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ADVANCES IN Cancer IMMUNOTHERAPY™

What's Next for Cancer Immunotherapy?

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AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE
CHAMPION OF THE EMERGENCY PHYSICIAN

ACCC Association of Community Cancer Centers

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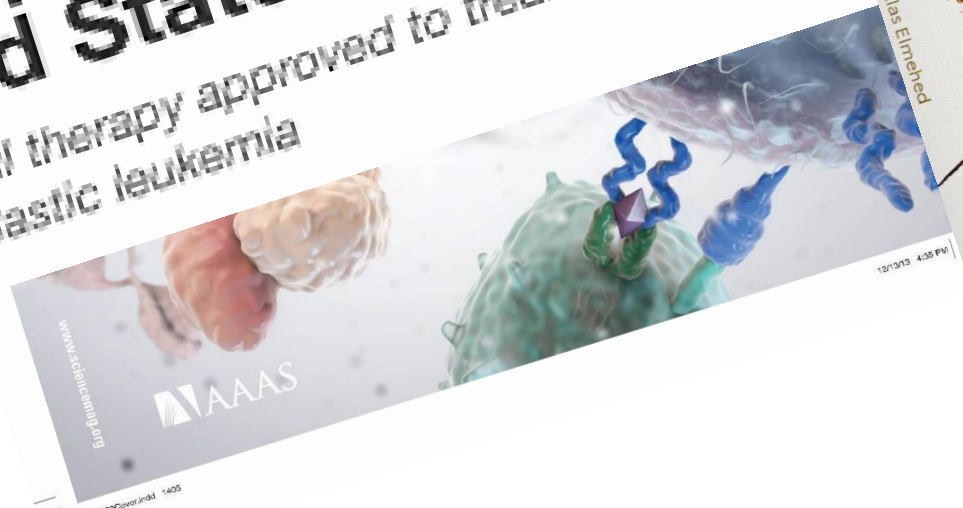
FDA News Release

FDA approval brings first United States

CAR T-cell therapy approved to treat certain childr
lymphoblastic leukemia



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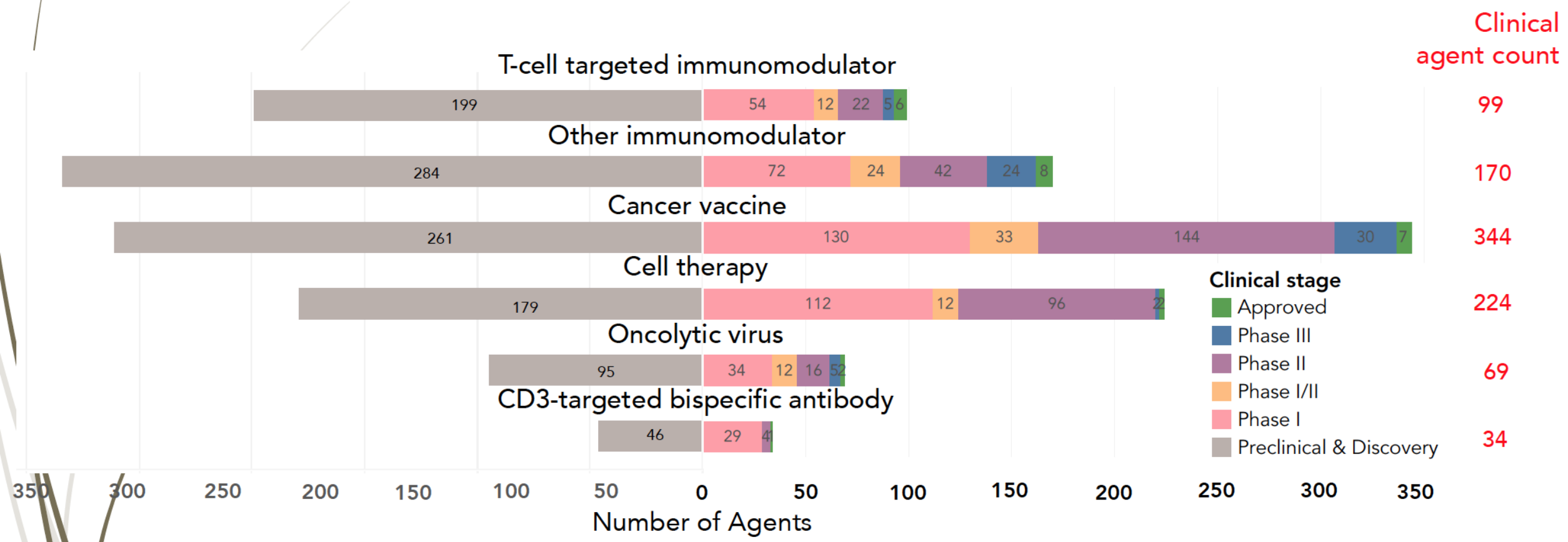
Key Challenges of IO Development

- Identification of the most promising agents for clinical development
- Complexities of IO phase I trials
- Development of IO combinations
- Biomarker development and validation in IO

