

Intismeran Autogene: the End-to-End Process From Tumor Biopsy to Individualized Neoantigen Therapy for Patients With Cancer

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BACKGROUND

- Individualized neoantigen therapy (INT) is a new type of therapy that aims to induce an immune response tailored to a patient's cancer with minimal additional toxicity¹
- Intismeran autogene (intismeran; formerly V940 or mRNA-4157) represents a first-in-class INT that enables delivery of up to 34 neoantigens identified from a patient's unique tumor mutation profile
- Intismeran is under clinical evaluation across a range of solid tumor types (**Table 1**)
 - Early phase studies have shown intismeran to be well tolerated as monotherapy and in combination with pembrolizumab²⁻⁴
 - In a phase 2 study in patients with resected high-risk melanoma, intismeran plus pembrolizumab significantly improved recurrence-free survival and distant metastasis-free survival vs pembrolizumab alone^{3,4}
- Because it is an individualized therapy, the process for generating intismeran doses and delivering them to patients differs from current therapies

Table 1. Ongoing Intismeran Clinical Studies

Study Name	ClinicalTrials.gov Identifier	Cancer Type	Setting	Phase	Estimated Enrollment	Year Initiated	Status
INTerpath-001	NCT05933577	High-risk, resected melanoma	Adjuvant	3	1089	2023	Active, not recruiting
INTerpath-002	NCT06077760	NSCLC	Adjuvant	3	868	2023	Active, recruiting
INTerpath-004	NCT06307431	RCC	Adjuvant	2	272	2024	Active, not recruiting
INTerpath-005	NCT06305767	MIBC	Adjuvant	2	230	2024	Active, recruiting
INTerpath-007	NCT06295809	cSCC	Neoadjuvant/adjuvant	2/3	1012	2024	Active, not recruiting
INTerpath-009	NCT06623422	NSCLC	Adjuvant, post prior neoadjuvant immunotherapy	3	680	2024	Active, recruiting
INTerpath-011	NCT06833073	High-risk NMIBC	Two cohorts: adjuvant and neoadjuvant/adjuvant	2	308	2025	Active, recruiting
INTerpath-012	NCT06961006	Melanoma	Unresectable stage III or IV disease	2	160	2025	Active, recruiting
mRNA-4157-P201/KEYNOTE-942	NCT03897881	High-risk melanoma	Adjuvant	2	267	2019	Active, recruiting
mRNA-4157-P101/KEYNOTE-603	NCT03313778	Solid tumors	Neoadjuvant/adjuvant	1	242	2017	Active, not recruiting

cSCC, cutaneous squamous cell carcinoma; MIBC, muscle-invasive bladder cancer; NMIBC, non-muscle-invasive bladder cancer; NSCLC, non-small-cell lung cancer; RCC, renal cell carcinoma.

