Percutaneous hepatic injection of rose bengal disodium (PV-10) in metastatic uveal melanoma

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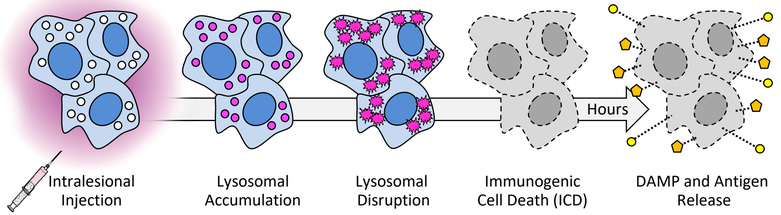
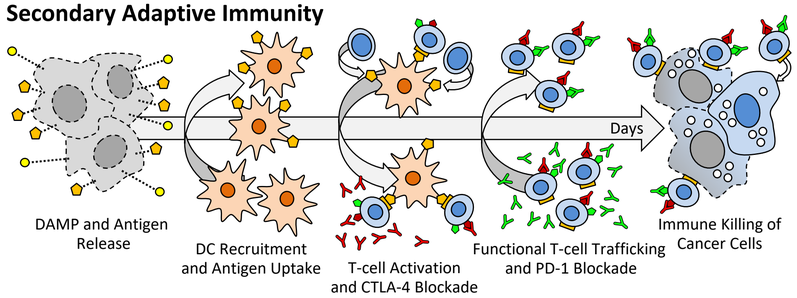
Background:

- PV-10 is a small molecule autolytic immunotherapy in clinical development for the treatment of solid tumors [1-8].
- When administered by intralesional (IL) injection, PV-10 can produce immunogenic cell death (ICD) that may induce a T cell-mediated immune response against treatment refractory and immunologically cold tumors [9-11]. Adaptive immunity can be enhanced through combination with immune checkpoint blockade (CB) [4,8].

Primary Tumor Autolysis



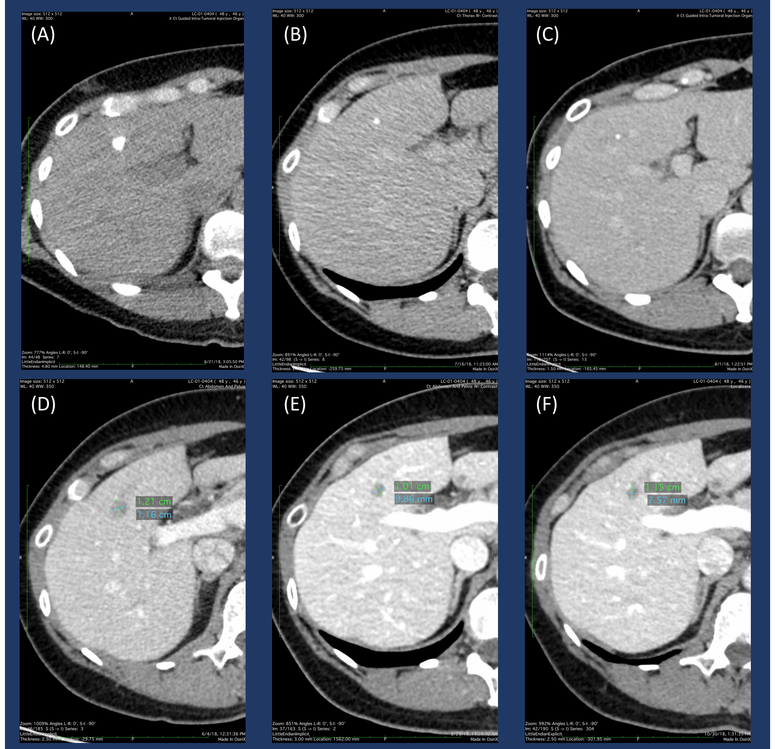
Secondary Adaptive Immunity



- Given this mechanism and clinical data that metastatic uveal melanoma (MUM) generates low response rates to CB alone, we investigated treatment of MUM with percutaneous PV-10.

Methods:

- This open-label Phase 1 basket study (**NCT00986661**) is evaluating the safety, tolerability, and preliminary efficacy of intralesional PV-10 in patients (pts) with solid tumors of the liver; the study population includes a defined sub-group of MUM pts.
- PV-10 is injected percutaneously into one or more designated hepatic tumor(s) with a maximum sum of diameters of ≤4.9 cm in the initial PV-10 treatment cycle.
- Response assessments using 2D EASL criteria [12] are performed at Day 28, and then every 3 months.
- Pts with additional injectable tumors may receive further PV-10 cycles after Day 28.
- Pts can receive standard of care CB immunotherapy during the study.