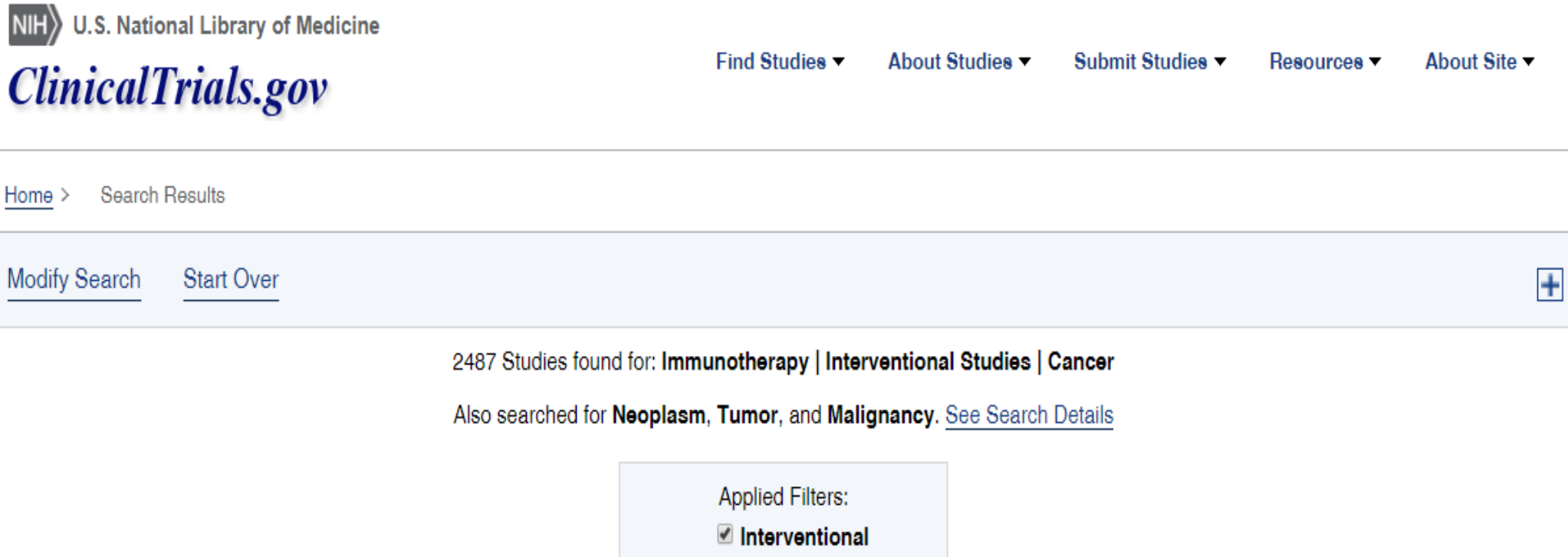
A REVOLUTION IS UNDERWAY: 2,004 IO AGENTS IN DEVELOPMENT

940 Agents are in Clinical Stages, and 1,064 in Preclinical



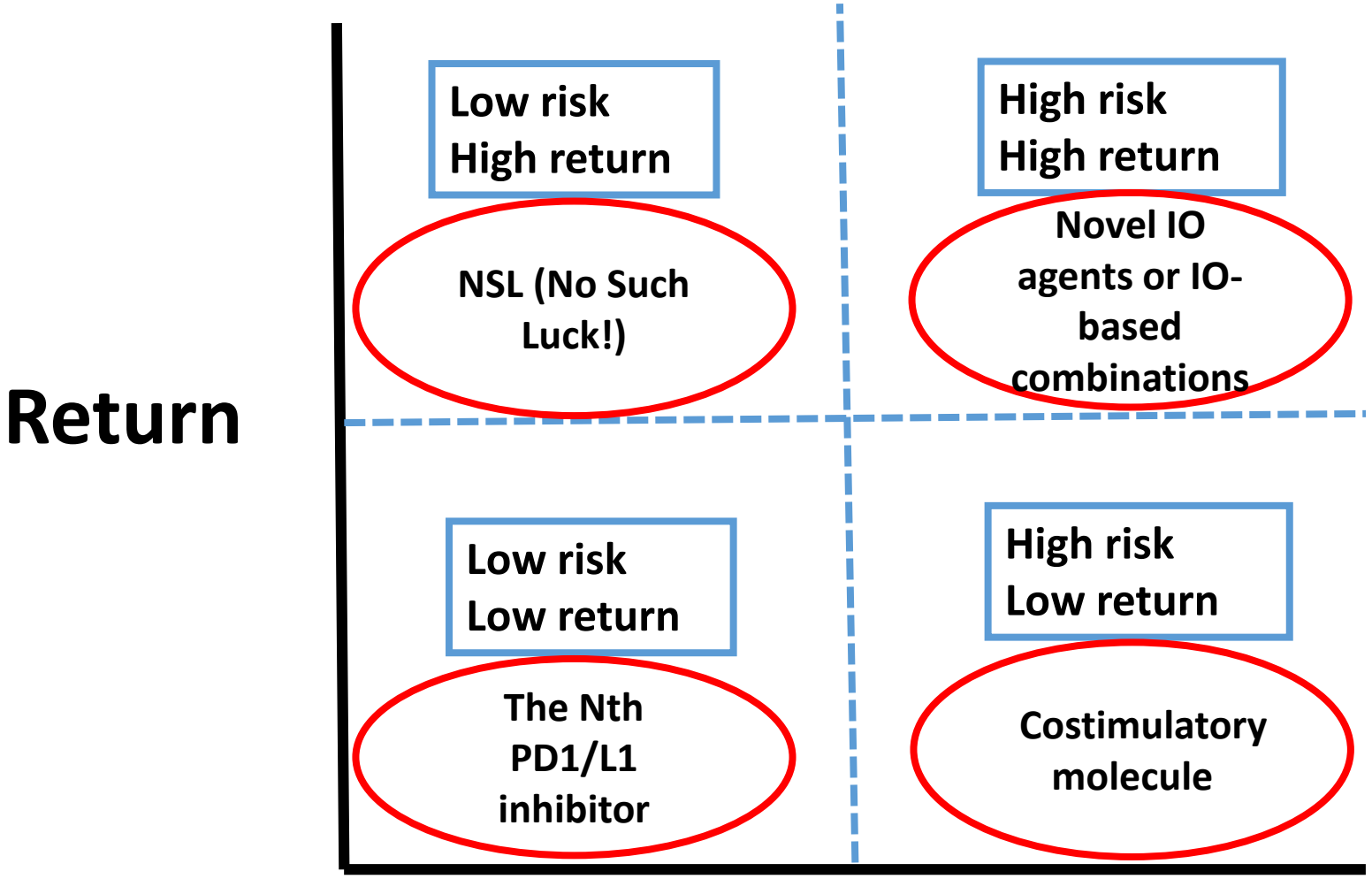
Tang, et al. Annals of Oncology 2017

Over 2,400 Immunotherapy Interventional Studies in Cancer



Accessed March 10, 2019

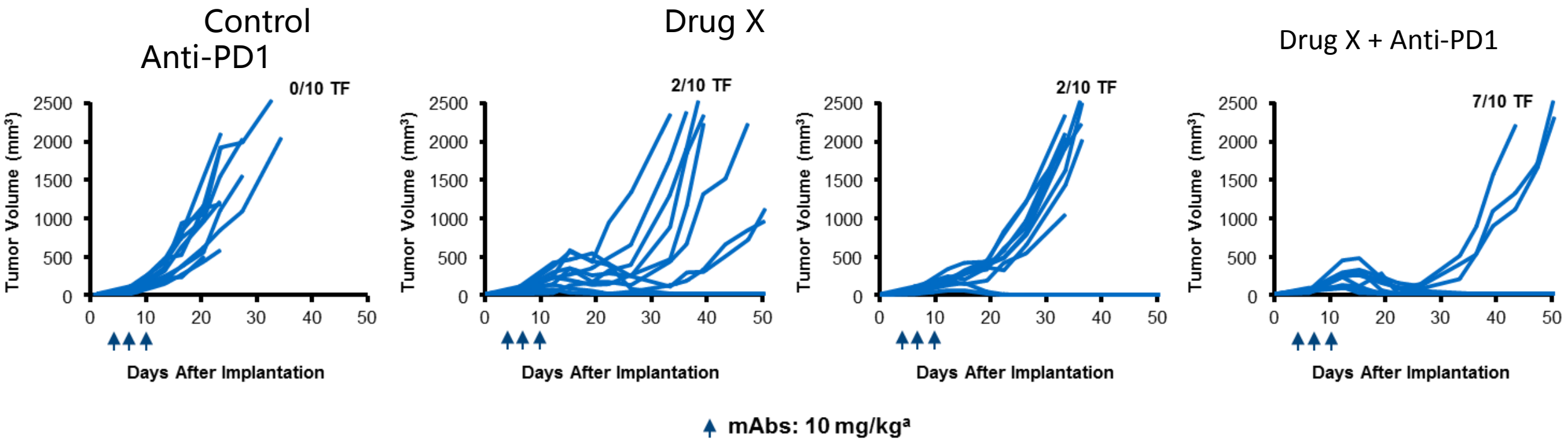
Trade-off in IO Drug Development



IO Combinations in Clinical Trials: Basis for Combination – Limited Nonclinical Data and Lack of Reliable Animal Models

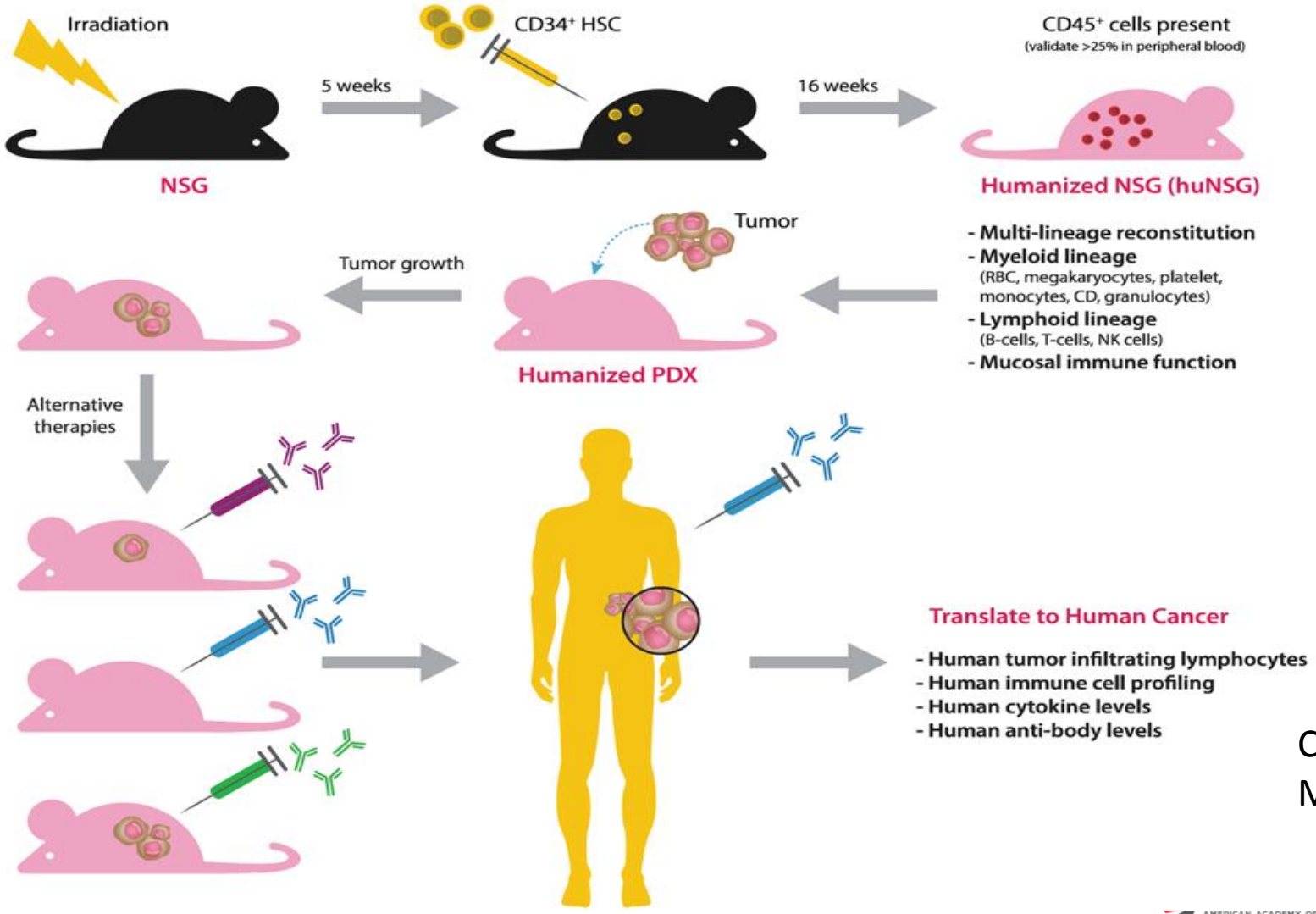
Phase	Agents	Targets	Basis for Combination	NCT
Ib	PF-05082566 (utomilumab) pembrolizumab	4-1BB PD-1	**B16F10 melanoma and MC38 colorectal cancer models**	02179918
Ib	MOXR0916 atezolizumab	OX40 PD-L1	**MC38 colorectal model**	02410512
I/II	Epacadostat various PD-1/PD-L1 inhibitors	IDO PD-1/PD-L1	**B16.SIY 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

