**Phase 1 Study of mRNA-2752, a Lipid Nanoparticle Encapsulating mRNAs Encoding huOX40L, IL-23, and IL-36γ Intratumoral (iTu) Injection +/- Durvalumab in Advanced Solid Tumors and Lymphoma**


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**Background**

- **mRNA-2752** is a novel mRNA-based therapeutic encoding OX40L, IL-23 and IL-36γ pro-inflammatory cytokines.
- Expression of pro-inflammatory cytokines within a treated tumor along with T-cell co-stimulation mediates the tumor microenvironment (TME) to allow a more robust immune response.

**Study Design**

- **Objectives:**
  1. Assess the safety and tolerability of mRNA-2752 +/- durvalumab.
  2. Characterize the pharmacokinetics of mRNA-2752 +/- durvalumab.
  3. Characterize protein expression from introduced mRNAs and biomarkers in tumors.
  4. Assess preliminary anti-tumor activity in select expansion cohorts of TME, HNSCC, NHL, urothelial carcinoma, and immune checkpoint-refractory melanoma and NSCLC.

**Clinical Efficacy**

- **Pharmacokinetic-Pharmacodynamic Modeling**
  - Pro-inflammatory cytokines, including IFN-γ, TNF-α, IL-23, and OX40L mRNAs.
  - Durable PRs seen in a PD-L1-low squamous-cell bladder cancer patient, and a DLBCL after progression on CAR-T.
  - Median IL-23 plasma levels maintained at < 1 ng/mL with dose ranges up to 8 mg supports the therapeutic goal of ITu mRNA-2752 given as monotherapy and in combination with durvalumab. The recommended dose for expansion (RDE) is up to 8 mg mRNA-2752 + durvalumab.

**Conclusions**

- mRNA-2752 given as monotherapy and in combination with durvalumab is tolerable at all dose levels studied.
- The recommended dose for expansion (RDE) is up to 8 mg mRNA-2752 + durvalumab.
- Median IL-23 plasma levels maintained at ~1 ng/mL with dose ranges up to 8 mg supports the therapeutic goal of ITu mRNA-2752 given as monotherapy and in combination with durvalumab.
- Durable PRs seen in a PD-L1-low squamous-cell bladder cancer patient, and a DLBCL after progression on CAR-T.
- Treatment response of the injected lesion was seen in a melanoma patient progressed on pembrolizumab and T-VEC.
- Durable PRs seen in a PD-L1-low squamous-cell bladder cancer patient, and a DLBCL after progression on CAR-T.
- Treatment response of the injected lesion was seen in a melanoma patient progressed on pembrolizumab and T-VEC.
- Evidence of immunomodulation/expected pharmacodynamics in the TME of both injected and un-injected lesions, in both monotherapy and combination cases, as indicated by increases in pro-inflammatory cytokines, IL-23, PD-L1 levels (marker of interferon signaling), and T-cell induced (IL-23) and transcriptional signature score, with greatest changes observed in patients with clinical benefit.
- Pro-inflammatory cytokines, including IFN-γ, are predominantly transiently elevated post-monotherapy treatment, peaking at 24 hours post-treatment, trend toward further elevated levels with a spike of cytokines, including TNF-α in combination with durvalumab.
- PD-1/PD-L1 modeling supports ITu dosing which is being explored in cutaneous melanoma in the neoadjuvant setting.
- Exenatide is ongoing in expansion cohorts of TNBC, urothelial carcinoma, lymphoma, and immune-checkpoint inhibition-refractory melanoma and NSCLC.

**References**