FRIENDS OF CANCER RESEARCH

Annual Meeting

Panel 2

Identifying and Establishing the Role of Circulating Tumor DNA in Cancer Drug Development

#FriendsAM18

Wifi: RitzCarlton_CONFERENCE Password: fcr18

Panel 2 Participants

Moderator: Geoffrey Oxnard, Dana Farber Cancer Institute

- Darya Chudova, Guardant Health
- Jamie Holloway, Patient Advocate
- David Shames, Genentech, A Member of the Roche Group
- Jean-Charles Soria, MedImmune
- Julia Beaver, U.S. FDA
- Reena Philip, U.S. FDA

EXPLORING THE USE OF CIRCULATING TUMOR DNA AS A MONITORING TOOL FOR DRUG DEVELOPMENT

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Friends of Cancer Research Annual Meeting

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Background

- Circulating tumor DNA (ctDNA) refers to DNA shed by tumors when undergoing cell apoptosis and necrosis
- ctDNA assays are minimally-invasive and convenient, and are increasingly well validated
- Broadly, three potential applications for ctDNA assays
  1. Molecular characterization (at diagnosis of resistance)
  2. Cancer detection (screening or minimal residual disease)
  3. Cancer monitoring

IDENTIFYING AND ESTABLISHING THE ROLE OF CIRCULATING TUMOR DNA IN CANCER DRUG DEVELOPMENT

FOCUS: DISEASE MONITORING

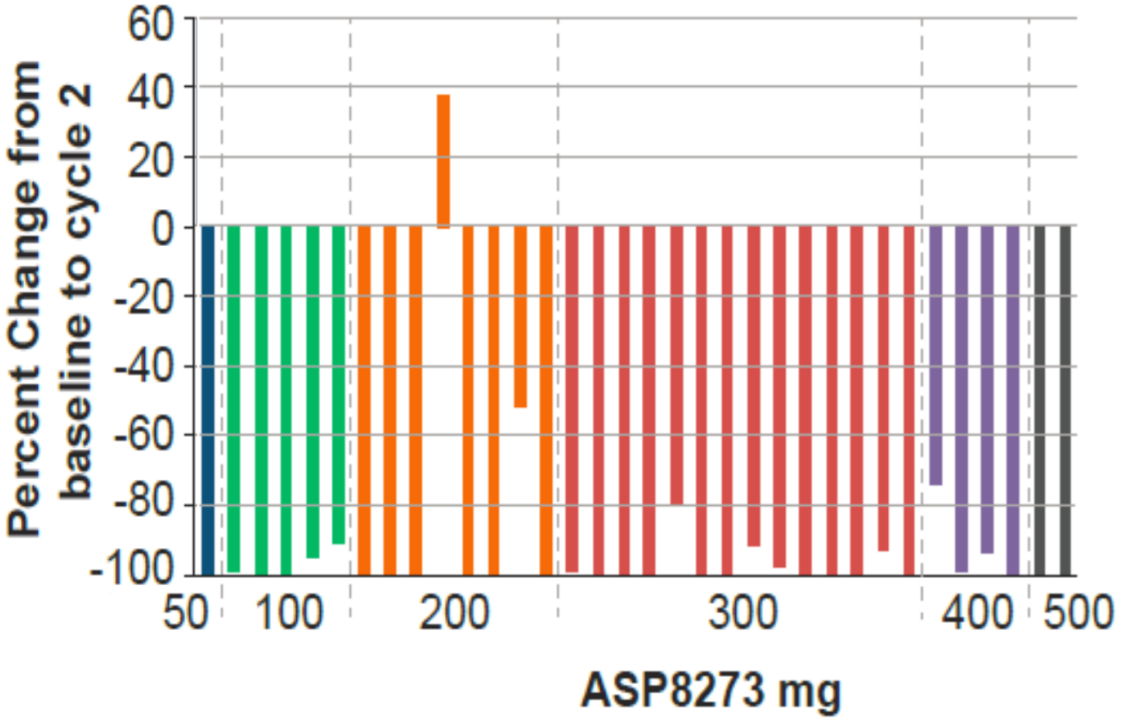
OBJECTIVES

1	2	3
Assess the current state of ctDNA as a monitoring tool	Suggest best practices for the use of ctDNA as a monitoring tool	Propose two potential opportunities for the operationalization of ctDNA in drug development