Non-Clinical Models



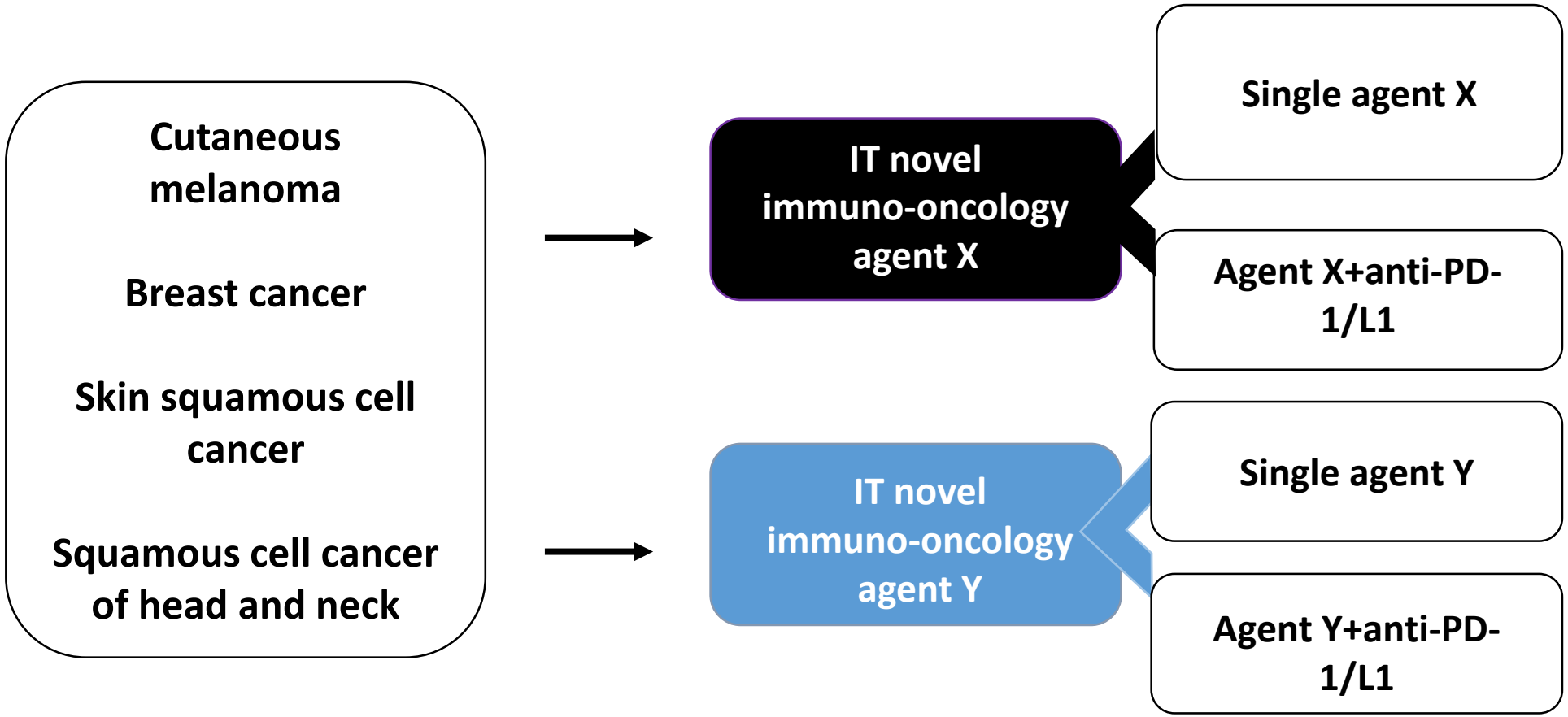
Syngeneic models

Humanized Mice for Immunotherapy Models



Choi et al. Experimental & Molecular Medicine 2018

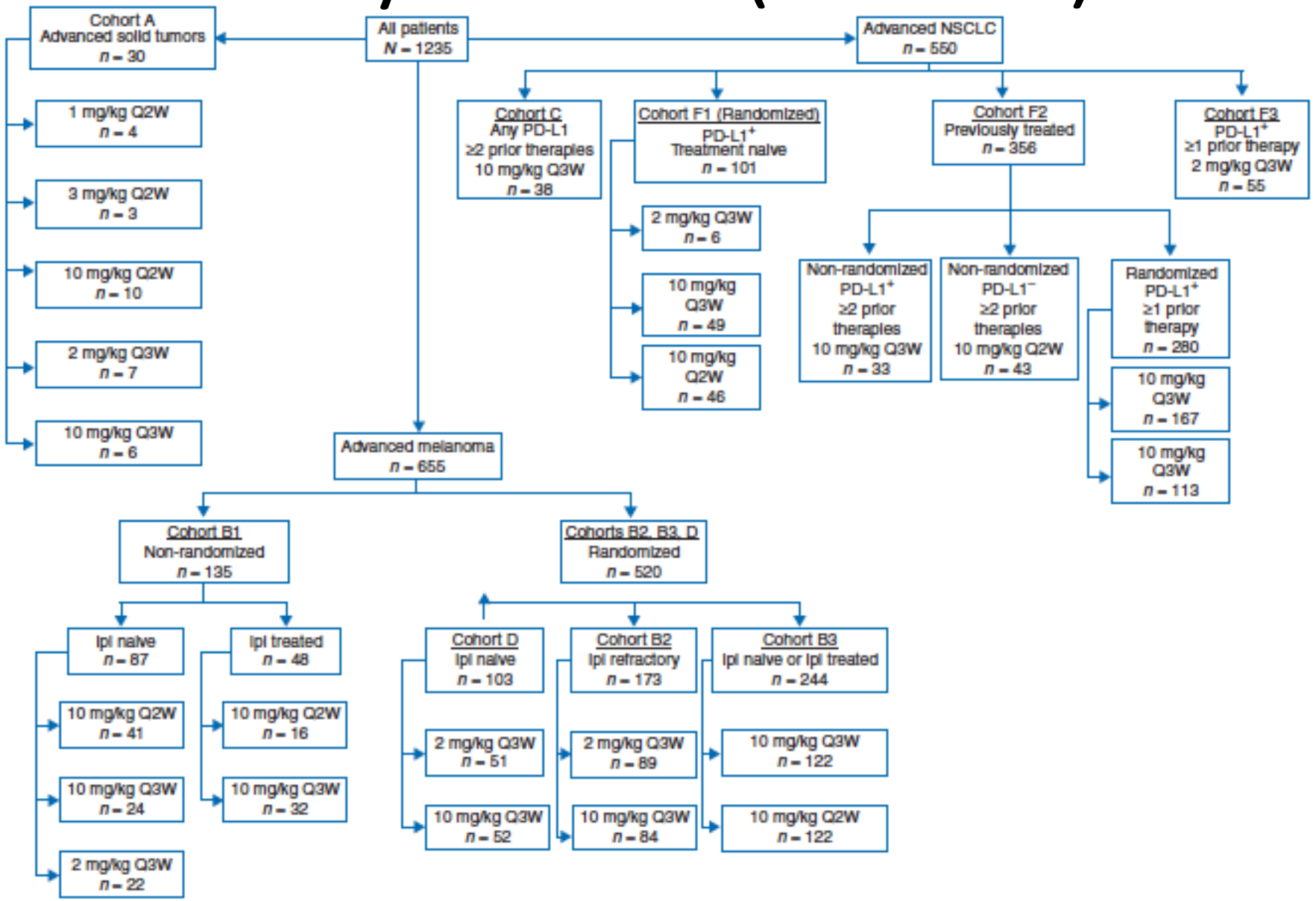
Phase 0 Evaluation of Novel IO Agents



Complexities of IO Phase I Trials

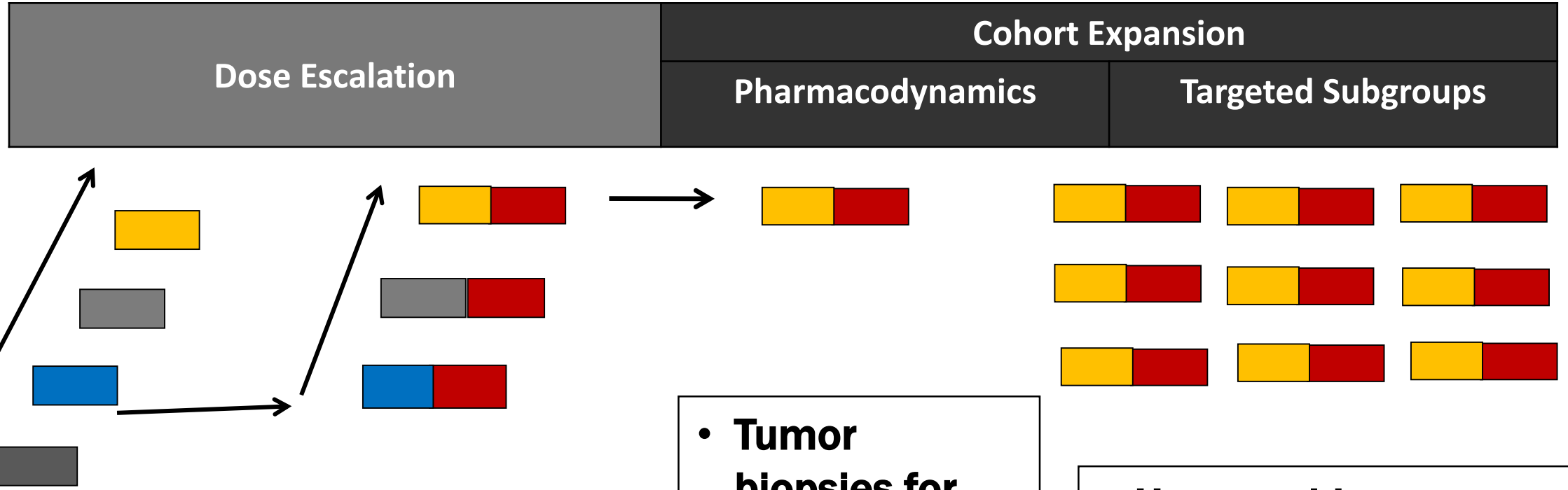
- Design
- Logistics and Economics
- Complexity and safe guards
- Dealing with new toxicities (e.g. CRS)

Keynote-001 (n = 1235)



Kang et al. Annals Oncology 2017

Common IO Phase I Study Design



Novel IO agent mono-therapy

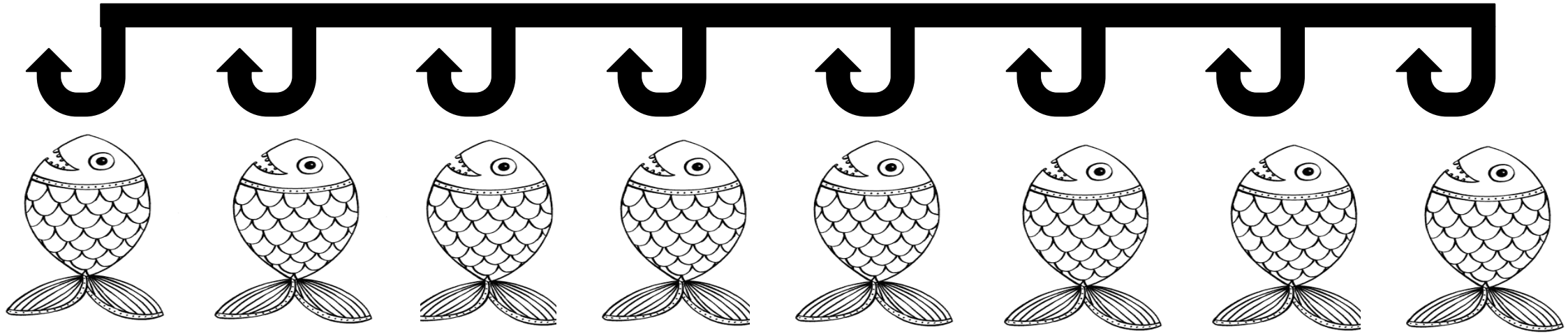
Novel IO agent + anti-PD-1/L1 antibody

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

- **Hot vs cold tumors**
- **IO naïve vs exposed pts**

Signal-Finding, Multiple Cohort Phase I Trials

Common Design with Immune Checkpoint Inhibitors



Cancer A | Cancer B | Cancer C | Cancer D | Cancer E | Cancer F | Cancer G | Cancer H

