Poster PP22

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

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ABSTRACT:

Exploratory biomarker analysis integrates data from early and late phase oncology trials to deliver translational insights for scientific presentations (AACR, ASCO, ESMO) and future publications. Using Next-Generation Sequencing and Multi-Omic profiling (Genomic, Transcriptomic, Proteomic), we analyse tumour tissue and liquid biopsy samples longitudinally to evaluate treatment-related biological changes.

In early-phase trials, we observe biomarkers indicating target engagement and pathway modulation, supporting pharmacodynamic activity and potential predictive value. Late-phase analyses reveal dynamic biomarker shifts associated with clinical outcomes, resistance mechanisms, and tumour evolution. Integrated data highlights signatures related to immune activation, DNA damage response, and adaptive resistance.

Although not included in the Clinical Study Report, these findings provide critical translational context. This work demonstrates the value of embedding biomarker research across development stages to inform trial design and guide precision oncology strategies. Key results will be presented through visual data displays, case examples, and comparative analyses to emphasize clinical relevance.

INTRODUCTION:

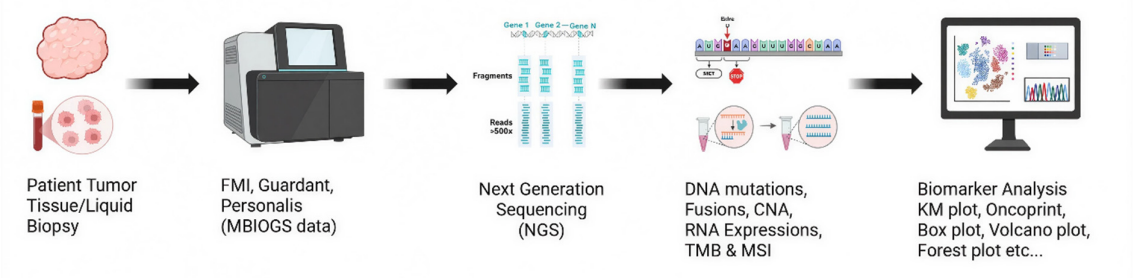
Exploratory biomarker analysis in oncology aims to identify potential biomarkers genes, proteins, or metabolites that are closely associated with cancer progression, treatment response, and resistance. By analyzing these biomarkers, we can develop personalized therapies that tailor treatments to individual patients, leading to improved outcomes. Additionally, this approach plays a crucial role in early-stage drug development, offering valuable insights for patient selection in clinical trials, monitoring safety, and enhancing our understanding of how treatments work, ultimately driving more effective and targeted cancer therapies.

Biomarker Focus in Clinical Phases

Early-Phase (Phase 1/2): Focuses on biomarkers that indicate target engagement and pathway modulation, crucial for understanding pharmacodynamics and predicting treatment success.

Late-Phase (Phase 3/4): Aims to track biomarker shifts over time, identifying changes linked to resistance mechanisms and tumor evolution, helping to predict long-term clinical outcomes.

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)

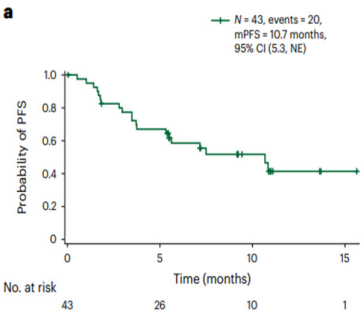
- KAT6A and KAT6B are histone lysine acetyltransferases driving tumor growth in ER+ breast cancer.
- Inhibition with Prifetrastat (PF-07248144) demonstrated proof-of-concept that these are druggable targets, improving outcomes.

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	*ESR1* MT *N*=24	*ESR1* WT *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[a]	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	6.5–46.1	15.3–54.2
Median duration of response (95% CI)[b]	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[a]	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[a]	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[b]	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)

[a]Clopper–Pearson method used. [b]Brookmeyer and Crowley method used. 2L, 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.

