Immuno-Oncology Combinations: Clinical Trial Design Consideration

Lillian L. Siu, MD
Professor, Director of Phase I Program
Co-Leader of Tumor Immunotherapy Program
BMO Chair in Precision Genomics
Princess Margaret Cancer Centre, Toronto, Canada

UHN Princess Margaret Cancer Centre

UNIVERSITY OF TORONTO

Tumor Immunotherapy Program

Disclosures (2017)

I have the following financial relationships to disclose:

- Consultant for: Merck (compensated), AstraZeneca/Medimmune (compensated), Symphogen (compensated), Morphosys (compensated)
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- Stockholder in: None

26 IMMUNO-ONCOLOGY AGENTS APPROVED GLOBALLY

.... MOSTLY DISCOVERED BY EXPERTS IN ACADEMIC CENTERS

Therapy type	Therapy name	Company	Target
T-cell targeted immunomodulator (6 in total)	Ipilimumab	Bristol-Myers Squibb Co	CTLA-4
	Nivolumab	Bristol-Myers Squibb Co	PD-1
	Pembrolizumab	Merck & Co Inc	PD-1
	Atezolizumab	Roche/Genentech Ltd	PD-L1
	Avelumab	Merck KGaA	PD-L1
	Durvalumab	AstraZeneca/MedImmune LLC	PD-L1
Other immunomodulator (8 in total)	Aldesleukin	Novartis AG	IL2R
	Imiquimod	Valeant Pharmaceuticals Intl Inc	TLR7
	Interferon alfa	Sumitomo Dainippon Pharma Co Ltd	IFNAR1; IFNAR2
	Interferon alfa-1b	Shenzhen Kexing Biotech Co Ltd	IFNAR1
	Interferon alfa-2a	Cadila Healthcare Ltd	IFNAR1; IFNAR2
	Interferon alfa-2b	Merck & Co Inc	IFNAR1; IFNAR2
	Interferon beta	Toray Industries Inc	IFNAR1
	Interferon gamma-1a	Otsuka Pharmaceutical Co Ltd	IFNAR1

Therapy type	Name of Therapy	Company	Target
Cancer vaccine (7 in total)	BCG Live	Shire Plc	TLR
	ImmuCyst	Sanofi	TLR
	Immuno BCG	Ataulpho Paiva Foundation	TLR
	Mycidac-C	Cadila Pharmaceuticals Ltd	TLR2
	Sipuleucel-T	Dendreon	Unspecified TAA
	TICE BCG	Merck & Co Inc	TLR
	Uro-BCG	Medac Inc	TLR
Cell therapy (2 in total)	Tisagenlecleucel	Novartis AG	CD19
	Axicabtagene ciloleucel	Gilead	CD19
Oncolytic virus (2 in total)	Oncorine	Shanghai Sunway Biotech Co Ltd	CD40L
	Talimogene laherparepvec	Amgen Inc	GMCSFR
CD3-targeted bispecific ab	Blinatumomab	Amgen Inc	CD19 X CD3

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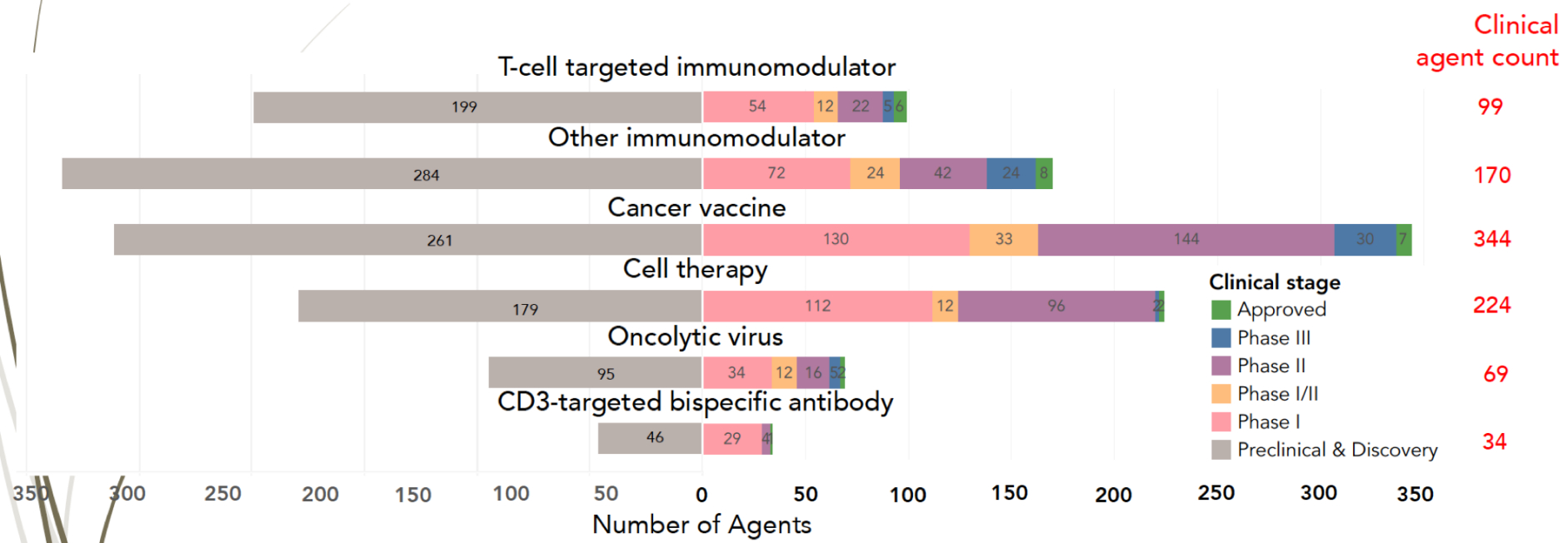
A REVOLUTION IS UNDERWAY: 2,004 IO AGENTS IN DEVELOPMENT