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 – potentially exposing them to subtherapeutic or toxic doses
- Increased complexity often with multiple amendments
- Challenges in disseminating new safety information to investigators, IRBs, regulators in a timely manner
- Objectives, endpoints and statistical analysis plans often lacking
- Diluted clinical experience due to large number of participating sites

Adapted in part from FDA Draft Guidance:
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM616325.pdf

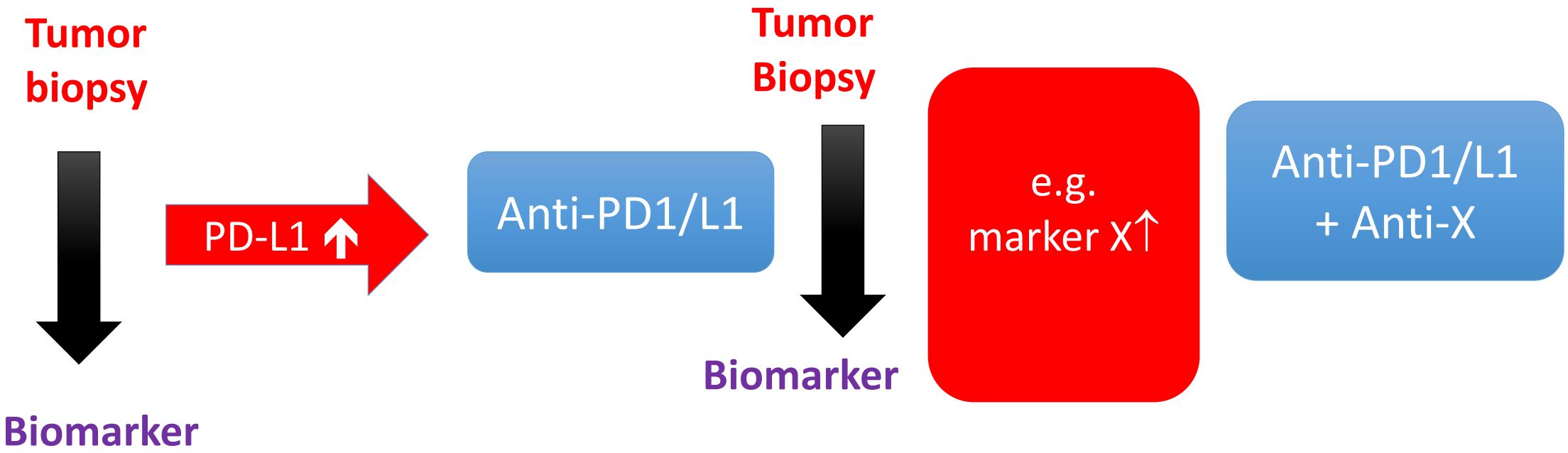
Statistical Considerations and Challenges for Seamless Trials

- Must clear
- Se
- nu
- Interim safet
- Futility analysis to limit enrollment of patients to ineffective regimens

"We are phase I trialists carrying the responsibilities of phase III trialists!"

Hobbs and CTEP Clinical Trials Design Task Force. JNCI, 2019

Adaptive/Preemptive IO Dynamic Trial



- Can we individualize each patient's treatment dynamically?

