ESMO Virtual Congress 2020
September 19-21, 2020

PROVECTUS BIOPHARMACEUTICALS, INC.

Subject 0602: A Combination Therapy Trial of PV-10® and KEYTRUDA® for Immune Checkpoint Blockade-Refractory to Advanced Cutaneous Melanoma

Developing a New Generation of Immunotherapy Medicines

ESMO 2020: Clinical Example, Presentation 1126P

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Rose Bengal Disodium (RBD)

- RBD is 4,5,6,7-tetrachloro-2',4',5',7'-tetraiodofluorescein disodium, a halogenated xanthene and Provectus' proprietary lead small molecule
- Provectus' current Good Manufacturing Practices (cGMP) RBD is a proprietary pharmaceutical-grade drug substance produced by the Company's quality-by-design (QbD) manufacturing process to exacting regulatory standards that avoids the formation of uncontrolled impurities currently present in commercial-grade rose bengal
- Provectus' RBD and cGMP RBD manufacturing process are protected by composition of matter and manufacturing patents as well as trade secrets

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Small Molecule Autolytic Cancer Immunotherapy

IL PV-10 is an injectable formulation of Provectus' proprietary RBD

- Intralesional (IL) (aka intratumoral) administration of PV-10 for the treatment of solid tumor cancers can yield immunogenic cell death and induce tumor-specific reactivity in circulating T cells[1-3]
- This IL PV-10-induced functional T cell response may be enhanced and boosted in combination with immune checkpoint blockade (CB)[4]
- In CB-refractory advanced cutaneous melanoma, IL PV-10 may restore disease-specific T cell function, which may also be prognostic of clinical response.

1. Wachter et al. Functional Imaging of Photosensitizers using Multiphoton Microscopy. *Proceedings of SPIE* 4620, 143, 2002.
2. Liu et al. Intralesional rose bengal in melanoma elicits tumor immunity via activation of dendritic cells by the release of high mobility group box 1. *Oncotarget* 7, 37893, 2016.
3. Qin et al. Colon cancer cell treatment with rose bengal generates a protective immune response via immunogenic cell death. *Cell Death and Disease* 8, e2584, 2017.
4. Liu et al. T cell mediated immunity after combination therapy with intralesional PV-10 and blockade of the PD-1/PD-L1 pathway in a murine melanoma model. *PLoS One* 13, e0196033, 2018.

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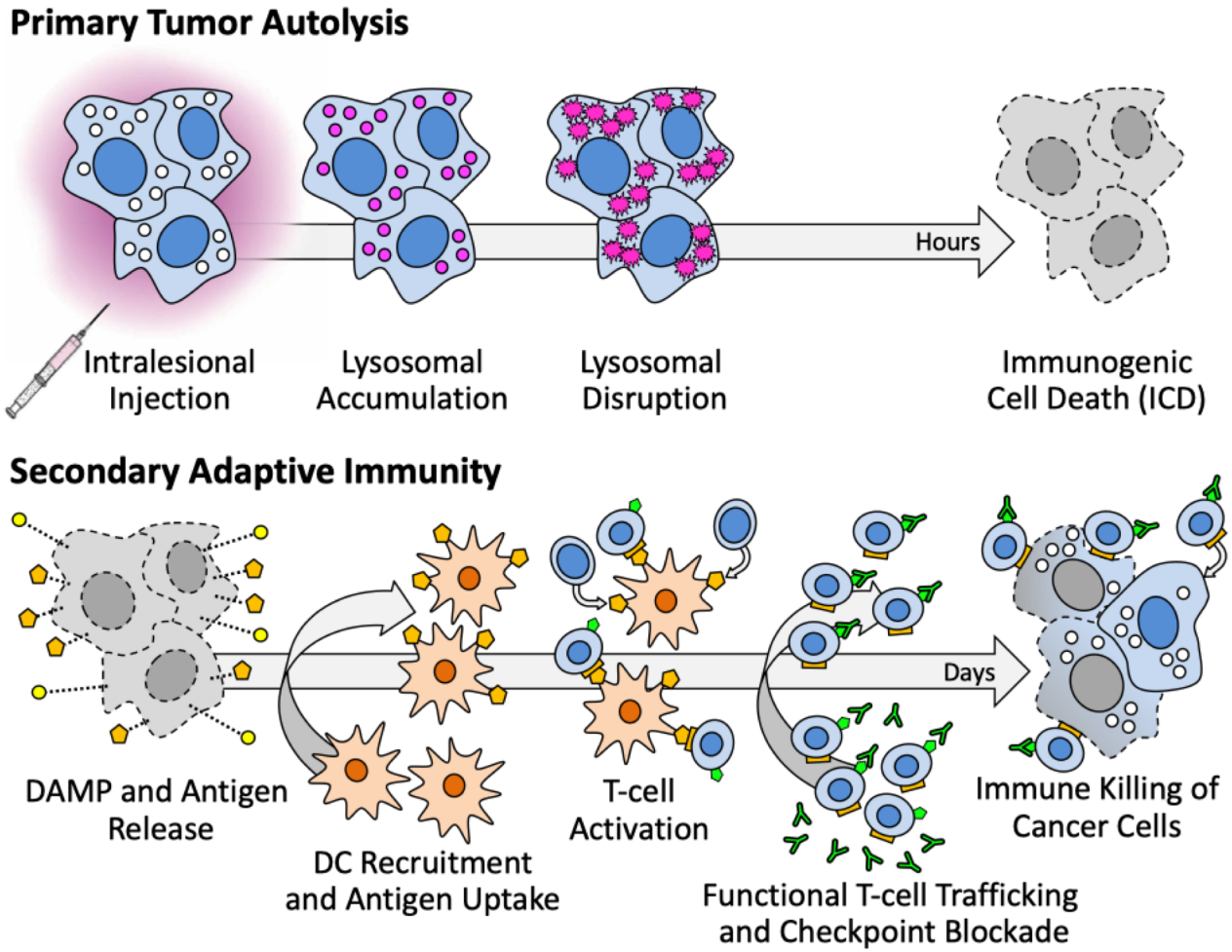
Mechanism of Action: IL PV-10+Checkpoint Blockade



