

Analysis of Individualized and Overlapping Neoantigens in Intismeran Autogene (mRNA-4157/V940) From the mRNA-4157-P201 (KEYNOTE-942) Trial

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BACKGROUND

- Intismeran autogene (intismeran; formerly mRNA-4157 or V940) is specifically designed using a patient's tumor sample, from which a unique neoantigen "fingerprint" is identified; up to 34 neoantigens are encoded in an mRNA encapsulated in a lipid nanoparticle and used to elicit an individualized antitumor response¹
- Intismeran generates de novo T-cell responses and expands preexisting neoantigen-specific T-cell responses, inclusive of both cytotoxic CD8 and CD4 T-cell responses; such neoantigen-specific T-cell responses are sustained for at least 100 days following last dose of intismeran²
- In the phase 2 mRNA-4157-P201 (KEYNOTE-942; NCT03897881) study, patients with completely resected stage IIIB–IV melanoma receiving intismeran plus pembrolizumab (pembro) had prolonged recurrence-free survival (RFS) vs those receiving pembro alone, with benefit maintained across multiple patient subgroups, including by tumor mutational burden and *BRAF* mutation status²
- Expansion of novel T-cell clonotypes was significantly higher with pembro plus intismeran compared with pembro alone and was associated with RFS with intismeran plus pembro but not pembro alone³