Risk-Based Management of Novel Therapies

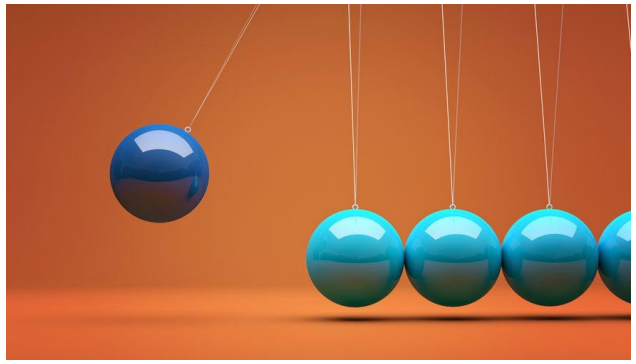
CRS / CRES

Cytokine Release Syndrome (CRS)/CAR-related Encephalopathy Syndrome (CRES)

Risk Category	Example	Severe CRS Rate	Timing of CRS	Inpatient Requirement	Inpatient CAR-T Package
High	*CAR-T*	CRS or CRES >10%	Within 1 week of infusion	At least 7 days on cell therapy unit	Required
Medium	*TCR Transgenic*	CRS 5-10% Or any known CRES	Within 1 week of infusion	4-7 days on cell therapy unit	Can be considered
Low	*Bispecific antibodies*	CRS Unknown or <5% No known CRES risk	Within 2 days of infusion	At least 2 days for first dose on unit with expertise in CRS management	Not required

From the Princess Margaret Cancer Center Cell Therapy Program

The Swinging Pendulum……



Cytotoxic Chemotherapy

Inpatients for complex regimens

Molecularly Targeted Agents

Largely outpatient ambulatory care

Some Immunotherapy

Some require observation for cytokine release syndrome or even ICU admissions

Development of IO Combinations

- Often tested initially as expansion cohort in phase I studies or in seamless studies

- Go-no-go decisions frequently made based on objective response rates (ORR) in single-arm cohorts without comparators

Examples of Successful IO Combinations

Combination	Indication	ORR	PFS	OS	Toxicity
Ipilimumab + Nivolumab (CheckMate-067)	**Melanoma**	CR+PR: I: 19% N: 44% I+N: 58%	3-year PFS: I: 10% N: 32% I+N: 39%	3-year OS: I: 34% N: 52% I+N: 58%	Gr 3/4 TRAE: I: 28% N: 21% I+N: 59%
Pembrolizumab + Chemotherapy (Keynote-189)	**NSCLC**	CR+PR: C: 19% P+C: 48%	1-year PFS: C: 17% P+C: 34%	1-year OS: C: 49% P+C: 69%	Gr 3-5 AE: C: 66% P+C: 67%
Hu5F9-G4 (anti-CD47) + Rituxumab	**NHL (rituximab-refractory)**	CR+PR: 36%+14% = 50%	-	-	Mainly Gr 1-2

Wolchok et al. NEJM, 2017; Gandhi et al. NEJM, 2018; Advani et al. NEJM, 2018

Examples of Less Successful IO Combinations

- MYSTIC (Durvalumab + Tremelimumab vs Platinum-based SOC Chemotherapy) in 1L NSCLC with PD-L1 ≥25% of tumor cells – PFS and OS endpoints not met
- Pembrolizumab + Epacadostat vs Pembrolizumab + Placebo in stage III/IV melanoma – OS endpoint not met

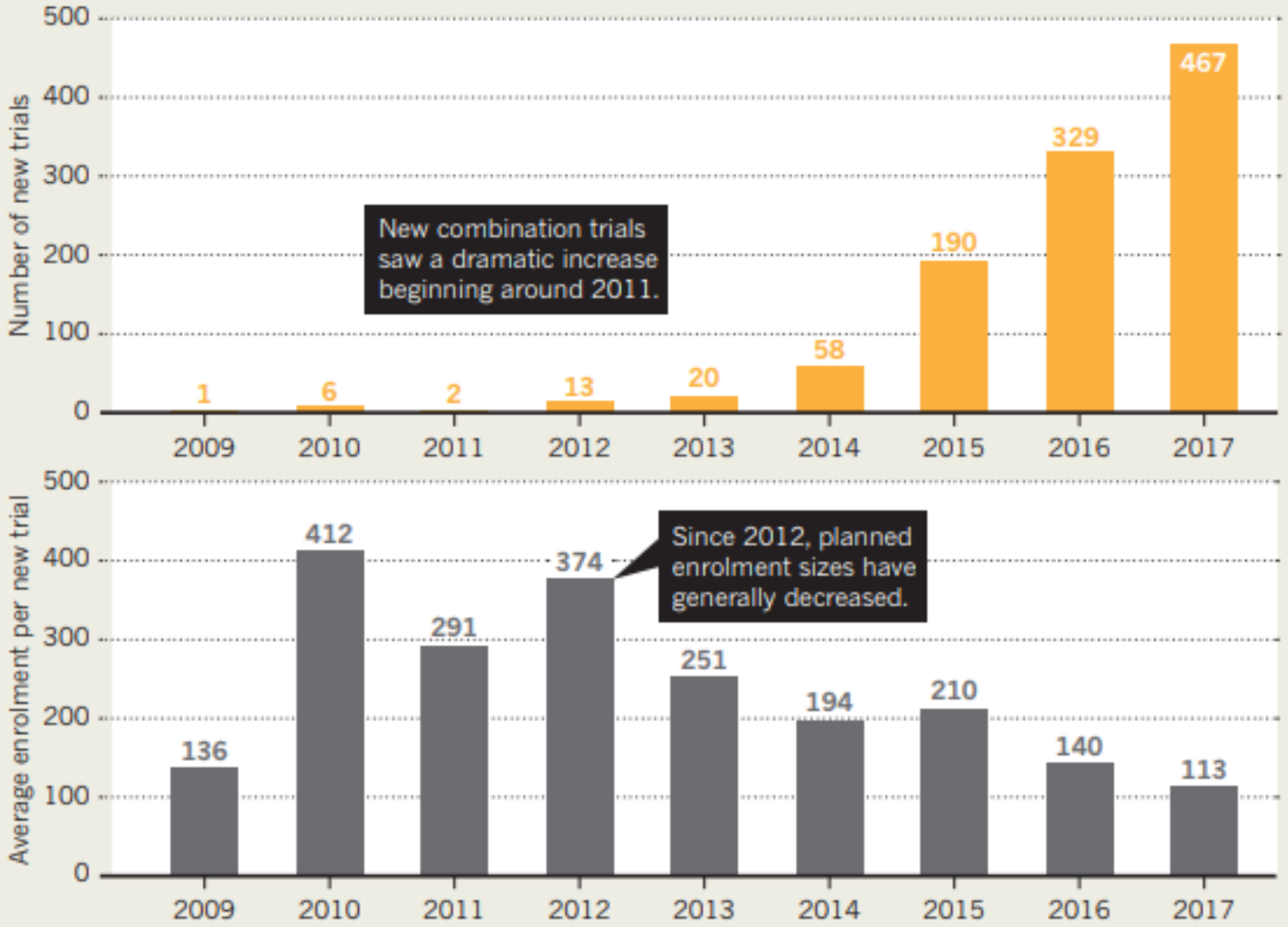
Long et al ASCO 2018

Challenges in Designing Rational IO Combinations

- Need to understand the biological 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
- Biomarker-driven combination studies are needed

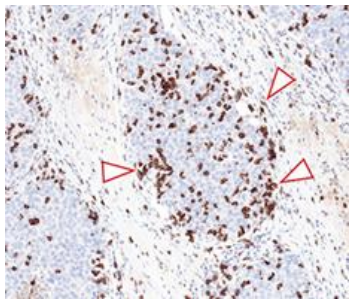
IN COMBINATION: MORE TRIALS, BETTER TARGETED

The number of new clinical trials that combine checkpoint inhibitors targeting PD-1 or PD-L1 with other treatments is soaring worldwide. At the same time, the average planned enrolment for each trial is dropping, partly reflecting more targeted study populations.