940 AGENTS ARE IN CLINICAL STAGES, AND 1,064 IN PRECLINICAL



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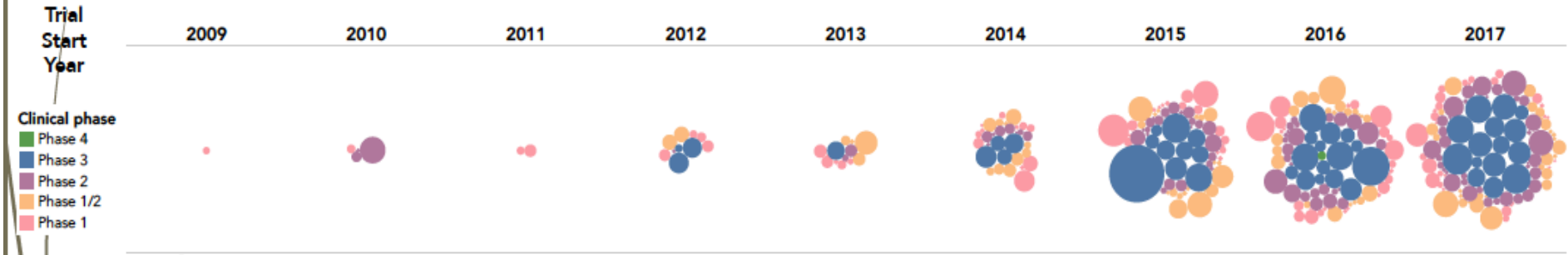
INCREASE OF NEW PD-1/L1 COMBO TRIALS, BUT SMALLER STUDIES



Trial Start Year	2009	2010	2011	2012	2013	2014	2015	2016	2017
Number of new trials	1	5	2	13	20	58	190	329	469
Planned new enrollment	136	2,473	582	4,867	5,031	11,276	39,821	46,153	52,539
Planned enrollment per new trial	136	495	291	374	252	194	210	140	112

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Immunotherapy can be Used in Combination with Other Therapeutic Agents

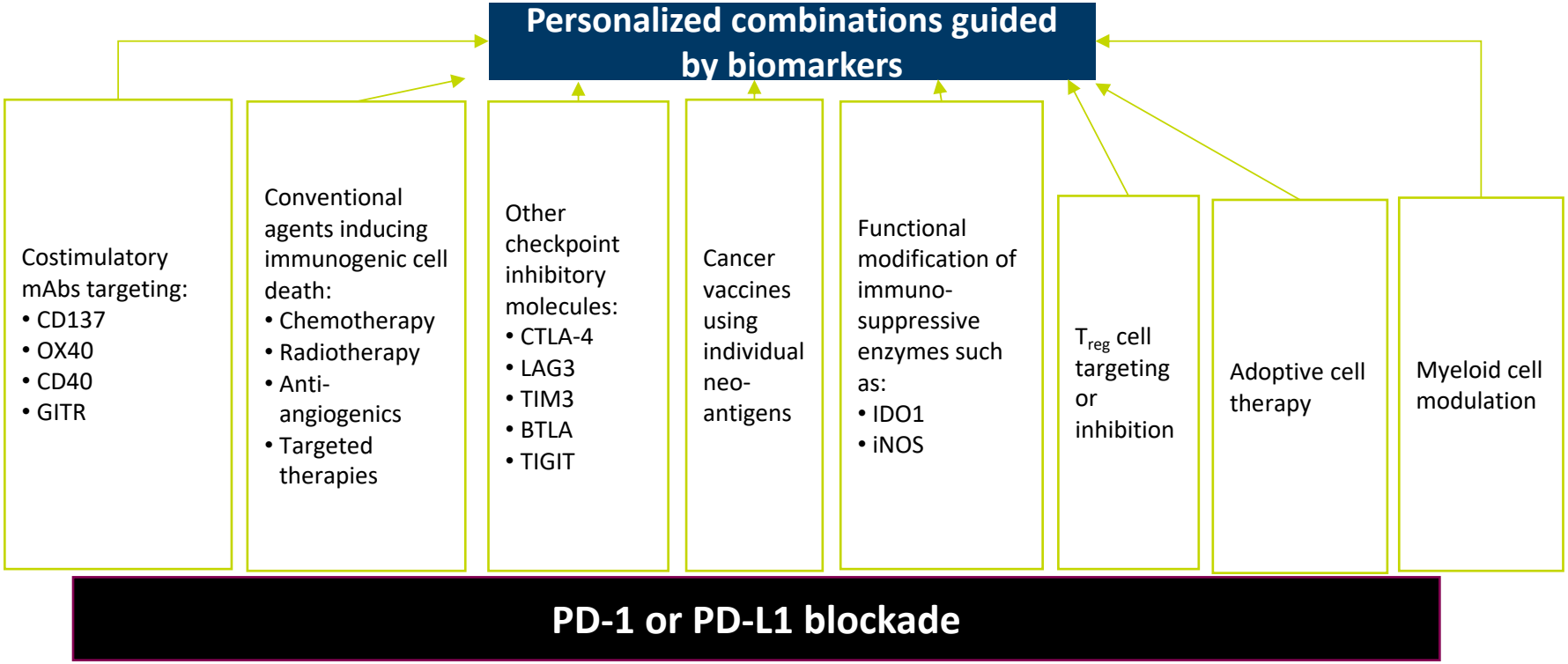


Figure adapted from *Clin Cancer Res*. Copyright 2012, vol 18 (2): pp336-341.

