Evolution of Comprehensive Genomic Profiling in Precision Medicine

Dave Fabrizio
Foundation Medicine
VP, Early Clinical Development

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Disclosures

I am an employee of Foundation Medicine and stock-holder in Roche

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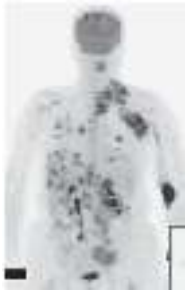
Increasing Precision Medicine Complexity Requires Biomarker Innovation

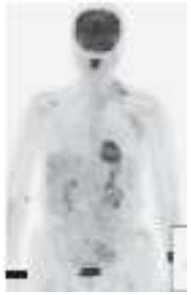
Precision medicine has evolved from simplified single agent targeted therapy to include more complex immunotherapy, synthetic lethality and combination treatment strategies

Vemurafenib in *BRAF* V600E mutated melanoma

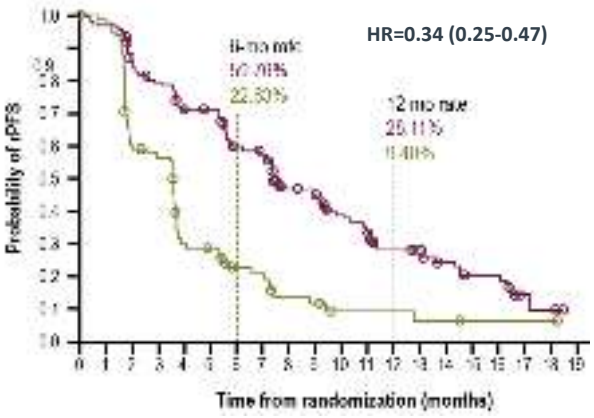
Baseline



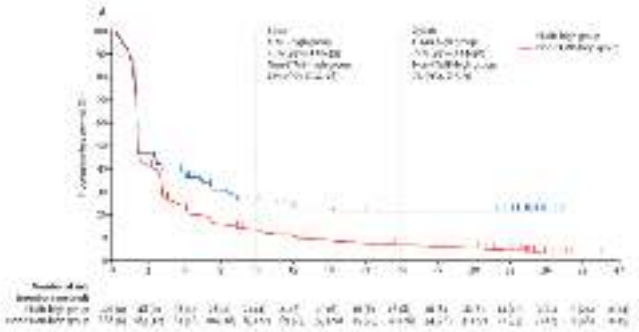
15 days



HRD Associated PFS of olaparib Treated mCRPC



TMB Associated PFS of pembrolizumab in solid tumors



Flaherty, et al. (2010) *N Engl J Med* | Hussain, et al. (2019) *N Engl J Med* | Marabelle, et al. (2020) *Lancet Onc*

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Real-World Clinico-Genomic Database is the Sandbox to Test Novel Biomarker Hypotheses

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Comprehensive genomic profiling across hundreds of cancer-related genes for each patient's tumor

+

flatiron

Real-world, longitudinal patient-level clinical data from Electronic Health Records (EHRs) from cancer clinics

Real-World Clinico-Genomic Database:

- ☐ New biomarker discovery
- ☐ Hypothesis testing
- ☐ Elucidate complex decision trees

