Sparkathon Project TimIOs:
A Pooled Analysis of Durable versus Transient Responders on Immunotherapy Trials

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On behalf of Team TimIOs

SITC Hurdle

- Understanding tumor heterogeneity is critical for developing the tools for predicting clinical responses

Problem

- Immunotherapy is a standard of care for many solid tumor types

- 20-40% of patients respond to checkpoint inhibitors

- The majority of patients do not respond

Problem

• Compartmentalization of clinical and tissue-derived data

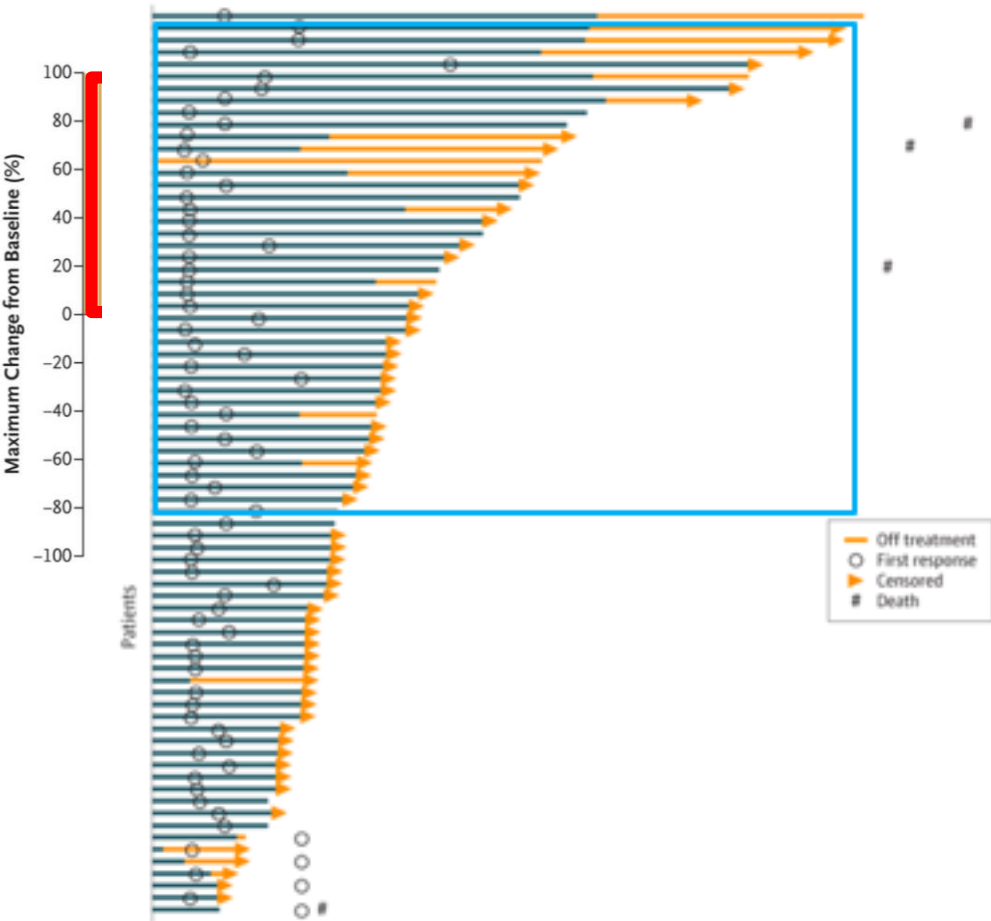• Need for a unified platform to analyze existing data

Innovative Solution

- A unified public/private consortium

- Honest broker to facilitate cross- institution collaboration

- Build a platform to identify fundamental differences between
  - **Durable vs transient responders**
  - Elite responders vs rapid progressors

Immunotherapy Trial X

Standard Definitions (RECIST 1.1):
1. Complete Response CR
2. Partial response PR (≥30% decrease in sum product diameters)
3. Stable disease (29% decrease to 19% increase)
4. PD (≥20% increase)

Non-Standard definitions
5. Aggressive PD (≥50% increase) by 12 weeks
6. Transient response (PR or CR lasting shorter than 6 months)
7. Durable response (PR or CR lasting longer than 2 years)

Comparative populations to analyze:
(A) durable vs transient response. (6 vs 7)
(B) complete response (so called 'elite' responders) vs patients with rapidly progressive disease
(1 vs 5)