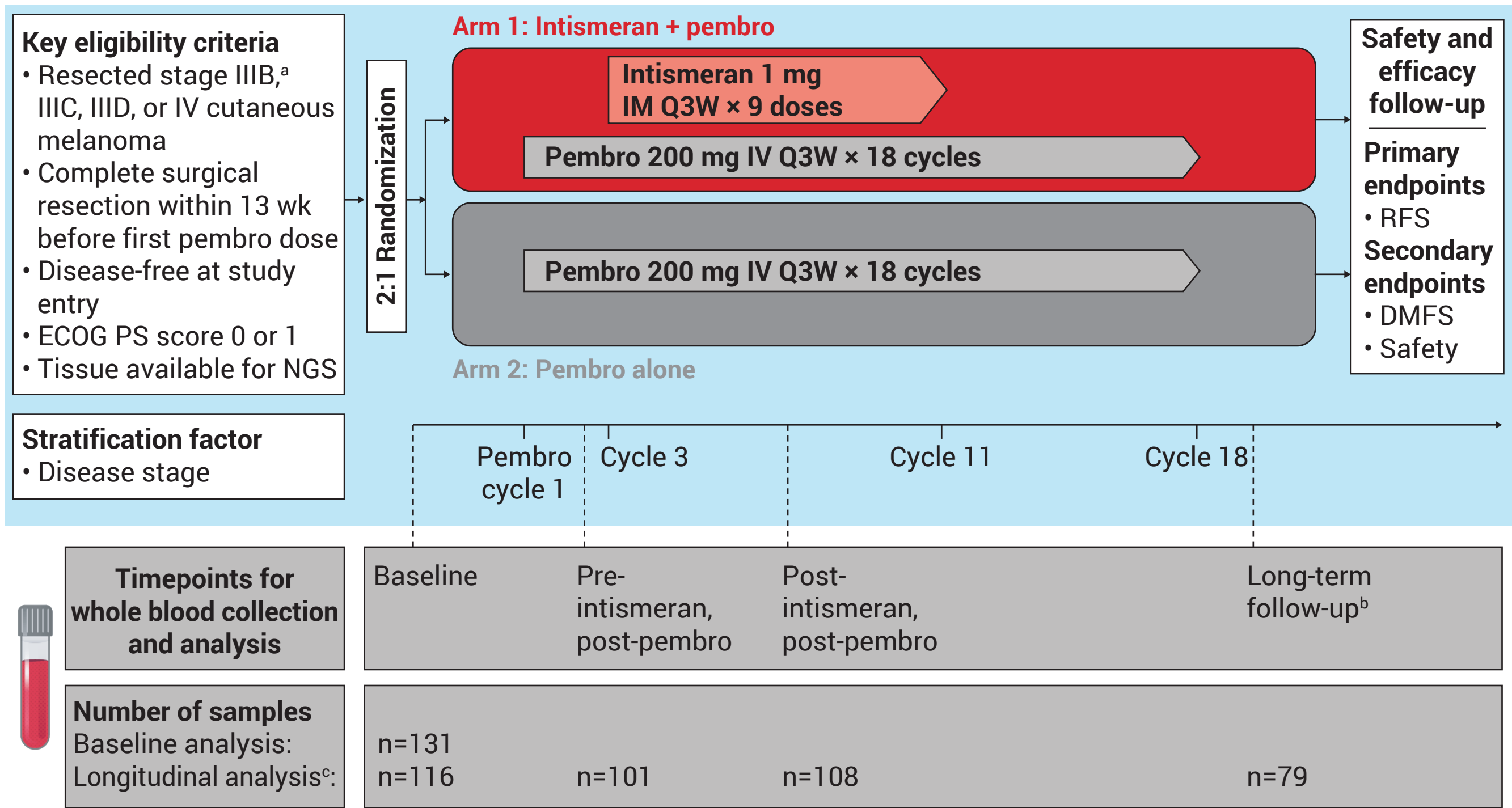
OBJECTIVE

- To characterize the overlap of neoantigens in intismeran design in the mRNA-4157-P201 study

METHODS

- As previously described,¹ patients were randomized 2:1 to receive intismeran plus pembro (n=107) or pembro alone (n=50)
- Tumor resection samples or biopsies and peripheral blood were collected from eligible patients and subjected to next-generation sequencing (NGS)
 - Neoantigens were analyzed for all patients treated with intismeran plus pembro
- Bulk T-cell receptor (TCR) sequencing was performed on longitudinal blood samples. TCR beta chains were downsampled and normalized to the top 10,000 clones by rank sum unique molecular identifier

