Acute and Early Circulating Tumor DNA Dynamics in Metastatic Triple-Negative Breast Cancer Targeted Therapy Phase Ib/II Clinical Trials

Briana To[1,2*], Vishnu Prasath[1,2*], Deloris Veney[1,2], Christian Rolfo[1,2], Viktor Adalsteinsson[4], Nancy U. Lin[5], Sara Tolaney[5], Heather A. Parsons[5], Robert Wesolowski[1,2,3+], Dionisia Quiroga[1,2,3+], Daniel Stover[1,2,3]

[1]Ohio State University College of Medicine, Columbus, OH, USA
[2]The Ohio State University Comprehensive Cancer Center, Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, Columbus, OH, USA
[3]Stefanie Spielman Comprehensive Breast Center, Columbus, OH, USA
[4]Broad Institute of Harvard and Massachusetts Institute of Technology; Massachusetts Institute of Technology, Cambridge, MA, USA
[5]Dana-Farber Cancer Institute, Boston, MA, USA

The James
THE OHIO STATE UNIVERSITY
COMPREHENSIVE CANCER CENTER

Background

- For patients with advanced cancer, the proportion of tumor-derived DNA in circulation ('tumor fraction'/TF) has been shown to be prognostic across multiple cancer types, including metastatic breast cancer (MBC).
- Metastatic triple-negative breast cancer (mTNBC) is a poor prognosis subset of breast cancer characterized by higher circulating ctDNA TF relative to other breast cancer subtypes.
- There is evidence that early change in TF may correlate with response to therapy, potentially offering a rapid response biomarker for early phase studies.
- While ctDNA has a half-life of minutes to hours, little is known regarding TF dynamics during and in the hours immediately after infusion of targeted or cytotoxic therapies.
- Additionally, prior ctDNA studies have suggested a potential 'surge' or 'transient peak' of ctDNA immediately following therapy initiation due to induction of rapid cell death.
- In this study, we characterize ctDNA dynamics during the peri-infusion period of targeted and cytotoxic therapies. Using banked samples from four phase Ib/II clinical trials, we further assessed whether changes in TF were associated with treatment response and progression-free survival.

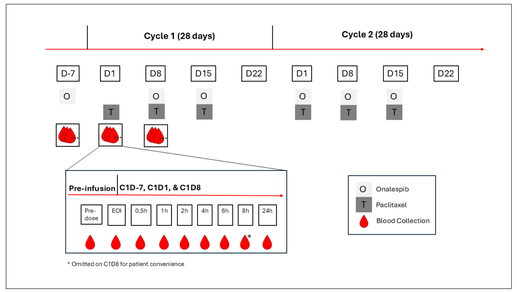
Methods

Banked plasma samples were identified from four phase Ib/II clinical trials:

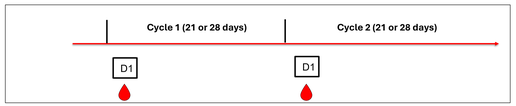
1. Heat shock protein 90 (HSP90) inhibitor Onalespib with Paclitaxel (NCT02474173)
2. MEK inhibitor Trametinib alone and in combination with AKT inhibitor GSK2141795/Uprosertib (NCT01964924)
3. Multi-kinase inhibitor Cabozantinib monotherapy (NCT02260531)
4. JAK1/2 inhibitor Ruxolitinib monotherapy(NCT01562873).

Study design

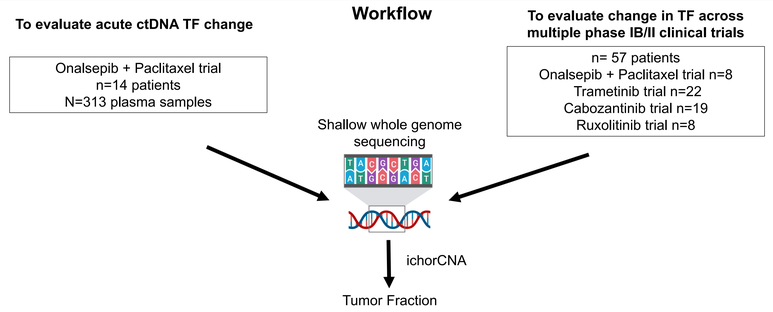
1. Onalespib with Paclitaxel (NCT02474173)



3-4. Remaining studies (NCT01964924, NCT02260531, NCT01562873)



Methods



Results

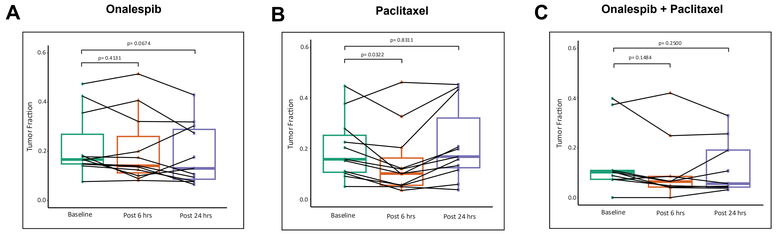


Figure 1 Tumor fraction change from baseline compared to 6 and 24 hours post-infusion of Onalespib (A), Paclitaxel (B) and combination of Onalespib and Paclitaxel (C). There was significant decline in TF from pre-infusion to 6 hours for Paclitaxel alone (Wilcoxon signed rank p=0.03) but no significant change for Onalespib alone or Onalespib + Paclitaxel from pre-infusion to 6- or 24-hours.