Subject 0404 (F age 47 with multifocal hepatic MUM). Intralesional injection of radiopaque PV-10 on Day 0 (A) illustrates local retention that remains evident after 25-41 days (B-C). Regression of injected lesion vs baseline (D, Day -17) is observed on follow-up at 2.3 months (E) and 4.3 months (F). Partial response per 2D-EASL achieved after injection of 2 tumors in 2 treatment cycles.

Conclusions:

- Percutaneous IL PV-10 exhibited acceptable safety and tolerability alone and in combination with CB.
- Response indicative of regression or stabilization in a majority (83%) of injected lesions is encouraging in a rare disease of major unmet need.
- Enrollment and follow-up for safety, duration of response, and OS are ongoing.
- A companion study is assessing PV-10 in neuroendocrine tumors metastatic to the liver (NCT02693067) [13].

Study sponsor: Provectus Biopharmaceuticals, Inc.
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Results:

- As of a data cut-off of mid-May 2020, a defined sub-group of 14 pts with MUM (5 refractory to prior CB) had received at least 1 cycle of PV-10 (range 1-5 cycles), with an average of 2 hepatic lesions injected per pt (range 1-8 lesions):
  - 3 pts received PV-10 alone;
  - 3 pts received PV-10 + anti-PD-1; and
  - 8 pts received PV-10 + anti-PD-1 + anti-CTLA-4.
- Acceptable safety was observed; adverse events (AEs) were consistent with established patterns for each agent:
  - AEs attributed to PV-10 were transient and included Grade 3/4 transaminitis that resolved within 72 hrs, injection site pain, photosensitivity, and pink discoloration of skin, urine or feces; and
  - AEs attributed to CB included nausea, decreased WBC, and fatigue.
- Response assessments on 24 injected tumors were: 2 complete response (8%), 7 partial response (29%), and 11 stable disease (46%), per 2D EASL.
- Among the 5 CB-refractory pts, median overall survival (OS) was 11.4 months (range 6.9 – 17.5 months, with 2 pts alive at 9.4 and 17.5 months). Among the 9 CB-naïve pts, median OS was estimated at 11 months (range 5.7 – 24.7 months, with 5 pts alive at 6.4 to 24.7 months). Pts receiving PV-10 alone (1 CB-refractory, 2 CB-naïve) achieved a median OS of 7.9 months, with one CB-naïve pt alive with partial overall response at 24.7 months.

Subject	Disease Status / Treatment History	Study Therapy [1]	Overall Status
0401 F 69	2 hepatic tu	3 cycles to 3 tu + Ipi-Nivo	Alive (24.7 mos)
0404 F 46	Multiple hepatic tu	2 cycles to 2 tu + Ipi-Nivo	Alive (20.7 mos)
0407 F 63	2 hepatic tu + ex-hepatic mets / Ipi + Nivo	2 cycles to 2 tu + Nivo	Alive (17.5 mos)
0410 F 56	Multiple hepatic tu + ex-hepatic mets / Pem and ^{90}Y	1 cycle to 2 tu + Ipi-Nivo	Alive (9.4 mos)
0412 M 32	5 hepatic tu + ex-hepatic mets	2 cycles to 2 tu + Ipi-Nivo	Alive (9.0 mos)
0415 M 57	Hepatic + ex-hepatic mets	1 cycle to 1 tu + Ipi-Nivo	Alive (6.5 mos)
0414 M 71	1 hepatic tu	1 cycle to 1 tu + Ipi-Nivo	Alive (6.4 mos)
0402 F 64	2 hepatic tu / adjuvant Ipi and Ipi+Nivo	1 cycle to 1 tu + Nivo	Expired (DP, 11.4 mos)
0408 F 60	2 hepatic tu + ex-hepatic mets	3 cycles to 3 tu + Autologous T cells + Pem	Expired (DP, 11.0 mos)
0409 M 54	Multiple hepatic tu	3 cycles to 5 tu + TIL + Ipi-Nivo	Expired (DP, 9.2 mos)
0411 M 75	Multiple hepatic tu + ex-hepatic mets / Nivo	5 cycles to 8 tu + Ipi-Nivo	Expired (DP, 8.7 mos)
0406 F 61	1 hepatic tu	1 cycle to 1 tu + hepatic embolization	Expired (DP, 7.9 mos)
0210 M 81	>6 tu / Ipi and Pem	2 cycles to 2 tu + hepatic embolization	Expired (DP, 6.9 mos)
0413 M 66	Multiple hepatic tu + ex-hepatic mets / immunoembolization and ^{90}Y	1 cycle to 1 tu + Ipi-Nivo	Expired (DP, 5.7 mos)

Abbreviations: DP, disease progression; Ipi, ipilimumab; Ipi-Nivo, combination ipilimumab and nivolumab; Nivo, nivolumab; Pem, pembrolizumab; TIL, tumor infiltrating lymphocyte therapy; tu, hepatic tumor. [1] Number of injection cycles and number of hepatic tumors injected with PV-10; concomitant therapy listed when applicable.

References

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