1. Morelo et al. *Nat Rev Can* 2015;(15):457-472 .
2. Drake CG. *Ann Oncol* 2012;23(suppl 8):viii41-viii46

Management of Cancer in the Post-Anti-PD-1/L1 Era

Inflamed

Anti-PD-1/L1 naive

1

Response to Anti-PD-1/PD-L1

Progress with interval therapy

2

Progress without interval therapy

3

Immune excluded, Immune Dessert

Likely primarily resistant to Anti-PD-1/L1

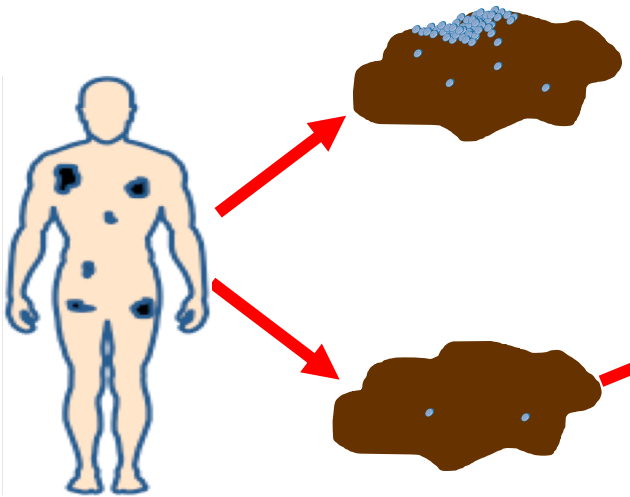
Bring T cells into tumors

4

Generate/Expand T cells

5

Management of Cancer in the Post-Anti-PD-1/L1 Era



Anti-PD-1/anti-PD-L1

Bring T cells into tumors:

+ anti-CTLA4, other immune checkpoint inhibitors
+ radiation/SBRT
+ immune activating antibodies or cytokines
+ TLR agonists or oncolytic viruses
+ IDO or macrophage inhibitors
+ targeted therapies
+ chemotherapy

Generate/Expand T cells:

Vaccines
TCR engineered ACT
CAR engineered ACT
Expanded T cells/TIL

What are the Key Challenges with IO Combinations?

- What nonclinical data are sufficient to support rational IO combinations?
- How to make go-no-go decisions from early phase IO combination trials?
- How do we optimize efficiencies and reduce redundancies in performing IO combination trials?

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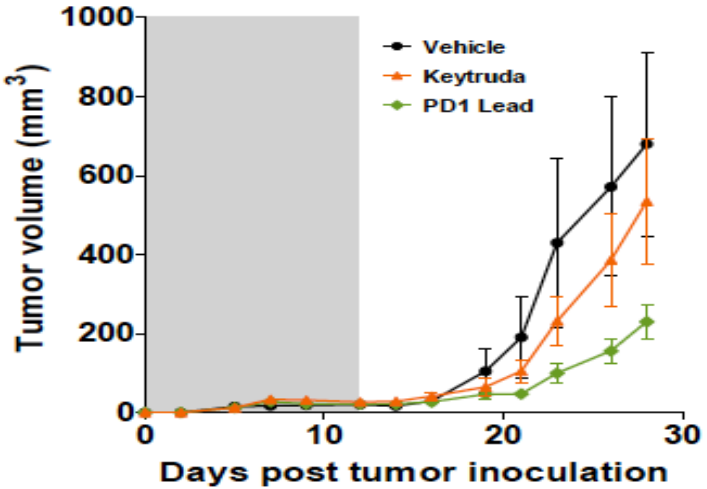
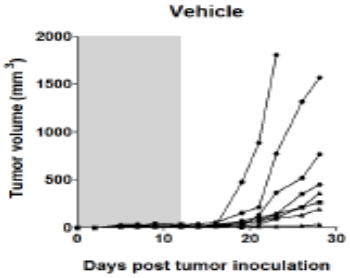
Presented IO Combinations in Clinical Trials: Basis for Combination – Limited Nonclinical Data

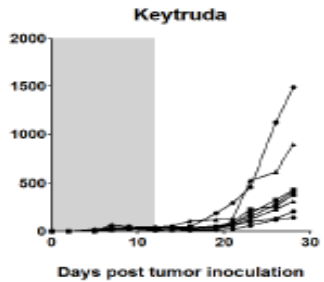
Phase	Agents	Targets	Basis for Combination	NCT
Ib	PF-05082566 (utomilumab) pembrolizumab	4-1BB PD-1	**B16F10 melanoma and MC38 colorectal cancer models**	02179918
Ib	MOXR0916 atezolizumab	OX40 PD-L1	**MC38 colorectal model**	02410512
I/II	BMS-986205 nivolumab	IDO PD-1	**Not shown**	02658890
I/II	Epacadostat various PD-1/PD-L1 inhibitors	IDO PD-1/PD-L1	**B16.SIY melanoma model**	multiple trials
I/II	Indoximod nivolumab	IDO PD-1/PD-L1	**4T1 breast cancer model**	01866319
I/II	BMS-986156 nivolumab	GITR PD-1	**MC38 colorectal cancer**	02598960

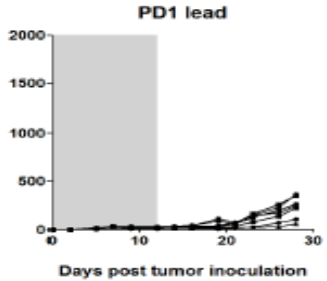
“Humanized” Mouse Models to Test IO Drugs

- Co-grafting human CD8+/CD4+ T cells with A375 (melanoma, MHC-II, PDL1+) *s.c.* in NOD/*scid* mice