Figure 1. mRNA-4157-P201 (NCT03897881) study design and whole blood collection schedule



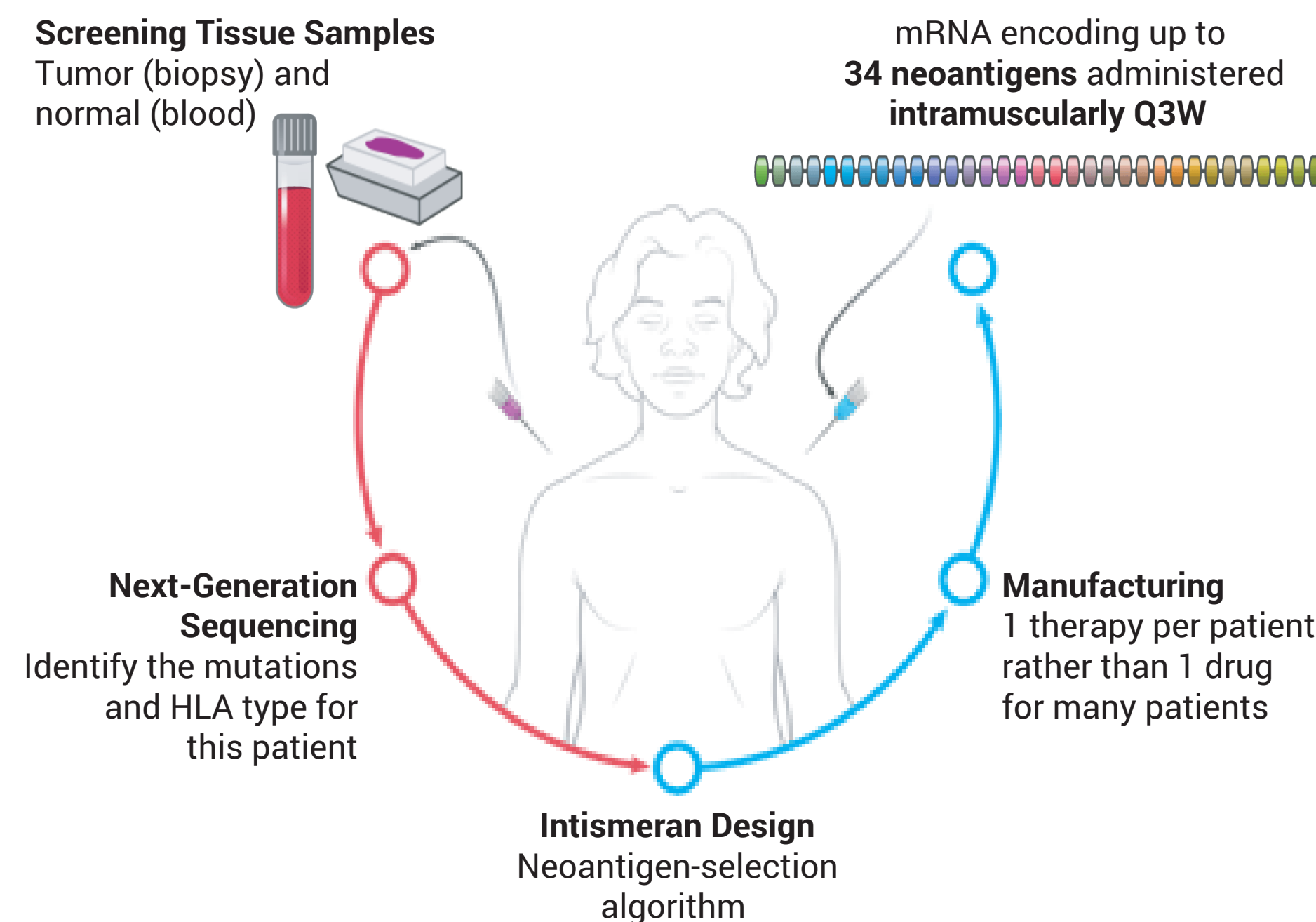
DMFS, distant metastasis–free survival; ECOG PS, Eastern Cooperative Oncology Group performance status; IM, intramuscular; IV, intravenous; Q3W, every 3 weeks.
^aPatients with stage IIIB disease were eligible only if their cancer had relapsed within 3 months of prior surgery of curative intent.
^bLong-term follow up visit occurred after 18 cycles of pembro (~400 days from the start of treatment).
^cFor longitudinal analysis, only patients with screening and ≥1 sample in the post-intismeran/post-pembro phase were included.