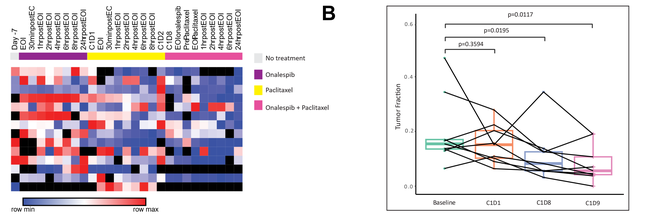


Figure 2 (A) Heatmap depicting tumor fraction at various timepoints post-treatment during cycle 1. **(B)** Changes in TF at baseline compared to C1D1, C1D8 and C1D9. There was a significant decline in TF from baseline day -7 to pre-infusion on day 8 and 24 hours after the last treatment of cycle 1 (C1D9).

Results

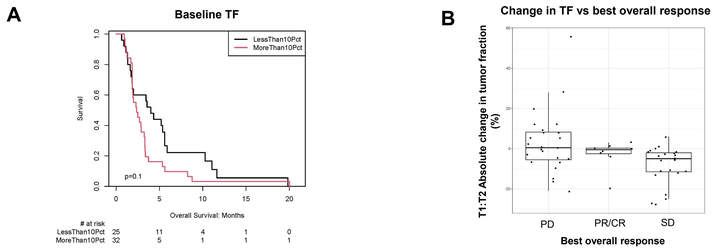


Figure 3 (A) Patients who had TF below 10% at baseline was not associated with improve progression free survival (PFS) (log-rank p=0.01). **(B)** The absolute change in tumor fraction from pre-treatment (T1) to 14-28 days after treatment initiation (T2) was significantly associated with best overall response (ANOVA p=0.01). PD= progressive disease, PR= partial response, CR= complete response, SD= stable disease.

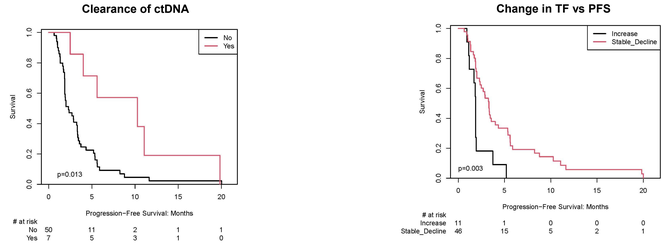


Figure 4 (A) Clearance of ctDNA from T1:T2 was associated with significantly longer PFS (median PFS 10.3 months clearance vs. 2.3mo no clearance; log-rank p=0.013). **(B)** A stable or decline in ctDNA post-treatment was significantly associated with improved PFS (long-rank p=0.003).

Conclusion

There was no significant 'surge' in ctDNA TF within minutes to 24-hours of infusion of a targeted therapy, cytotoxic chemotherapy, or both in combination. Stability or decline of ctDNA TF 14-28 days after initiation of targeted therapy trial was associated with objective response and prolonged PFS. This supports further research on ctDNA dynamics immediately after systemic therapy initiation, particularly in the context of early phase trials for mTNBC.

References

- Stover, Daniel G., Heather A. Parsons, Gavin Ha, Samuel S. Freeman, William T. Barry, Hao Guo, Alish D. Choudhury et al. "Association of cell-free DNA tumor fraction and somatic copy number alterations with survival in metastatic triple-negative breast cancer." *Journal of Clinical Oncology* 36, no. 6 (2018): 543-553.
- Lo, YM Dennis, Sing-Fai Leung, Lisa YS Chan, Anthony TC Chan, Kwok-Wai Lo, Philip J. Johnson, and Doly P. Huang. "Kinetics of plasma Epstein-Barr virus DNA during radiation therapy for nasopharyngeal carcinoma." *Cancer research* 60, no. 9 (2000): 2351-2355.
- Tie, Jeanne, Isaac Kinde, Yuxuan Wang, Hui-Li Wong, Justin Roebert, Michael Christie, Mark Tacey et al. "Circulating tumor DNA as an early marker of therapeutic response in patients with metastatic colorectal cancer." *Annals of Oncology* 26, no. 8 (2015): 1715-1722.
- Tolaney, Sara M., David R. Ziehr, Hao Guo, Mei R. Ng, William T. Barry, Michaela J. Higgins, Steven J. Isakoff et al. "Phase II and biomarker study of cabozantinib in metastatic triple-negative breast cancer patients." *The oncologist* 22, no. 1 (2017): 25-32.
- Prasath, Vishnu, Hinda Boutrid, Robert Wesolowski, Mahmoud Abdel-Rasoul, Cynthia Timmers, Maryam Lustberg, Rachel M. Layman et al. "Phase II study of MEK inhibitor trametinib alone and in combination with AKT inhibitor GSK2141795/uprosertib in patients with metastatic triple negative breast cancer." *Breast cancer research and treatment* 210, no. 1 (2025): 179-189.
- Stover, Daniel G., Carlos R. Gil Del Alcazar, Jane Brock, Hao Guo, Beth Overmoyer, Justin Balko, Qiong Xu et al. "Phase II study of ruxolitinib, a selective JAK1/2 inhibitor, in patients with metastatic triple-negative breast cancer." *NPJ Breast cancer* 4, no. 1 (2018): 10.
- Williams, Nicole O., Dionisia Quiroga, Courtney Johnson, Adam Brufsky, Mara Chambers, Saveri Bhattacharya, Maria Patterson et al. "Phase Ib study of HSP90 inhibitor, onalespib (AT13387), in combination with paclitaxel in patients with advanced triple-negative breast cancer." *Therapeutic Advances in Medical Oncology* 15 (2023): 17588359231217976.

Funding: PELOTONIA UH3 CA239105