Does platinum therapy impact somatic mutation burden?

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Background & Motivation

- Somatic mutation burden correlates with response to checkpoint blockade immunotherapy[1-3]
- If the mutagenic chemotherapy cisplatin substantially contributes to mutation burden, it might sensitize a cancer to immunotherapy
- Cisplatin induces mutations in *C. Elegans* with a bias toward C>A in CpC context, small deletions, and certain dinucleotide substitutions[4]

Hypothesis: Platinum-associated mutations are enriched in samples from patients who received adjuvant platinum chemotherapy

Cohort: 15 donors diagnosed with high grade serous ovarian carcinoma with next generation sequencing of pre-treatment primary tumors and post-treatment relapse or recurrence samples

Study	Donors (Samples)	Sequencing
Australian Ovarian Cancer Study[5]	12 (27)	WGS
TCGA[6]	3 (6)	WES

References

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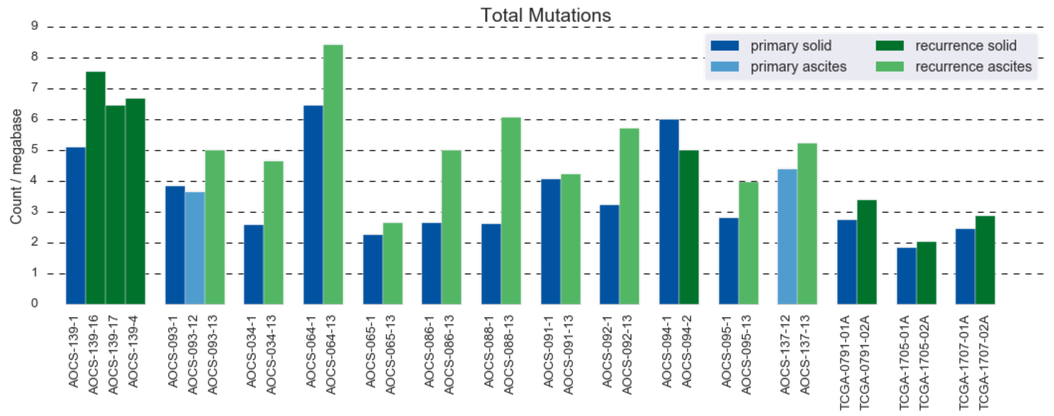
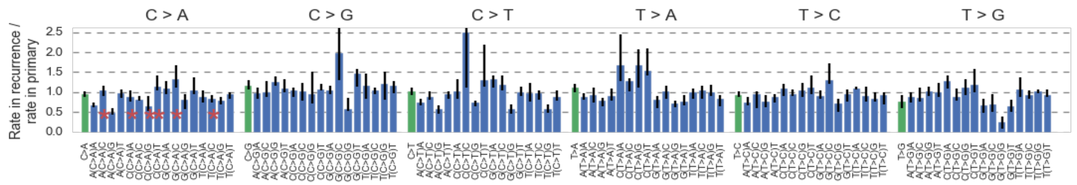
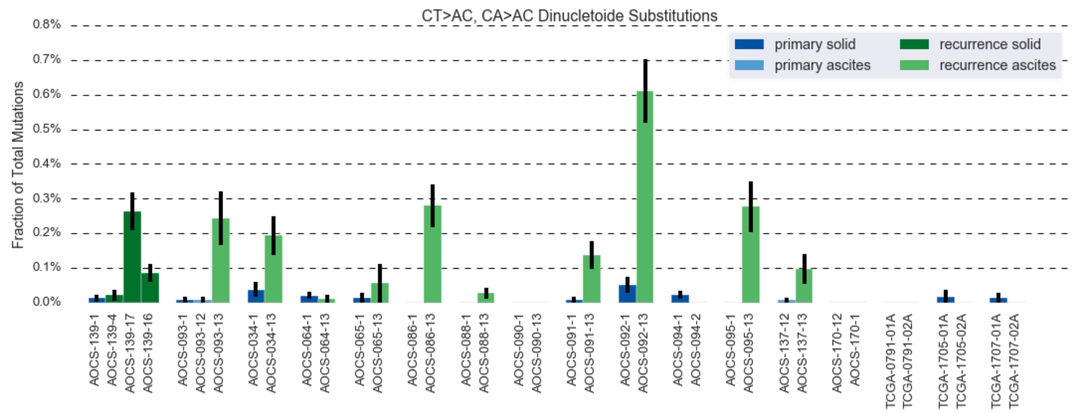


Total detected mutations per megabase sequenced. On average, about a third (31%) of the mutations in treated samples have no evidence in the primary.



Single nucleotide variants in trinucleotide contexts. Each bar gives the ratio of a mutation's rate in the treated vs. untreated samples (> 1 indicates enrichment in treated). The platinum associated C>A mutations in CpC contexts, highlighted with red asterisks, are not significantly enriched in the treated samples.



Platinum-associated dinucleotide substitutions CT>AC and CA>AC as a fraction of total mutations. For the recurrence samples (green) we consider only mutations with no evidence in the primary. The recurrence samples are substantially enriched for these mutations.

Results

- No enrichment for the C>A or deletion signature
- Enrichment for the dinucleotide substitution signature in 10/15 patients. Mean increase was 9.7-fold [95% CI 6.6-13.8]
- The dinucleotide mutations occur at low absolute rates, accounting for < 0.5% of total mutations and < 4 protein changing mutations in any sample

Conclusion

This data suggests the increased somatic mutation burden found at recurrence is not predominantly due to direct mutagenic impact of platinum therapy

- Other processes dominate single-nucleotide variants and indels, which are the vast majority of mutations
- However, due to their extremely low background rate, we can detect enrichment for platinum-associated dinucleotide substitutions
- Further work is required to validate if these dinucleotide substitutions are in fact an indicator of platinum exposure in human cancers