RESULTS

Intismeran design

- Tumor tissue and peripheral blood were collected from patients to perform comprehensive NGS and human leukocyte antigen (HLA) typing to identify tumor-specific mutations
- The intismeran neoantigen-selection algorithm then predicted immunogenicity of identified neoantigens for each patient and subsequently ranked the top 34 neoantigens for individualized intismeran
- A single mRNA sequence encoding the 34 neoantigens was designed and incorporated into a lipid nanoparticle for IM administration

Figure 2. Overview of the manufacture of intismeran



- In total, 3433 neoantigens were selected across 107 patients in the intismeran plus pembro arm (median, 34; range, 9–34)
 - 32 neoantigens (0.9%) overlapped in ≥1 patient, and the remaining 3401 neoantigens (99.1%) were unique (Figure 3)
 - 24 patients (22.4%) had no overlapping neoantigens, and the other 83 patients (77.6%) had a median of 97.1% unique neoantigens
 - The most frequent overlapping neoantigens identified in patients arose from *BRAF* V600E (n=31), *NRAS* Q61R (n=12), and *BRAF* V600K (n=10) mutations (Figure 4), rendered by algorithmic prioritization during neoantigen ranking

Figure 3. Number of unique and overlapping neoantigens for all patients in the intismeran plus pembro arm

