The Changing Landscape in Phase I and Early Phase Clinical Trials

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Disclosures (2015-2016)

I have the following financial relationships to disclose:

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Honoraria from: None

Employee of: None

The Traditional Drug Development Paradigm

Phase I	Phase II	Phase III
o Safety, tolerability o Pharmacokinetics o Pharmacodynamics o Preliminary antitumor activity	o Efficacy observed in selected tumor types, e.g. ORR, TTP, PFS	o Meaningful benefit obtained in a randomized setting against existent standard e.g. OS

The Current Drug Development Paradigm

Proof of Mechanism	Proof of Concept	
	Early	Late
o Safety, tolerability – on target and off target effects o Preliminary antitumor activity o Evidence of target engagement in valid pharmacodynamic biomarkers	o Predictive biomarkers explored o Antitumor activity seen using surrogate endpoints e.g. ORR, TTP or PFS	o Predictive biomarkers confirmed o Proof of concept using a validated clinical endpoint e.g. OS

Objectives

- Describe features related to the changing nature of phase I clinical trials in the era of novel onco-therapeutics

- Understand the reasons that may have resulted in such changes in phase I trials and their implications in the drug development process

Changing Nature of Phase I Trials

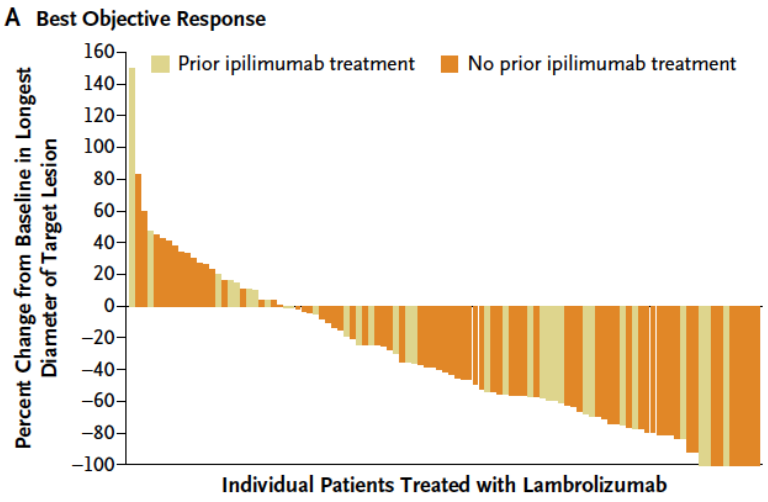
1. Trend of increase in the sample size of phase I trials
2. Expansion cohorts being conducted for multiple purposes
3. Enrichment strategies – histology and/or genotype
4. Emergence of immuno-oncology era
5. Novel dose escalation methods being applied
6. Research biopsies
7. Driving go-no-go decisions based on their ability to provide proof-of-concept

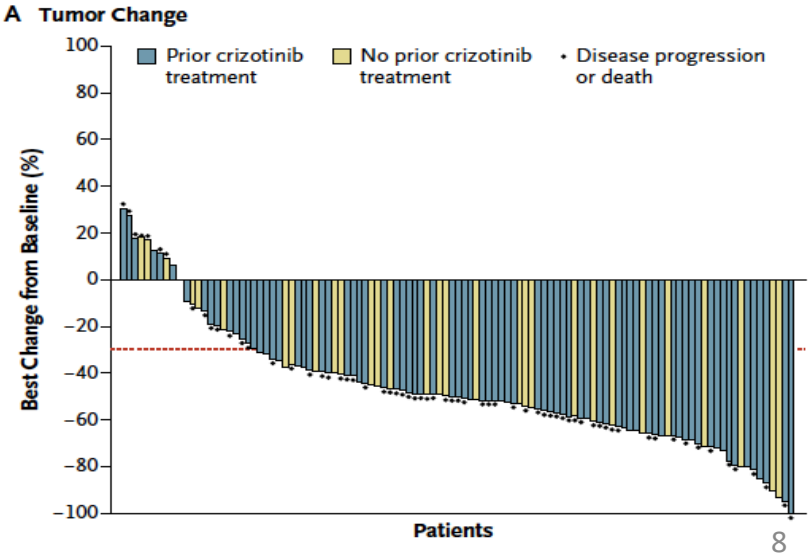
Why Are Phase I Trials Changing?