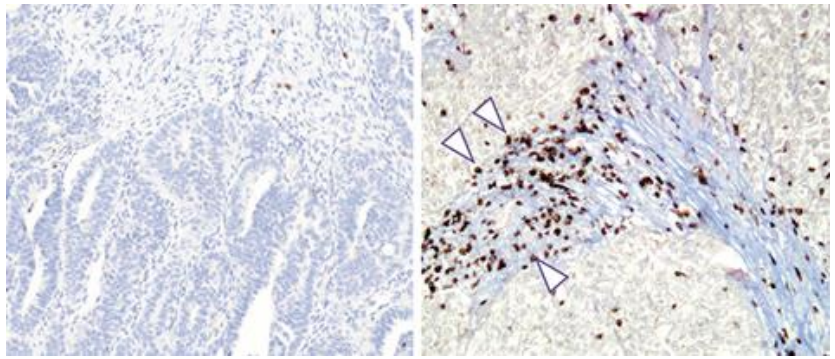


Schmidt, Nature 2017, Tang, et al. Annals of Oncology 2017

Combination Strategies in the Post-Anti-PD-1/L1 Era



Inflamed



Immune desert

Immune excluded

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

Adopted from Marc Butler

Biomarker Identification and Validation in IO

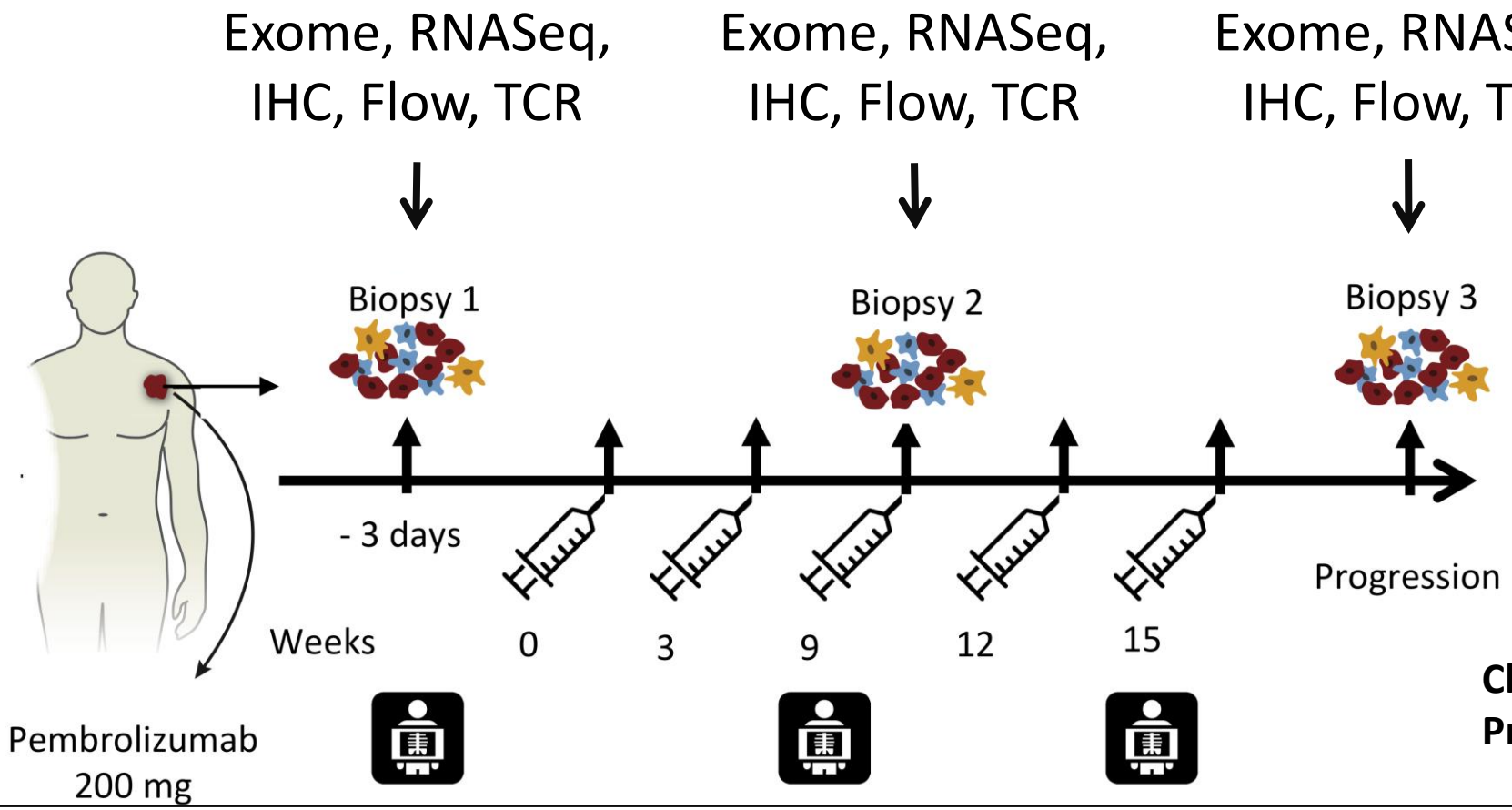
- Early phase trials offer an excellent opportunities for investigator-initiated efforts especially in the understanding of pharmacodynamics and predictive biomarkers

- Need for data sharing and cross-validation given that most academic investigator-initiated studies are small and lack the power to draw definitive conclusions

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**

INSPIRE: Investigator-initiated Phase II Study of Pembrolizumab Immunological Response Evaluation



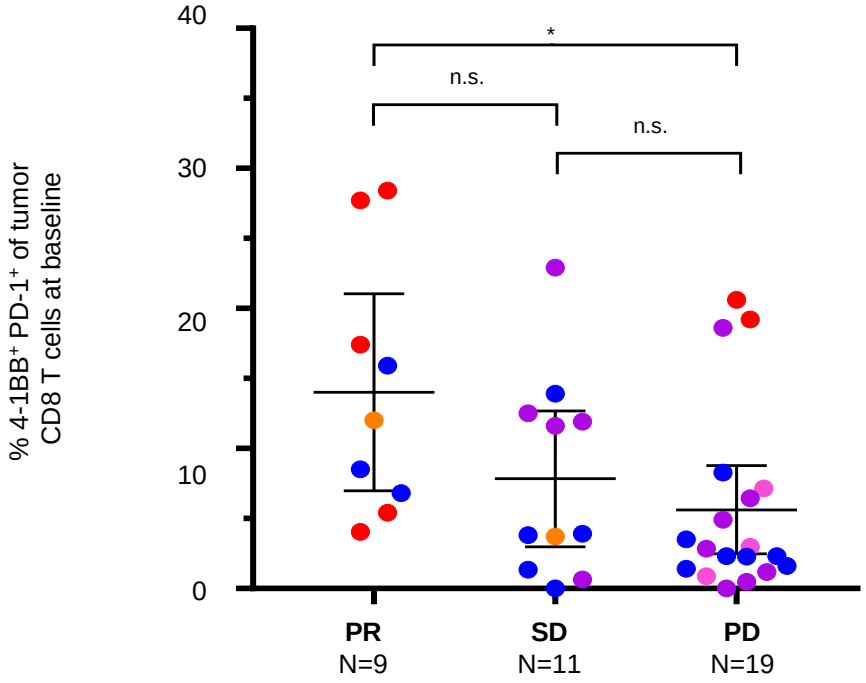
Clouthier et al. JITC, In Press 2019

Head & Neck, Breast, Ovarian, Melanoma, mixed solid tumours (20 each)

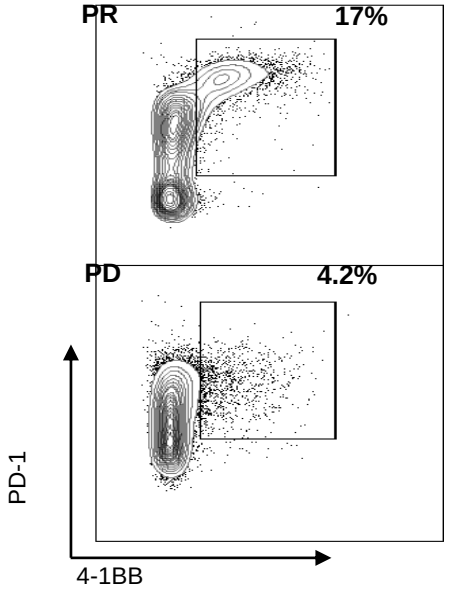
Drug Only Support from Merck

Patients with a confirmed PR had approximately 2-fold more 4-1BB+ PD-1+ CD8 T cells at baseline than patients with a best response of PD ($p<0.05$) or SD (n.s.) (N = 33 with evaluable paired biopsies)

