Trial in Progress: Phase 1/2 Study of mRNA-4359 Administered Alone and in Combination With Immune Checkpoint Blockade in Adult Participants With Advanced Solid Tumors

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Background

- mRNA-4359 is a lipid nanoparticle–encapsulated mRNA-based cancer therapy encoding concatemerized PD-L1 and IDO1 antigens that can be administered as an intramuscular injection
  - PD-L1 is a cell-surface receptor expressed on both tumor and regulatory immune cells and functions as a checkpoint to inhibit T-cell function[1]
  - IDO1 is an L-tryptophan–metabolizing enzyme involved in T-cell suppression and immune tolerance[2-4]
- Both PD-L1 and IDO1 have been hypothesized to contribute to an inhibitory tumor microenvironment that allows tumor cells to bypass immune monitoring and clearance[5,6]
- T cells that can target PD-L1 and IDO1 have been shown to pre-exist in patients with cancer[7-9]
- mRNA-4359 encodes immunogenic peptides hypothesized to generate anti–PD-L1/IDO1-specific T cells to eliminate immunosuppressive regulatory cells, as well as cancer cells that express those antigens, potentially tipping the balance towards an inflammatory and/or immune-permissive tumor microenvironment
  - Combination with checkpoint inhibition may further amplify this antitumor immunostimulatory effect

IDO1, indoleamine 2,3-dioxygenase 1; PD-L1, programmed death ligand-1.

1. Zhang X, et al. *Immunity*. 2004;20(3):337-347. 2. Badawy AAB. *Int J Tryptophan Res*. 2017;10:1178646917691938. 3. Kolawole AO, et al. *Arch Biochem Biophys*. 2015;570:47-57. 4. Yeung AWS, et al. *Clin Sci (Lond)*. 2015;129(7):601-672. 5. Munn DH, Mellor AL. *Trends Immunol*. 2013;34(3):137-143. 6. Jiang X, et al. *Mol Cancer*. 2019;18(1):10. 7. Sørensen RB, et al. *PLoS One*. 2009;4(9):e6910. 8. Sørensen RB, et al. *Blood*. 2011;117(7):2200-2210. 9. Wu Y, et al. *Front Immunol*. 2019;10:2022.

Methods

Study Design

mRNA-4359-P101 (NCT05533697) is an ongoing, open-label, multicenter, first-in-human, phase 1/2 study of mRNA-4359 as monotherapy and in combination with immune checkpoint blockade with 3 treatment arms (**Figure 1**)

- Arm 1a (dose escalation) will enroll adults with locally advanced or metastatic solid tumors and investigate mRNA-4359 monotherapy
  - Eligible tumors include cutaneous melanoma, NSCLC, non–muscle invasive bladder cancer, head and neck squamous cell carcinoma, microsatellite stable colorectal cancer, basal cell carcinoma, or triple-negative breast cancer
- Arm 1b (dose confirmation) will enroll adults with locally advanced or metastatic and checkpoint inhibitor–refractory melanoma or NSCLC and investigate mRNA-4359 in combination with pembrolizumab
- Arm 2 (expansion) will enroll adults with locally advanced or metastatic melanoma or NSCLC with a PD-L1 tumor proportion score ≥1% and investigate mRNA-4359 in combination with pembrolizumab as first-line therapy

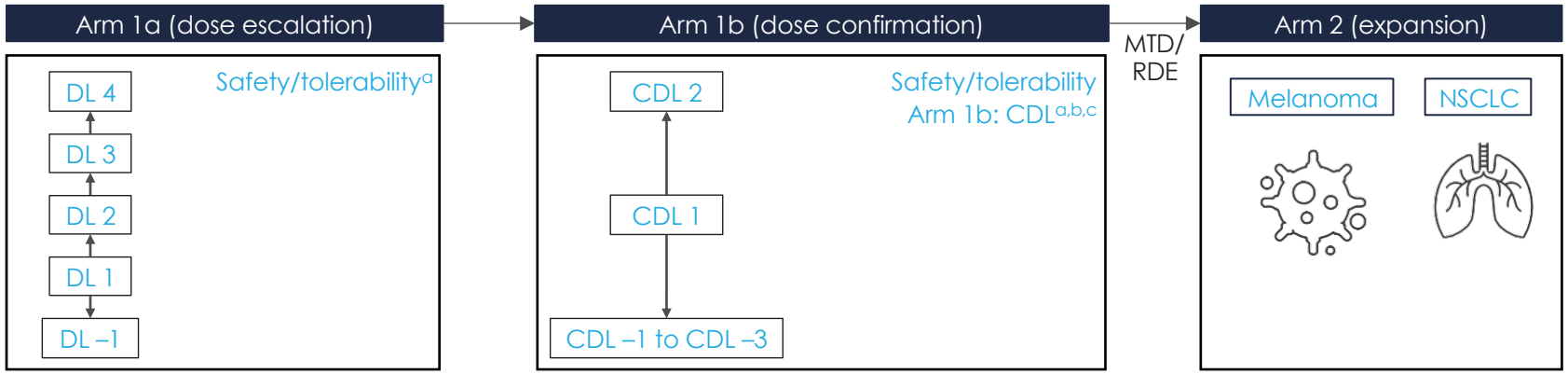
NSCLC, non–small cell lung cancer; PD-L1, programmed death ligand-1.

