A ctDNA-directed, multi-center phase II study of molecular response adaptive immuno-chemotherapy in patients with non-small cell lung cancer: Analysis of Stage 1 of CCTG BR.36

#CT212

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Study Design and Endpoints

- BR.36 was designed to validate (stage 1) and implement (stage 2) ctDNA molecular response in precision immuno-oncology decision making
- Primary Endpoints: establish definition, timing and concordance of ctDNA molecular response with radiographic RECIST response
- Secondary Endpoints: time to molecular response, correlation with PFS, OS

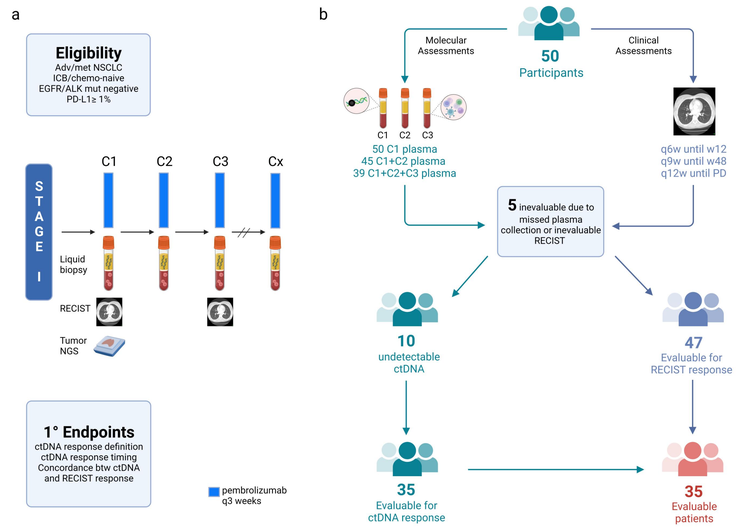


Figure 1. CONSORT diagram for stage 1 BR.36 (NCT04093167).

Next-generation sequencing approach

- Tumor agnostic WBC DNA-informed hybrid capture 33-gene NGS (PGDx EPR)
- ctDNA molecular response (mR): Max MAF clearance at C2D1 or C3D1
- ctDNA molecular disease progression (mPD): Max MAF persistence

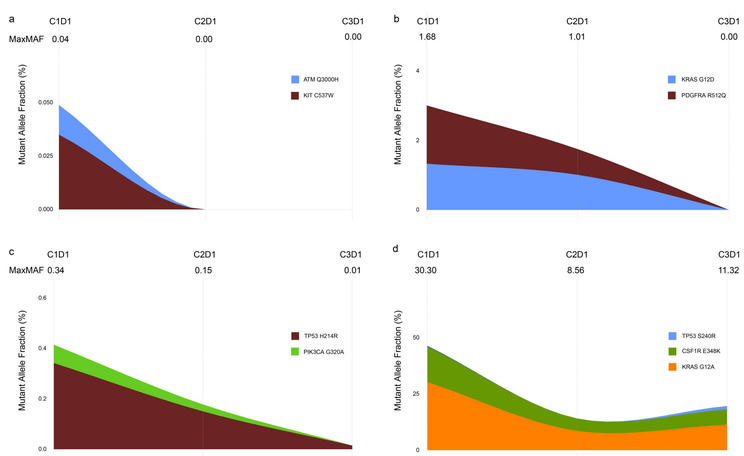


Figure 2. Representative ctDNA dynamics patterns.

Results

- Trial activation: Oct 17, 2019, closed to accrual: Apr 5, 2022
- 98% ever-smokers, 98% stage IV, 52% female, 76% AC, 96% PD-L1+
- 50 enrolled patients followed for a minimum of 12 weeks
- BOR by RECIST 32%, by irRECIST 36%
- 45 evaluable patients, 35 with detectable ctDNA
- Evaluable mR rate 43% (90% CI: 29-58%)
- **BR.36 (stage1) met its primary endpoint for concordance between ctDNA molecular and RECIST radiographic response**

RECIST response (BOR)	Molecular response	
	mR	*mPD*
CR/PR	9 (**82%**)	2 (18%)
No RECIST response	6 (25%)	18 (**75%**)
iRECIST response		
iCR/iPR	10 (**83%**)	2 (17%)
No iRECIST response	5 (22%)	18 (**78%**)

- ctDNA response particularly informative in patients with RECIST SD
- Patients with mR had longer PFS and OS; RECIST less optimally distinguished patients wth CR/PR from patients with SD

