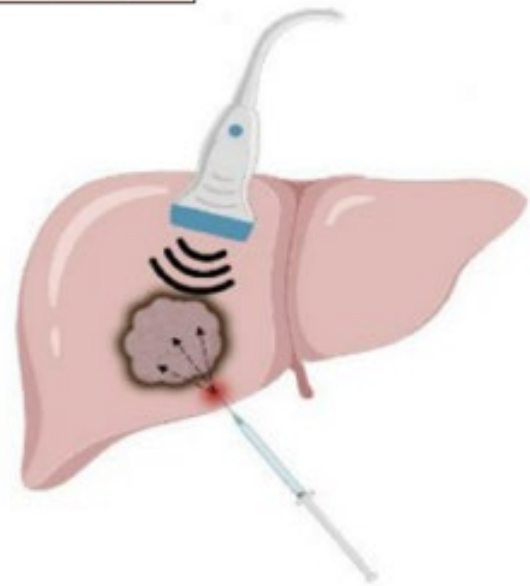
For ulcerated superficial tumor



Inject around the ulcer

Injection administration for deep tumors

Radial injection or coaxial injection may be used via image guidance with ultrasound or CT



CT, computed tomography.

Baseline clinical characteristics

- A “real world” anti–PD-1–failed melanoma population was enrolled

Patients, n (%)	N = 140
Age, median (range), y	62 (21–91)
Sex	
Female	45 (32.1)
Male	95 (67.9)
Stage	
IIIb/IIIc/IVM1a	72 (51.4)
IVM1b/c/d	68 (48.6)
BRAF status	
Wild-type	87 (62.1)
Mutant	53 (37.9)
LDH level	
LDH ≤ULN	92 (65.7)
LDH >ULN	47 (33.6)
Unknown	1 (0.7)
Baseline PD-L1 tumor expression	
Positive (≥1%)	44 (31.4)
Negative (<1%)	79 (56.4)
Undetermined or missing	17 (12.1)

Patients, n (%)	N = 140
Prior therapy	
Anti–PD-1	
Anti–PD-1 only as adjuvant therapy	36 (25.7)
Anti–PD-1 other than as adjuvant therapy	104 (74.3)
Anti–CTLA-4	
Anti–PD-1 combined with anti–CTLA-4	61 (43.6)
Anti–PD-1 treated with anti–CTLA-4 sequentially	4 (2.9)
Received BRAF/MEK therapy	17 (12.1)
Anti–PD-1 resistance category	
Primary resistance[a]	92 (65.7)
Secondary resistance[b,c]	48 (34.3)

Due to the requirement that patients must have confirmed PD on an immediate prior anti–PD-1–based therapy, most patients had 1 or 2 prior lines of therapy

The median (range) follow-up at the time of the primary analysis was 15.4 months (0.5–47.6 months)

[a]Primary resistance: Progressed within 6 months of starting the immediate prior course of anti–PD-1 therapy. [b]Secondary resistance: Progressed after 6 months of treatment on the immediate prior course of anti–PD-1 therapy. [c]Includes 1 patient with unknown resistance status.
CTLA-4, cytotoxic T-lymphocyte antigen 4; LDH, lactate dehydrogenase; PD, progressive disease; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; ULN, upper limit of normal.