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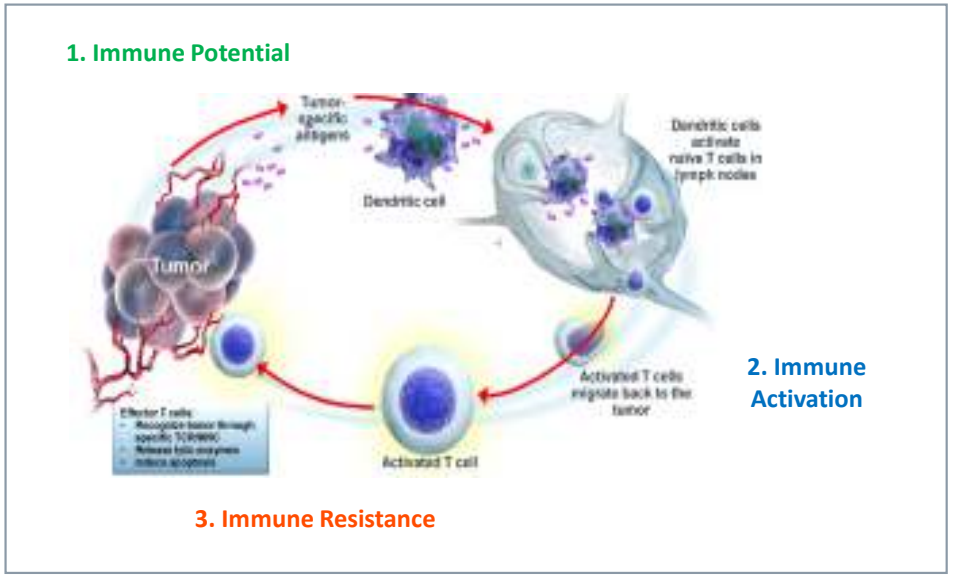
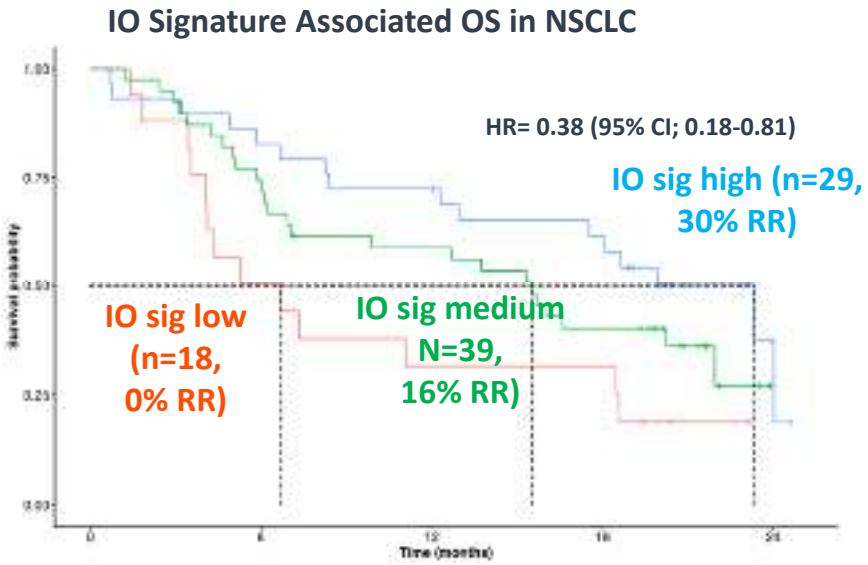
Complex Biomarkers Often Integrate Multiple Solutions

- IO signatures may be multi-modal, including TMB, gene expression and resistance mechanisms
- We must identify rational combinations of individual components to build better utility provide more insight into clinical decision making

Precision Medicine Guided Immunotherapy Combinatorial Solutions





Fabrizio et al., SITC 2022, to be presented

Picture adapted from Chen, Mellman; ***Immunity***; 2013, v.39, issue 1, p.1-10

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The Patient Journey Today

How do tissue and plasma-based testing fit into the typical cancer patient's journey?

Detection	Diagnosis	Early disease		Metastasis	Next line
Early disease detection	Disease classification Prognosis Treatment decision	Risk of recurrence	Molecular Relapse	Treatment decision Id site of metastasis	Resistance Mechanism based treatment decision ID site of metastasis

