1670P: Circulating tumor DNA dynamics of response and resistance in *BRAF* V600E mutant metastatic colorectal (mCRC) and other cancers: data from EVICT (Erlotinib and Vemurafenib In Combination Trial)

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Introduction

- In the phase Ib/II EVICT trial, the combination of vemurafenib and erlotinib demonstrated promising efficacy with responserates of 32% (10/31; 16%- 5/31 confirmed) in patients (pts) with *BRAF* V600E mt mCRC and 43% (3/7) in pts with other cancers.
- The overall clinical benefit rate (partial response + stable disease) was 71% (27/38).
- Here we report the utility of circulating tumor DNA (ctDNA) as a biomarker to predict outcomes and understand mechanisms of treatment resistance.

Methods

- Serial plasma samples were available from 25 pts.
- Paired baseline and progression samples were analyzed by targeted sequencing (AVENIO ctDNA expanded assay, Roche diagnostics).
- Droplet digital PCR was used to serially monitor mutations of interest.

Summary

EVICT demonstrates that the combination of vemurafenib and erlotinib is well tolerated, with promising activity in *BRAF* V600E mCRC and other tumor types. Our findings highlight that ctDNA analysis can reveal important insights into mechanisms of treatment resistance and provides an early biomarker of treatment response.

Results

Baseline ctDNA analysis

- *BRAF* V600E mt ctDNA was detected at baseline in 21/25 pts (84%).
- Other frequently altered genes included *TP53 (60%), EGFR* (52%), and *MET* (40%).
- Mutational burden was higher in pts who did not derive a clinical benefit (*P*=0.04).
- *MET* amplification was associated with inferior overall survival (OS) (median 4.9 vs 8.8 months; HR 2.2; 95% CI 0.8-6.0, *P*=0.04).

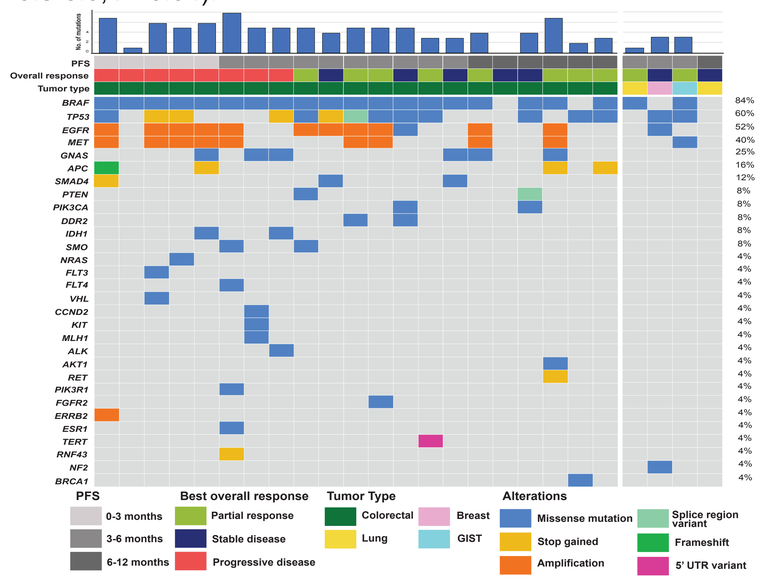

Figure 1. Landscape of somatic mutations detected through targeted sequencing of baseline plasma DNA in 25 pts enrolled on the EVICT trial.

ctDNA dynamics

- Decline in ctDNA levels between baseline and week 2 was greater in pts who derived clinical benefit (*P*<0.001).
- Decline in ctDNA variant allele fraction at 2 weeks predicted longer PFS (median 1.8 vs 6.4 months, HR 3.6, 95% CI 1.3-9.8, *P*<0.001) and OS (median 5.6 vs 9.9 months, HR 2.9, 95% CI 1.0-8.4, *P*<0.01).

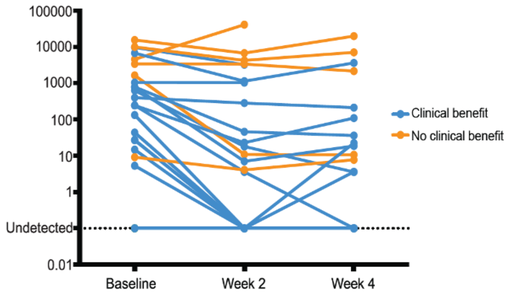

Figure 2. Dynamics of *BRAF* V600E mutant DNA copies/mL between baseline, week 2 and week 4 of treatment according to clinical benefit

Genomic evolution following treatment

- Of the 18 pts with available plasma at progression, 9/18 (50%) showed emergence of ≥ 1 *KRAS* or *NRAS* mutation.
- Polyclonal *KRAS* mutations were observed in 6/9 pts (67%).
- Other frequently acquired MAPK pathway alterations included *MAP2K1* mutations (22%) and *MET* amplification (17%).

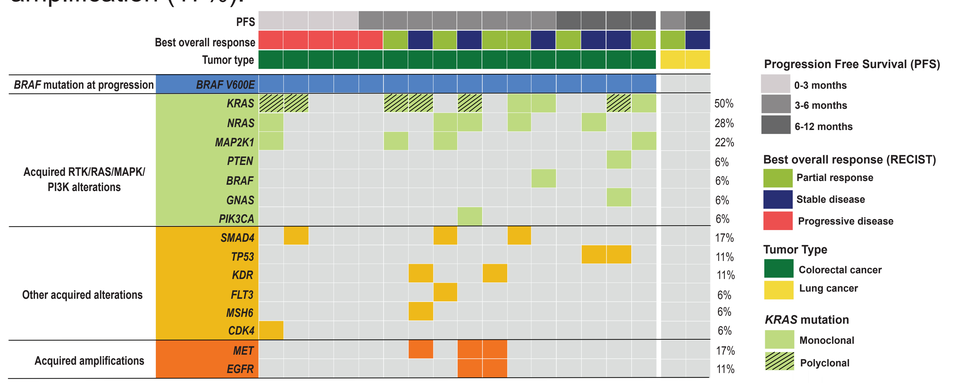

Figure 3. Summary of ctDNA genomic features at disease progression in 18 pts.

Conclusion

In pts with *BRAF* V600E mt cancers treated with vemurafenib and erlotinib, baseline ctDNA profile and an early decline in ctDNA were predictive of clinical outcomes. ctDNA analyses provided a mechanistic understanding of intrinsic and acquired resistance, revealing frequent evidence of convergent evolution and MAPK pathway reactivation as the dominant mechanim of therapeutic escape.

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Disclosures: No conflicts of interest