Primary efficacy analysis

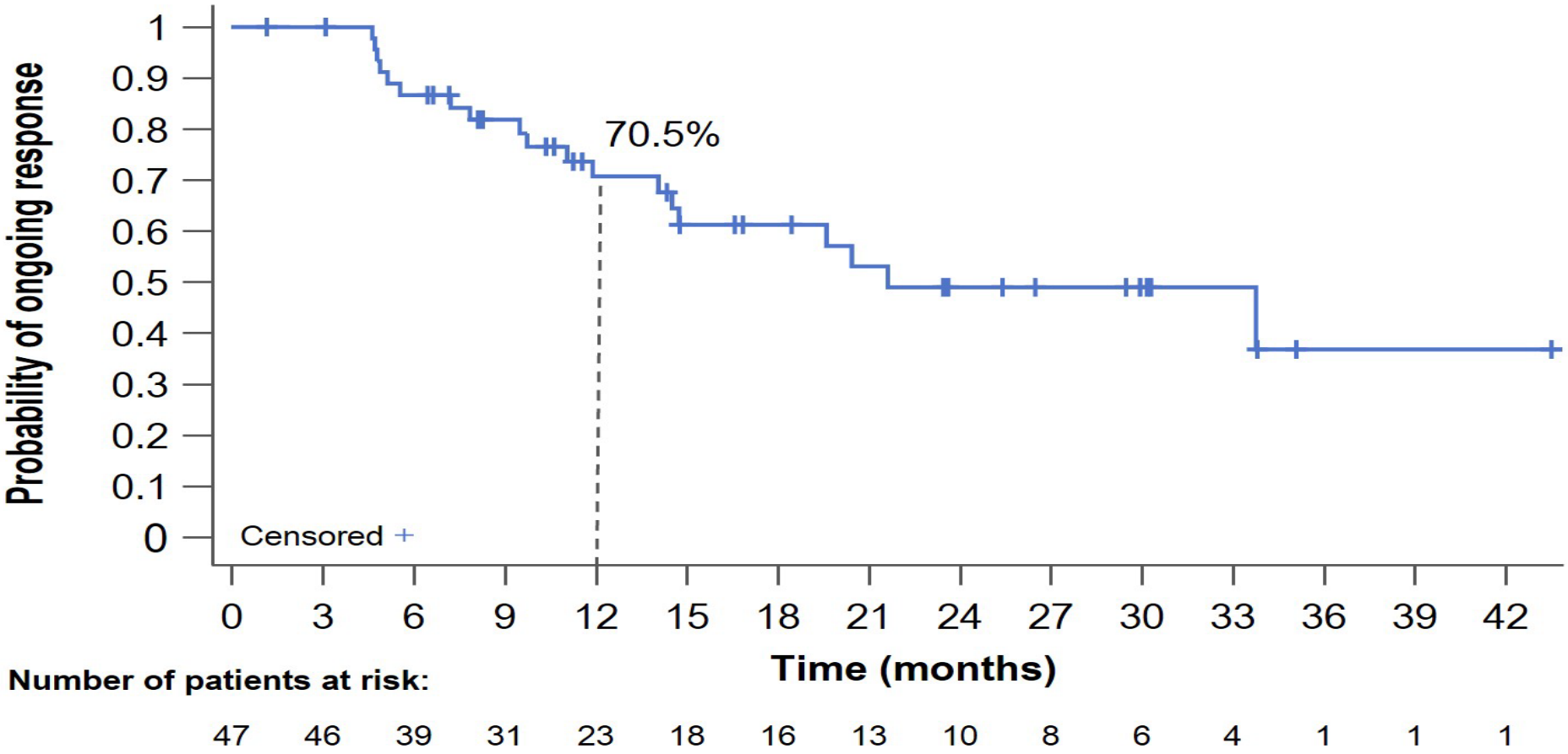
By blinded, independent central review

	Primary endpoint mRECIST v1.1 (N = 140)	Sensitivity analysis RECIST v1.1 (N = 140)
Confirmed best response, n (%)		
CR	21 (15.0)	21 (15.0)
PR	26 (18.6)	25 (17.9)
SD	41 (29.3)	31 (22.1)
PD	43 (30.7)	54 (38.6)
ORR (confirmed CR+PR), n (%)	**47 (33.6)**	**46 (32.9)**
95% CI	(25.8, 42.0)	(25.2, 41.3)

- 1 in 3 patients (33.6%) experienced a confirmed objective response, 15.0% CR

CI, confidence interval; CR, complete response; mRECIST, modified RECIST; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Duration of response



- Median (range) duration of response was 21.6 months (1.2+ to 43.5+ months)

Efficacy

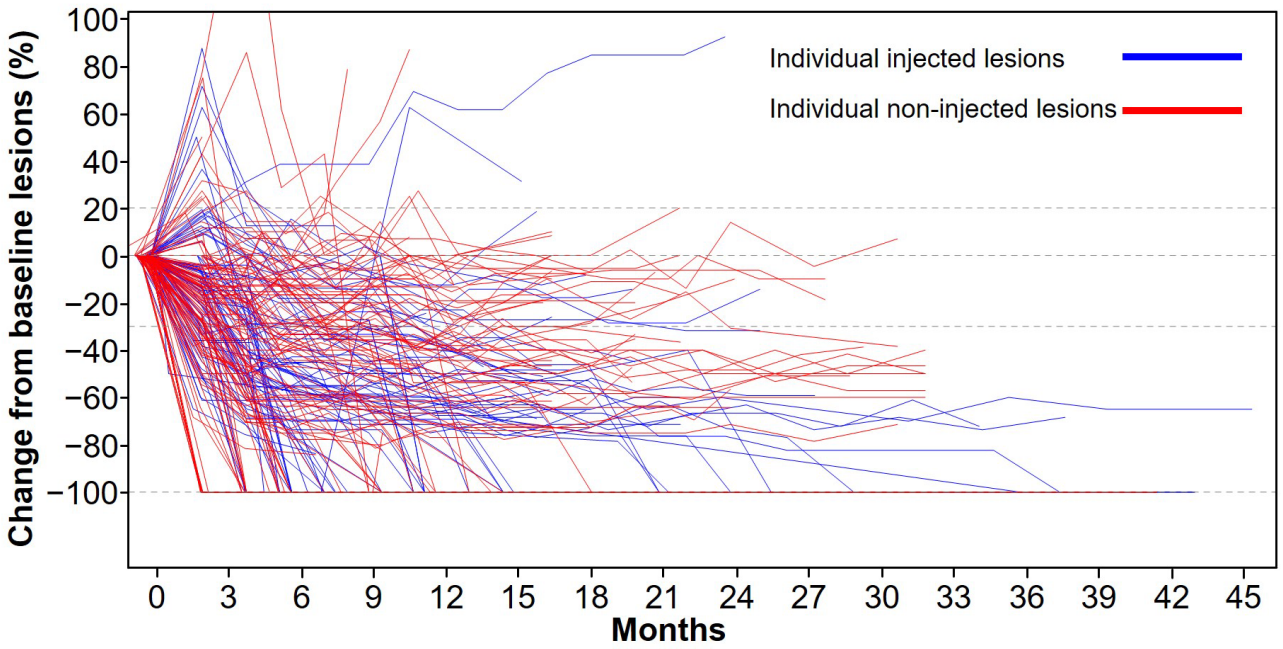
- Centrally reviewed mRECIST v1.1 responses (per protocol); all patients have ≥12 months follow-up

BOR n (%)	All patients (N = 140)	Single-agent anti–PD-1 (n = 75)	Anti–PD-1/ CTLA-4 (n = 65)	Stage IIIb–IVa (n = 72)	Stage IVb–IVd (n = 68)	Primary resistance (n = 92)	Secondary resistance (n = 48[a])	Anti–PD-1 adjuvant (n = 36)	Anti–PD-1 not adjuvant (n = 104)
CR	21 (15.0)	16 (21.3)	5 (7.7)	17 (23.6)	4 (5.9)	16 (17.4)	5 (10.4)	11 (30.6)	10 (9.6)
PR	26 (18.6)	13 (17.3)	13 (20.0)	12 (16.7)	14 (20.6)	17 (18.5)	9 (18.8)	5 (13.9)	21 (20.2)
SD	41 (29.3)	20 (26.7)	21 (32.3)	24 (33.3)	17 (25.0)	22 (23.9)	19 (39.6)	10 (27.8)	31 (29.8)
PD	43 (30.7)	24 (32.0)	19 (29.2)	18 (25.0)	25 (36.8)	31 (33.7)	12 (25.0)	9 (25.0)	34 (32.7)
ORR	**47 (33.6)**	**29 (38.7)**	**18 (27.7)**	**29 (40.3)**	**18 (26.5)**	**33 (35.9)**	**14 (29.2)**	**16 (44.4)**	**31 (29.8)**

- Consistent response rates were seen across patient subgroups, including the following:
  - **27.7% ORR** in patients who had **prior anti–PD-1 and anti–CTLA-4**
  - **35.9% ORR** in patients who had **primary resistance to anti–PD-1**

[a]Includes 1 patient with unknown resistance status.
BOR, best overall response; CR, complete response; CTLA-4, cytotoxic T-lymphocyte antigen 4; mRECIST, modified Response Evaluation Criteria in Solid Tumors; ORR, objective response rate; PD, progressive disease; PD-1, programmed cell death protein 1; PR, partial response; SD, stable disease.