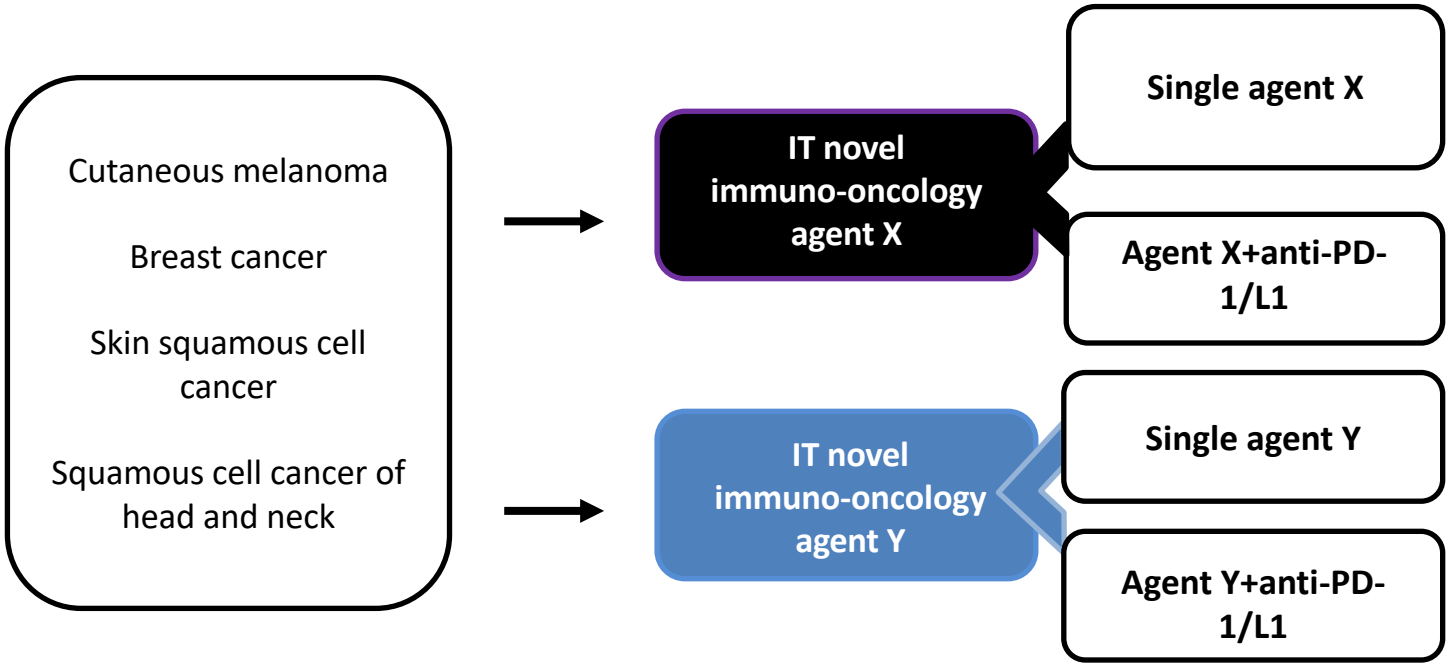






Treatment schedule
10 mg/kg, 3x weekly, 6 doses

Phase 0 Evaluation of Novel IO Agents



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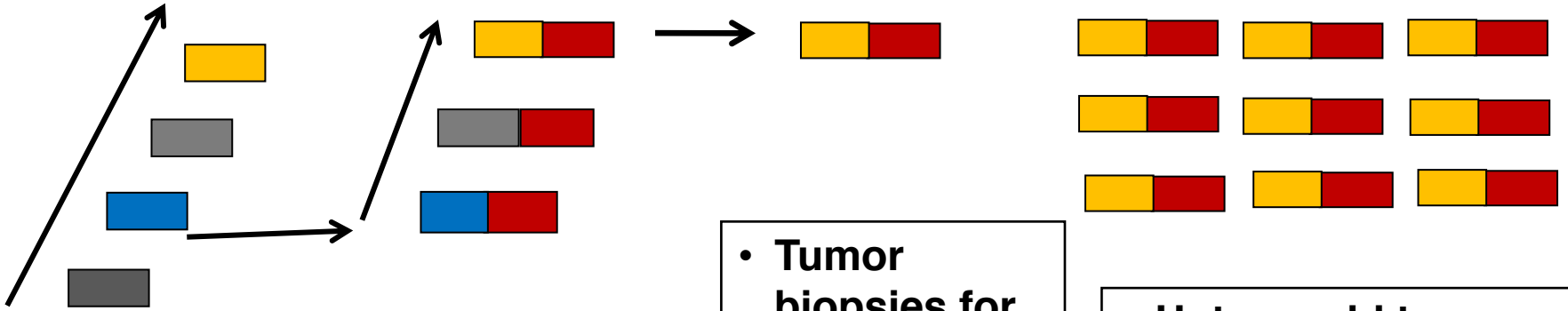
Common IO Phase I Study Design