FMI today

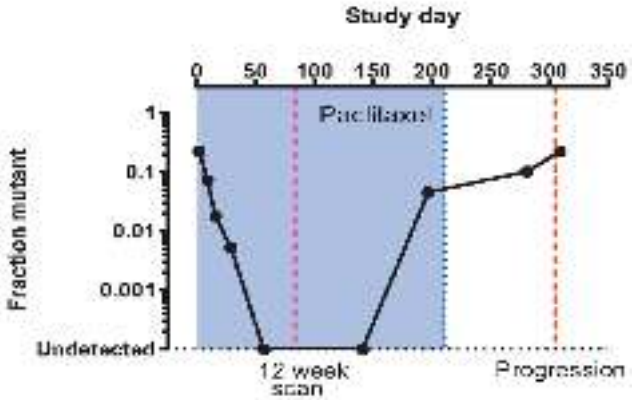
Relevance of tissue vs. plasma

*Opportunity for FMI to expand with **new platforms***

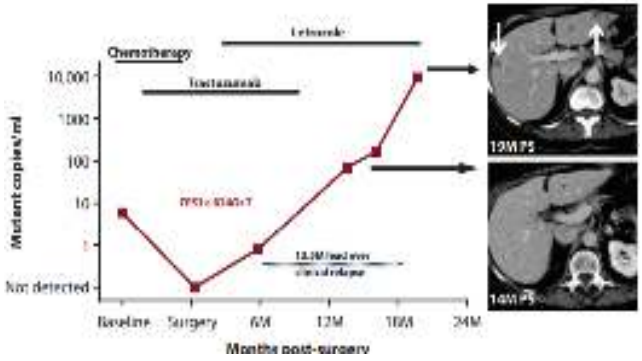
*Opportunity for FMI to expand **existing platforms***

PLASMA **TISSUE**

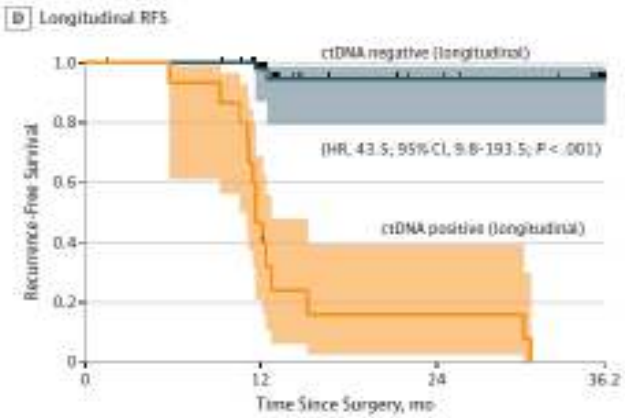
Monitoring ctDNA for Therapy Utilization or Minimal Residual Disease



Late-stage therapy monitoring



Recurrence detection



MRD detection

Change in ctDNA levels can associate with response to therapy or risk of recurrence

- Solutions can be both tumor informed (tracking personalized variants) or uninformed (e.g. methylations signatures)

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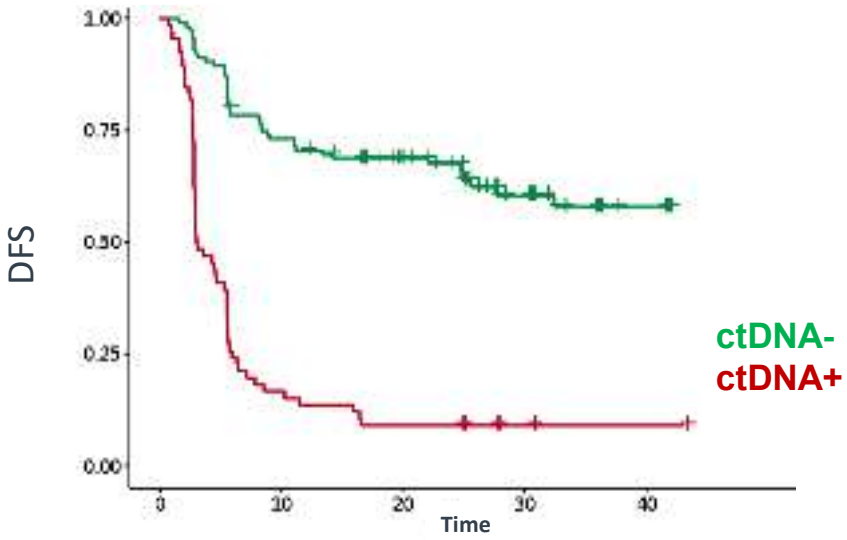
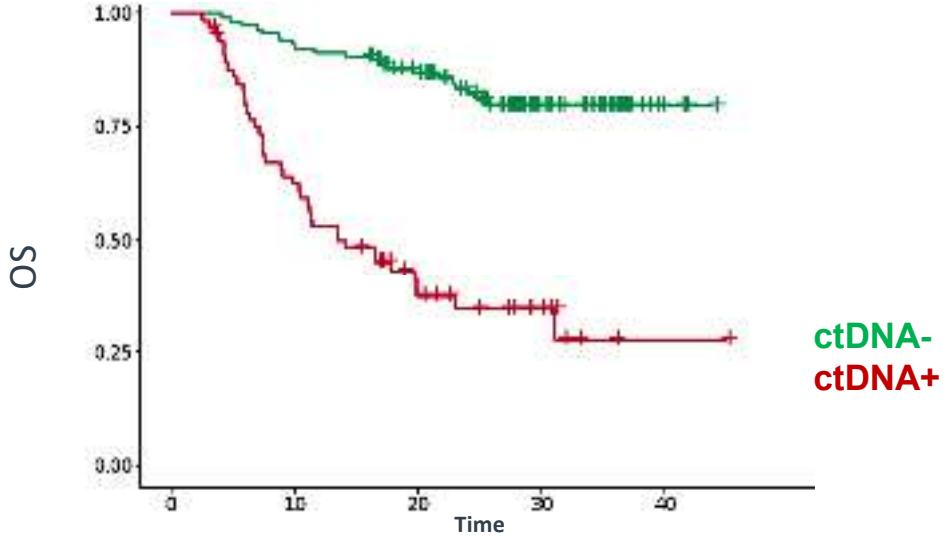
Circulating Tumor DNA Associates with Worse Survival In Early-stage Bladder Cancer (IMvigor 010- Observation arm)