Change in size of individual injected and non-injected lesions for responding patients (superficial and deep/visceral)



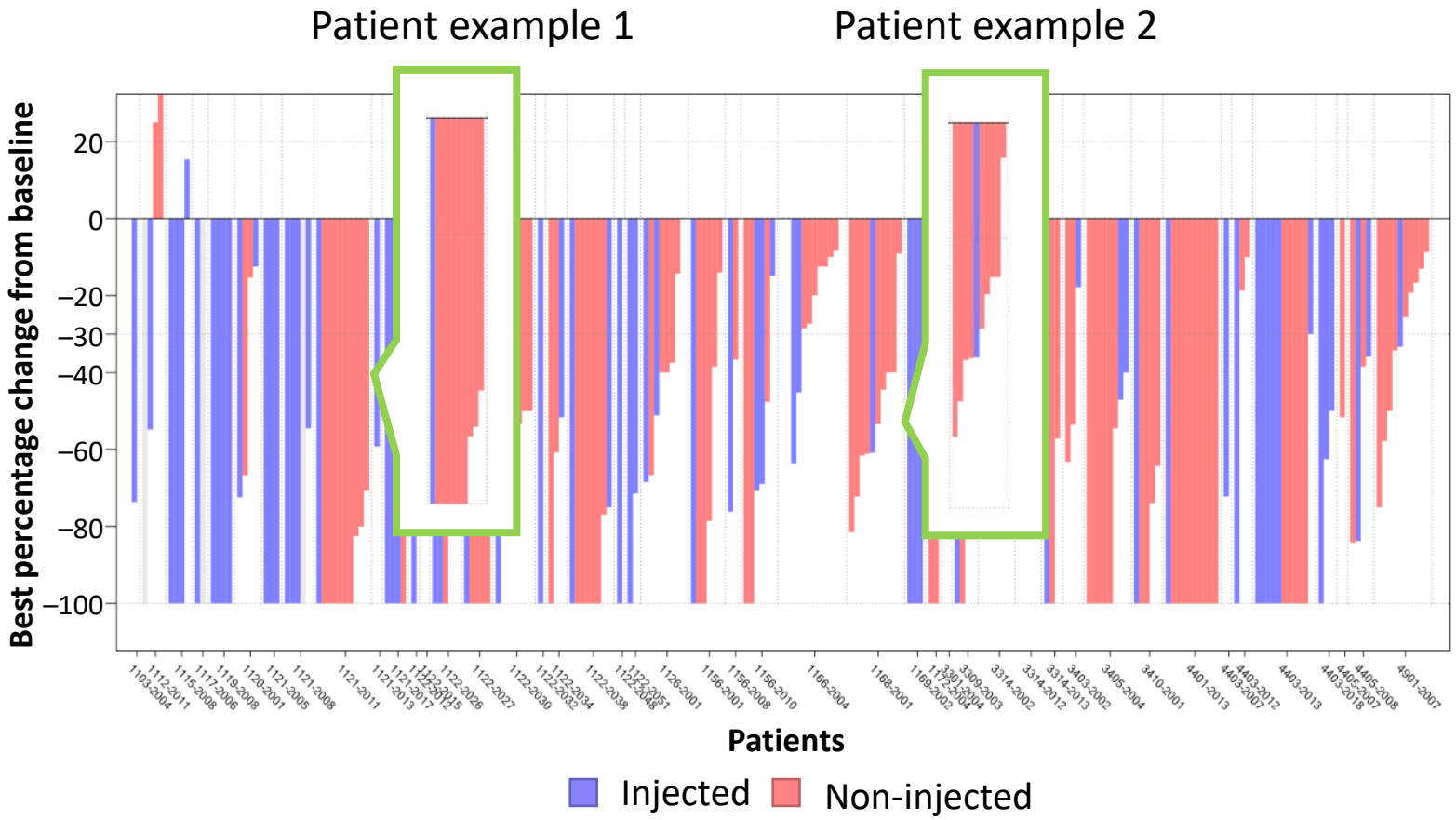
	Number (%) of measured lesions for responders (CR or PR; N = 47)	
	Injected (n = 79)	**Non-injected (n = 123)**
Number of lesions with:		
No reduction	1 (1.3)	4 (3.3)
Any reduction	78 (98.7)	119 (96.7)
Best reduction >0% to <30%	4 (5.1)	21 (17.1)
Best reduction ≥30% to <100%	**31 (39.2)**	**48 (39.0)**
Best reduction of 100%	**43 (54.4)**	**50 (40.7)**

- Injected and non-injected lesions responded with similar frequency, depth, duration, and kinetics
- **Most lesions (85%) had a reduction ≥30%**

All measurable lesions (10 max if >10 were present) measured by central review for each patient with a best response of confirmed CR or PR (excludes new lesions). Central reviewers were blinded to lesion injection status.
CR, complete response; PR, partial response.