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IL PV-10+KEYTRUDA (pembrolizumab) for Advanced Cutaneous Melanoma Refractory to Immune Checkpoint Blockade

About the Phase 1b/2 Combination Therapy Trial (NCT02557321)

- A first expansion cohort of the Phase 1b portion of the study began enrolling patients with metastatic cutaneous melanoma who were CB-refractory in December 2018
- This CB-Refractory Cohort extended an exploratory group of refractory patients enrolled into the study's main cohort, which primarily enrolled CB-naïve patients
- Patients with at least 1 injectable lesion and who were candidates for KEYTRUDA were eligible
- Eligible subjects received the combination treatment of PV-10 and KEYTRUDA every 3 weeks for up to 5 cycles (i.e., over a period of up to 12 weeks), followed by only KEYTRUDA every 3 weeks for up to 24 months
- The primary endpoint for the Phase 1b trial was safety and tolerability
- Overall response rate (ORR) and progression-free survival were key secondary endpoints (both assessed via RECIST 1.1 after 5 treatment cycles, and then every 12 weeks thereafter)

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Subject 0602: Partial Response (RECIST 1.1)

- Male, age 74
- Stage IV M1d (N3) disease
  - Multiple injectable subcutaneous (SQ) metastases of the left front lower quadrant
  - Multiple distant non-injected metastatic sites: right inguinal lymph nodes, lung, and cerebellum
- Refractory to BRAK-MEK and CB treatments, and twice-radiotherapy to the cerebellum
- 9 cycles of IL PV-10 to 5 injectable SQ lesions over a 5-month period of time
  - Median dose 0.32 mL PV-10 per cycle (range 0.15-2.46 mL)
- At 28 weeks
  - Complete response (CR) of target lesions
  - Overall: Partial response (PR) by RECIST 1.1 with regression in all metastatic sites
- **Slide No. 8:** Clinical photographs of the injected SQ lesions at screening, day 1 (prior to IL PV-10 injection), week 3 (after the first cycle of PV-10), week 6, and week 15; CT scans of injected SQ lesions at screening, week 15, and week 28
- **Slide No. 9:** CT scans of non-injected inguinal nodes (1st and 2nd rows), non-injected lung metastasis (3rd row), and MRI (T1) scan of 1 of 2 metastases of the cerebellum

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Complete Response of Injected Lesions from IL-PV-10