Dose Escalation	Cohort Expansion	
	Pharmacodynamics	Targeted Subgroups



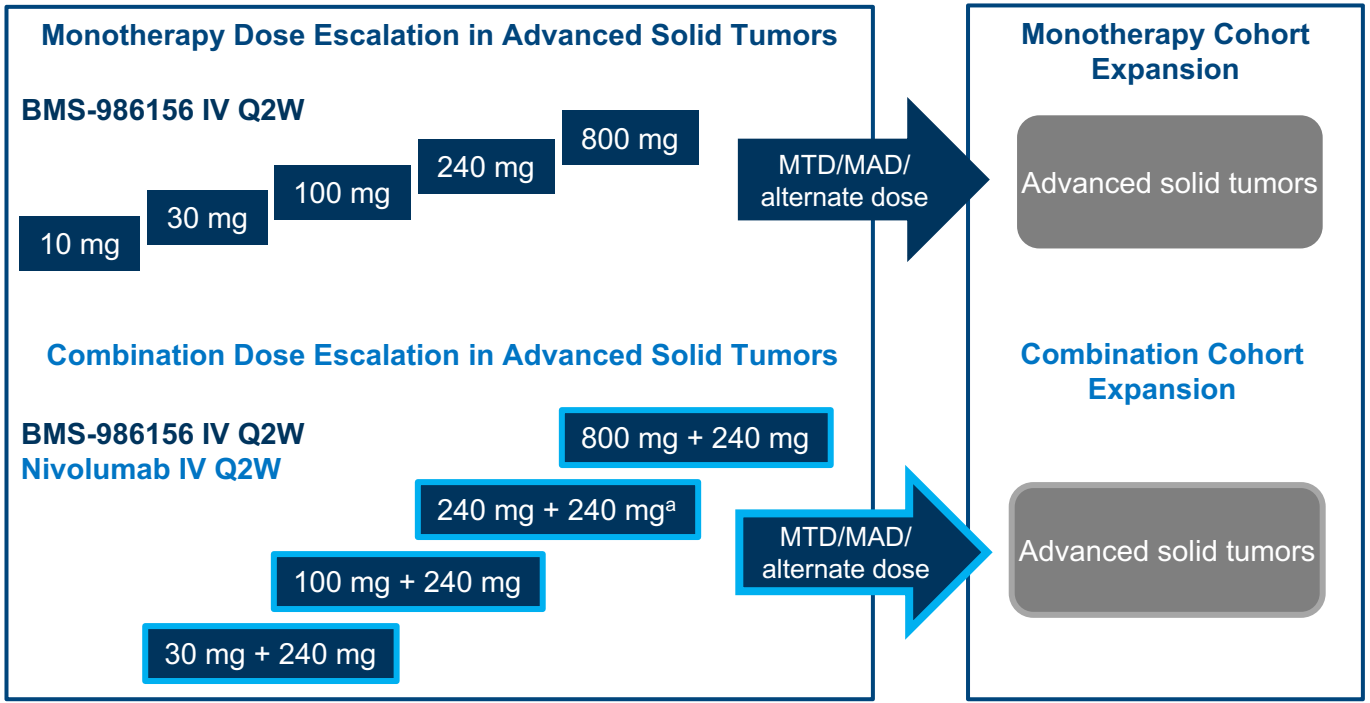
Novel IO agent mono-therapy

Novel IO agent + anti-PD-1/L1 antibody

- Tumor biopsies for immune biomarker evaluations e.g. TILs

- Hot vs cold tumors
- IO naïve vs exposed pts

Phase 1/2a Study of BMS-986156 ± Nivolumab in Patients With Advanced Solid Tumors (NCT02598960)



- Primary objectives
  - Safety, tolerability, DLTs, and MTD, MAD, or alternate dose
- Secondary/exploratory objectives
  - Immunogenicity
  - PK
  - PD
  - Preliminary antitumor activity

Data cutoff: March 31, 2017

Siu et al. ASCO 2017

[a]Dose currently being evaluated in the expansion phase.
DLT, dose-limiting toxicity; IV, intravenously; MAD, maximum administered dose; MTD, maximum tolerated dose; PD, pharmacodynamics; PK, pharmacokinetics; Q2W, every 2 weeks.

Pros and Cons of Seamless Phase I-II Trials

Pros:

- Efficiency, time-saving
- Compelling data can lead to accelerated regulatory approval
- Frequent investigator-sponsor communications are critical to ensure safety

Cons:

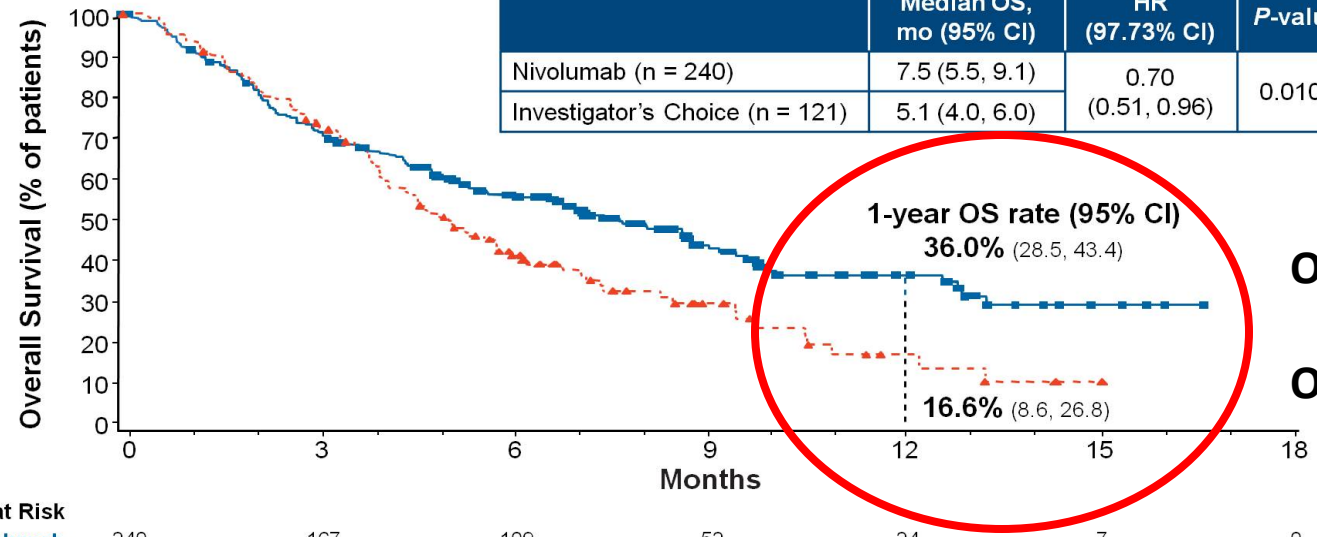
- Often huge studies with 100s-1000s of patients
- Increased complexity often with multiple amendments
- Objectives, endpoints and statistical analysis plans often lacking
- Diluted clinical experience due to large number of participating sites