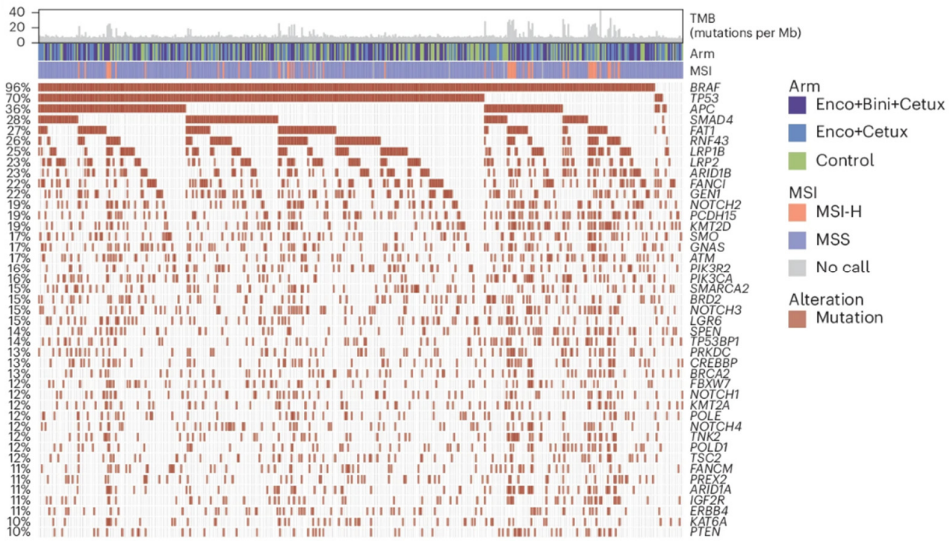
Impact of the biomarker (BRAF V600E)