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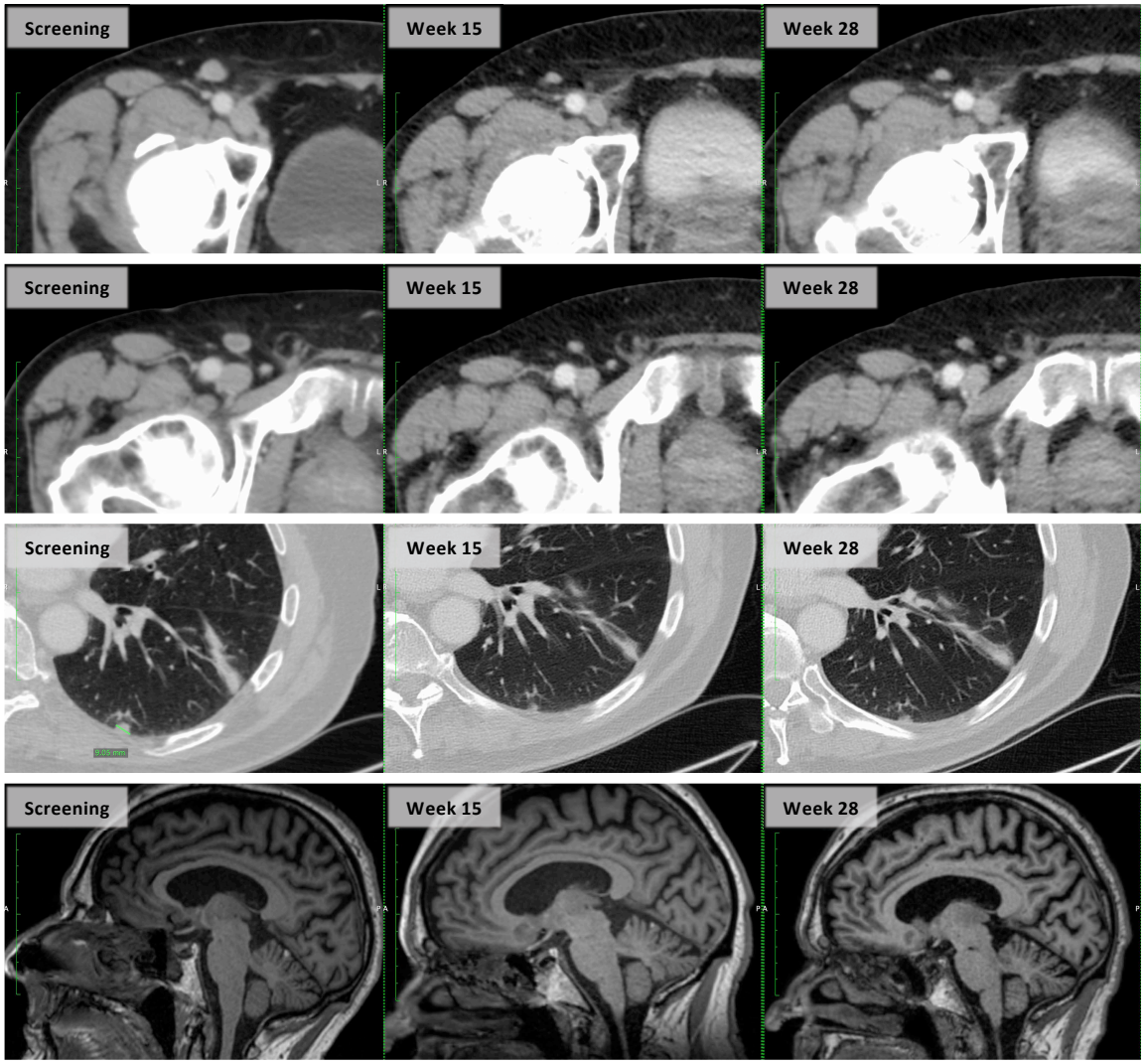
Regression in all Non-Injected Metastatic Sites from IL PV-10+KEYTRUDA: Inguinal Nodes, Lung, and Brain



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Summary Study Comments: CB-Refractory Cohort

Combination Therapy Trial of PV-10 and KEYTRUDA for Immune Checkpoint-Blockade Refractory Advanced Cutaneous Melanoma (NCT02557321)

- Preliminary data
  - 15 patients evaluable for safety; 11 evaluable for efficacy
- Refractory to single- and dual-agent checkpoint blockade; 60% Stage IV M1b-d
- Stable, non-overlapping safety profile
- CB-Refractory Cohort: preliminary response data
  - 9% CR, 36% ORR, and 64% disease control rate (DCR)
- Immune correlative analytes of the combination therapy exhibited systemic release similar to that previously shown in CB-naïve patients receiving single-agent PV-10
  - Including damage-associated molecular pattern (DAMP) high mobility group box protein 1 (HMGB1) and tumor-specific functional T cell activity
- Data compare favorably to other investigational therapies for this patient population (e.g., CB, TLR9 agonists, HDAC, cytokines, TIL)

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