Responses in injected and non-injected lesions

Responses observed, including visceral non-injected lesions



- Tumor reduction seen in 53 out of 60 non-injected visceral organ lesions
- Injected and non-injected lesions responded with similar frequency, depth, and duration
- Responses were not driven by injected lesions alone

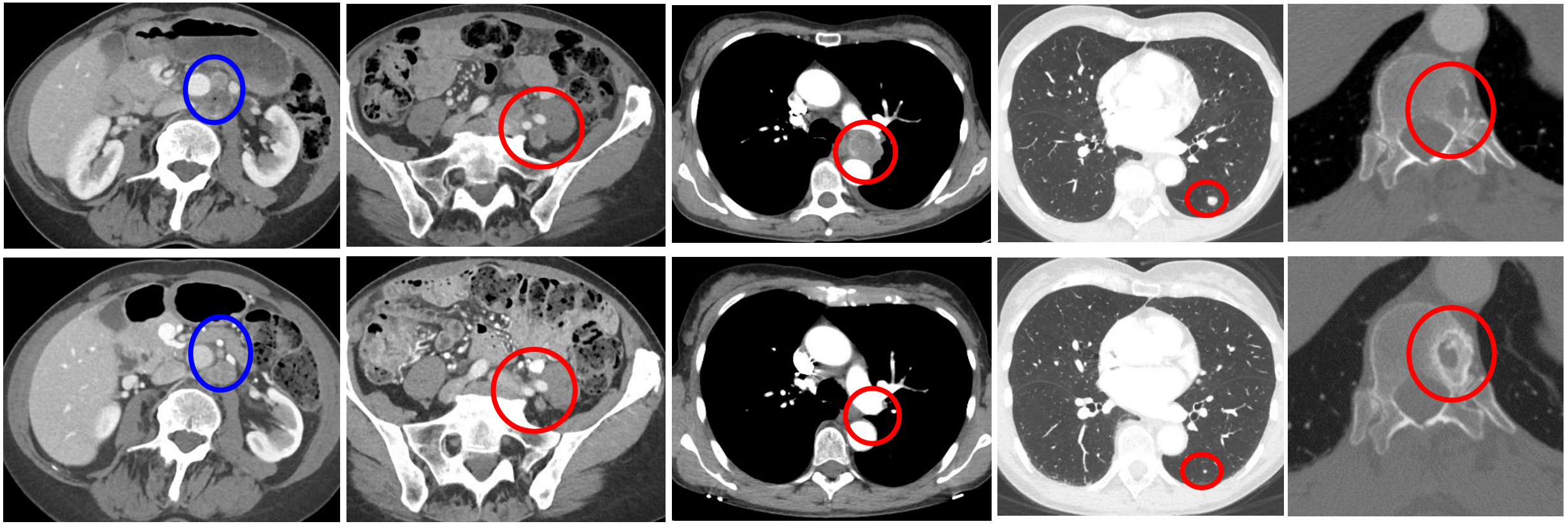
Anti-tumor effect of non-injected lesions in visceral organs of responding patients (N = 47)

Location of visceral lesions	n* (lesions)	Any Reduction	>0 to <30%	≥30% to <100%	100%
Lung	29	28 (96.6%)	7 (24.1%)	9 (31%)	12 (41.4%)
Liver	15	15 (100%)	4 (26.7%)	5 (33.3%)	6 (40%)
Adrenal	3	1 (33.3%)	0	0	1 (33.3%)
Ovary	1	1 (100%)	0	0	1 (100%)
Spleen	6	5 (83.3%)	5 (83.3%)	0	0
Pleura	2	2 (100%)	0	1 (50%)	1 (50%)
Brain	3	1 (33.3%)	1 (33.3%)	0	0
Pancreas	1	0	0	0	0
Total	**60**	**53 (88.3%)**	**17 (28.3%)**	**15 (25%)**	**21 (35%)**

- RP1 + nivolumab induced deep responses in non-injected lesions in visceral organs, including those distant from the injection site

*Includes 6 new lesions that appeared while on study

Patient example: Prior atezolizumab + cobimetinib, ipilimumab, SX-682 (CXCR inhibitor) + atezolizumab, ipilimumab + nivolumab



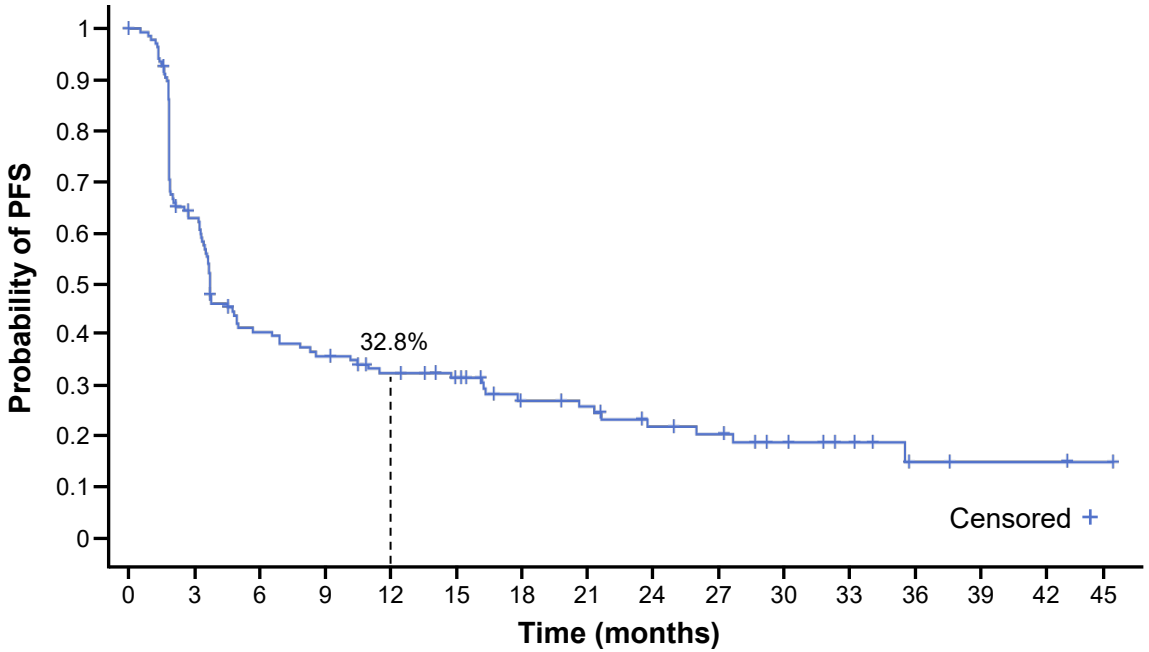
- Responses in non-injected distant and visceral tumors, including healing response in lytic bone lesions (new marginal sclerosis and internal bone formation)

Injected Non-injected

Based on measured lesions by Independent Central Review assessment.