A



B



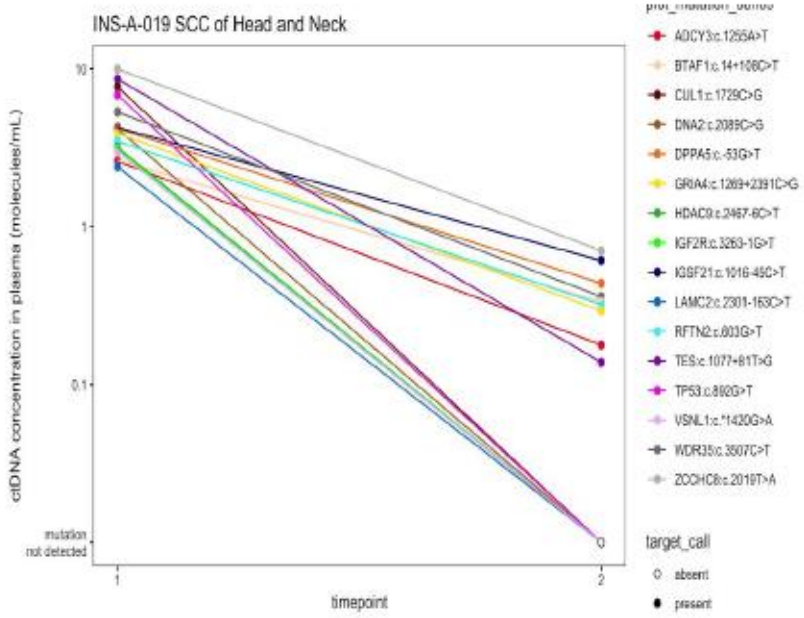
Clouthier et al. JITC, In Press 2019

SCCHN; TNBC; HGSC; MM; MST

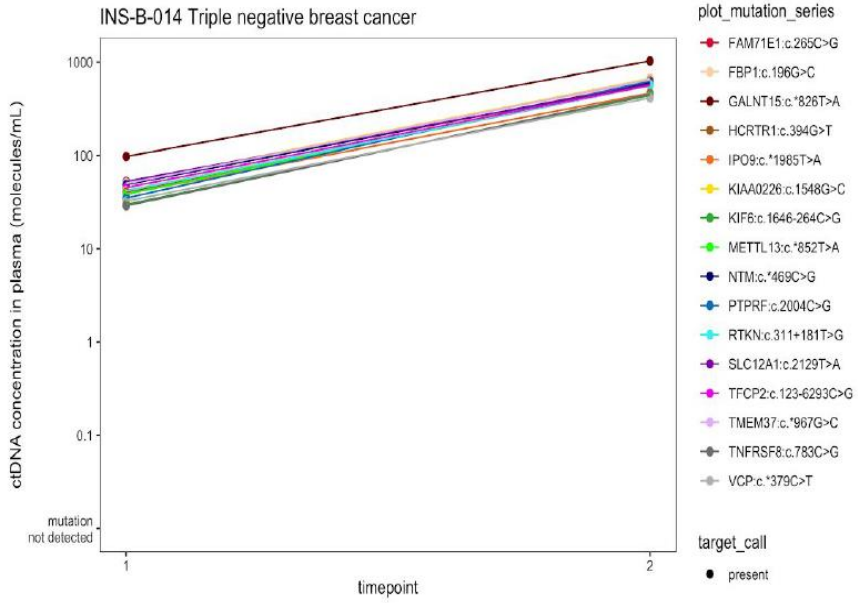
Confidential – Do Not Post

Bespoke ctDNA Analysis and Correlation with Clinical Outcome (Baseline vs at C3D1 [Week 7])

INS-A-019



INS-B-014



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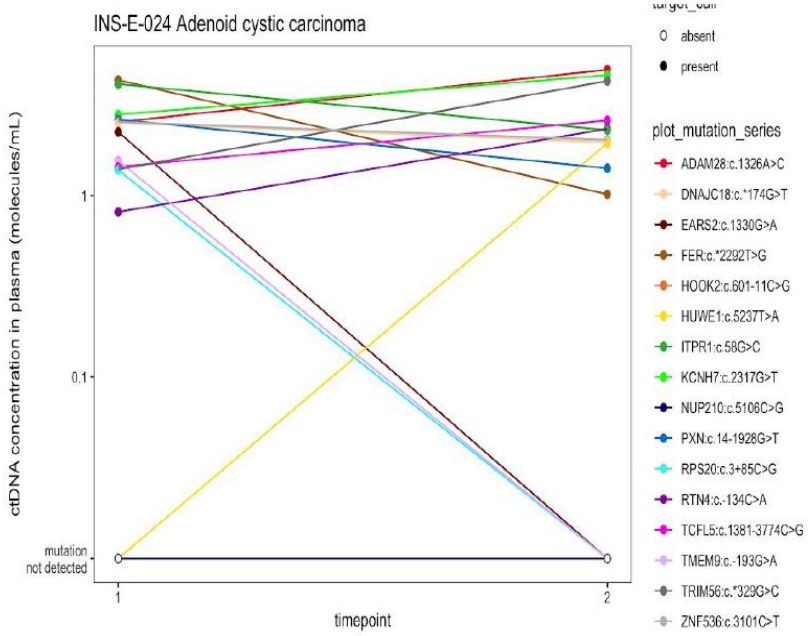


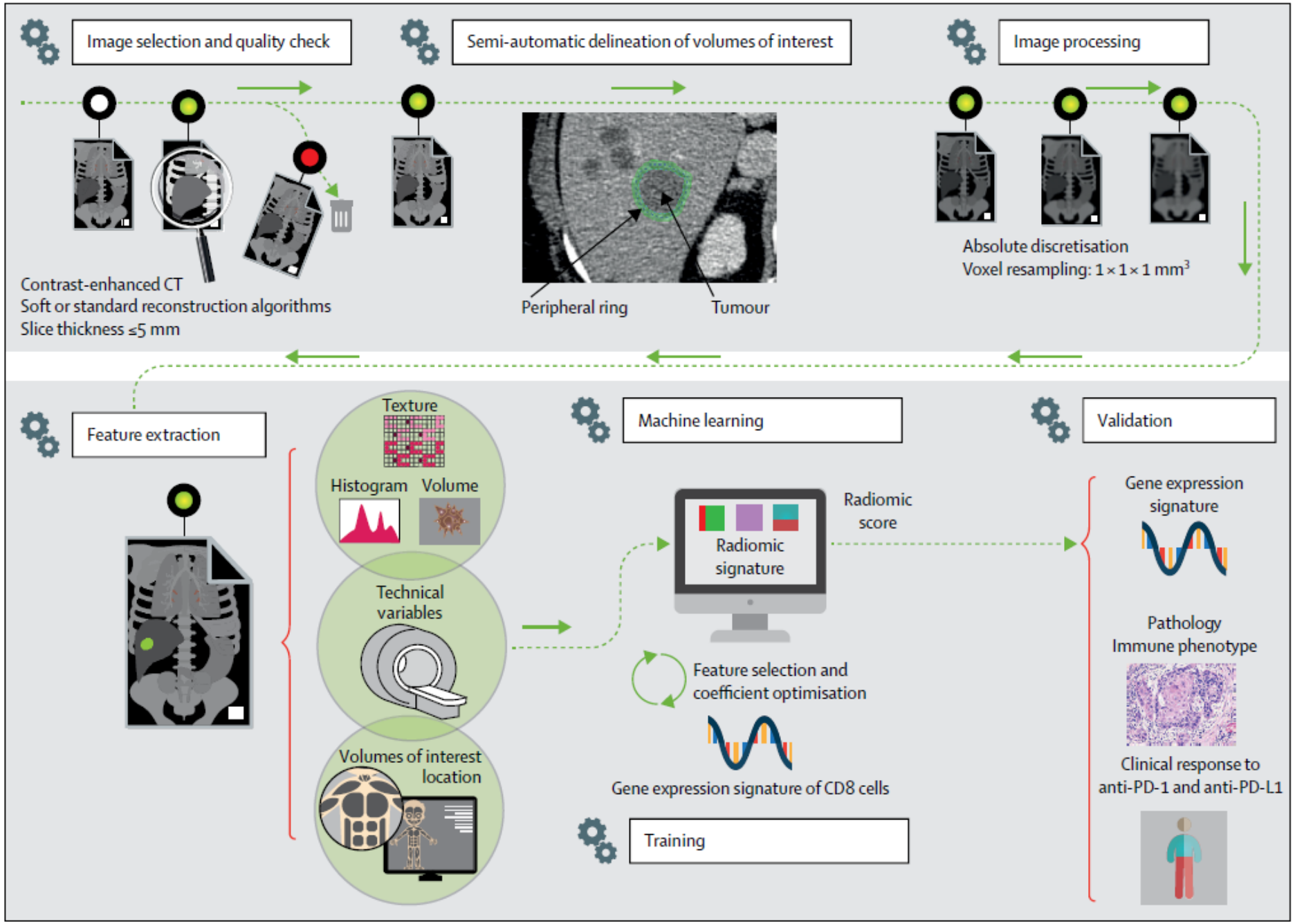
Head and neck cancer: Partial Response

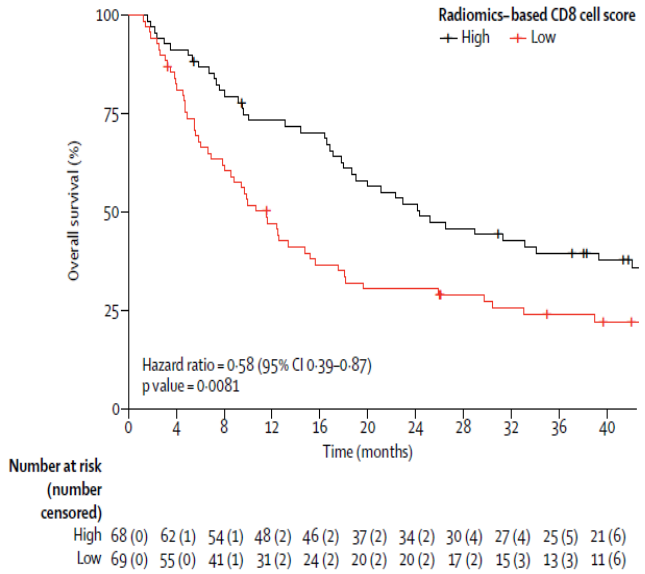
Triple negative breast cancer: Disease Progression