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

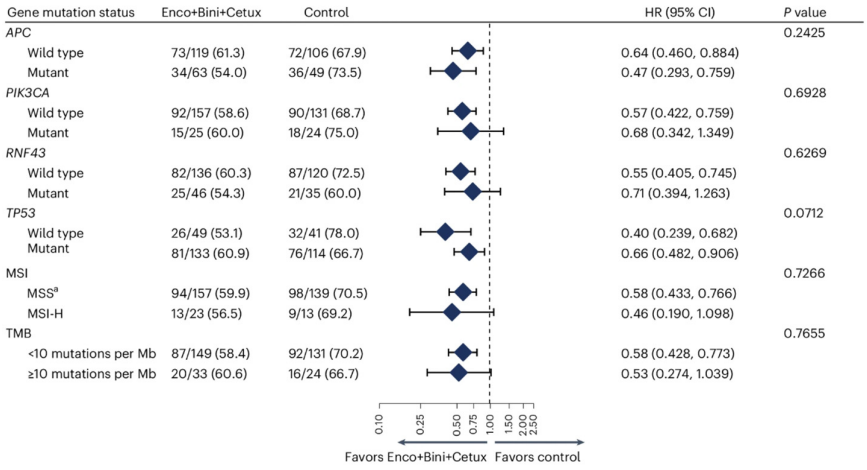
How the analysis happened & conclusion

- 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

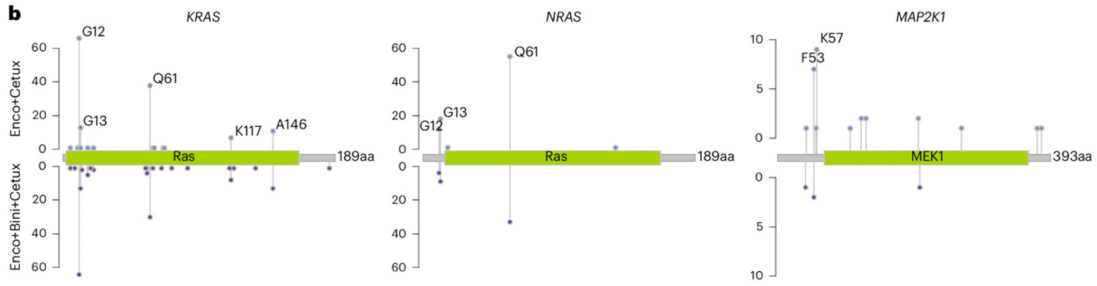


Association between OS and tumor baseline mutational status

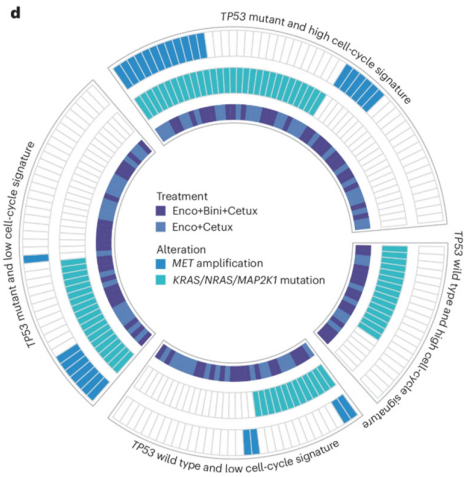


Gene mutation status	Enco+Bini+Cetux	Control	HR (95% CI)	*P* value
APC				0.2425
Wild type	73/119 (61.3)	72/106 (67.9)	0.64 (0.460, 0.884)	
Mutant	34/63 (54.0)	36/49 (73.5)	0.47 (0.293, 0.759)	
PIK3CA				0.6928
Wild type	92/157 (58.6)	90/131 (68.7)	0.57 (0.422, 0.759)	
Mutant	15/25 (60.0)	18/24 (75.0)	0.68 (0.342, 1.349)	
RNF43				0.6269
Wild type	82/136 (60.3)	87/120 (72.5)	0.55 (0.405, 0.745)	
Mutant	25/46 (54.3)	21/35 (60.0)	0.71 (0.394, 1.263)	
TP53				0.0712
Wild type	26/49 (53.1)	32/41 (78.0)	0.40 (0.239, 0.682)	
Mutant	81/133 (60.9)	76/114 (66.7)	0.66 (0.482, 0.906)	
MSI				0.7266
MSS[a]	94/157 (59.9)	98/139 (70.5)	0.58 (0.433, 0.766)	
MSI-H	13/23 (56.5)	9/13 (69.2)	0.46 (0.190, 1.098)	
TMB				0.7655
<10 mutations per Mb	87/149 (58.4)	92/131 (70.2)	0.58 (0.428, 0.773)	
≥10 mutations per Mb	20/33 (60.6)	16/24 (66.7)	0.53 (0.274, 1.039)	

Top acquired resistance alterations



Characterization of acquired putative resistance alterations.



BREAKWATER (NCT04607421)

Why the indication is important

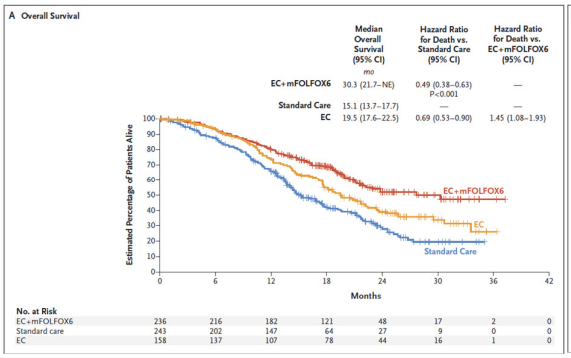
- BRAF V600E-mutated mCRC is aggressive with poor survival; median OS with standard care was 15.1 months.
- First-line EC+mFOLFOX6 doubled OS to 30.3 months (HR for death 0.49; P<0.001).