Progression-free survival and overall survival

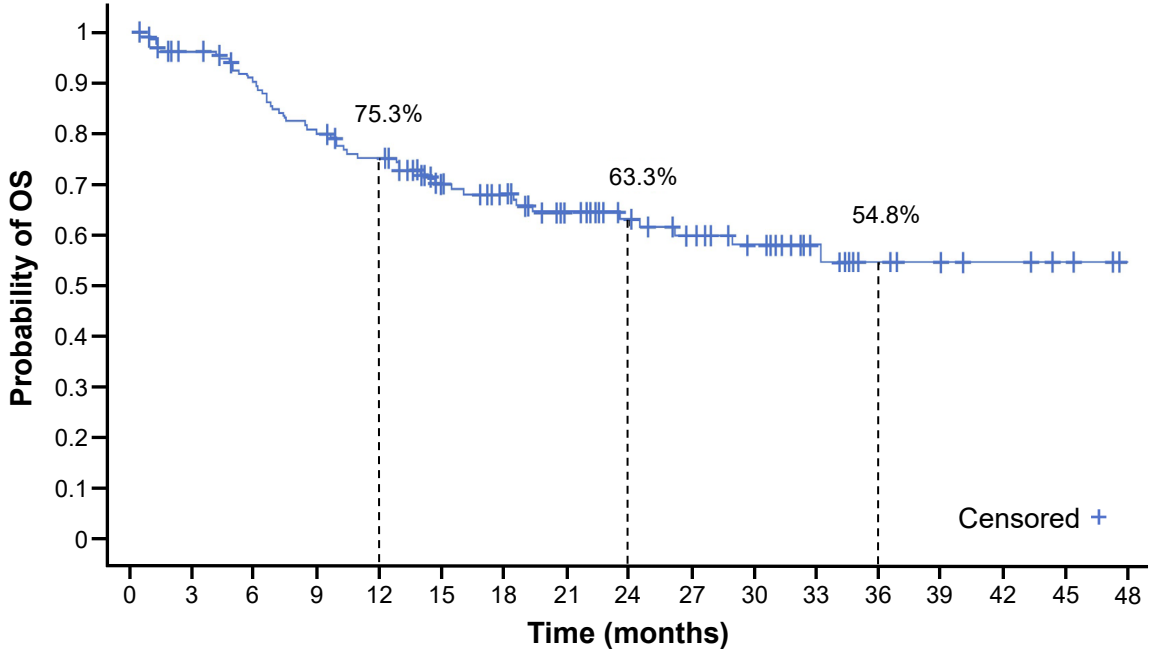
Progression-free survival



Number of patients at risk:

140	83	52	46	39	32	23	21	16	14	10	7	3	2	2	1

Overall survival



Number of patients at risk:

140	127	116	104	95	72	63	52	43	35	29	17	9	6	5	3	0

- Twelve-month PFS was 32.8%; median PFS was 3.7 months (95% CI, 3.4–5.0)
- One-, 2-, and 3-year OS rates were 75.3%, 63.3%, and 54.8%, respectively; median OS has not been reached

CI, confidence interval; PFS, progression-free survival; OS, overall survival.

Safety profile: Treatment-related AEs (N = 141)

Related to either RP1 or nivolumab

Preferred term, n (%)	TRAEs occurring in ≥5% of patients (N = 141)	
	All Grades	Grade 3–4
≥1 TRAE	**126 (89.4)**	**18 (12.8)**
Fatigue	46 (32.6)	1 (0.7)
Chills	45 (31.9)	0 (0.0)
Pyrexia	43 (30.5)	0 (0.0)
Nausea	31 (22.0)	0 (0.0)
Influenza-like illness	25 (17.7)	0 (0.0)
Injection-site pain	21 (14.9)	0 (0.0)
Diarrhea	20 (14.2)	1 (0.7)
Vomiting	19 (13.5)	0 (0.0)
Headache	18 (12.8)	0 (0.0)
Pruritus	18 (12.8)	0 (0.0)
Asthenia	14 (9.9)	1 (0.7)
Arthralgia	10 (7.1)	1 (0.7)
Decreased appetite	9 (6.4)	1 (0.7)
Myalgia	9 (6.4)	0 (0.0)
Cough	8 (5.7)	0 (0.0)
Rash	8 (5.7)	0 (0.0)
Injection-site reaction	7 (5.0)	0 (0.0)
Vitiligo	7 (5.0)	0 (0.0)

RP1 combined with nivolumab is generally well tolerated

- Predominantly grade 1 and 2 constitutional-type side effects
- Low incidence of grade 3 events (none occurring in >5% of patients); five grade 4 events in total
- No grade 5 events