Serial genotyping of ctDNA in plasma

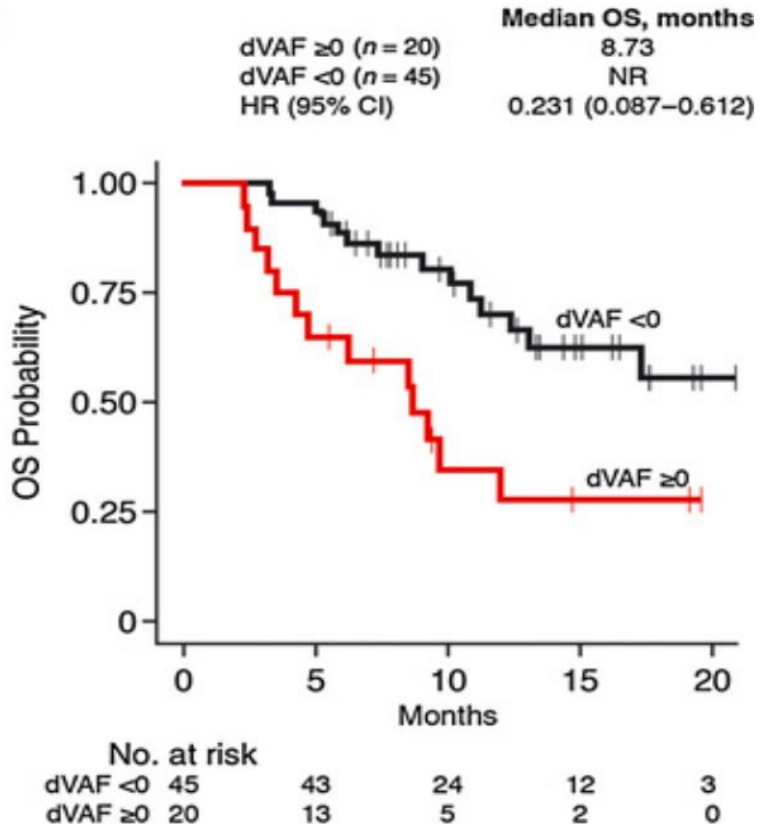
- In phase I dose escalation studies to complement dose finding:

Plasma EGFR T790M levels



Yu et al, CCR, 2017

- In phase II studies for evaluating treatment outcome:



Raja et al, CCR, 2018

Case Studies

Very little consistency across studies

Table 1: Case studies and study parameters

Parameters/Study	Mok et al., Clinical Cancer Research, 2015[14]	Yu et al., Clinical Cancer Research, 2017[15]	Raja et al., Clinical Cancer Research, 2018[16]
Histology	Stage IIIB and IV NSCLC	Advanced NSCLC patients with disease progression after EGFR TKI treatment	NSCLC and UC
# of patients	305	93	100 (28 discovery, 72 validation) and 29 (validation) from 2 different studies
Clinical trial	FASTACT-2 study	NCT02113813	ATLANTIC and Study 1108
ctDNA/cfDNA	cfDNA	cfDNA	ctDNA
Technology	Semi-quantitative—Cobas 4800 blood test (RT-PCR)	Quantitative—BEAMing PCR	Quantitative—NGS, targeted panel (Guardant 360)
Gene	EGFR	EGFR	Gene panel (73 genes)
Units	Copy/mL	% mutant EGFR cfDNA	Mean VAF
Timepoints	Baseline, cycle 3 (~12 weeks) and progression (PD)	Baseline, cycle 2	Baseline and 6 weeks-prior to 4th treatment
Median follow up time	Not specified	Not specified	Ranged between 9-15 months depending on study
Drug(s) being tested	Erlotinib (after gemcitabine/platinum)	ASP8273 (3rd generation EGFR TKI)	Durvalumab (anti PD-L1)
Clinical Response/ Outcome	ORR, PFS, OS	ORR	Tumor volume, PFS, OS
Tube	"collected according to standard procedures"	n/a	K2-EDTA
Timing of processing	"collected according to standard procedures"	n/a	n/a

Abbreviations: cfDNA, cell-free DNA; ctDNA, circulating tumor DNA; EDTA, ethylenediaminetetraacetic acid; *EGFR*, epidermal growth factor receptor; NGS, next generation sequencing; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-L1, programmed death-ligand 1; PFS, progression free survival; RT-PCR, real time- polymerase chain reaction; TKI, tyrosine kinase inhibitor; UC, urothelial carcinoma; VAF, variant allele fraction.

Best Practices

- Standardized practices that will help improve consistency across studies
- Consistency of ctDNA collection and reporting will help aggregate data from multiple studies

Table 2: Best practices for the use of ctDNA in disease monitoring

Best Practice	Recommendations
Material collection	
Timing	1. Collection at cycle 1, day 1 (screening sample may not be representative) 2. Early collection after 2-4 weeks 3. Collection at the time of restaging scans 4. Collection at or after progression (prior to next therapy)
Amount of material	• One 10ml tube is usually adequate for analysis • Recommend collection of a second 10mL tube for future bridging studies • Recommend saving the cell pellet to allow study of white blood cells if needed.
Tube type	• If site has capacity to spin down tubes locally within a few hours after collection, EDTA tubes would be adequate. Otherwise tubes including a DNA stabilization agent (e.g. Streck tubes) are preferred to allow delayed spinning of specimens
Detection platform technology	• Should be able to measure ctDNA changes quantitatively • Recommend quantification of variant allelic fraction, which can be calculated across various assays (e.g. ddPCR, NGS) • Platform should be validated to show optimal commutability against other assays (orthogonal approaches)
Analysis	• Consider calculation of percent change from baseline, similar to approach used for tumor measurements in imaging • Analysis should account for the possibility of mutations derived from clonal hematopoiesis. Sequencing of white blood cells can be useful for distinguishing this