Objective Response Rate is not Best Predictor of Clinical Benefit

Overall Survival

Nivolumab in R/M SCCHN After Platinum Therapy

	Median OS, mo (95% CI)	HR (97.73% CI)	*P*-value
Nivolumab (n = 240)	7.5 (5.5, 9.1)	0.70 (0.51, 0.96)	0.0101
Investigator's Choice (n = 121)	5.1 (4.0, 6.0)		



No. at Risk							
Nivolumab	240	167	109	52	24	7	0
Investigator's Choice	121	87	42	17	5	1	0

ORR (Nivo) = 13%

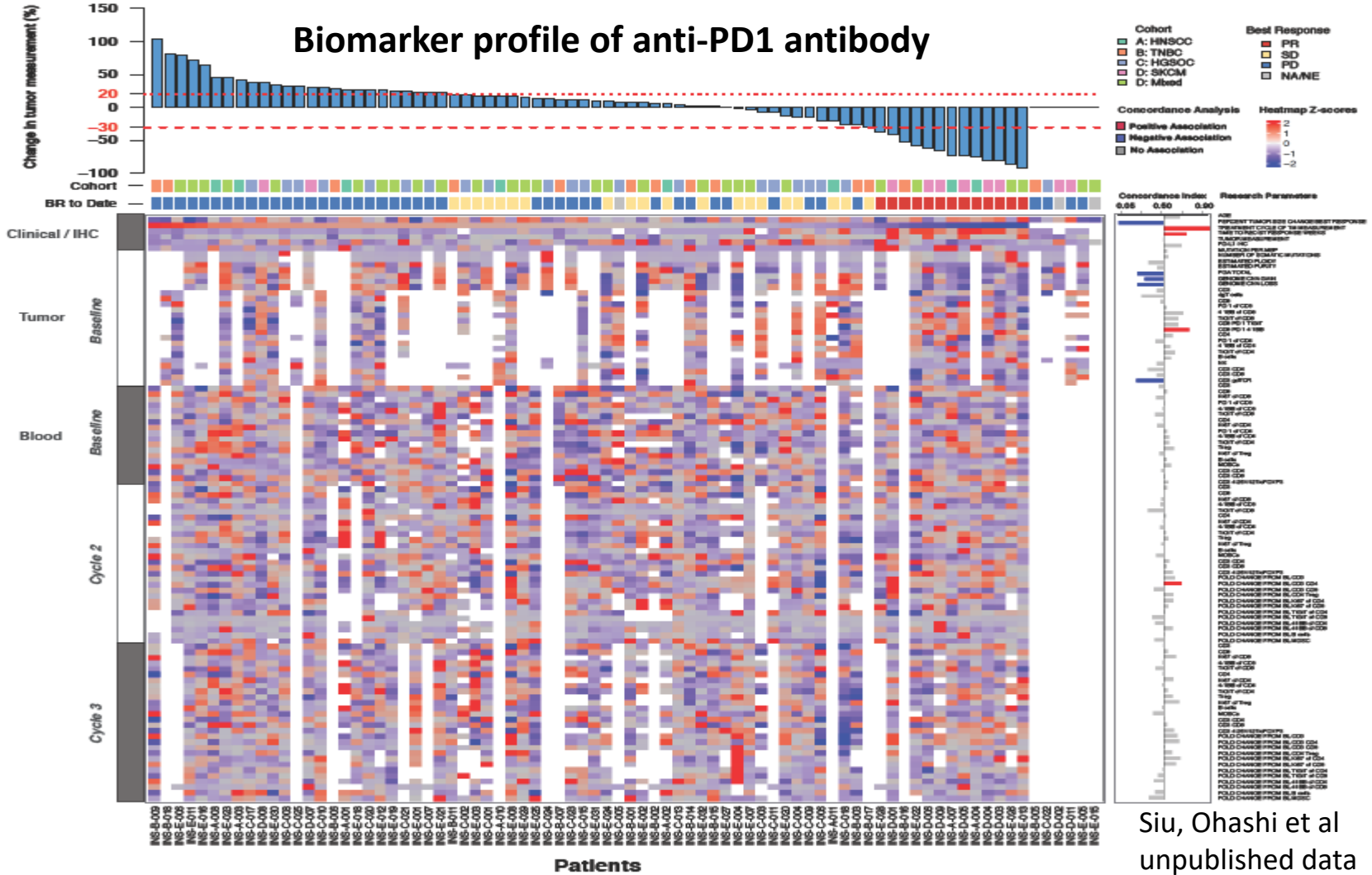
ORR (IC) = 5.8%

Ferris et al New Engl J Med 2016

Challenges in Designing Rational IO Combinations

- Need to understand the effects different IO agents have on T cells, other immune cells and the tumor microenvironment to design rational combinations
- Beyond ORR, what are the best endpoints for go-no-go decisions? What thresholds define potential antitumor efficacy? The readouts are complicated by heterogeneous pt populations some of whom may be responding to anti-PD1/L1 antibody alone
- Optimal sequencing of IO agents in combination is also uncertain
- Biomarker-driven combination studies that are agnostic of histology (e.g. high TMB, POLE mutations, LAG3 overexpression, etc) are being developed