Adenoid cystic cancer: Stable Disease

Confidential – Do Not Post

Using Radiomics to Predict Response to IO

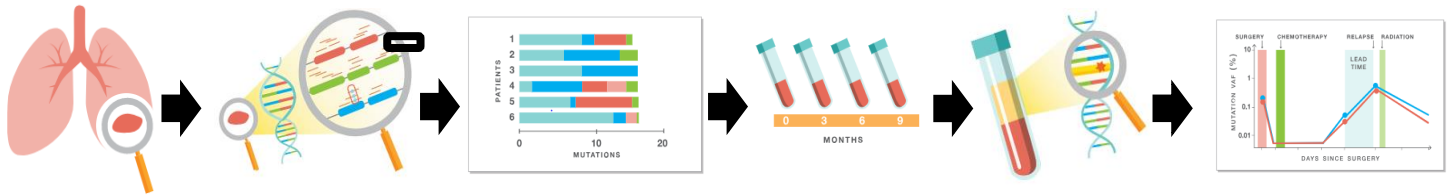




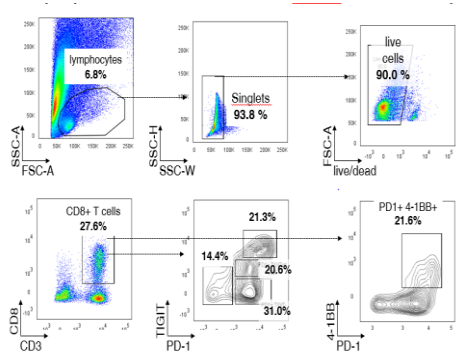
Sun et al. Lancet Oncology 2018

Multi-Omic Assessment for Predictive Signature Identification

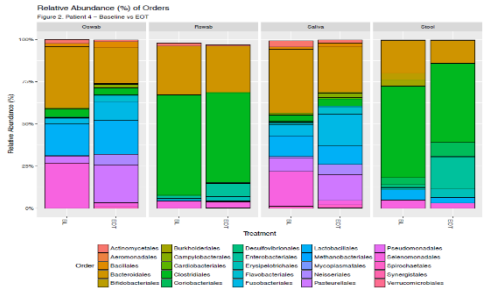
Longitudinal ctDNA Assessment



Immunophenotyping

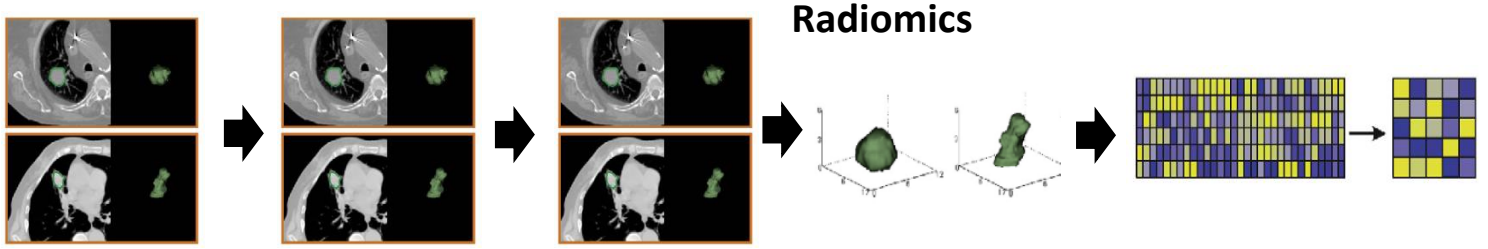


Microbiome



Computational Modelling

Radiomics



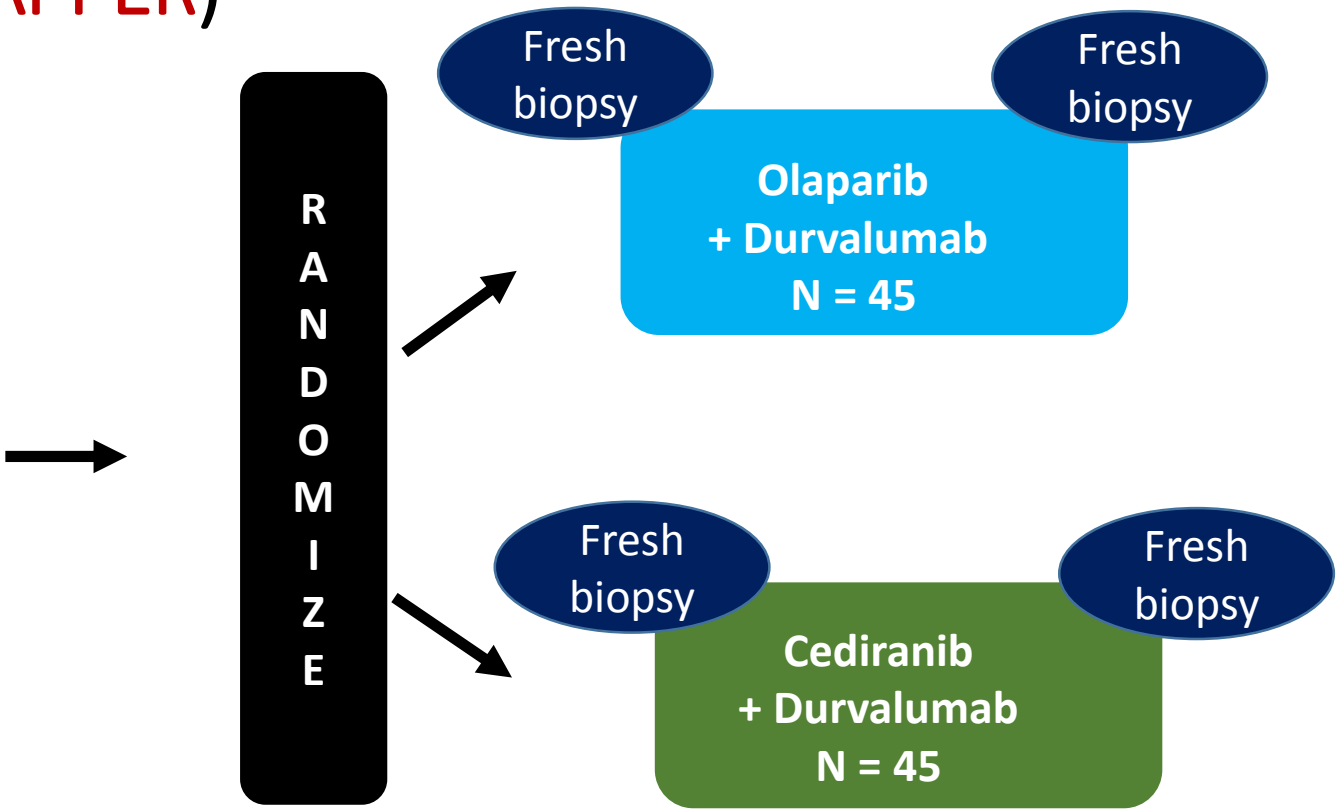
Basket Combination Study of Inhibitors of DNA Damage Response, Angiogenesis and Programmed Death Ligand 1 in PatiEnts with Advanced Solid TumoRs (DAPPER)

Histologies (cold tumors):

- **MSS CRC**
- **Pancreas**
- **Soft tissue sarcoma**

- **ECOG PS 0 – 1**

- **Prior anti- PD-1/ PD-L1, anti-angiogenesis, DDR pathway inhibitor therapies allowed**



To open March 2019

Conclusions

- The emergence of IO era has posed new challenges in multiple aspects:
  - Need better ways to choose the most promising agents to the clinic
  - Rethinking of phase I trial designs that maintain efficiency without comprising on safety or stringency
  - Go-no-go decisions especially for rational IO combinations need to be biology-based and biomarker driven
  - Academia and pharma need to share knowledge to maximize our understanding to provide precision immuno-oncology

Phase I Program
Cancer Genomics Program
Tumor Immunotherapy Program
at Princess Margaret