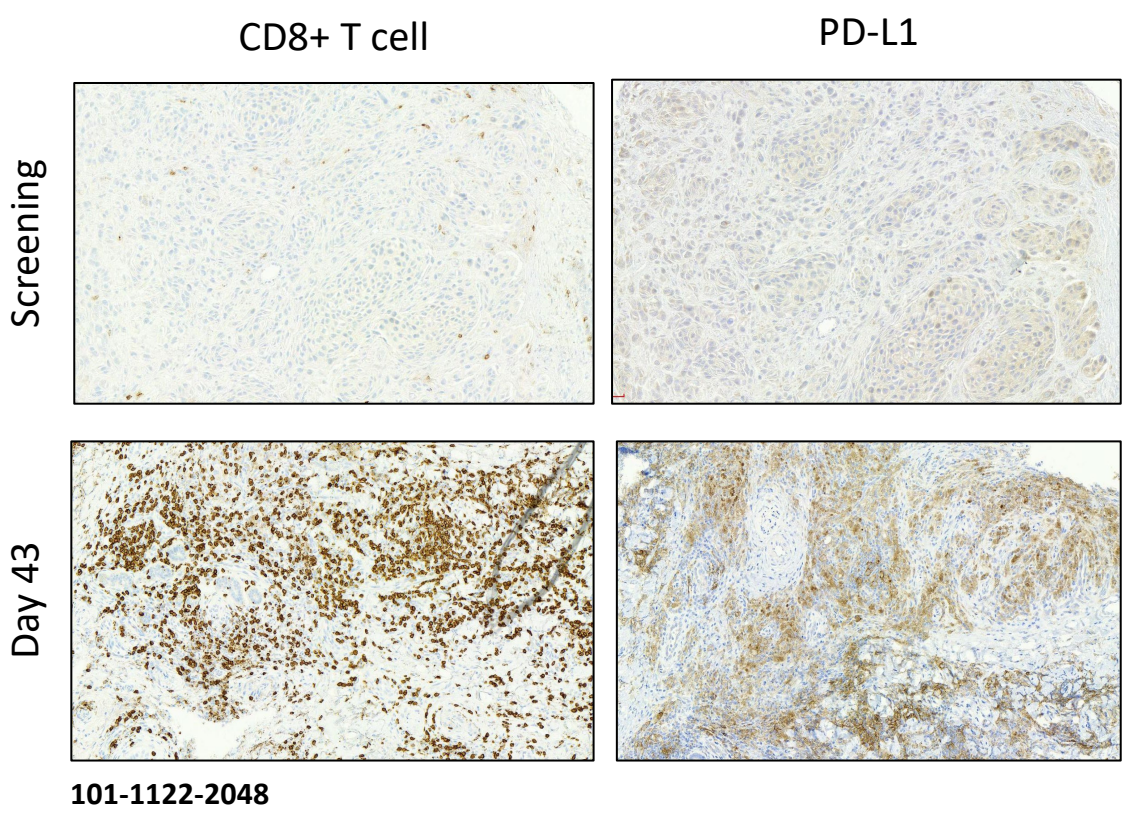
Additional grade 3/4 TRAEs (grade 4 TRAEs are italicized):

- **Two events each (1.4%):** Hypophysitis and rash maculo-papular
- **One event each (0.7%):** Abdominal pain, acute left ventricular failure, amylase increased, cancer pain, *cytokine release syndrome*, eczema, enterocolitis, extranodal marginal zone B-cell lymphoma (MALT type), *hepatic cytolysis*, hyponatremia, immune-mediated enterocolitis, infusion-related reaction, left ventricular dysfunction, *lipase increased*, memory impairment, meningitis aseptic, muscular weakness, *myocarditis*, palmar-plantar erythrodysesthesia syndrome, paresthesia, peripheral sensory neuropathy, radiculitis brachial, sinus arrhythmia, *splenic rupture*, tricuspid valve incompetence, tumor pain, type 1 diabetes mellitus

AE, adverse event; MALT, mucosa-associated lymphoid tissue; TRAE, treatment-related AE.

RP1 + nivolumab increased T-cell infiltration and PD-L1 expression

Reversal of T-cell deficiency



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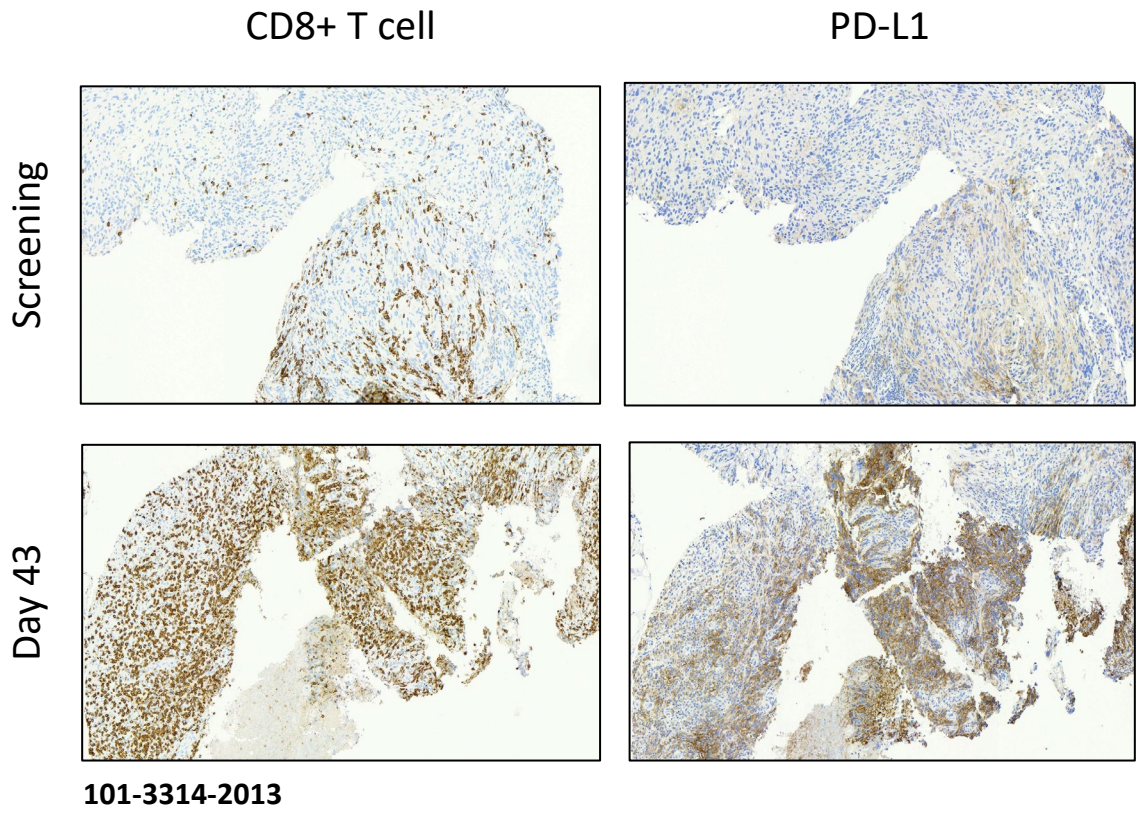
Increase of T-cell infiltration