Biomarker profile of anti-PD1 antibody

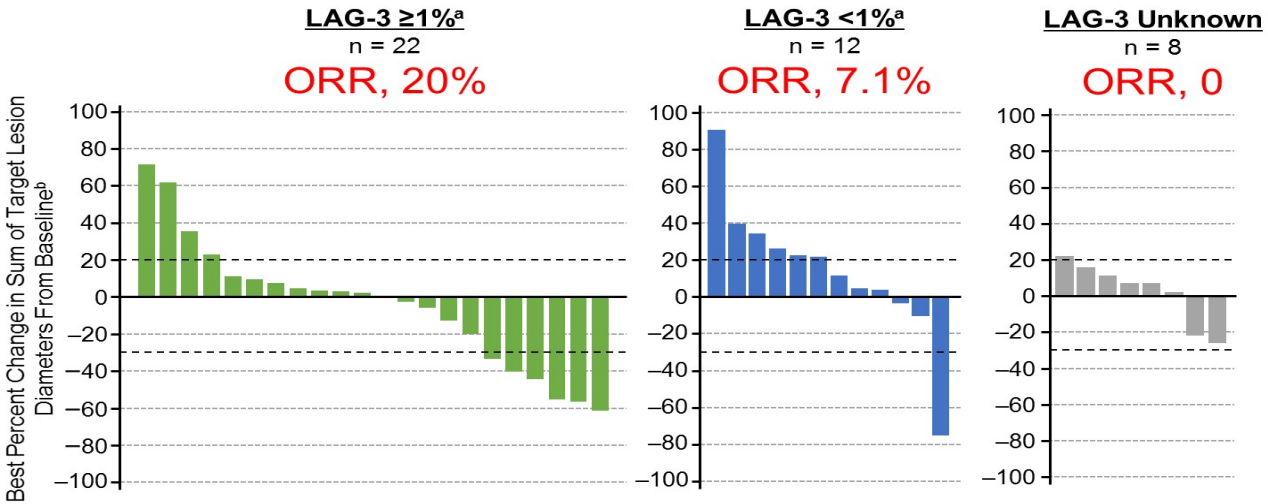


Siu, Ohashi et al unpublished data

Abstract 9520

LAG-3 Expression Enriches for Response

Melanoma Prior-IO Cohort



- LAG-3 expression enriched for responses in IO-experienced patients
- Nearly a 3-fold increase in ORR was observed in patients with LAG-3 ≥1% vs LAG-3 <1% (20% vs 7.1%)
- Overall response rate was 13%

6 PRs: 2 prior PD; 3 prior PR; 1 unk

DCR, disease control rate; ORR, objective response rate.
[a]LAG-3 expression (percent of positive cells within invasive margin, tumor, and stroma) evaluated using immunohistochemistry (IHC) assays on formalin-fixed, paraffin-embedded tumor sections. Immune cell LAG-3 expression (≥1% or <1%) determined using mouse antibody clone 17B4. [b]Response-evaluable patients (n = 48; all progressed on prior anti–PD-1/PD-L1 therapy). Six patients had clinical progression prior to their first scan and are not included in the plot. One patient with best change from baseline >30% had an unconfirmed best response of SD.

Ascierto et al. ASCO 2017

Predictive Biomarkers for IO Agents

- **PD-L1** – Not a perfect predictive biomarker
- **Microsatellite status/Mismatch repair proteins**
- **Genomics-based** – Tumor mutation burden, neoantigens, other genomic-based biomarkers, TCR sequencing, single cell sequencing
- **Immunophenotyping** – Flow cytometry, CyTOF, multiplexed immunohistochemistry/ immunofluorescence
- **Transcriptomic based** – RNAseq, Nanostring
- **Imaging-based** – Radiomics, PET functional imaging
- **Microbiome-based**