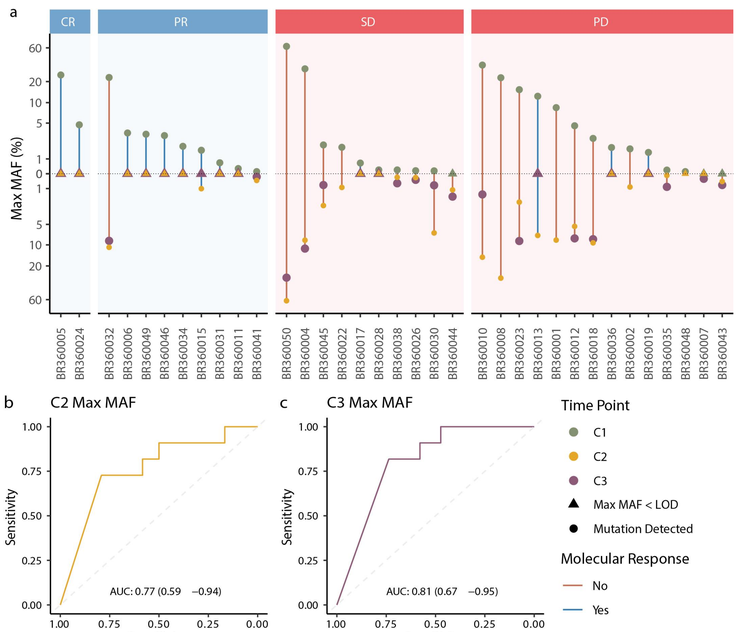
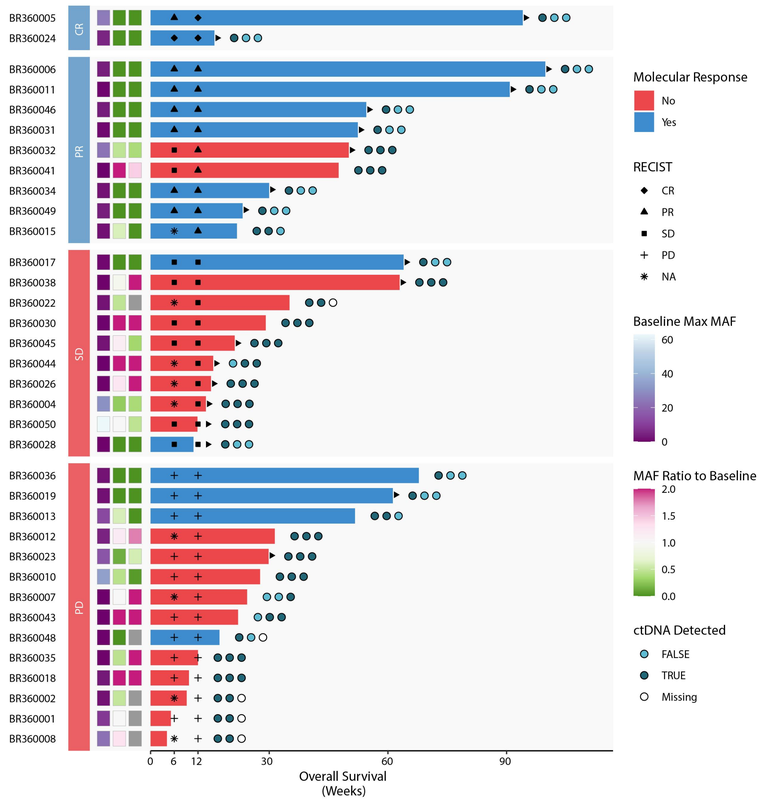


Figure 3. Depth of ctDNA response in RECIST response groups.



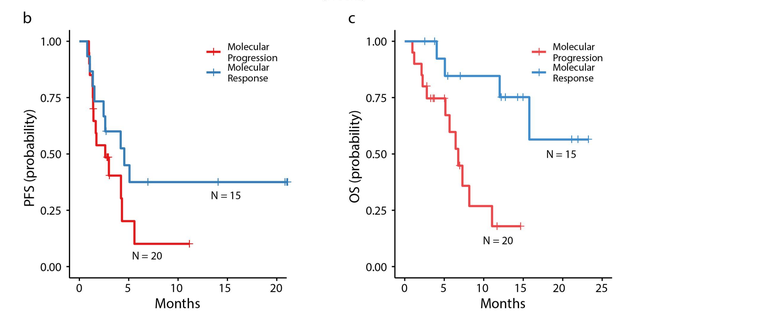


Figure 4. Swimmer's plot and survival analyses for mR vs. mPD.

Conclusions

BR.36 stage 1 established the definition, timing and concordance of ctDNA molecular response with radiographic response. These findings are incorporated in the randomized, ctDNA-interventional second stage of the trial, which utilizes ctDNA molecular response after 2 cycles of pembrolizumab to identify patients with mPD who are randomized to treatment intensification with pembrolizumab and chemotherapy.

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