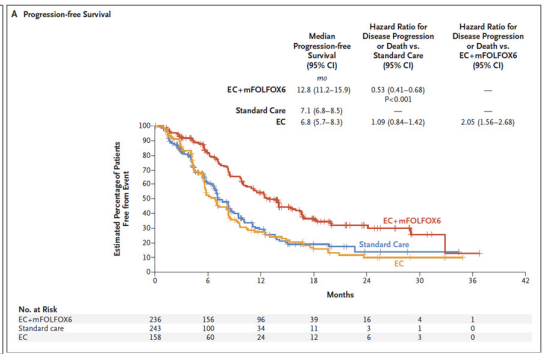
Impact of the biomarker (BRAF V600E)

- 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).

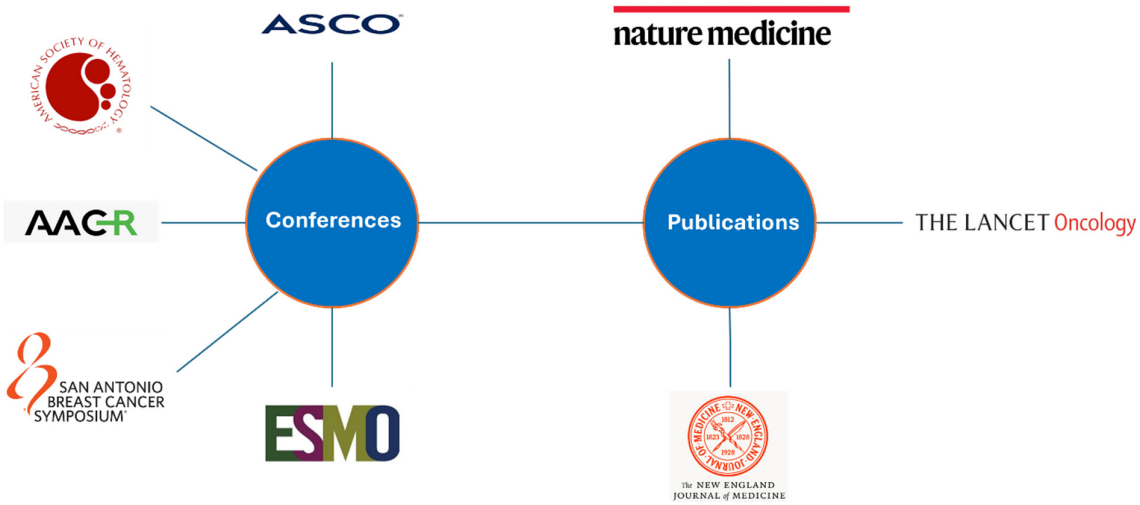
How the analysis happened & conclusion

- 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:

Biomarker discovery in exploratory analyses marks just the beginning of a long and complex journey. Translating these initial findings into clinical trial design requires a deep biological understanding, rigorous validation, and often, years of research. Well-established examples of biomarker-driven trial design include BRAF V600 mutations in melanoma and colorectal cancer, which enable targeted therapies; ALK fusions in non-small cell lung cancer (NSCLC), used in enrichment designs; HER2 amplification in breast cancer, leading to HER2-targeted therapies; and PD-L1 expression in immuno-oncology, crucial for patient selection. In Pfizer's biomarker-informed trials, ESR1 mutations led to the creation of a biomarker cohort in VERITAC-2, and IB6 high expression informed an SV ADC trial. Notably, these biomarkers were already well-characterized before the trials were designed. A discovery example like CCNE1 expression in the PALOMA-3 trial shows potential as a biomarker for CDK4/6 inhibitors (like Palbociclib), though the findings are still promising but not yet validated for trial design. The key takeaway is that the impact of biomarkers on trial design is a marathon, not a sprint. Discovery is just the first step; validation and biological insight are essential before clinical application.

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ACKNOWLEDGMENTS:

We would like to express our sincere thanks to the following individuals and teams for their contributions to this presentation:

- Douglas Laird
  Translational Oncology Scientist | Pfizer

- Shibing Deng & Michelle Saul
  Translational Biomarker Statistics | Pfizer

- Vikram Venugopal & Muhammed Farzan K
  Specialized Data Programmers - Exploratory Biomarker Analysis | Pfizer

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