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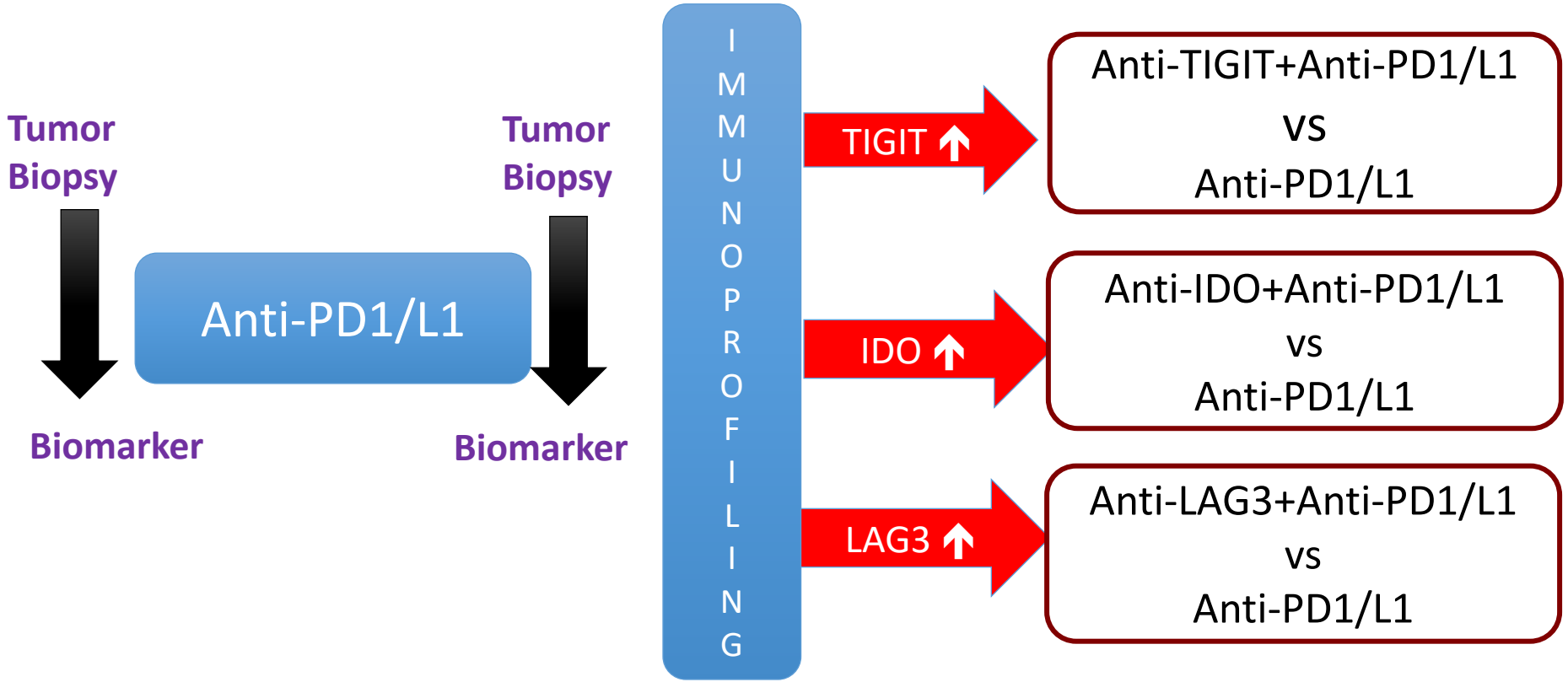
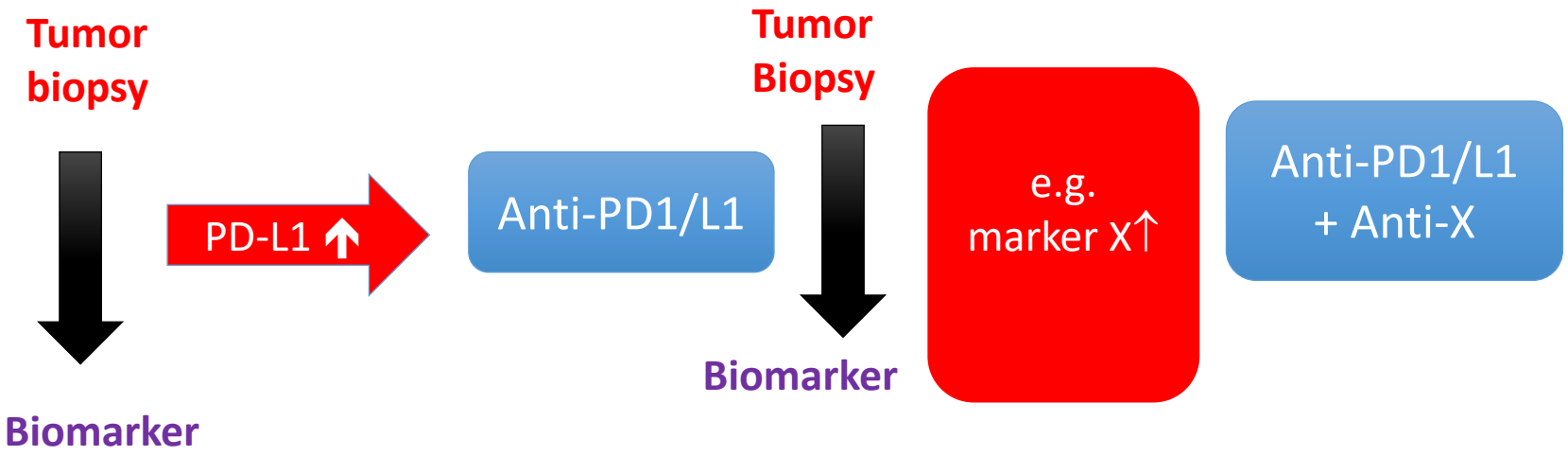
Question		MDICT 2018
MDICT	Strong hypothesis?	**Yes, but preferably not the only data supporting**
	Each agent active?	**Preferred, if not, robust hypothesis and non clinical data**
	Non clinical efficacy?	**Preferred, but may not be directly relevant to human**
	Combo toxicology	**Has limitations**
	Combo PK, PD	**PD critical**
	Explore sequence?	**Yes, and in clinic**
Trial design	Formal phase 1?	**More important than ever to have formal phase I/ PD studies**
	Escalation plan	
	Randomise?	**Yes, for schedule and to evaluate efficacy**
	PK in all?	**If DDI possible**
	PD in all	**PD critical prior to go/no-go decisions**
	Adaptive?	**Novel designs critical to maximize knowledge**
	Other	**Clear objectives and Go/No-Go criteria**
Other	Drugs	**Best in class, do not retest failed combo unless justified**
	Sharing	**Critical**

courtesy L Seymour on behalf of MDICT

Adaptive/Preemptive IO Basket Trial



Adaptive/Preemptive IO Dynamic Trial



- Can we individualize each patient's treatment dynamically?

Conclusions

- PD-1/PD-L1 inhibition is safe and broadly active; serves as the backbone of I/O combination therapy
- There are more rationale combinations than can be feasibly tested
  - Selection of patients and early demonstration of proof of concept
  - How to determine if there is additivity or synergy beyond just objective response rate
- Important to understand the effects of different IO agents on immune cells and TME
- Innovative trial designs and integration of validated predictive and resistance biomarkers are critical to inform the most effective way to deliver IO regimens