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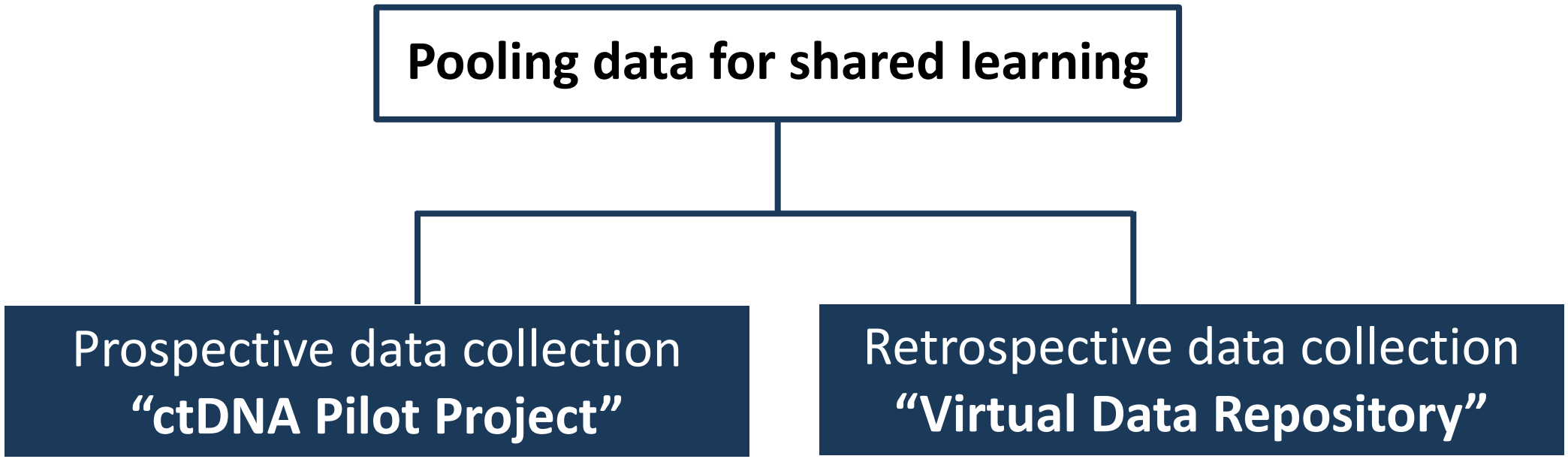
Friends ctDNA multi-stakeholder consortium



ctDNA Pilot Project: Monitoring therapeutic effect of immune checkpoint inhibitors

- Prospective collection of ctDNA data in standardized manner
- Ongoing or planned trials could include framework as part of their data collection strategy
- ctDNA data will be aggregated for multi-study analysis

Table 3: *Friends* ctDNA pilot project framework

Parameter	Proposed Pilot
Patient population	Patients with advanced/metastatic disease
Population size	As determined by the clinical trial or drug sponsor
Drug class	Immune checkpoint inhibitors
Trial phase	All phases
Technology for ctDNA assessment	ddPCR or NGS gene panel
Minimum Limit of Detection	0.2-0.25% VAF
Test tubes	If site has capacity to spin down tubes locally within a few hours after collection: EDTA. Otherwise tubes including a DNA stabilization agent (e.g. Steck tubes)
Timepoints	1. Collection at cycle 1, day 1 (screening sample may not be representative) 2. Early collection after 2-4 weeks 3. Collection at the time of restaging scans 4. Collection at or after progression (prior to next therapy)
Median follow up	6 months
Diagnostic endpoints	Relative percent change from baseline
Alterations (definition)	Mutations, insertions, deletions, amplifications, and fusions
Clinical endpoints	Raw tumor size/volume, ORR and PFS and/or OS, if applicable (trial dependent)
Adjustment factors	Age, gender, smoking status, baseline ECOG score, previous line of therapy, and histology

Virtual ctDNA Data Repository

Explore a framework for how to bring data together

- Existing data
- Prospective data

Analyze data from multiple studies

Table 4: Considerations for a virtual data repository

Issues	Questions
Core dataset	• What is the minimum core set of data elements that sponsors would feel comfortable sharing as part of a pilot project? • Should raw or analyzed data be uploaded to the repository? • What kind of case report data on clinical response is necessary?
Legal, ethical, and privacy concerns	Are there any legal, ethical, and/or privacy concerns for contributing data to a virtual repository?
Logistical concerns	
Data storage	Where would the data be stored? Would there be a maximum data storage value? Could this data be hosted on a cloud?
Data transfer	How would data be transferred/uploaded?
Blinding	Does the data need to be blinded?
Analytical opportunities	Will the data be analyzed as a meta-analysis, or could the data be combined and analyzed together?

Friends ctDNA multi-stakeholder consortium

Next steps:

1. *Friends* will seek to develop a multi-stakeholder consortium: interested members of the academic, diagnostics, government, pharmaceutical, and patient advocacy communities should request to join the ctDNA multi-stakeholder consortium;

2. The consortium will meet to discuss the feasibility of the initiatives discussed in this white paper; and

3. The consortium will implement the optimal approach to advance our understanding of ctDNA use in drug development

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