1. Knowledge of molecular biology is accumulating and technology is rapidly advancing
2. Molecularly targeted agents and immuno-oncology agents have become important parts of the oncology therapeutic armamentarium
3. Patient and infrastructure resources are limited
4. Accelerated regulatory approval is possible for compelling results
5. The desire to accelerate the drug development process to bring active compounds to the clinic and improve cancer cures have fueled these changes

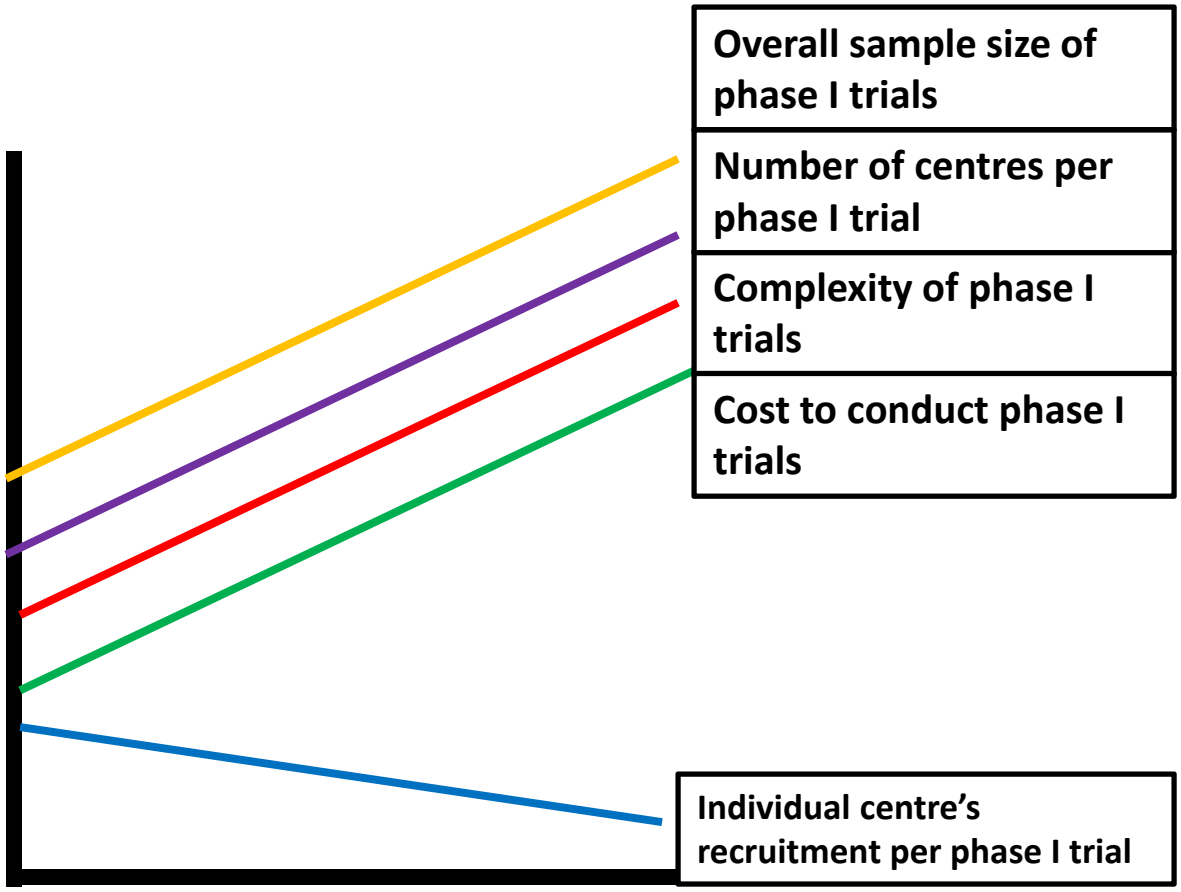
Accelerated Approvals of New Drugs: 2 Examples

Drug	Phase I to Approval by FDA	Time (years)
Pembrolizumab (anti-PD-1 antibody)	February 2011 to September 2014	3.6 years
Ceritinib (ALK inhibitor)	January 2011 to April 2014	3.3 years





Economics and Logistics of Phase I Trials



Consequences:

- Each centre needs to open multiple studies to be economically viable
- Greater regulatory burden (protocol amendments, SUSARs, etc)
- Cost per case is increased
- Limited experience being accumulated per centre
- Collection of trial data by sponsor – there must be sharing of toxicity data by grade and frequency on a regular basis throughout protocol conduct