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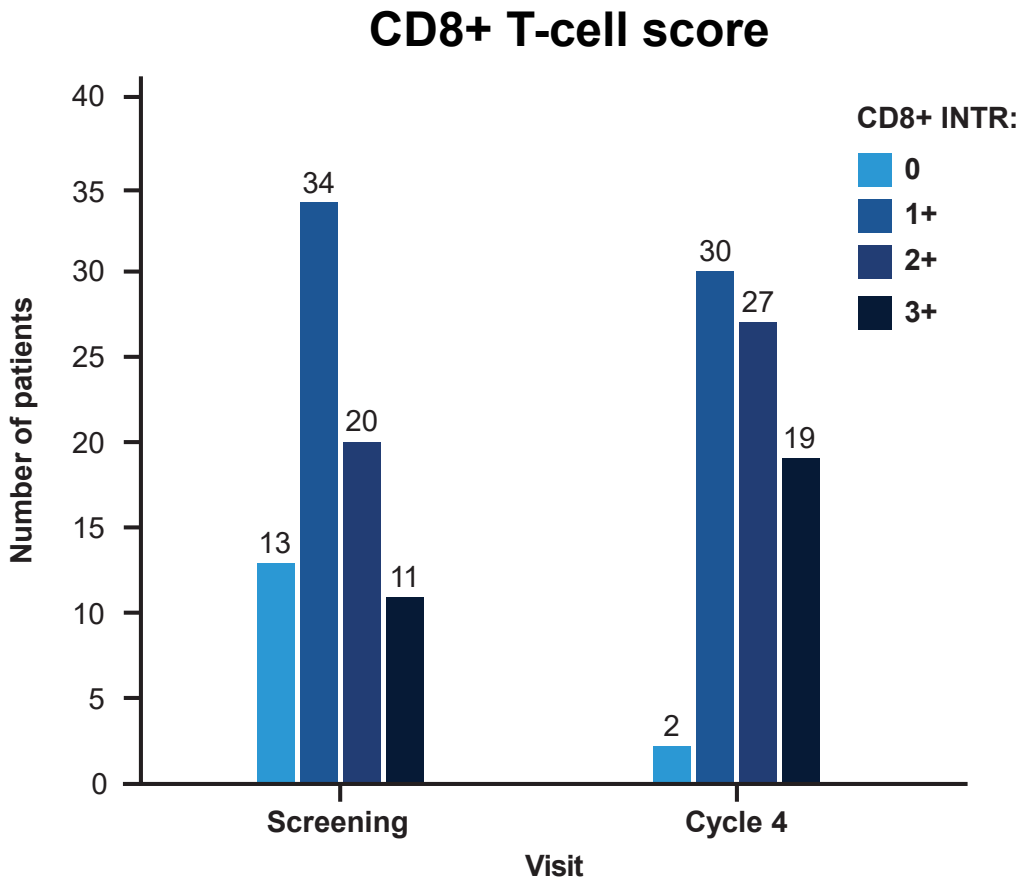
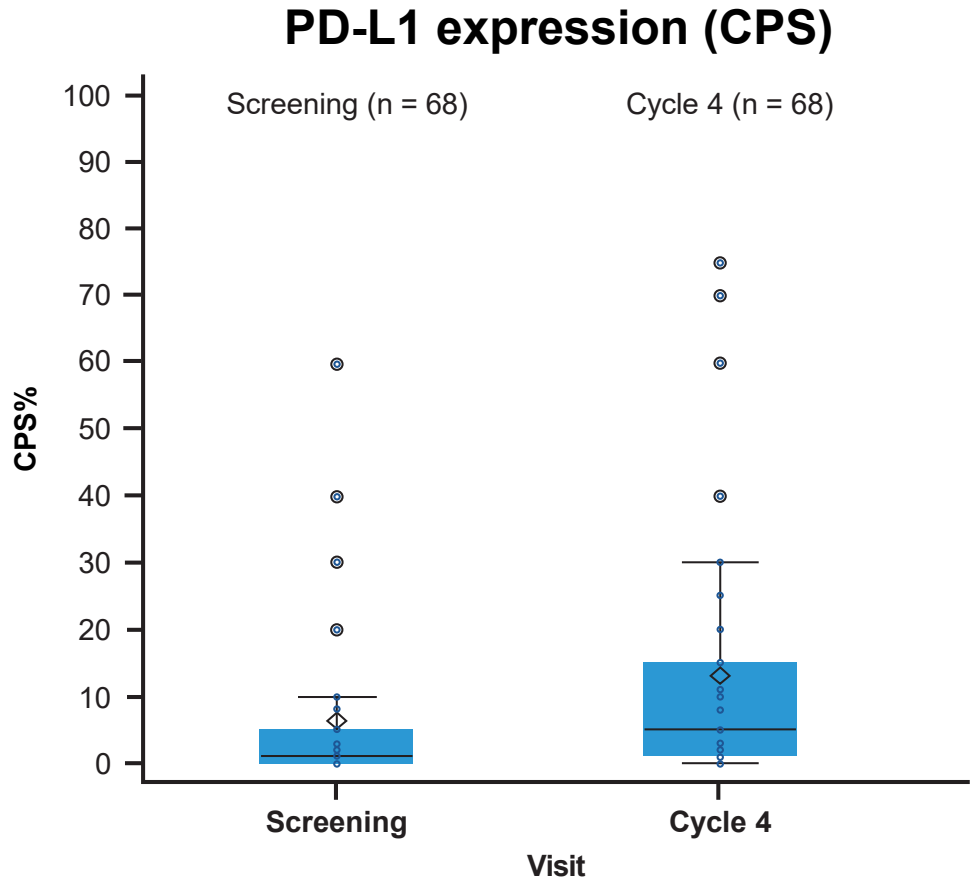
PD-L1, programmed death-ligand 1.