Stage 1

Integrate transcriptomic data sets from completed anti-PD1 clinical trials to conduct a retrospective analysis

- Evaluate differences in durability of response
- Increase our understanding of the biology of durable vs transient responders and elite vs non-responders
- Generation of standardized transcriptomic signatures
- Development of predictive algorithms for patient response stratification
- Resulting data to be shared between all participants

Core Teams
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Primary Objectives

1A) Utilize existing transcriptomic data from RNA seq to develop immune gene expression signatures distinguishing

- transient vs durable responders (primary analysis)
- aggressive progression of disease vs elite responders (secondary analysis)

- Hypothesis: Tumors from durable vs transient responders have different immune gene expression profiles, which can be identified and used to identify novel biologic features of the host-tumor immune interaction, predict response, and improve patient selection.

- Defining immunosuppressive signatures associated with resistance to immunotherapy with checkpoint blockade may
  - inform the design of more effective combination therapies based on concurrent inhibition of relevant immune checkpoints
  - spare patients potential toxicity if unlikely to respond

Primary Objectives

- 1B) Utilize existing transcriptomic data from RNA seq to determine the relative expression of potentially pharmacologically targetable IS molecules in the TME, and to analyze data to identify new pathways and molecules critical to outcome.

  - Foxp3, PD-1, LAG3, TIM3, IDO1, PD-L1, PD-L2, TIGIT, ITGAM, arginase 1, adenosine receptor A2A, CD39, CD73 and TGF- beta

- Hypothesis: Negative immune regulators are over-expressed by tumor and immune cells in the TME of transient responders vs durable responders and patients with aggressive progression of disease vs complete responders.

Secondary Objective

- To compare tumor mutation load and T cell clonality of pre-treatment tumor infiltrating T cell populations between transient vs durable responders through exome sequencing, if data from DNA (exome) sequencing is available.

- Hypothesis: Tumor mutational load and T cell clonal diversity are higher in durable vs transient responders and patients with aggressive PD vs complete responders.

	Name of Trial	Tumor Type	Phase	Drug	No of Patients	ORR (%)	CR	PR	PD	PR /CR with PFS<1 yr	PR/CR who lived > 2 years (superior PFS)	
AstraZeneca	PACFIC	NSCLC	III	Durvalumab	709	28.4		9	232	73 (16.5%)	72.80%	
BMS	CHECKMATE-040	HCC	I/II	Nivo	214	19	3 (n)		39	68		
BMS	CHECKMATE-142	Colon-MSI-H	II	Nivo	74	32	2	22	21		57	6
BMS	CHECKMATE-037	Melanoma	III	Nivo	120	38	4	34	42			
BMS	CHECKMATE-067	Melanoma	III	Nivo	316	44	52	88	121		197	96
BMS	NCT02267343	Gastric or GE ju	III	Nivo	330	11.2						
BMS	CHECKMATE- 025	Renal	III	Nivo	410	25	4	99			329	11
BMS	CHECKMATE 141	HNSCC	III	Nivo	240	13.3	6	26			236	0
BMS	CHECKMATE 017	SquamousNSCLC	III	Nivo	135	20	1 (n)	26	56		114	0
BMS	CHECKMATE 057	Adeno NSCLC	III	Nivo	292	19	4	52	129		246	2
BMS	CHECKMATE 066	Melanoma	III	Nivo	210	40	16	68	69			
BMS	CHECKMATE 275	Urothelial	II	Nivo	270	19.6	6	46	104			
Genentech	NCT02108652	Urothelial	II	Atezolizumab	119	27 (23%)	11 (9%)	16 (13%)	43 (36%)		4	0
Genentech	OAK	NSCLC	III	Atezolizumab	425	58 (14%)	6 (1%)	52 (12%)	187 (44%)		75	2
Merck	KEYNOTE-055	HNSCC	II	Pembro	171	16	1 (n)					
Merck	KEYNOTE-059	Gastric	II	Pembro	259	11.2	1.90% only able to find presentations of the data and not a peer-reviewed publication					
Merck	KEYNOTE-001	NSCLC	III	Pembro	495	19.40%	0.8% (n=4)	23.6% (n=117)	34.5% (n=171)		24	2
Merck	KEYNOTE-002	Melanoma	III	Pembro	361 (intent to tre	22 and 28% (Per	9 (n) based on in	75 (n) based on i	170 (n) based on	Not readily avaliable, will need to	29+40 (Pembro 2mg/kg vs 10mg/kg) based on fi	
Merck	KEYNOTE-052	Urothelial	III	Pembro								
Merck	KEYNOTE-006	Melanoma	III	Pembro	556 (intent to tre	37 and 36% (Per	33 and 36 (n, Pe	70 and 64 (n, Pe	107 and 115 (n,	367 (total pop less number at risk	29 (Pembro q2+q3 wk tx populations)	
Merck	SARC 0128	Sarcoma	II	Pembro	80 (evaluable pt	18% and 5% for	1 (n, soft tissue)	6 and 2 (n, for S	18 and 29 (n, fo	4, (2 undif pleomorphic sarcoma,	2 (undif pleomorphic sarc) - expansion co-hort o	
Pfizer	Javelin Merkel-200	Merkel cell carc	II	Avelumab	88	31.80%	8	20	5		10	1
Merck	KEYNOTE-001	Melanoma	Ib	Pembro	655	33	105	273				
Merck	KEYNOTE-055	HNSCC	II	Pembro	171	16	1	27				
Merck	KEYNOTE- 010	NSCLC	II/III	Pembro	691					104 (at 10months)	2 (at 20 months)	