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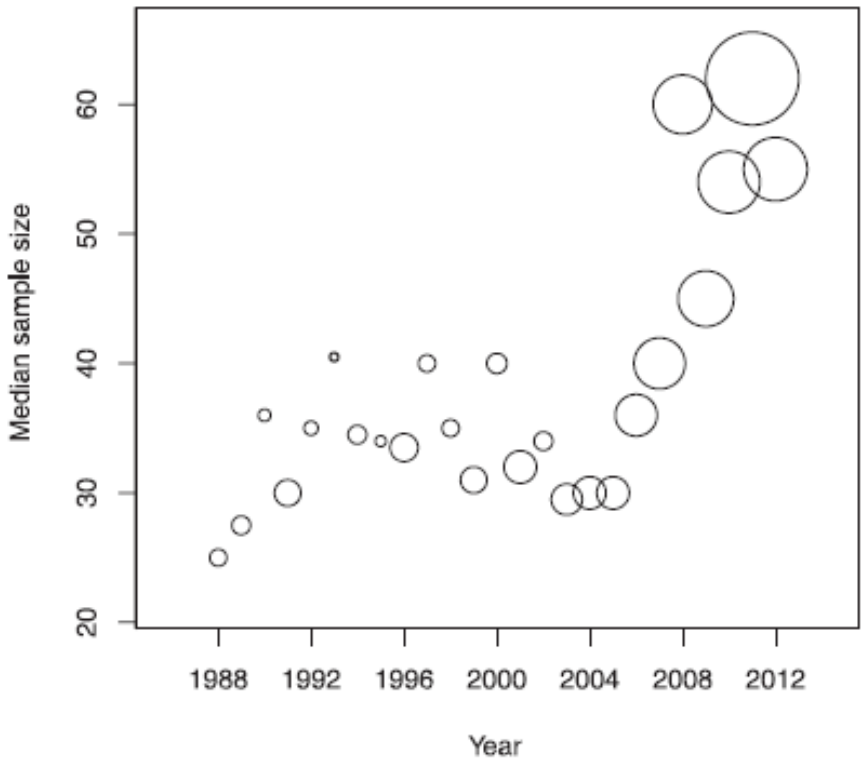
Increase in Overall Sample Size of Phase I Trials



The average sample size of a phase I study has increased from 33.8 patients (1988-1992) to 73.1 patients (2008-2012)

