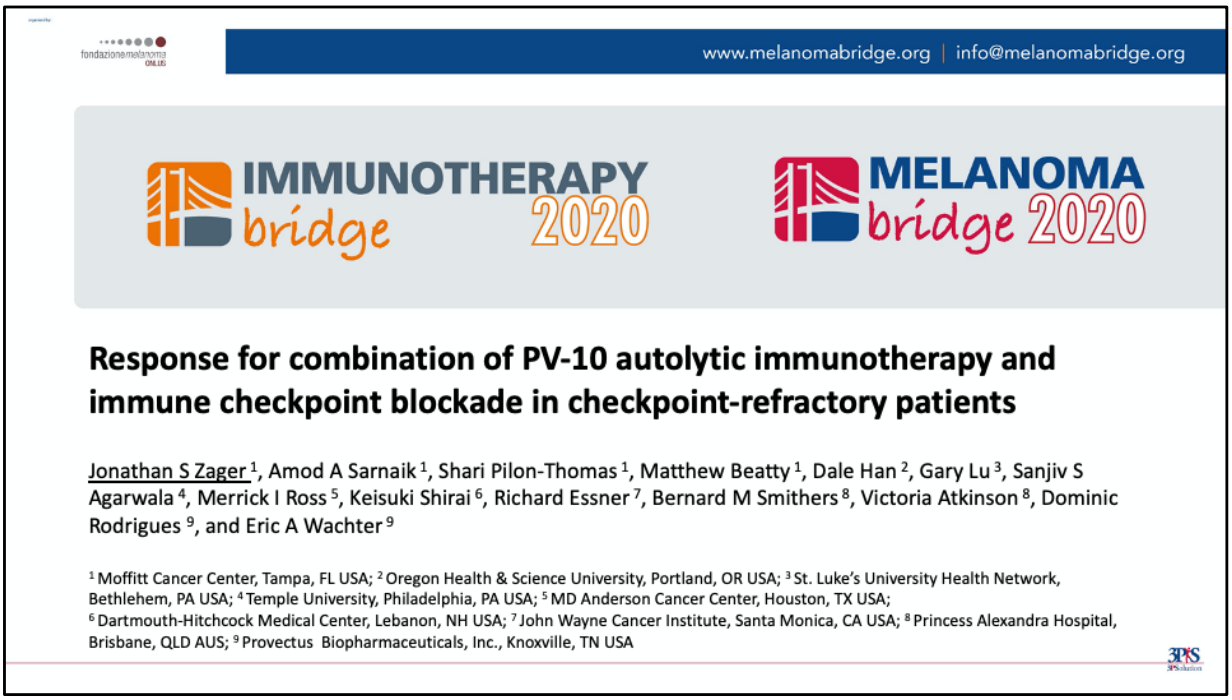


Hi, I'm Jonathan Zager of Moffitt Cancer Center, and it's my pleasure to present this overview of preliminary safety and efficacy data on the combination of PV-10 and pembrolizumab in checkpoint-refractory melanoma.

Disclosures

- Funding for this research was provided by Provectus Biopharmaceuticals, Inc.

Here are my disclosures.

Background

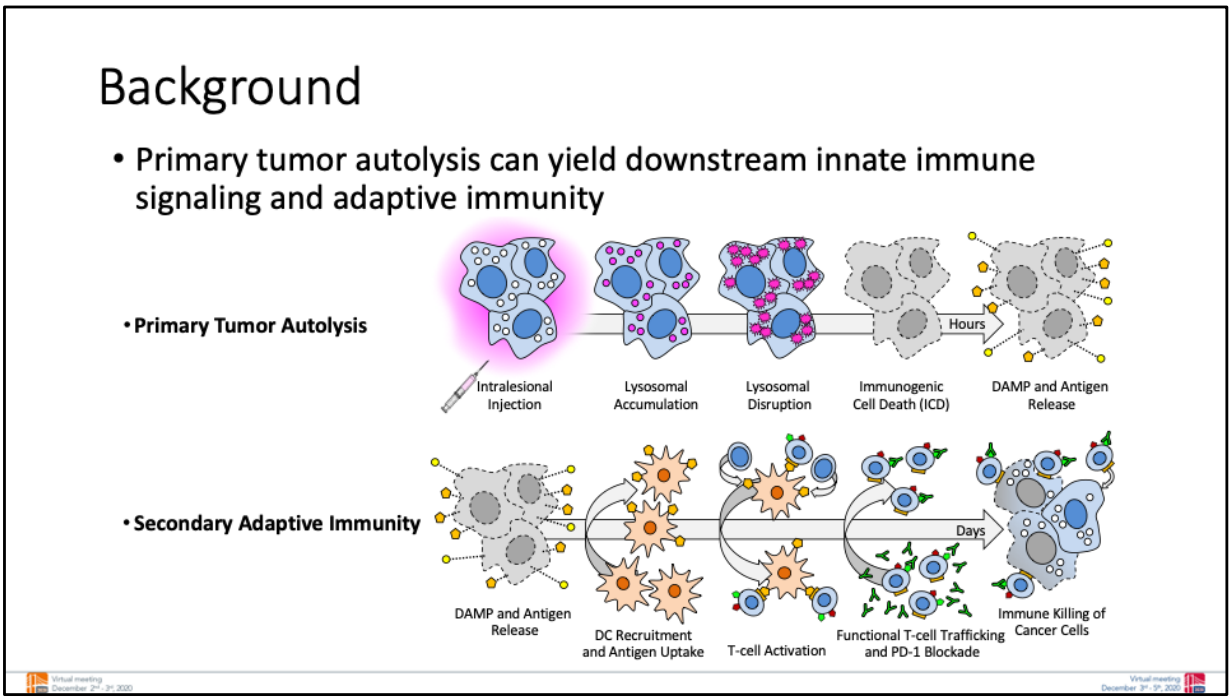
- PV-10 is an injectable formulation of rose bengal disodium, a small molecule autolytic immunotherapy, in development for solid tumors
- Intralesional (IL) injection can yield immunogenic cell death (ICD) and tumor-specific reactivity in circulating T cells [1-4].
- PV-10 is currently the subject of a Phase 1b/2 study in combination with immune checkpoint blockade (CB) in patients with advanced cutaneous melanoma (NCT02557321).