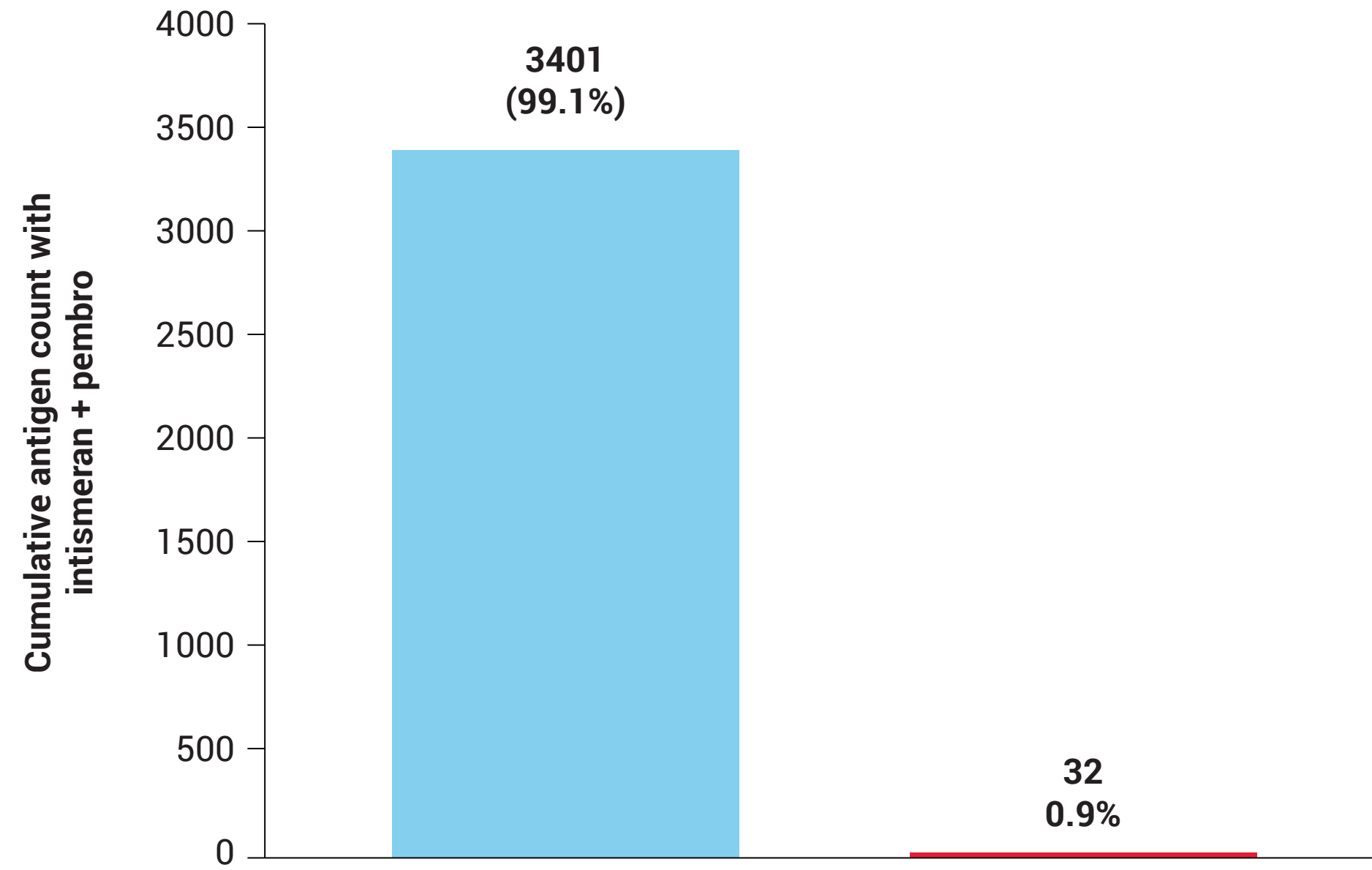
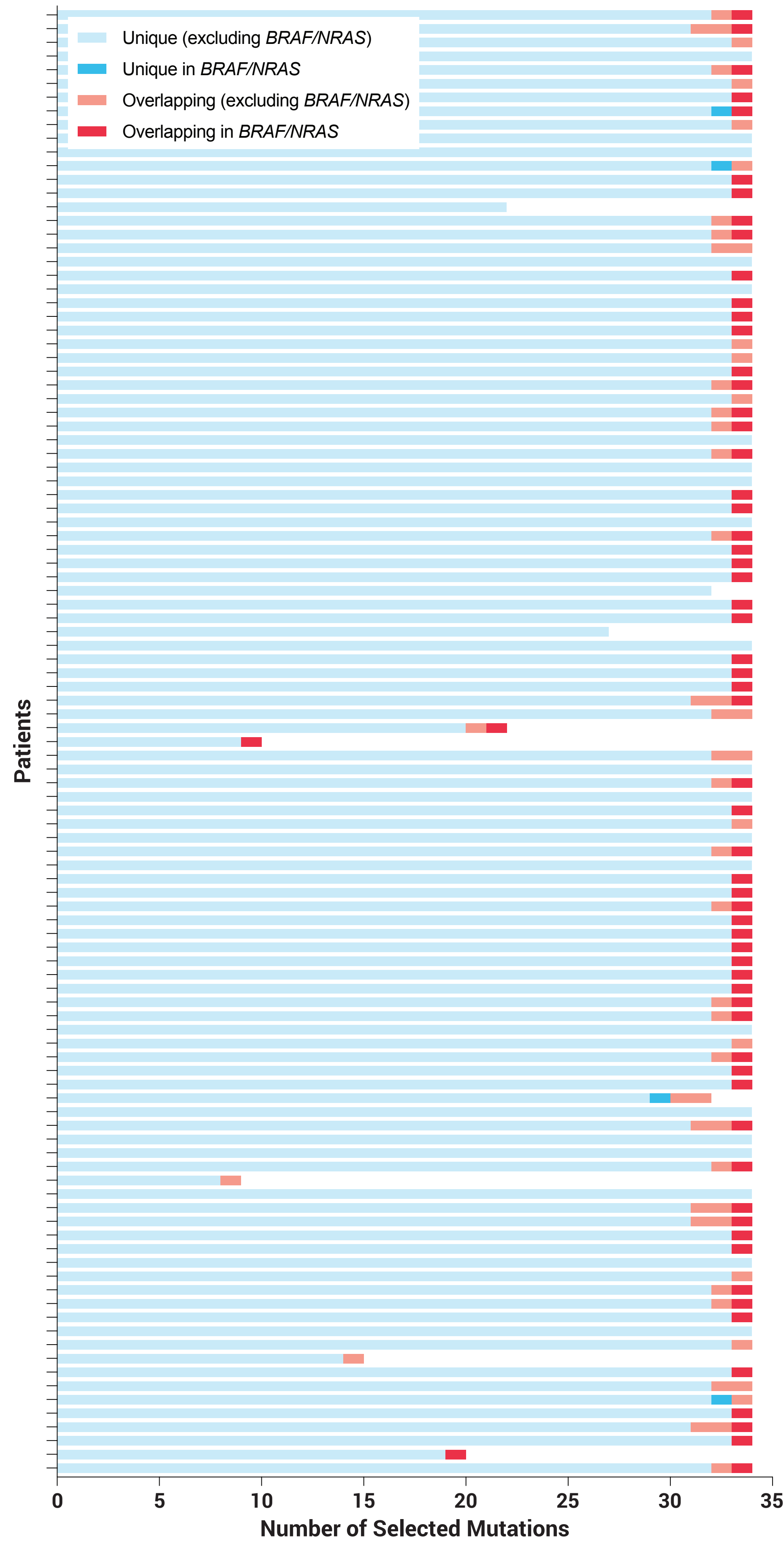