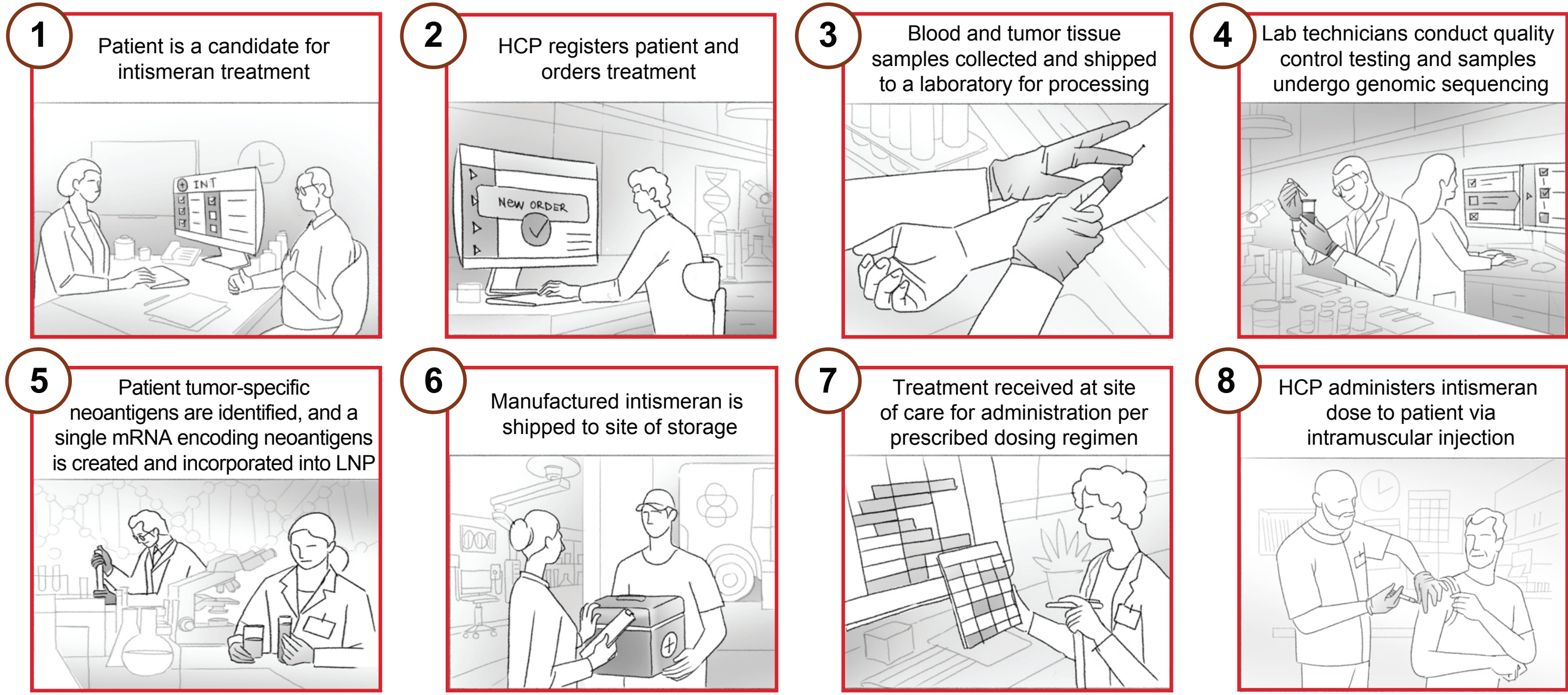
OBJECTIVE

- To describe the process by which intismeran doses are generated and delivered to clinical sites, with an emphasis on individualized operational and manufacturing processes

THE INTISMERAN END-TO-END JOURNEY: OVERVIEW

- As an individualized cancer therapy, the design and delivery of intismeran relies on a well orchestrated, integrated process (**Figure 1**)

Figure 1. Individualized Process for Intismeran Generation and Manufacture



HCP, healthcare practitioner; LNP, liquid nanoparticle.

PHASE 1: DIAGNOSIS TO TUMOR SAMPLE

- Once diagnosis is confirmed, and a patient is deemed eligible for adjuvant or neoadjuvant intismeran treatment, a curative surgical approach is determined which allows for the collection of the minimal required tumor volume for intismeran design (~1 mm³) while employing a technique that maintains tumor tissue integrity
- Rapid and efficient transfer of the tumor sample to a designated pathology laboratory to initiate formalin fixation and paraffin embedding is recommended to optimize RNA and DNA integrity
 - It is important to follow tissue handling guidelines as described, for example, by the College of American Pathologists⁵
- Alternatively, an archival tumor biopsy sample that meets the recommended tumor quantity and nucleic acid preservation criteria can be used