Increase in CD8+ T-cell infiltration and PD-L1 expression



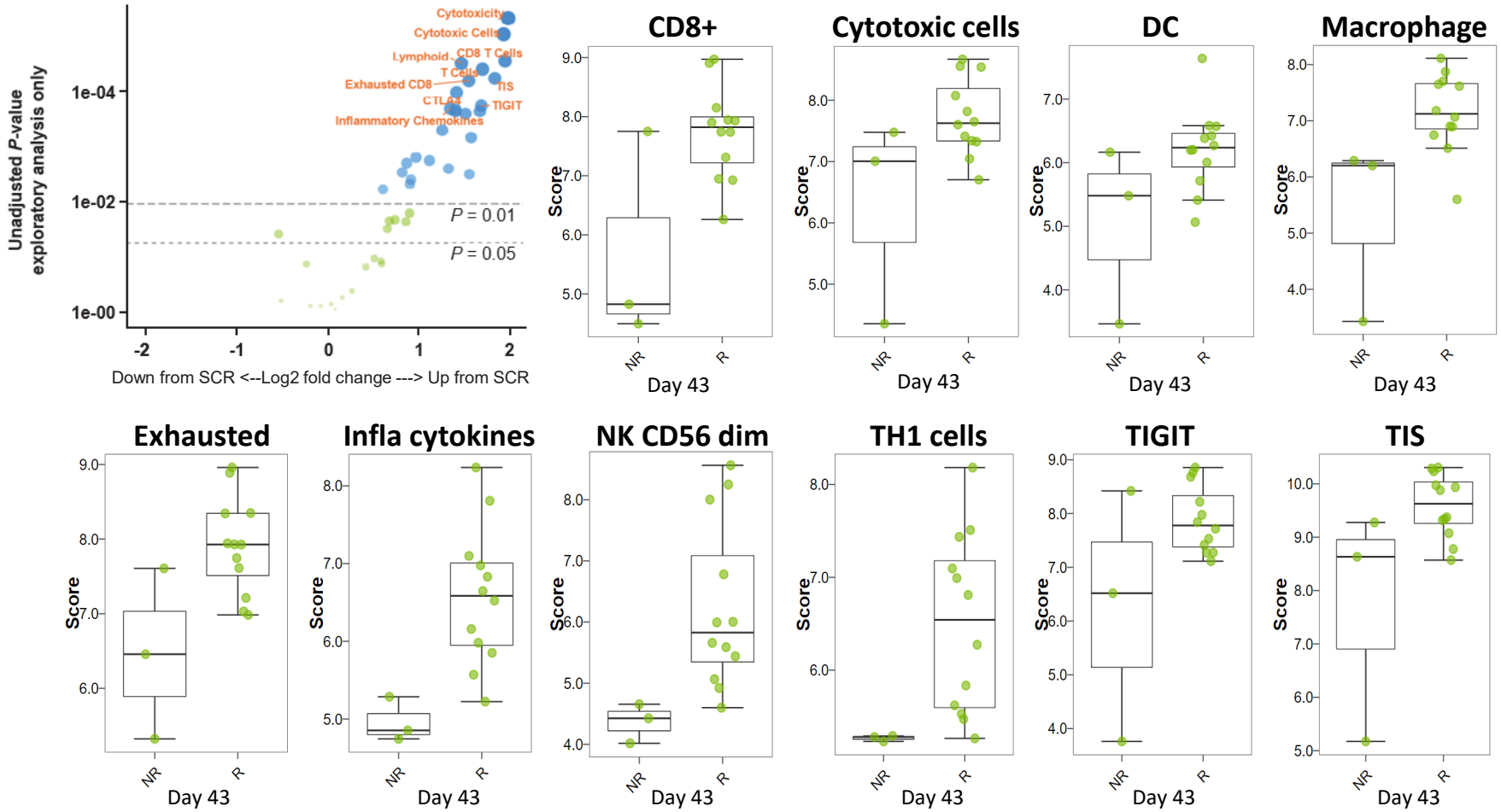


- Available tumor biopsies showed increased CD8+ T-cells score 37/78 (47%) and PD-L1 expression 39/68 (57%) at day 43 compared with baseline, demonstrating immune activation

CPS, combined positive score; PD-L1, programmed death-ligand 1.

Gene expression changes associated with immune activation*

Changes in genes from screening to day 43



NR = Non-responder

R = Responder

*Data from previous IGNYTE cohorts.

DC, dendritic cell; Infla, inflammatory; NK, natural killer cell; NR, non-responder; R, responder; SCR, screening; TH, T helper; TIGIT, T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains; TIS, tumor inflammation signature.

Conclusions

- **Efficacy**
  - RP1 combined with nivolumab after confirmed progression on anti–PD-1 therapy alone or combined with anti–CTLA-4 demonstrated a clinically meaningful rate and duration of response
    - ORR 33.6%; median DOR of 21.6 months
  - Responses occur in patients with advanced disease, including in non-injected visceral lesions
  - Clinically meaningful activity across all subgroups, including after combined anti–PD-1/CTLA-4 and in primary anti–PD-1 resistant disease
- **Survival**
  - While median OS has not yet been reached, 1- (75.3%), 2- (63.3%), and 3-year (54.8%) survival rates are promising and further demonstrate durable clinical benefit
- **Safety**
  - The safety profile was favorable, with generally transient grade 1–2 side effects
- **Biomarkers**
  - Initial biomarker data demonstrate increased CD8+ T-cell infiltration, PD-L1 expression, and interferon gene expression signature changes associated with the induction of an inflamed tumor phenotype
- **Next steps**
  - The IGNYTE-3 confirmatory phase 3 trial evaluating RP1 + nivolumab vs physician's choice in melanoma that has progressed on anti–PD-1 and anti–CTLA-4 is currently recruiting (NCT06264180)

CTLA-4, cytotoxic T-lymphocyte antigen 4; DOR, duration of response; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

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The IGNYTE study is currently recruiting patients with anti–PD-1–failed NMSC and anti–PD-1–failed MSI-H/dMMR solid tumors. To learn more about enrolling your patient, contact clinicaltrials@replimune.com or +1 (781) 222 9570.

Additional information can be obtained by visiting Clinicaltrials.gov (NCT03767348).