1. Wachter et al. SPIE 2002. 2. Liu et al. Oncotarget 2016. 3. Qin et al. Cell Death and Disease 2017. 4. Liu et al. PLoS One 2018.

PV-10 is a small molecule autolytic immunotherapy that has been administered to over 450 patients with cancers of the skin and of the liver, the majority having cutaneous melanoma. It's administered intralesionally under visual, palpation or ultrasound guidance to superficial malignancies, and under CT or ultrasound guidance to tumors of the liver. In the present work, PV-10 was administered to tumors located at cutaneous, subcutaneous, soft tissue and nodal sites; it was not administered to any visceral sites.

In the main cohort of the study, 21 patients naïve to checkpoint blockade received PV-10 and systemic pembrolizumab.

This presentation will focus on preliminary results of an expansion cohort, EC1, of patients refractory to prior checkpoint blockade who received PV-10 and pembrolizumab combination therapy.

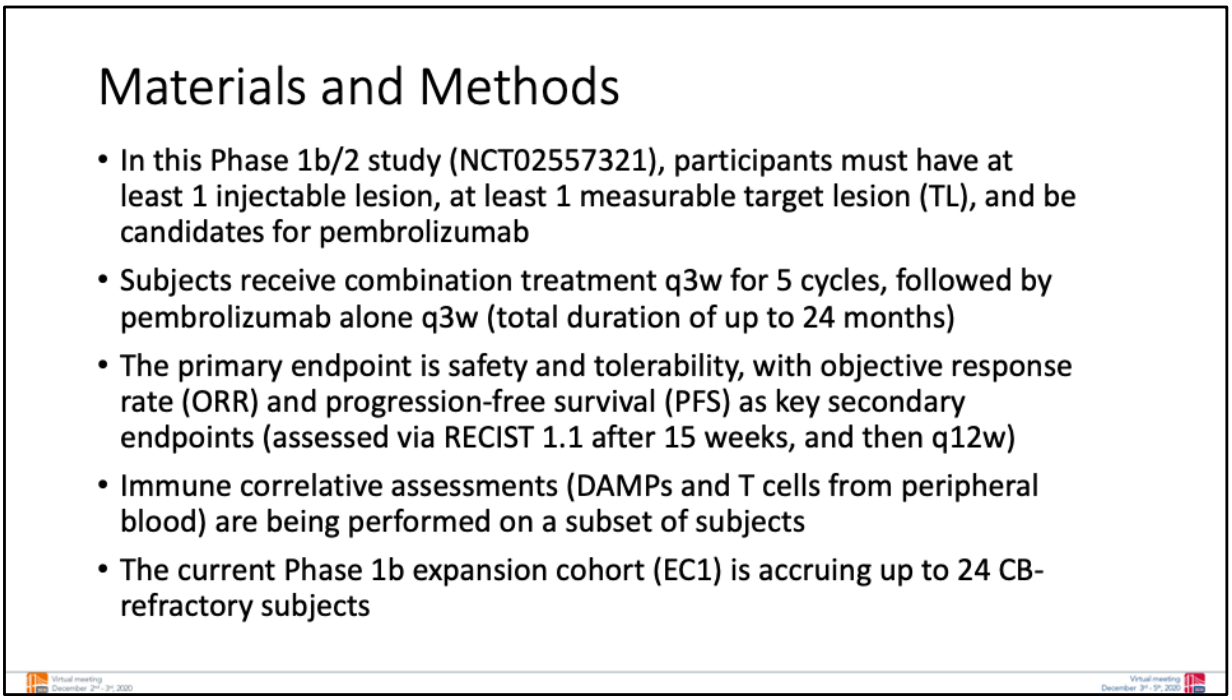


Injection of PV-10 into tumor tissue leads to rapid accumulation within tumor lysosomes, destabilizing these lysosomes and triggering lysosomal disruption and immunogenic cell death. This process can occur within hours of tumor injection.

