Translational Biomarkers : Key Drivers of Clinical Outcomes in Oncology: Insights from Next-Generation Sequencing and Multi - Omic Profiling

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What is Exploratory Biomarker Analysis In Oncology ?

- **Identifies Potential Biomarkers:** Investigates genes, proteins, or metabolites in cancer patients to uncover biomarkers associated with disease progression, treatment response, and resistance.
- **Enhances Personalized Treatment:** Aims to develop targeted therapies by tailoring treatment based on individual biomarkers, optimizing outcomes for specific patient subgroups.
- **Lays Foundation for Drug Development:** Provides critical insights for early-stage drug development, enabling better patient stratification, safety monitoring, and understanding of treatment mechanisms.

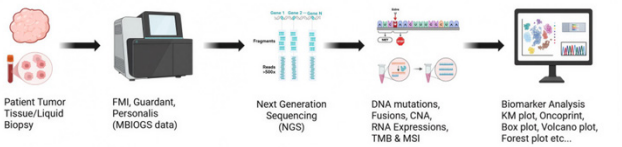
Early-Phase (Phase 1/2) Objective:

Focus on biomarkers indicating **target engagement** and pathway modulation, which support **pharmacodynamic activity** and potential **predictive value**.

Late-Phase (Phase 3/4) Objective:

Aim to reveal dynamic biomarker shifts associated with **clinical outcomes**, **resistance mechanisms**, and **tumor evolution**.

Data Collection (NGS Based)



Breast Cancer - (NCT04606446)

Why the indication is important

- ER+HER2− metastatic breast cancer often develops resistance after multiple lines of therapy.
- There is a strong unmet need for novel targets and drugs with durable antitumor activity in this heavily pretreated setting.

Impact of the biomarker (KAT6A/B)

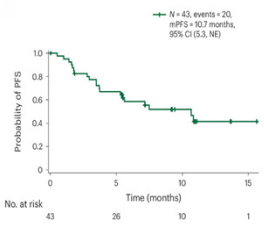
- KAT6A and KAT6B are histone lysine acetyltransferases driving tumor growth in ER+ breast cancer.
- Inhibition with PF-07248144 demonstrated proof-of-concept that these are druggable targets, improving outcomes.

How the analysis happened & conclusion

- Phase 1 trial (n=107) evaluated safety, PK/PD, and efficacy of (PF-07248144) as monotherapy and with fulvestrant.
- The combination showed **ORR 30.2% (95% CI 17.2–46.1) and median PFS 10.7 months**, with tolerable safety, supporting further development.

	PF-07248144 5mg q.d. Part 2A (N=35)	Combination PF-07248144 5mg q.d. + fulvestrant 500mg Parts 1B+2B (N=43)								
	N=35	Total N=43	2L N=23	3L+ N=20	Fulv treated N=5	Fulv naive N=38	ESR1MT N=24	ESR1WT N=18	PIK3CA/AKT1/ PTEN MT N=19	PIK3CA/AKT1/ PTEN WT N=23
Objective response (CR+PR), n (%)	4 (11.4)	13 (30.2)	5 (21.7)	8 (40.0)	3 (60.0)	10 (26.3)	8 (33.3)	5 (27.8)	5 (26.3)	8 (34.8)
95% CI*	3.2–26.7	17.2–46.1	7.5–43.7	19.1–63.9	14.7–94.7	13.4–43.1	14.5–52.2	7.1–48.5	8.5–46.1	15.3–54.2
Median duration of response (95% CI)*	12.0 (7.4–NE)	9.2 (7.2–NE)	NE (5.5–NE)	9.2 (7.2–NE)	N/A	N/A	9.2 (5.8–NE)	NE (NE–NE)	7.2 (5.5–NE)	NE (9.2–NE)
Disease control (CR+PR+SD+ non-CR/non-PD), n (%)	18 (51.4)	33 (76.7)	16 (69.6)	17 (85.0)	5 (100.0)	28 (73.7)	21 (87.5)	12 (66.7)	13 (68.4)	20 (87.0)
95% CI*	34.0–68.6	61.4–88.2	47.1–86.8	62.1–96.8	47.8–100.0	56.9–86.6	67.6–97.3	41.0–86.7	43.4–87.4	66.4–97.2
CBR, n (%)	11 (31.4)	22 (51.2)	10 (43.5)	12 (60.0)	4 (80.0)	18 (47.4)	12 (50.0)	10 (55.5)	9 (47.4)	13 (56.5)
95% CI*	16.9–49.3	35.5–66.7	23.2–65.5	36.1–80.9	28.4–99.5	31.0–64.2	29.1–70.9	30.8–78.5	24.4–71.1	34.5–76.8
mPFS, (95% CI)*	3.3 (2.0–5.8)	10.7 (5.3–NE)	NE (3.5–NE)	10.7 (5.5–NE)	N/A	N/A	10.7 (5.5–NE)	NE (3.5–NE)	7.2 (2.8–NE)	10.8 (5.6–NE)

*Clopper-Pearson method used. †Brookmeyer and Crowley method used. ‡L, with at least one prior line of treatment; 3L+, as third line and above; Fulv, fulvestrant; N/A, not available; NE, not evaluable.