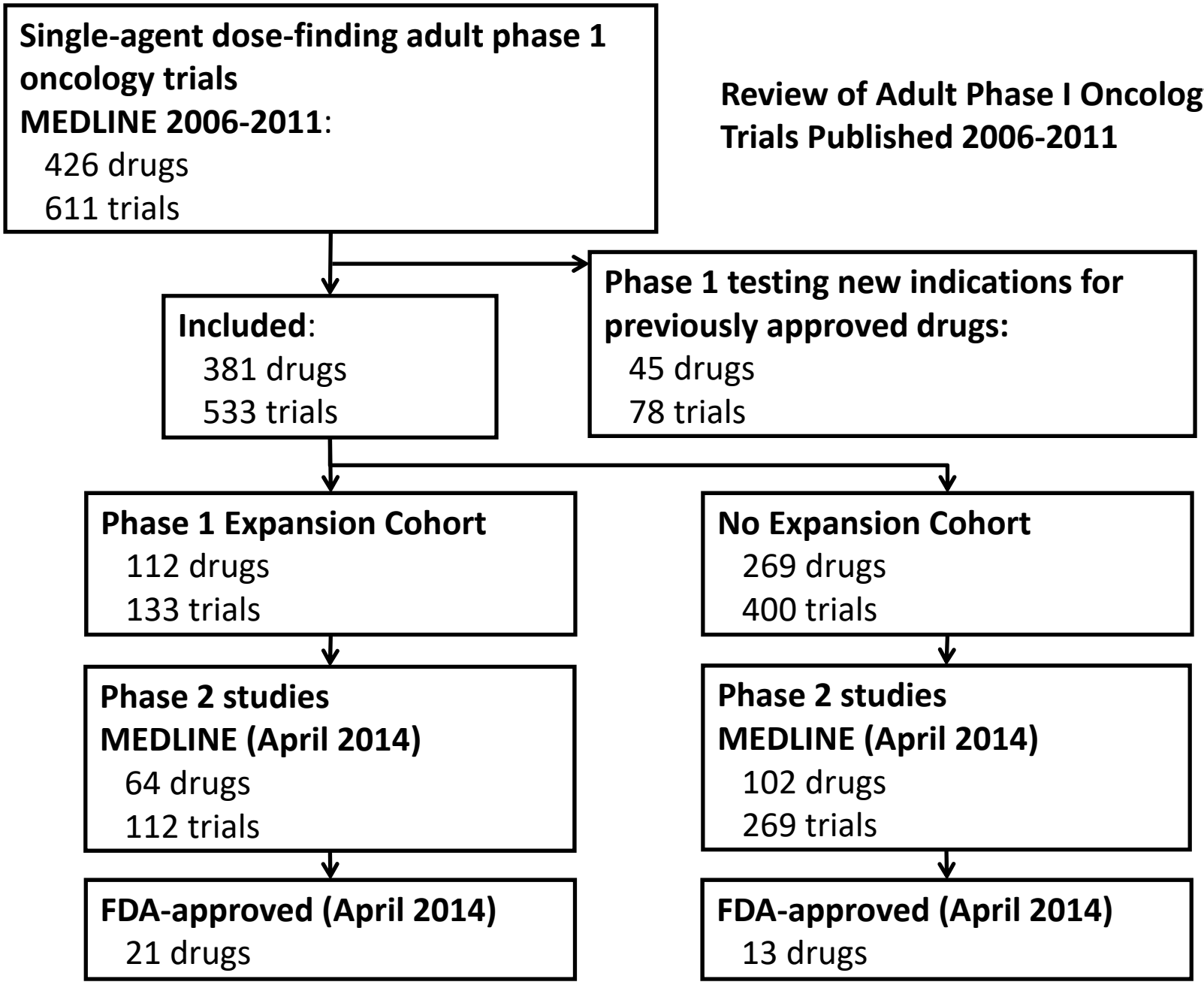
Dahlberg et al. J Natl Cancer Inst 2014

Expansion Cohorts (EC) in Phase I Trials

- Systemic review of adult single-agent phase I trials after 2006
- 149 (24%) of 611 trials used $\geq$ 1 EC, increased from 12% in 2006 to 38% in 2011
- Median number of pts: 22 in dose-escalation cohorts and 17 in EC
- Phase I trials more likely to include EC if multicentre (OR 1.8), non-cytotoxic agents (OR 2.0), industry sponsored (OR 1.6, p = 0.063)
- EC objectives reported in 74% of trials:
  - Safety (80%), efficacy (45%), PK (28%), pharmacodynamics (23%), patient enrichment (14%)
  - Among ECs assessing safety, MTD modified in 13% and new toxicities defined in 54%