	ctDNA+	ctDNA-
Patients with events	60 (91%)	41 (37%)
Median DFS [95CI]	3.0 [2.9-5.5]	Not reached
Hazard Ratio [95CI]; p-value	5.73 [3.81–8.63]; <0.0001	

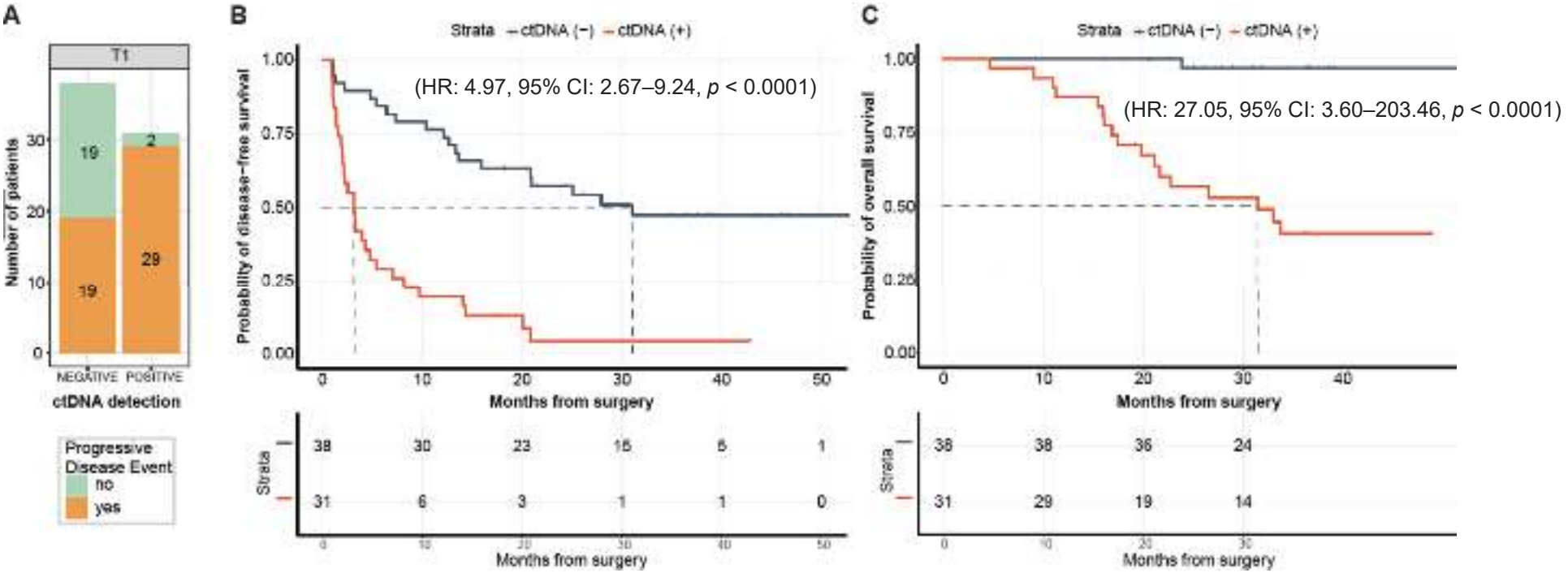
	ctDNA+	ctDNA-
Patients with events	41 (62%)	21 (18%)
Median OS [95CI]	14.1 [10.4–19.9]	Not reached
Hazard Ratio [95CI]; p-value	5.72 [3.35–9.74]; <0.0001	