ICD causes release of damage-associated molecular pattern molecules and tumor antigens that can lead to downstream adaptive immunity via dendritic cell recruitment and antigen uptake; presentation of these antigens to immature T cells can serve to educate and activate these T cells, leading to their maturation into functional T cells, primarily CD8 cytotoxic T cells, but also CD4 and NKT cells. Initiation of this adaptive immunity can occur within the first week following tumor injection.

Anti-tumor activity of these T cells may be enhanced by blockade of the PD-1 and/or CTLA-4 regulatory pathways.

The present study is assessing whether immune activation via PV-10-induced ICD can overcome acquired resistance to checkpoint blockade in checkpoint-refractory melanoma patients.

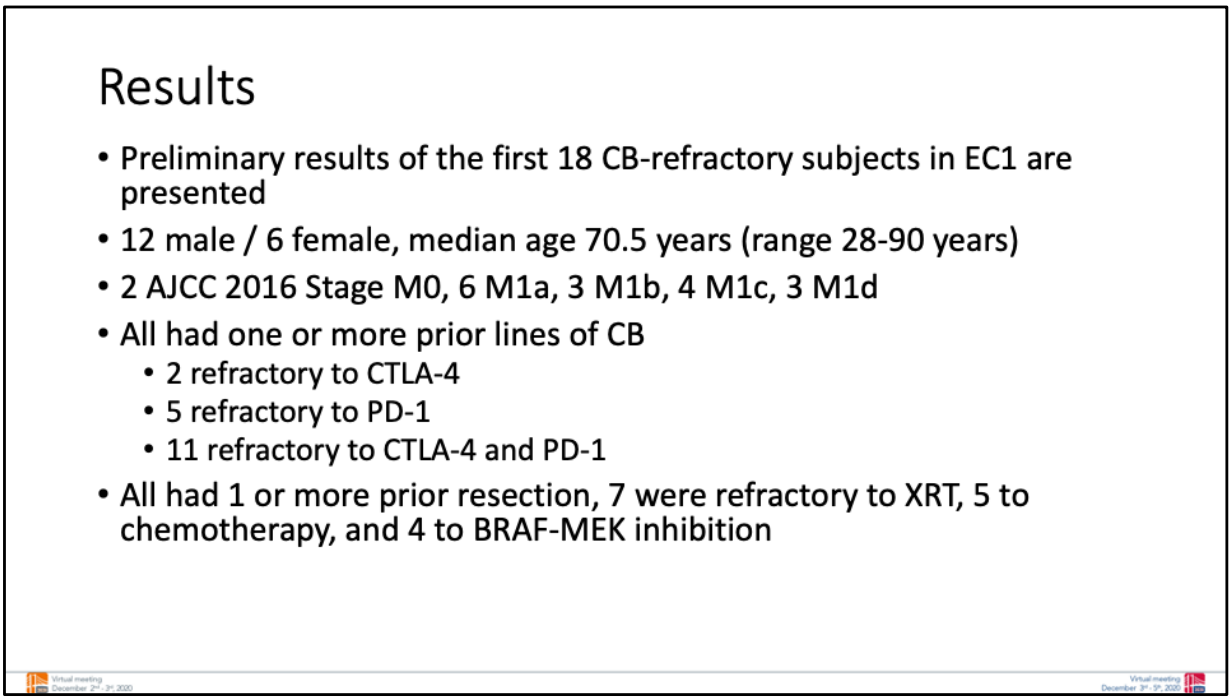


In this study, participants must have at least 1 injectable lesion, at least 1 measurable target lesion, and be candidates for pembrolizumab.

Subjects receive combination treatment q3w for 5 cycles, followed by pembro alone q3w for a total duration of up to 24 months. As understanding of this investigational combination has emerged, this PV-10 dosing schedule has been expanded to allow for additional cycles of PV-10 beyond the 5th cycle for patients with additional injectable disease.

The primary endpoint is safety, with objective response rate and progression-free survival as key secondary endpoints; efficacy is assessed via RECIST 1.1 starting after 15 weeks, and then q12w thereafter.

Immune correlative assessments are being performed on a subset of subjects.



Preliminary results of the first 18 checkpoint-refractory subjects enrolled in expansion cohort 1 are presented.

Baseline disease burden ranged from Stage M0 to M1d, with the majority of subjects having active visceral disease.

All subjects were refractory to one or more prior lines of checkpoint blockade, with 11 refractory to CTLA-4 and PD-1.

All subjects had 1 or more prior resection, and most were refractory to one or more additional line of therapy in addition to checkpoint blockade.