Study Population

- Goal for initial analysis to include patients with advanced melanoma (i.e. anti-PD1 Checkmate-037, Checkmate-067, Checkmate-066, Keynote-001, Keynote-002 and Keynote-006)

- GU cancers who received immunotherapy (i.e Checkmate-025, Checkmate-275, NCT02108652 and Keynote-052).

- Lung cancer patients (i.e PACIFIC trial, OAK trial, Checkmate-017, Checkmate-057, Keynote-001 and Keynote-010).
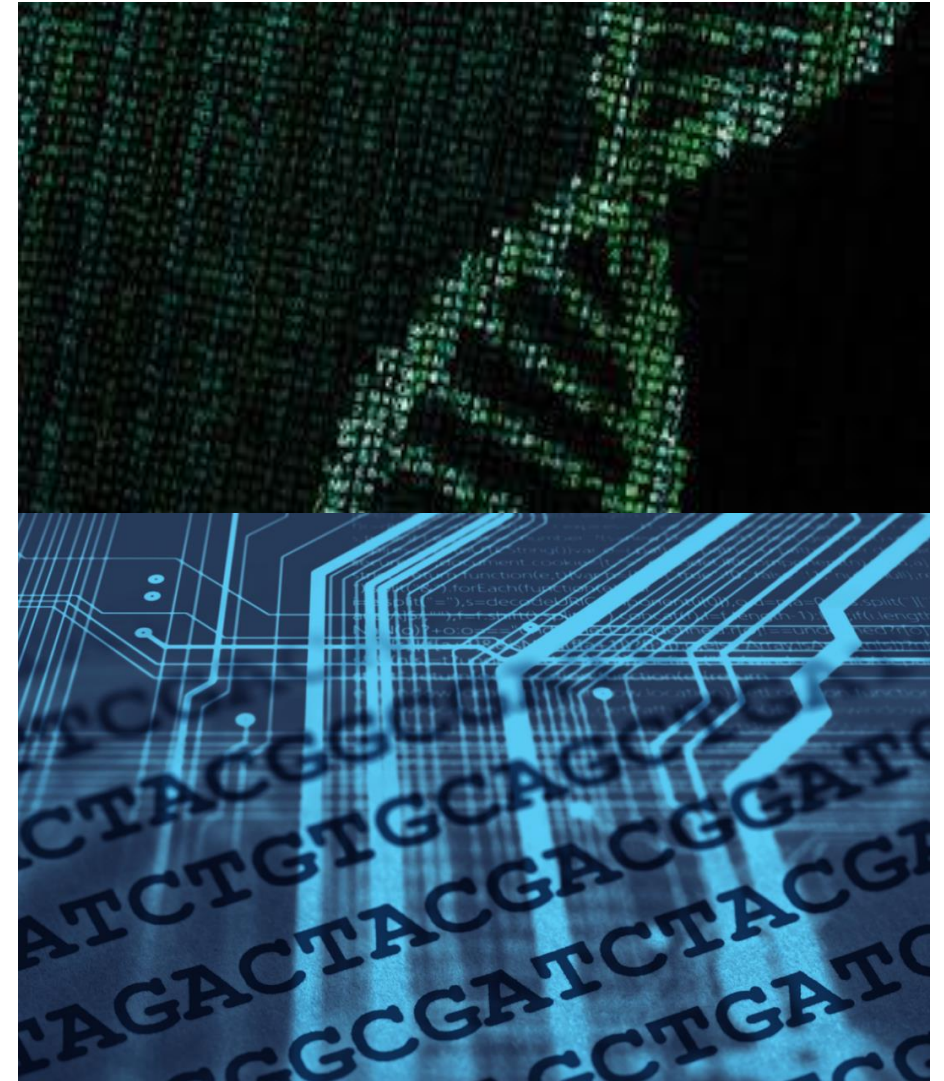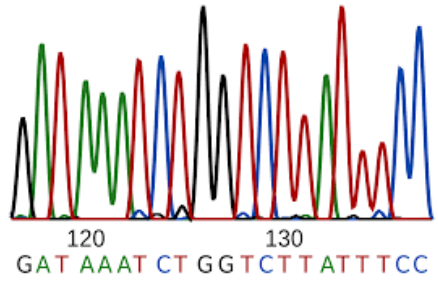
Clinical data