Methods (continued)

Additional Key Eligibility Criteria

- ≥18 years of age
- Eastern Cooperative Oncology Group performance status ≤1
- Adequate hematologic and biologic function based on laboratory assessments
- Absence of active central nervous system tumors or metastases
- Locally advanced or metastatic cancer with measurable disease as determined per RECIST v1.1

Figure 1. mRNA-4359-P101 (NCT05533697) study design



CDL, combination dose level; DL, dose level; MTD, maximum tolerated dose; NSCLC, non–small cell lung cancer; RDE, recommended dose for expansion; SRC, safety review committee.

[a]Intermediate dose levels may be explored based on SRC recommendation.

[b]CDL cohorts will begin at a DL that is deemed safe in monotherapy and is ≥1 DL below the DL that is being explored in monotherapy at that time.

[c]Arm 1b DLs will be determined based on preliminary clinical data from Arm 1a.

Study Objectives and Endpoints

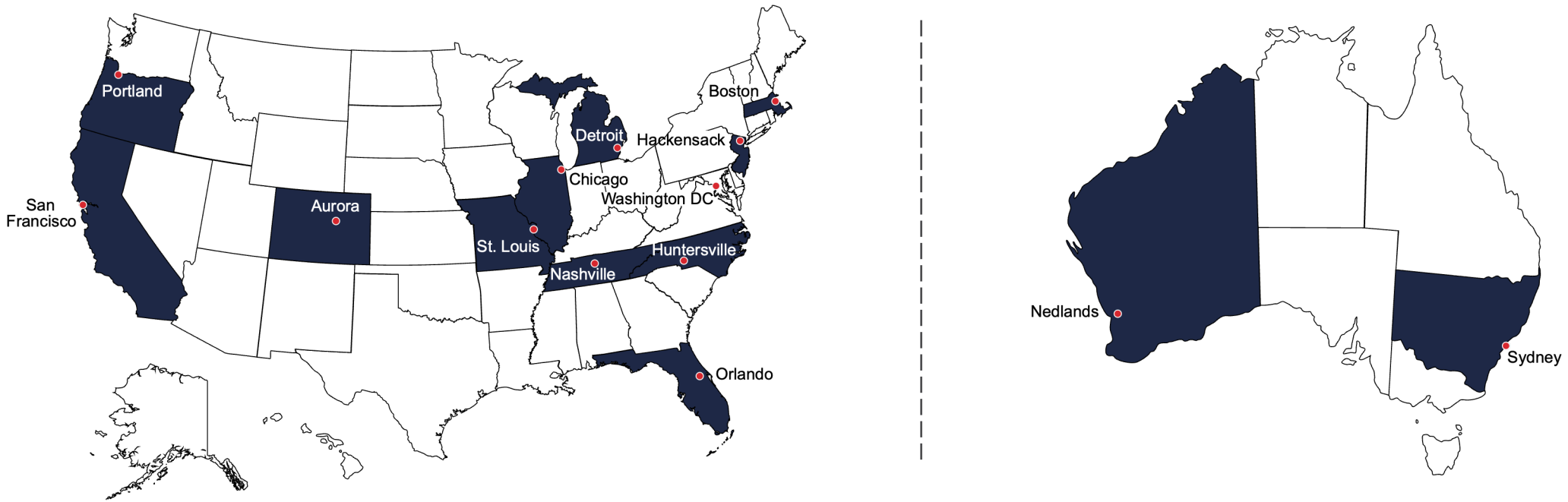
Primary objective	Endpoints
To assess the safety and tolerability of mRNA-4359 administered alone and in combination with pembrolizumab	• Define the MTD and/or RDE of mRNA-4359 • Identify the incidence, nature, and severity of DLTs, AEs, AEs of special interest, and serious AEs after the administration of mRNA-4359 alone and in combination with pembrolizumab
Secondary objectives	**Endpoints**
To assess the antitumor activity of mRNA-4359 alone and in combination with pembrolizumab	• ORR, DCR, DOR, and PFS based on RECIST v1.1
To measure and assess T-cell profile changes in both the periphery and in the tumor after the administration of mRNA-4359 with or without pembrolizumab	• Change (or percent change) from baseline in T-cell profile in the periphery and in the tumor

AE, adverse event; DCR, disease control rate; DLT, dose-limiting toxicity; DOR, duration of response; MTD, maximum tolerated dose; ORR, objective response rate; PFS, progression-free survival; RDE, recommended dose for expansion; RECIST, Response Evaluation Criteria in Solid Tumors.

Current Status

- Study enrollment is currently underway; for the United States, 12 sites are planned and 10 sites are active. For Australia, 3 sites are planned and 1 site is active (**Figure 2**)

Figure 2. Active study sites for mRNA-4359-P101 (NCT05533697)



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