Safety

- Adverse Events (AEs) were consistent with established patterns for each drug:
  - Injection site reactions attributed to PV-10
  - Immune-mediated reactions attributed to pembrolizumab
  - No significant overlap or unexpected toxicities
- This profile is similar to CB-naïve patients in the main cohort of the study [5]

5. Agarwala et al. ESMO 2020.

Treatment-Emergent Adverse Events (TEAEs) Occurring in >1 Subject, or Any Grade 3 or Higher (Phase 1b CB-Refractory Safety Population, N = 18)	TEAEs Related to PV-10		TEAEs Related to Pembrolizumab		TEAEs Related to Combination	
	All	≥ G3	All	≥ G3	All	≥ G3
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS						
Injection site pain	11	*1*	–	–	–	–
Injection site oedema	8	–	–	–	–	–
Injection site erythema	6	–	–	–	–	–
Injection site pruritus	6	–	–	–	–	–
Injection site discharge	5	–	–	–	–	–
Injection site vesicles	3	–	–	–	–	–
Injection site photosensitivity reaction	2	–	–	–	–	–
Injection site ulcer	2	–	–	–	–	–
Fatigue	–	–	8	–	–	–
EYE DISORDERS						
Periorbital oedema	1	*1*	–	–	–	–
Vision blurred	–	–	1	–	1	–
SKIN AND SUBCUTANEOUS TISSUE DISORDERS						
Rash maculo-papular	–	–	3	–	–	–
Pruritus	–	–	1	–	1	–
METABOLISM AND NUTRITION DISORDERS						
Decreased appetite	–	–	2	–	–	–
Hyperglycaemia	–	–	2	–	–	–
IMMUNE SYSTEM DISORDERS						
Myasthenia gravis	–	–	1	*1*	–	–
GASTROINTESTINAL DISORDERS						
Constipation	–	–	3	–	–	–
Vomiting	–	–	3	–	–	–
Diarrhoea	–	–	2	–	–	–
Nausea	–	–	2	–	–	–
INVESTIGATIONS						
Alanine aminotransferase increased	–	–	2	*1*	–	–
Aspartate aminotransferase increased	–	–	2	*1*	–	–
Lymphocyte count decreased	–	–	2	–	–	–
Lipase increased	–	–	1	*1*	–	–

All subjects receiving at least one dose of study medication are included in the safety population.

Treatment-Emergent Adverse Events in this population were consistent with established patterns for each drug, principally Grade 1-2 injection site reactions attributed to PV-10, and Grade 1-3 immune-mediated reactions attributed to pembrolizumab, with no significant overlap or unexpected toxicities.

All AEs deemed at least possibly related to PV-10 were Grade 1 or 2 except for single subjects experiencing Grade 3 periorbital oedema and Grade 3 injection site pain.

Grade 3 or higher AEs deemed at least possibly related to pembrolizumab were single subjects experiencing Grade 3 alanine aminotransferase increase; Grade 3 aspartate aminotransferase increase; Grade 4 lipase increase; and Grade 5 myasthenia gravis.

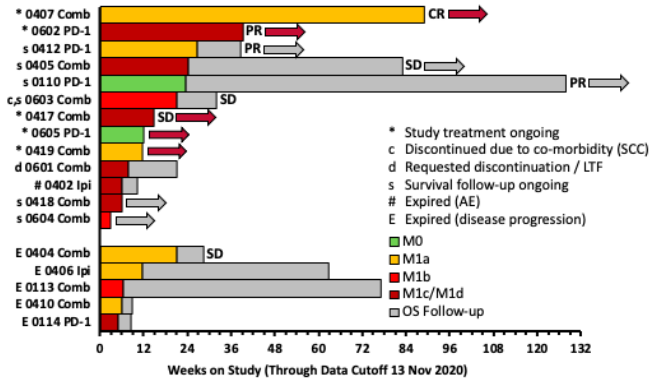
All AEs deemed at least possibly related to the combination were Grade 1 or 2.

Outcome

- As of the data cutoff of 13 Nov 2020, 14 subjects were evaluable for overall response by RECIST 1.1:

BOR by RECIST 1.1 (EC1 Evaluable Population)	All Participants (N = 14)	Prior PD-1 (N = 4)	Prior CTLA-4 (N = 1)	Prior CTLA-4 + PD-1 (N = 9)
Complete Response (CR)	1 (7%)	0	0	1
Partial Response (PR)	3 (21%)	3	0	0
Stable Disease (SD)	4 (29%)	0	0	4
Progressive Disease (PD)	6 (36%)	1	1	4
ORR (CR + PR)	4 (29%)	3	0	1
DCR (CR + PR + SD)†	8 (57%)	3	0	5

- As of the data cutoff date, 28% of all enrolled subjects had expired from melanoma



† Disease control rate (DCR) = CR + PR + SD

As of the data cutoff, 14 subjects were evaluable for overall response; of the remaining subjects enrolled, two had not yet reached initial response assessment; one requested discontinuation of active study participation prior to initial response assessment; and one withdrew prior to initial response assessment due to an AE, myasthenia gravis.

Four of the 14 evaluable subjects achieved an overall objective response, including 1 durable complete response, for an objective response rate of 29%. An additional 4 subjects achieved stable disease, for a disease control rate of 57%. Although the number of subjects is small when subdivided by prior treatment, these preliminary data suggest that subjects refractory to PD-1 fared well, as did subjects refractory to both CTLA-4 and PD-1.