Figure 4. Number of individualized and overlapping neoantigens in intismeran design in the intismeran plus pembro arm



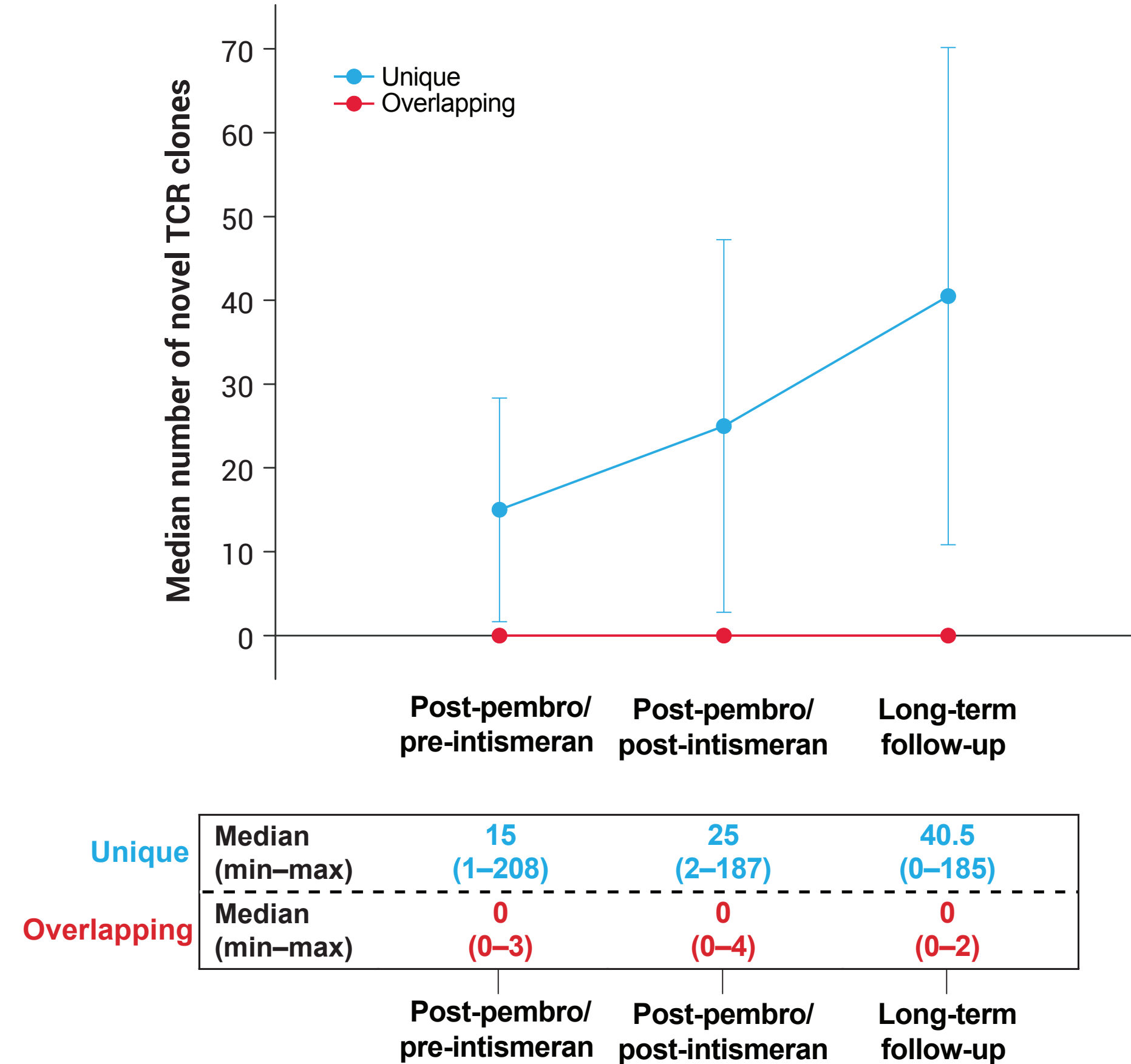
Each bar represents an individual patient from the intismeran plus pembro arm.

Intismeran induced novel T-cell clones

- Analysis of novel expanded TCR clones was performed at landmark timepoints, including at the post-pembro/pre-intismeran visit (cycle 2 day 1; all patients had only been treated with pembro alone); the post-pembro/post-intismeran visit (cycle 5 day 1); and the long-term follow-up visit