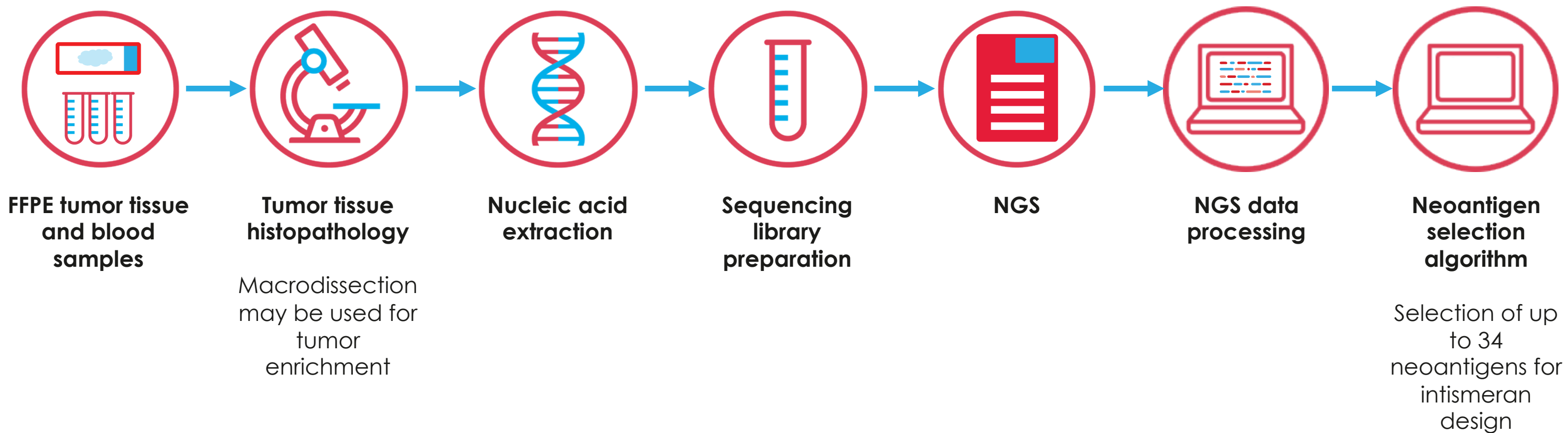
Sample Recommendations

- Formalin-fixed, paraffin-embedded (FFPE) tumor tissue samples
 - 20 freshly cut and unstained slides of 5 µm thickness (covering an optimal tumor volume of 1 mm³) with >20% tumor area are recommended
 - A greater number of slides may be needed (eg, samples with lower tumor area); in other instances, fewer slides (~10 slides) with higher tumor area may also be feasible
- Alternatively, an FFPE tumor block sample with the recommended tumor volume of 1 mm³ may be submitted, with further sample sectioning occurring at a manufacturer-approved central laboratory
- FFPE samples can be shipped at ambient temperatures
- Peripheral whole blood (~3 mL) must also be freshly collected for human leukocyte antigen (HLA)-type sequencing and to provide a “normal” control for tumor-specific mutation identification
- Tumor and blood samples should be shipped to a designated CAP/Clinical Laboratory Improvement Amendments (CLIA)- and ISO13485-certified sequencing laboratory operating as part of the intismeran manufacturing process

PHASE 2: TUMOR SAMPLE TO PATIENT-SPECIFIC NEOANTIGEN IDENTIFICATION

- The neoantigen selection process for intismeran comprises a workflow starting with processing of FFPE tumor and blood samples to identify patient-specific neoantigens for individualized intismeran design (**Figure 2**)
 - Patient samples are processed for tumor histopathology, nucleic acid extraction (RNA/DNA), next-generation sequencing (NGS), NGS data processing (somatic- and germline-variant calling and HLA typing), and proprietary bioinformatic analysis of DNA and RNA sequences (from both tumor and normal samples) to identify patient-specific somatic neoantigens
 - The intismeran neoantigen selection machine learning-based algorithm evaluates candidate mutations, integrating the HLA profile of each patient to prioritize epitopes most likely to induce strong CD8-positive and CD4-positive T-cell responses
 - Identified mutations are ranked according to somatic variant allele frequency, expression levels of intratumoral RNA, and amino acid sequence conservation. For each patient, intismeran is designed for up to 34 top-ranking neoantigens, which are unique to the individual patient (SMR Poster #P219: Sullivan RJ, et al. *Analysis of Individualized and Overlapping Neoantigens in Intismeran Autogene [mRNA-4157/V940] From the mRNA-4157-P201 [KEYNOTE-942] Trial*)
- Successful patient-specific neoantigen selection requires adequate FFPE tumor tissue and blood samples to analyze tumor histopathology and prepare RNA/DNA extraction for NGS and data processing for the manufacture of intismeran (**Figure 2**).

Figure 2. Intismeran Neoantigen Selection Process



FFPE, formalin-fixed, paraffin-embedded; NGS, next-generation sequencing.

PHASE 3: MANUFACTURE OF PATIENT-SPECIFIC INTISMERAN AND PATIENT DELIVERY

- Patient-specific neoantigen sequences are encoded into a single mRNA strand and synthesized under Good Manufacturing Practice conditions to produce an individualized formulation encapsulated in lipid nanoparticles (LNPs; similar to the previously described Spikevax LNP⁶)
- After submission of an adequate tumor sample and peripheral blood samples, manufacturing time to intismeran delivery to a clinical site is typically 6–8 weeks
- Each individualized set of intismeran doses undergoes comprehensive quality control, assessing potency, particle size, and endotoxin levels
 - One individualized batch is generated per patient to support delivery of 9 intramuscular doses
 - A full intismeran treatment course includes 9 doses delivered once every 3 weeks
 - Doses are delivered in frozen vials with defined thawing and storage protocols; doses can be refrigerated for up to 24 hours and at room temperature up to 6 hours after thawing

CONCLUSIONS

- Intismeran demonstrates the potential of INT through a validated, patient-specific mRNA approach
- Intismeran is supported by a streamlined delivery infrastructure, centered around intramuscular injections and standardized clinical workflows
- The manageable tolerability profile and coordinated end-to-end process has the potential to position intismeran for broad integration into the real-world oncology treatment setting
- Results are pending from ongoing registrational studies

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Disclosures

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