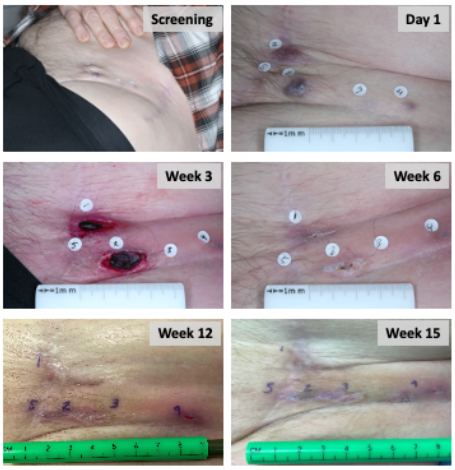
Outcome and temporal landmarks are shown in the swimmers plot, which is color coded by disease stage. Red arrows denote response follow-up is ongoing; grey arrows denote that survival follow-up is ongoing; and grey bars denote duration of survival follow-up. Checkpoint history is also coded for each subject using a suffix after each subject number. There was no obvious correlation between outcome and disease stage; however, responses were observed in subjects with M0 to M1d

disease.

Five of the 18 enrolled subjects, shown at the bottom of the swimmers plot, have expired from disease progression.

Response of PV-10-Injected Lesions

- The 14 RECIST-evaluable subjects (as of the data cutoff) had:
  - 33 Target lesions
  - 16 injected Target lesions
  - Injected Target lesions achieved 38% CR, 50% ORR and 69% DCR
  - Response in injected lesions consistent with that observed in CB-naïve patients [5]