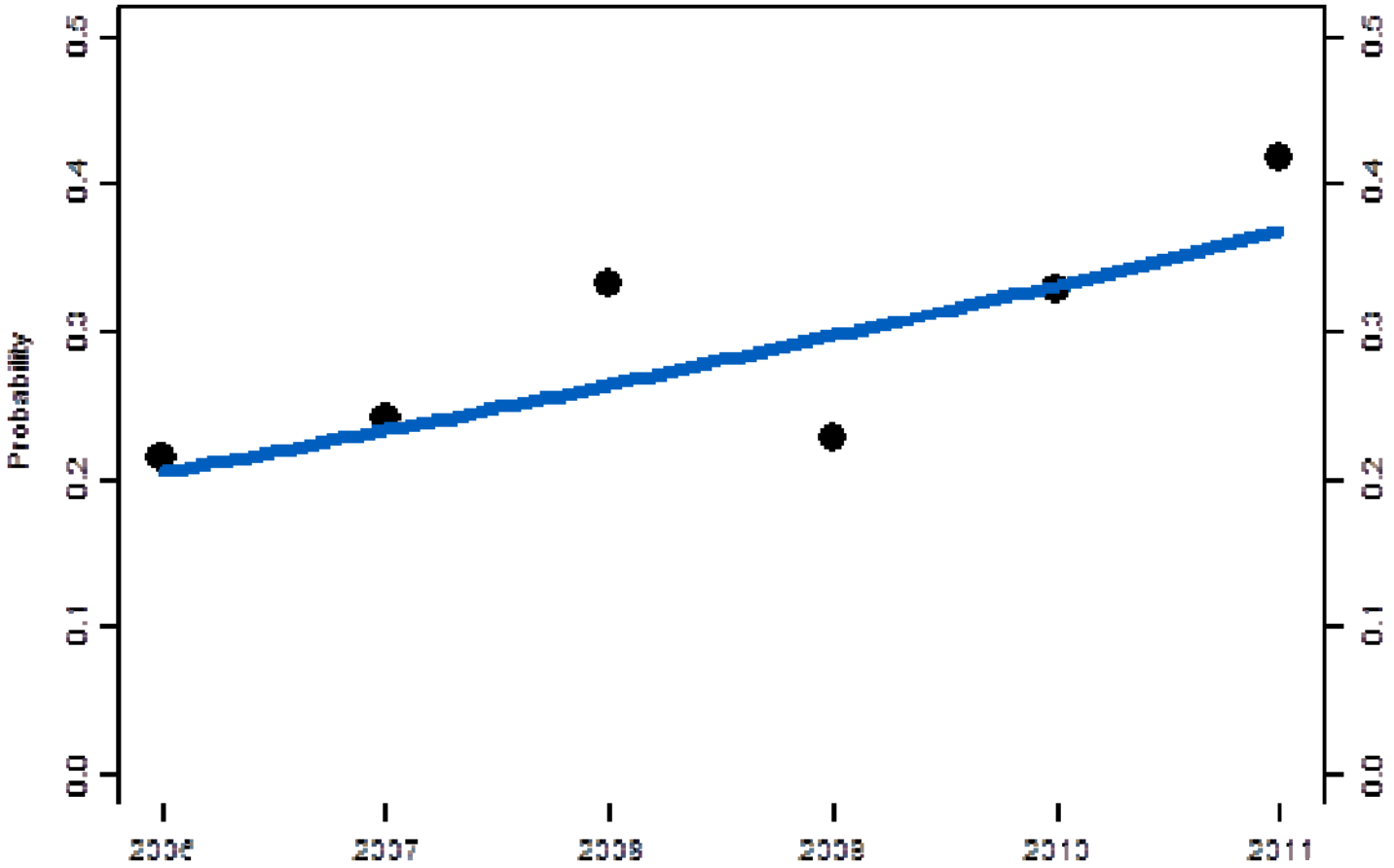
Manji et al. JCO 2013

Review of Adult Phase I Oncology Trials Published 2006-2011



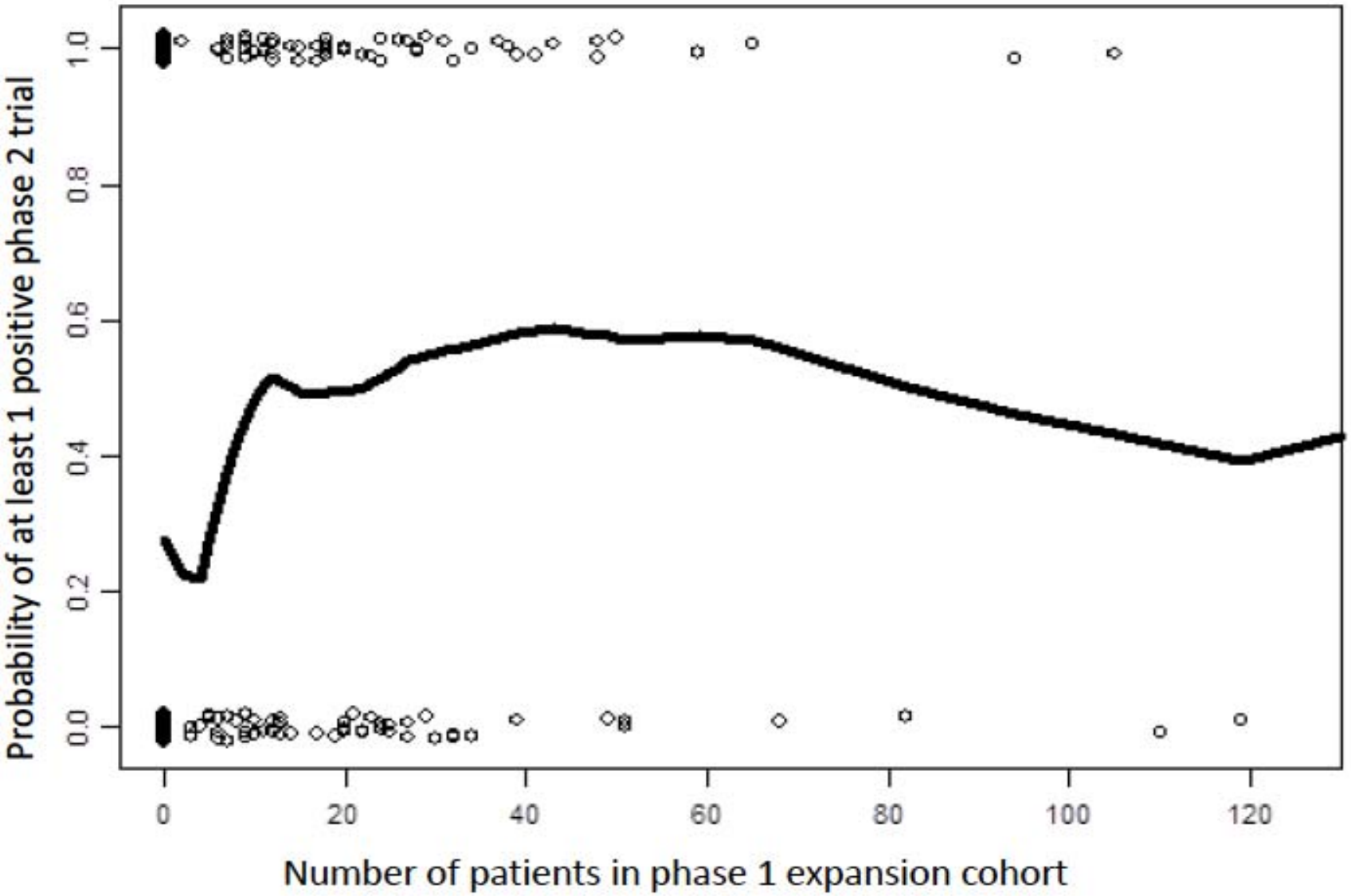
Bugano, Hess, Siu, Meric-Bernatam, Razak, Hong, In Press CCR