- Minimum patient and specimen data elements:
  - Age, sex, race
  - date of primary diagnosis
  - date of metastatic occurrence
  - date of biopsy, biopsy site
  - prior therapies, treatment on trial, # of cycles
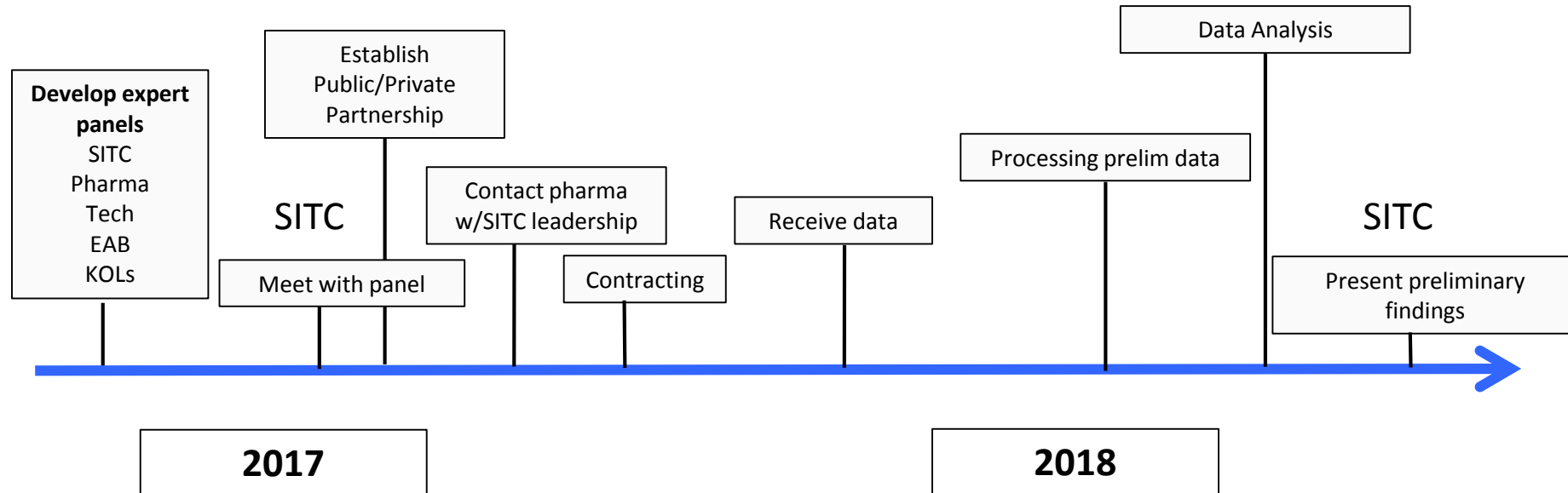 - DFS, PFS, OS on trial
  - date of sequencing

Bioinformatic data

- Tier 1 data
  - RNA seq
- Tier 2
  - DNA whole exome
  - TCR seq
- Format
  - BAM/FASTQ

Timeline

- Letter of intent developed and reviewed by Advisory Committee

- Initial contacts made with multiple pharmaceutical companies

- Received preliminary responses - setting up meetings

Key next steps:

- Secure collaboration for data aggregation and analysis

- Develop pipeline and initial analysis of pilot data

Thank you

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