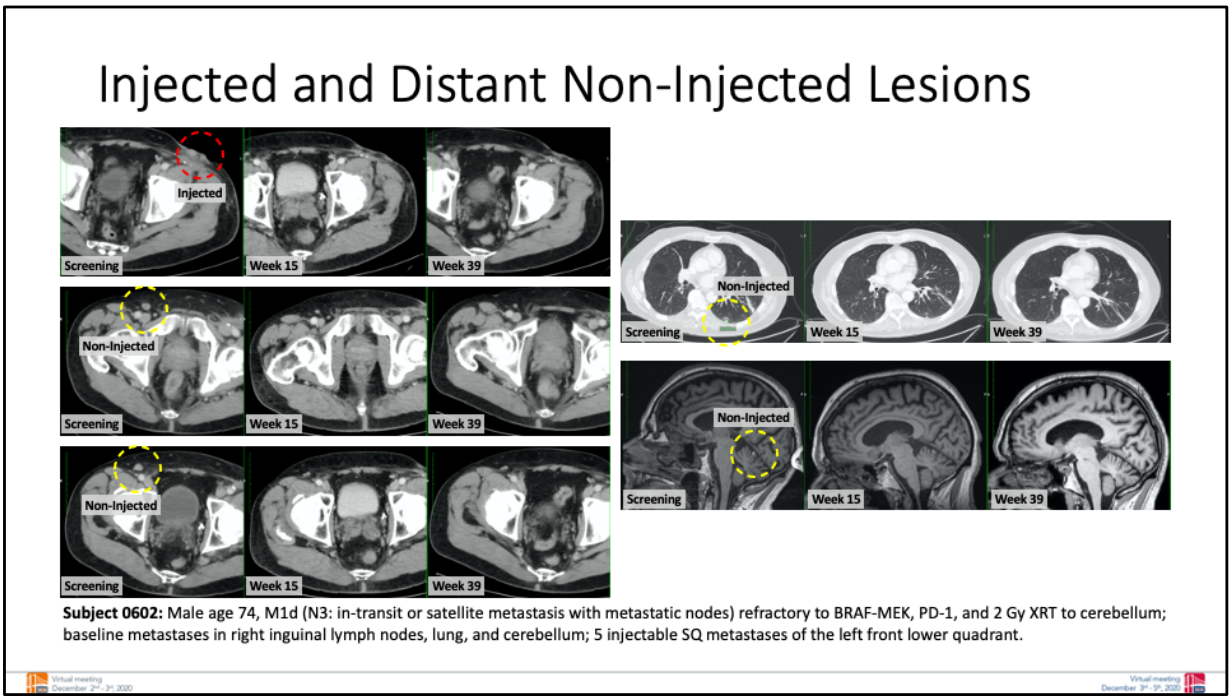


5. Agarwala et al. ESMO 2020: 75% CR, 79% ORR and 86% DCR of injected lesions.

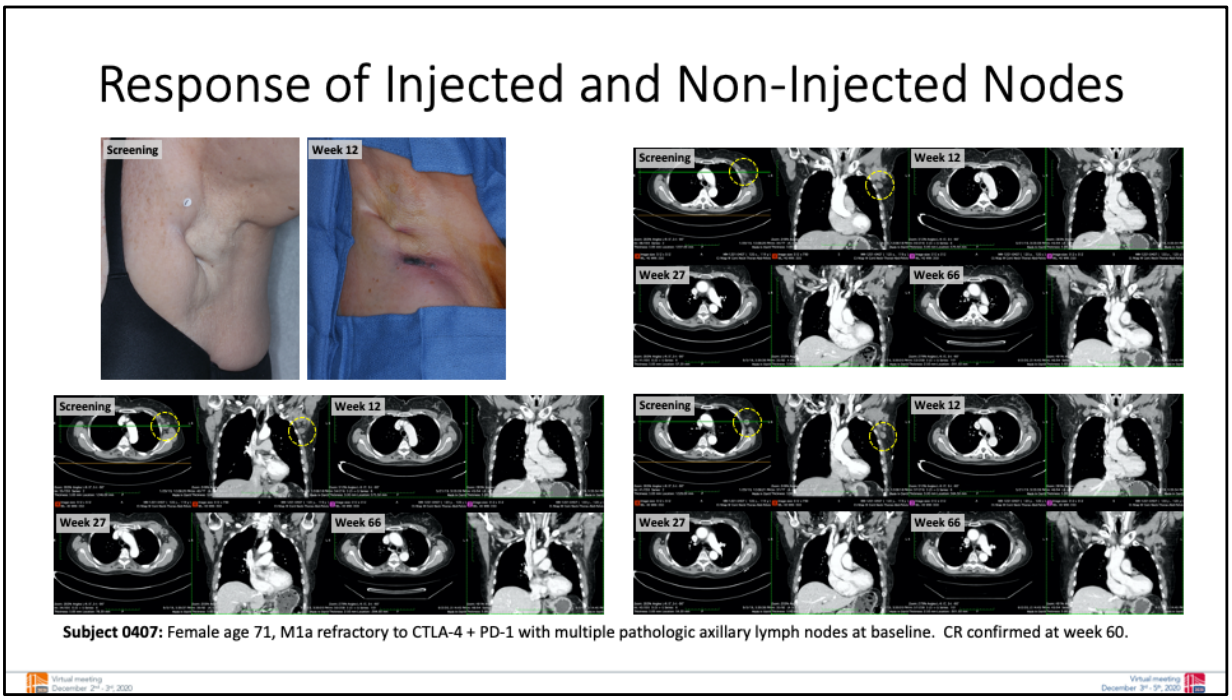
Subject 0602: Male age 74, M1d (N3: in-transit or satellite metastasis with metastatic nodes) refractory to BRAF-MEK, PD-1, and 2 Gy XRT to cerebellum; baseline metastases in right inguinal lymph nodes, lung, and cerebellum. Five injectable SQ metastases of the left front lower quadrant received PV-10.

The 14 evaluable subjects had 33 target lesions designated for RECIST assessment. Sixteen of these target lesions were injected with PV-10, achieving complete response in 38% of injected lesions, and an objective response in 50% of lesions. This response is consistent with that observed in checkpoint-naïve subjects in the main cohort of the study, where a complete response was observed in 75% of injected lesions.

An example of injected lesion response is evident in Subject 602, a 74 year old male with M1d disease. He received 9 cycles of PV-10 to 5 injectable subcutaneous lesions of the left lower quadrant over a period of 5 months. No other lesions were injected. He exhibited typical evidence of local response of his injected lesions at week 3, including eschar of the most superficial lesions, with partial response at week 15 and complete response of his injected lesions at his next response assessment at week 27.



In addition to complete response of his injected subcutaneous lesions, shown in the upper left panel, Subject 602 achieved an overall RECIST PR as of the data cutoff date. This included full regression of non-injected pathological inguinal lymph nodes in his right quadrant; full regression of his pulmonary metastases; and partial regression of his two metastases of the cerebellum.



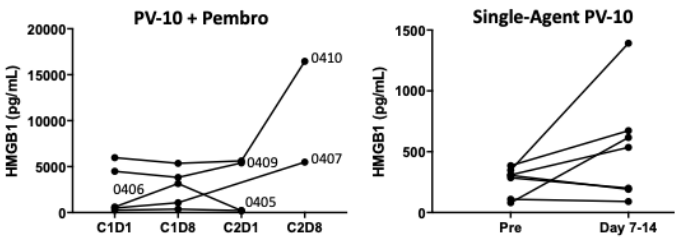
Response of injected and non-injected lesions is further illustrated by another checkpoint-refractory subject. Three years after excision of the primary in her forearm followed by ipi-nivo and further nivolumab, Subject 407 had axillary involvement that included 1.9 to 2.2 cm pathologic nodes at baseline.

Regression of her injected and non-injected nodal lesions was observed, with 14 total injections given in 9 cycles of PV-10 over a 6 month period.

Complete response was confirmed by PET-CT at week 60.