Probability of Having an Expansion Cohort According to Year of Publication of the Phase I Trial



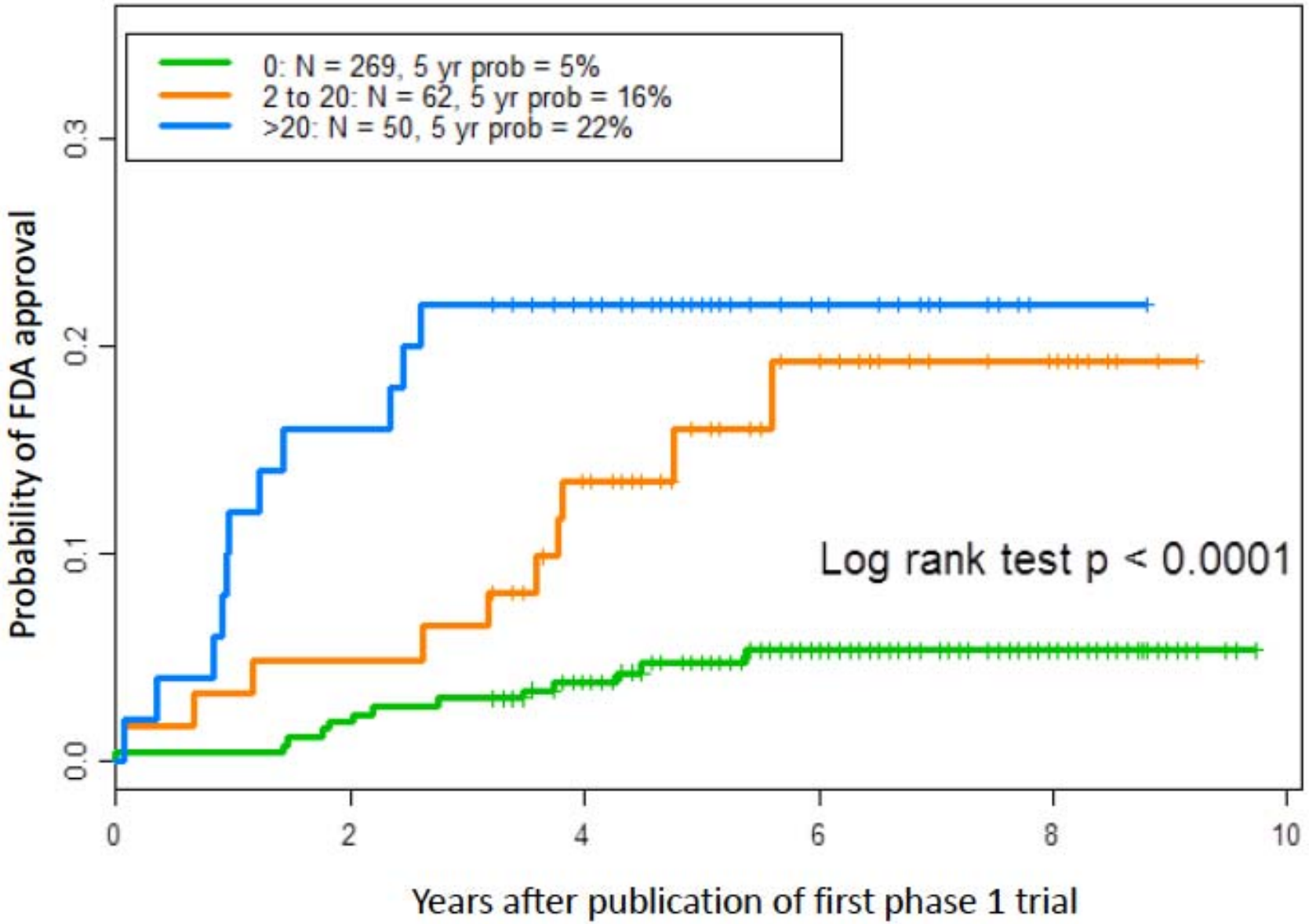
Bugano, Hess, Siu, Meric-Bernatam, Razak, Hong, In Press CCR