ctDNA+ Prevalence for F1 Tracker was 36% in 182 patients analyzed ~10 weeks post-surgery from the IMvigor010 urothelial carcinoma study -observational arm only

FoundationOne Tracker ctDNA positivity identified patients with worse prognosis in IMVigor010

Circulating Tumor DNA Associates with Worse Survival In Metastatic Colorectal Cancer (PREDATOR)

Post-operative timepoint was used to assess molecular residual disease with F1 Tracker



Lonardi, et al., Int. J. Mol. Sci., 2022

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Tumor naive strategy for monitoring

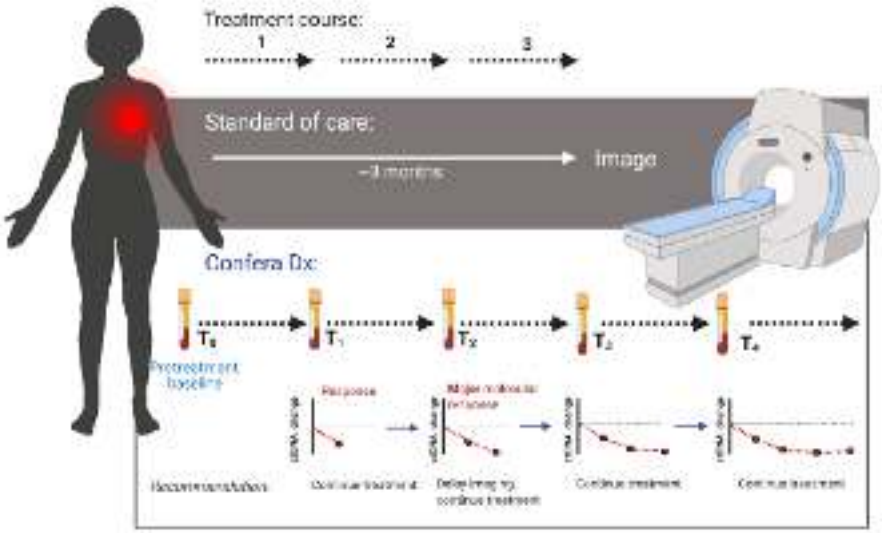
Confera monitoring assay

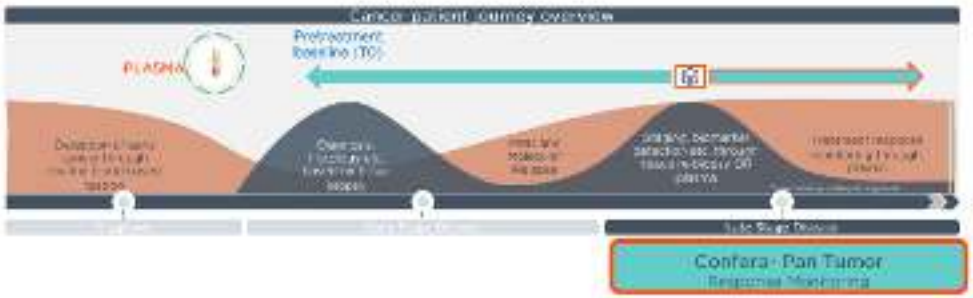
Confera monitors for circulating tumor DNA (ctDNA) in blood

- Low pass whole genome sequencing
- Assessing global copy number changes and methylation
  - Combined model to assess change in ctDNA levels over time
- Uses pretreatment liquid sample baseline
  - No tissue required

Goal: Treatment response monitoring

- Late stage monitoring
- Monitoring timepoints compared to pretreatment baseline





The Patient Journey Tomorrow

Expanded solutions to meet the needs for the future of precision medicine

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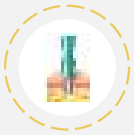
PLASMA



TISSUE