Immune Correlative Assessments: DAMPs

- Five subjects in EC1 have completed immune correlative assessment
- The DAMP HMGB1 exhibited changes comparable to that observed in CB-naïve subjects following treatment with single-agent PV-10



- CB-refractory Subjects 0406 and 0407 exhibited marked elevation of HMGB1 one week after their 1st cycle of PV-10 + pembro
- HMGB1 continued to increase for 0407 after the 2nd cycle (reaching 11.1x baseline a week after the second cycle at C2D8)
- CB-naïve melanoma subjects treated with single agent PV-10 showed similar elevation 7-14 days after PV-10 treatment (data adapted from [2])
- Pattern of DAMP release may be characteristic of treatment success and tumor histology [6]

2. Liu et al. Oncotarget 2016. 6. Innamrtato et al. SITC 2020.

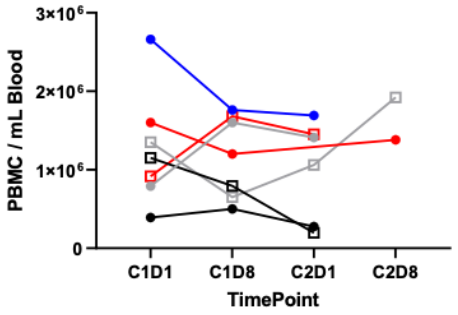
Correlative assessments have been completed on five checkpoint-refractory study participants, probing for possible changes in DAMPs and T cells in peripheral blood indicative of innate and adaptive immune signaling, respectively. Changes in these biomarkers were noted in an earlier study of PV-10 in the single-agent setting, and in the present group of refractory subjects comparable changes appear to occur in high-mobility group box 1, a DAMP that has also been observed in animal models of melanoma.

Of particular note among this refractory group, Subject 407 exhibited increased HMGB1 one week after initiation of study treatment, which increased further after her second treatment cycle; this preceded ultimate attainment of a durable CR.

Similar changes were noted in several other DAMPs examined, including S100A9 and HSP90a. Release of multiple DAMPs following administration of PV-10 in murine models of pancreatic adenocarcinoma was reported by the Pilon-Thomas laboratory last month at SITC 2020, and the specific pattern of DAMP release may be characteristic of successful treatment for a given tumor histology.

Immune Correlative Assessments: PBMCs

- PBMCs isolated from peripheral blood exhibited no clear trend in absolute counts during the first two treatment cycles



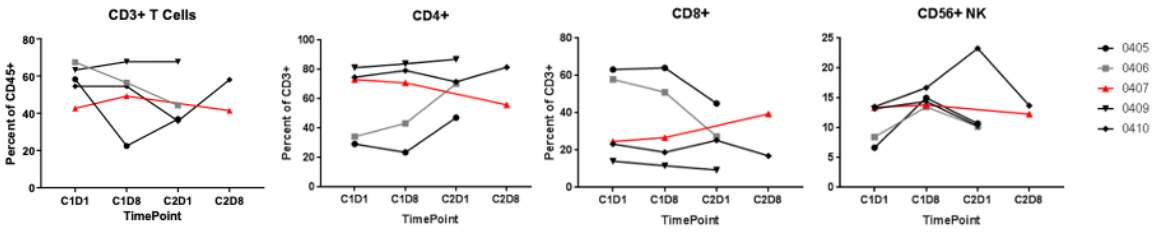
0405 : M1c (refractory to CTLA-4+PD-1, achieved SD)
0406 : M1a (refractory to PD-1, achieved PD)
0407 : M1a (refractory to CTLA-4+PD-1, achieved durable CR)
0409 : IIIB (CB-naïve enrolled to EC2, achieved durable CR)
0410 : M1a (refractory to CTLA-4+PD-1, achieved PD)
0411 : IIIB (CB-naïve enrolled to EC2, achieved durable CR)
0412 : IIIC (refractory to PD-1, achieved PR)

Subjects 0409 and 0411 (Stage III CB-naïve) enrolled to Expansion Cohort 2 (EC2) of the study
C1D1 = start of PV-10 + pembro study treatment / first treatment cycle
C1D8 = 1 wk after start of first treatment cycle
C2D1 = 3 wks after start of study treatment / start of second treatment cycle
C2D8 = 1 wk after start of second treatment cycle

Gross changes in levels of peripheral blood mononuclear cells showed no clear trend following initiation of study treatment. This is consistent with single-agent experience and neither PV-10 nor pembrolizumab are expected to directly affect total PBMCs.

Immune Correlative Assessments: T Cells

- PBMCs also exhibited no clear trend in T cell populations
- Increases in CD8+, CD4+ and NKT cell levels have been observed within one week of initiation of single-agent PV-10 [2]

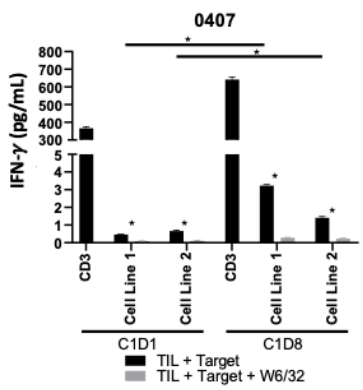


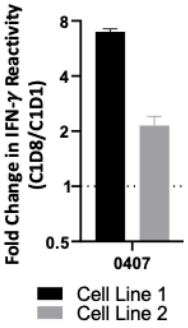
2. Liu et al. Oncotarget 2016.