Probability of Success in a Phase 2 Trial Relative to the Size of the Phase 1 Expansion Cohort



Bugano, Hess, Siu, Meric-Bernatam, Razak, Hong, In Press CCR

Probability of FDA Approval and the Number of Patients in the Phase 1 Expansion Cohort



Bugano, Hess, Siu, Meric-Bernatam, Razak, Hong, In Press CCR

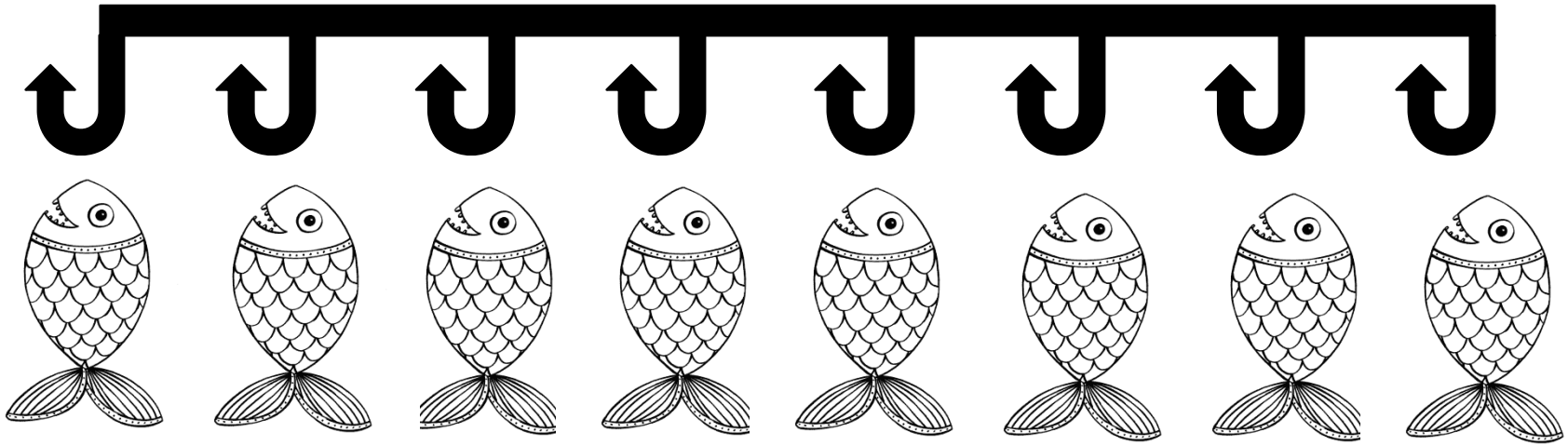
Cox Regression Model of Time-to-Drug-Approval

	Comparison	Univariate		Multivariate	
		HR(95% CI)	p	HR(95% CI)	p
Targeted agent	Y v N	0.7(0.3;1.7)	0.42	1.0(0.4;2.4)	0.95
Industry-sponsored	Y v N	4.4(1.1;18)	0.4	2.1(0.5;9.5)	0.33
Multicenter	Y v N	4.0(1.2;13)	0.02	2.4(0.7;8.5)	0.17
Pub >2008	Y v N	1.2(0.6;2.4)	0.57	1.0(0.5;2.2)	0.94
Tumor type	Hematologic v solid	4.0(1.3;12)	0.014	2.4(0.7;8.8)	0.17
	Hem+solid v solid	0.9(0.2;4.0)	0.91	0.6(0.1;4.6)	0.62
	Specific histology v any solid	1.6(0.8;3.4)	0.18	2.1(1.0;4.4)	0.066
Number of patients in dose escalation cohort	21-37 v < 21	0.8(0.3;2.1)	0.67	0.9(0.3;2.6)	0.88
	>37 v < 21	1.7(0.8;3.9)	0.19	1.4(0.6;3.4)	0.46
Number of patients in expansion cohort	2-20 vs 0	2.7(1.1;7.0)	0.034	2.1(0.8;5.4)	0.14
	21-271 vs 0	8.8(4.0;19.0)	<0.0001	6.6(2.9;15)	<0.0001