BEACON (NCT02928224)

Why the indication is important

- ~10% of mCRC harbors **BRAF V600E**, associated with poor prognosis.
- **BEACON CRC** established Enco+Cetux (±Bini) as an effective, approved treatment.

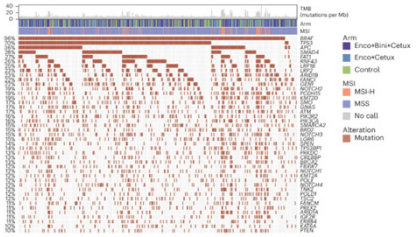
Impact of the biomarker (BRAF V600E)

- Benefit seen across subtypes, stronger in **immune-enriched tumors**.
- **ctDNA tracked outcomes**; resistance emerged via RAS, MAP2K1, MET, with TP53 linked to MET amplification.

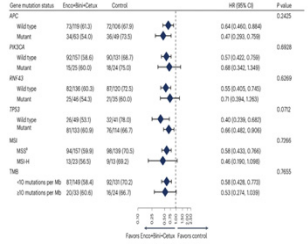
How the analysis happened & conclusion

- Integrated **WES, transcriptome sequencing, and ctDNA profiling** in >600 patients (largest BRAF V600E–mCRC dataset).
- Confirmed benefit of Enco+Cetux (±Bini), mapped **resistance pathways** and highlighted immune context in response.
- Provides insights to guide biomarker-driven treatment and resistance strategies.

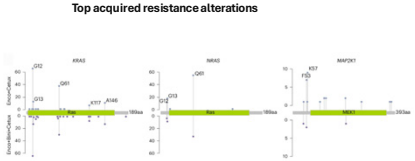
Mutational profiling of patients with BRAF-V600E-mutant mCRC



Association between OS and tumor baseline mutational status



Top acquired resistance alterations



Characterization of acquired putative resistance alterations.

BREAKWATER (NCT04607421)

Why the indication is important

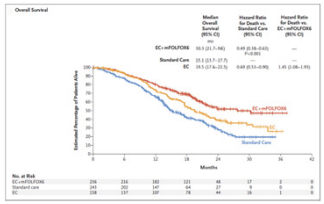
- BRAF V600E-mutated mCRC is aggressive with poor survival; median OS with standard care was **15.1 months**.
- First-line EC+mFOLFOX6 doubled OS to **30.3 months (HR for death 0.49; P<0.001)**.

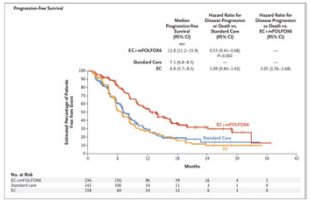
Impact of the biomarker (BRAF V600E)

- The mutation predicts poor response to standard chemo, with median PFS only **7.1 months**.
- Targeted therapy improved PFS to **12.8 months (HR for progression/death 0.53; P<0.001)**.

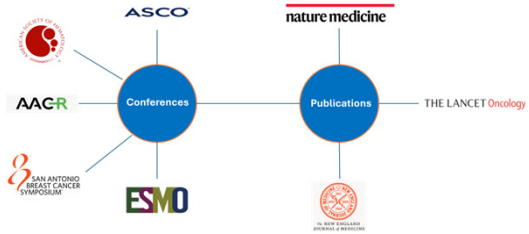
How the analysis happened & conclusion

- Phase 3 trial randomized patients to EC, EC+mFOLFOX6, or standard care; endpoints were ORR, PFS, OS.
- EC+mFOLFOX6 showed significantly higher response (ORR odds ratio **2.44; P<0.001**) and survival benefit.





Scientific Communities



Conclusion

From Discovery to Design - A Long Road for Biomarkers

Biomarker discovery in exploratory analyses is only the beginning. Translating these findings into clinical trial design requires deep biological understanding, extensive validation, and often, years of research.