There were also no clear changes in absolute levels of specific T cell populations, such as CD3, CD4, CD8 or NK T cells. This differs from changes observed when PV-10 is used in the single-agent setting, where increases in absolute levels of CD8, CD4 and NKT cells have been observed within 7-14 days of initiation of PV-10. However, any impact, or lack thereof, on PBMC levels when PV-10 and PD-1 are commenced concurrently remains to be confirmed once a larger number of patients are surveyed.

Immune Correlative Assessments: Reactivity

- IFN-γ expression in T cells demonstrates tumor-specific reactivity

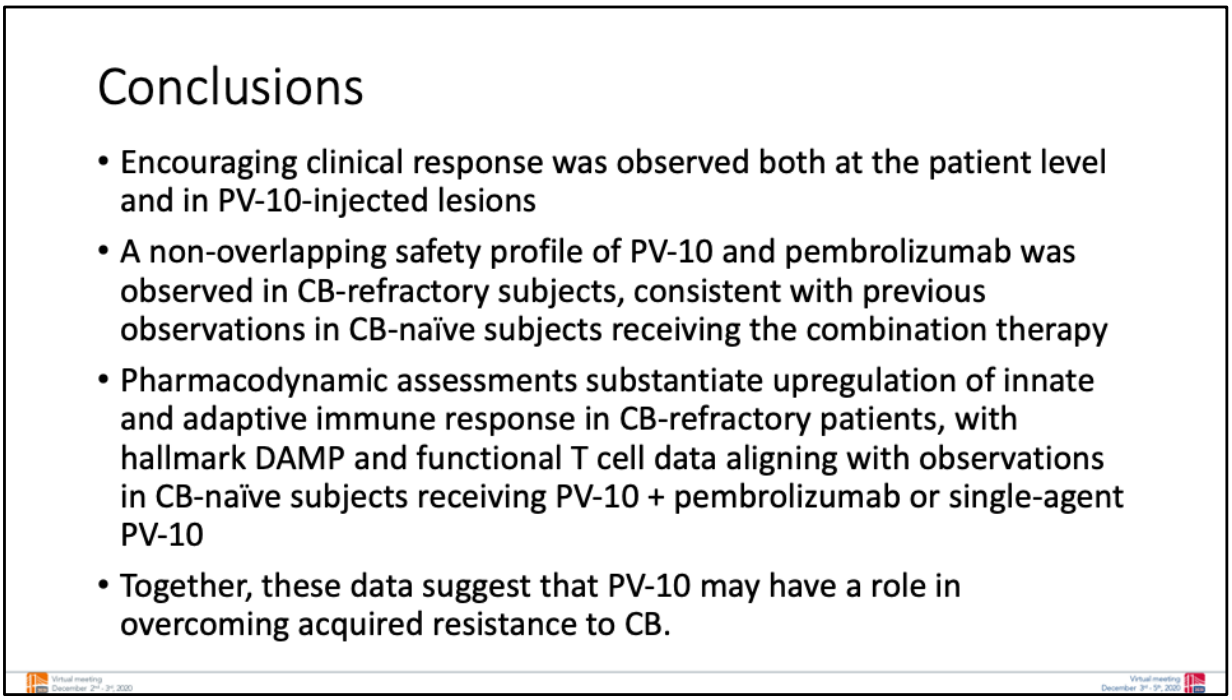




- CD8+ T cells were purified from isolated PBMCs and co-cultured with HLA-matched melanoma cell lines for 24 hrs
- MHC class I specific reactivity was verified by including an MHC-I blocking antibody (W6/32) to abrogate T cell activity
- Subject 0407 exhibited significant reactivity after 1st cycle of study treatment consistent with clinical outcome (CR)
- This reactivity is equivalent to that observed in CB-naïve melanoma subjects treated with single-agent PV-10 [2] and with PV-10 + pembrolizumab [7]

2. Liu et al. Oncotarget 2016. 7. Zager et al. ESMO 2020.

In contrast to equivocal absolute T cell numbers, a change in tumor-specific T cell reactivity was observed in at least one subject, 407, presented on several previous slides and who ultimately achieved a complete response. CD8 T cells isolated from peripheral blood collected one week after initiation of study treatment exhibited significantly increased reactivity against HLA-matched tumor cells. Similar reactivity has been observed in checkpoint-naïve patients treated with either single-agent PV-10 or PV-10 + pembrolizumab combination therapy, substantiating a common, systemic immune-mediated mechanism of PV-10 across each population.



In conclusion:

- Encouraging response was observed both at the patient level and in PV-10-injected lesions.
- The non-overlapping safety profile in checkpoint-refractory subjects is consistent with previous observations in checkpoint-naïve subjects.
- Upregulation of innate and adaptive immune response appears to be maintained in checkpoint-refractory subjects, with hallmark DAMP and functional T cell data consistent with observations in checkpoint-naïve subjects, whether receiving PV-10 + pembrolizumab or single-agent PV-10.
- Together, these data suggest that PV-10 may have a role in overcoming acquired resistance to checkpoint blockade.