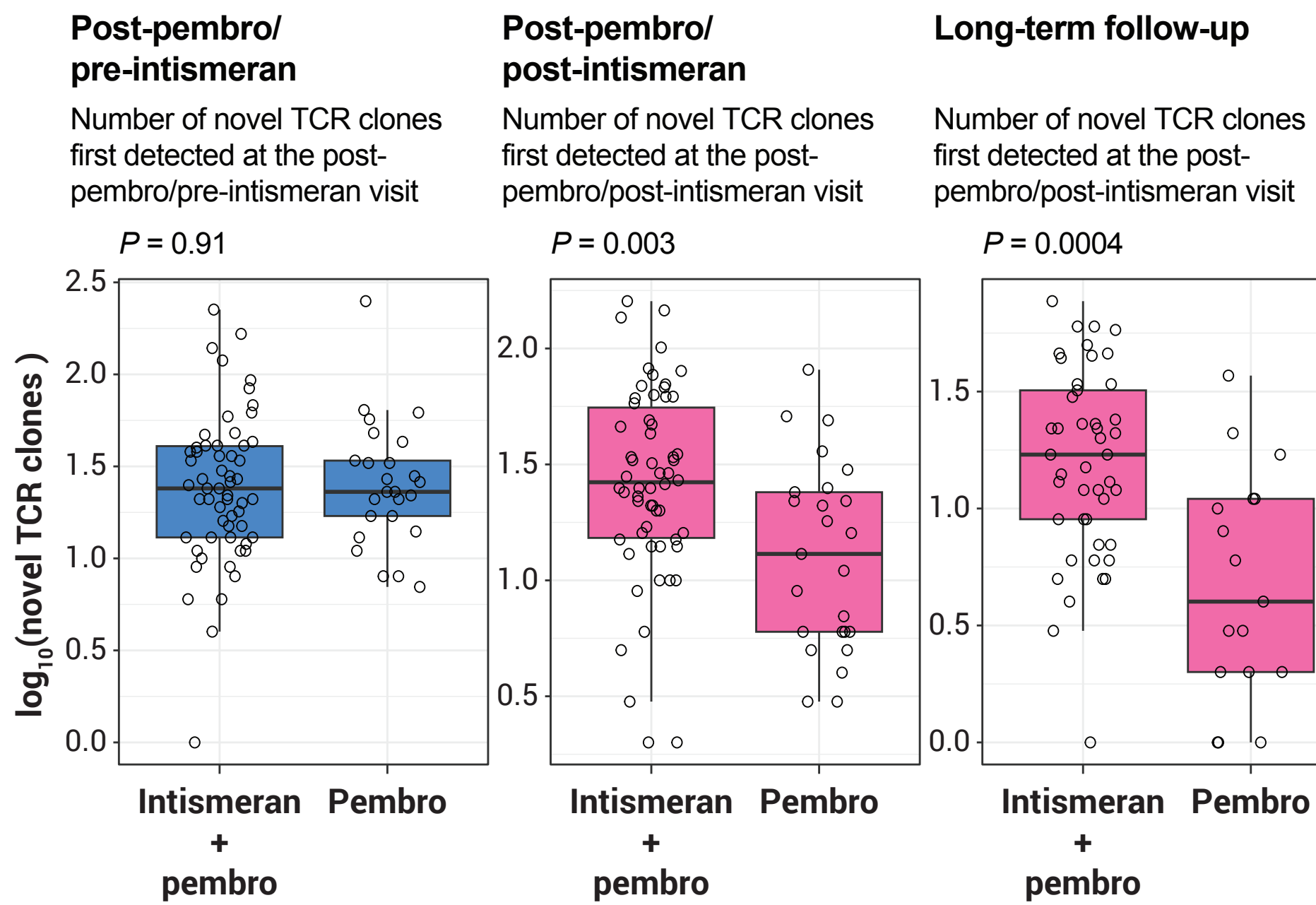
- Across these landmark timepoints, the median number of novel TCR clones in the intismeran plus pembro arm was primarily non-overlapping (Figure 5), suggestive of the individualized effects of intismeran
- Patients in the intismeran plus pembro and pembro alone arms had similar numbers of novel TCR clones at the post-pembro/pre-intismeran visit (Figure 6)
 - At the first post-pembro/post-intismeran visit, patients in the intismeran plus pembro arm generated a significantly higher number of novel TCR clones vs the pembro arm
 - At the long-term follow-up visit, the novel TCR clones detected at the post-pembro/post-intismeran visit remained significantly higher in the intismeran plus pembro arm vs pembro arm

Figure 5. Median number of TCR clones at landmark timepoints (post-pembro/pre-intismeran, post-pembro/post-intismeran, and long-term follow-up)



Errors bars show the median absolute deviation.

Figure 6. Frequency of novel TCR clones at landmark timepoints



CONCLUSIONS

- This analysis of neoantigen overlap demonstrated that more than 99% of neoantigens identified for treatment with intismeran were unique across the 107 patients assessed
- Consistent with the minimal overlap in neoantigen selection between patients for intismeran selection, treatment with intismeran plus pembro induced largely patient-specific novel T-cell clonal expansion, with the majority of expanded TCR clones identified as unique
 - Novel TCR clones induced by intismeran plus pembro were higher in frequency and had longer persistence compared with pembro alone
 - Individualized effects of intismeran can also be driven by the different HLA subtypes represented in intismeran design
- Work is ongoing to map intismeran-related neoantigen-specific T cells to identified novel TCR clones

References

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Disclosures

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