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Patterns of Response for Combination of PV-10 Oncolytic Immunotherapy and Checkpoint Inhibition

Small Molecule Oncolytic Immunotherapy

Primary Oncolytics

- Intratumoral Injection
- Lymphatic Accumulation
- Immunogenic Cell Death (ICD)

Secondary Adaptive Immunity

- T-cell Activation
- Antigen Presentation and Antigen Uptake
- Functional T-cell Activity

- Functional T-cell Activation in Peripheral Blood of Melanoma Patients [2]
- Immunomodulation of PV-10 Complementary to Checkpoint Inhibition in Murine Melanoma Models [3]

Extended Abstract and Background

PV-10 (rose bengal dextran) is the first small molecule oncolytic immunotherapy in development for solid tumors. Intratumoral injection of PV-10 can yield immunogenic cell death and stimulate tumor-specific reactivity in circulating T cells [1]. PV-10 has been administered as a single agent to 130 cutaneous melanoma patients in Phase I and 2 and 180 patients under expanded access, and is currently the subject of a Phase II/3 study in combination with systemic immune checkpoint inhibition (CI) for patients with advanced melanoma [5,6].

Materials and Methods

Study PV-10-DN-1201 (NCT02537323), an international, multicenter, open-label, sequential phase study, is assessing safety and efficacy of PV-10 in combination with anti-PD-1 therapy (pembrolizumab). Patients must have at least 1 measurable lesion, at least 1 measurable target lesion (T), and be candidates for pembrolizumab. In the Phase II portion of the study, patients receive combination treatment during the induction phase (4x5 cycles) and then pembrolizumab alone in the maintenance phase (total duration of up to 24 months); the primary endpoint is safety and tolerability with objective response rate (ORR) and progression-free survival as key secondary endpoints (assessed via RECIST 1.1 after 15 weeks then q2w).

Results

An initial Phase Ib cohort of predominantly Q-naive subjects reached full accrual in April 2018 (Main Cohort), with an intent-to-treat (ITT) population of 20 Stage IV and 3 Stage III/IIID patients (median age 70 years, range 28-90) receiving at least 1 dose of PV-10 and pembrolizumab. All Treatment-Emergent Adverse Events (TEAEs) were consistent with established patterns for both drugs, with no significant overlap of AEs or unexpected toxicities. All disease stages exhibited response after minimal PV-10 intervention (median of 4 cycles) ranging from 1 to 5; median of 5 infections of PV-10 per patient, range 1 – 82; with 9% complete response (CR) and 65% ORR (overall per RECIST) of a 1.7% 2018 data cutoff. Response of injected target lesions (77% CR and 80% ORR across all disease stages) was higher than historical data for single-agent PV-10 (46% CR and 53% ORR across all disease stages, NCT02502856). Although a combination rate of injected target lesions was also higher for MD disease in the Phase 1 Main Cohort than that observed in single-agent use: 87% CR (4 of 6 lesions) vs 54% CR (214 of 395 lesions).

Conclusion

Robust response was observed in injected and non-injected lesions across all disease stages. A first expansion cohort in the Phase II portion of the study is currently enrolling ex-CI refractory patients to further characterize response in this emergent population. Systemic therapy with CI is now recommended in the USA for Stage IIIB patients with satellite or in-transit disease [10], but the KEYNOTE-001 study demonstrated lower overall response in M0 vs M1 patients [11] and for subcutaneous vs visceral lesions [12]. To address this population, a second Phase Ib expansion cohort directed to patients with satellite or in-transit disease will be opened in early-2019.

Study Participants and Interim Clinical Data

- No M0 injection to cutaneous and subcutaneous lesions (not nodal or visceral lesions)
- Phase Ib Main Cohort eligibility restricted to checkpoint inhibitor-naive patients
- Subjects had substantial systemic disease burden in addition to their injectable lesions

Weeks on Study (Through Data Cut-off November 2018)

Change in Target Lesion Tumor Burden by RECIST 1.1 (Induction and Maintenance Phases)

- M0 17%
- M1a 23%
- M1b 32%
- M1c 18%

Overall response: 46% CR and 53% ORR across all disease stages, NCT02502856

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Single-Agent Injected Target Lesion Response (NCT02502856, N = 116 Target Lesions in 25 patients)

- High response rate for injected lesions across all disease stages
- In all patients, response rate for injected lesions was similar to single-agent PV-10 response and confirmed by biologic surrogates

- PV-10 induction phase can
- Rapidly reduce tumor burden (77% CR in injected lesions) with minimal PV-10 intervention
- Enhance checkpoint inhibition (CI) activity (synergy consistent with PV-10 mechanism)
- The combination may convey superior response rates than either therapy alone
- Combination was observed in a sparse population of Stage II and CI-refractory patients; dedicated expansion cohorts will explore potential utility in these important groups