Bugano, Hess, Siu, Meric-Bernatam, Razak, Hong, In Press CCR

Single Protocol, Multiple Cohorts Signal-Finding Trials:

Common Design with Immune Checkpoint Inhibitors

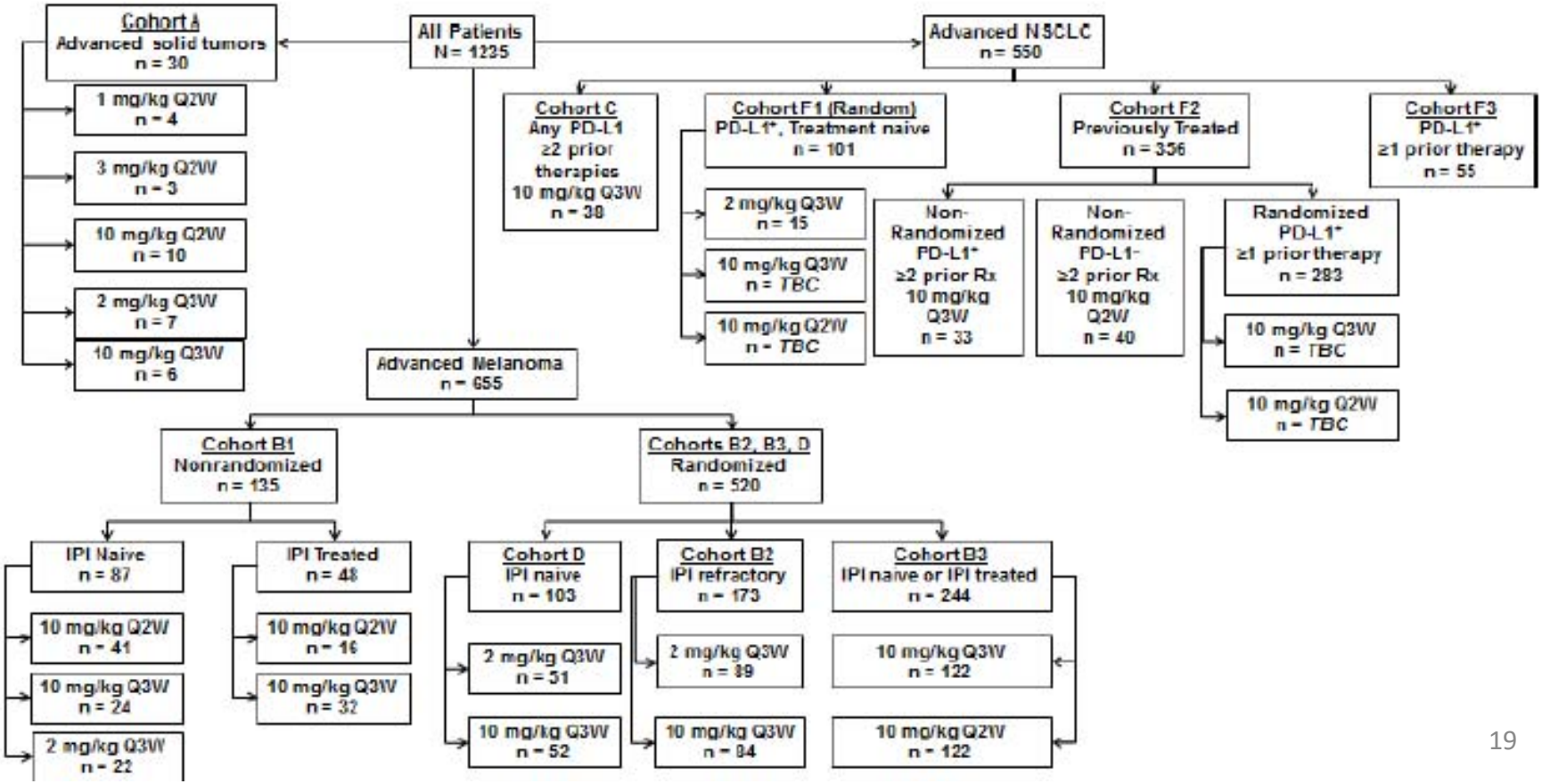


Protocol 001 (PN001) First in Human (FIH) to Registration

Cohort Expansion

From a small Phase 1-the study expanded to a 655-melanoma patient multi-part study

- 5 amendments, between Dec-2011 to Sep-2013, to answer emerging questions
- **4 "phase 2 study-like"** parts including 3 randomized dose comparison sub-studies



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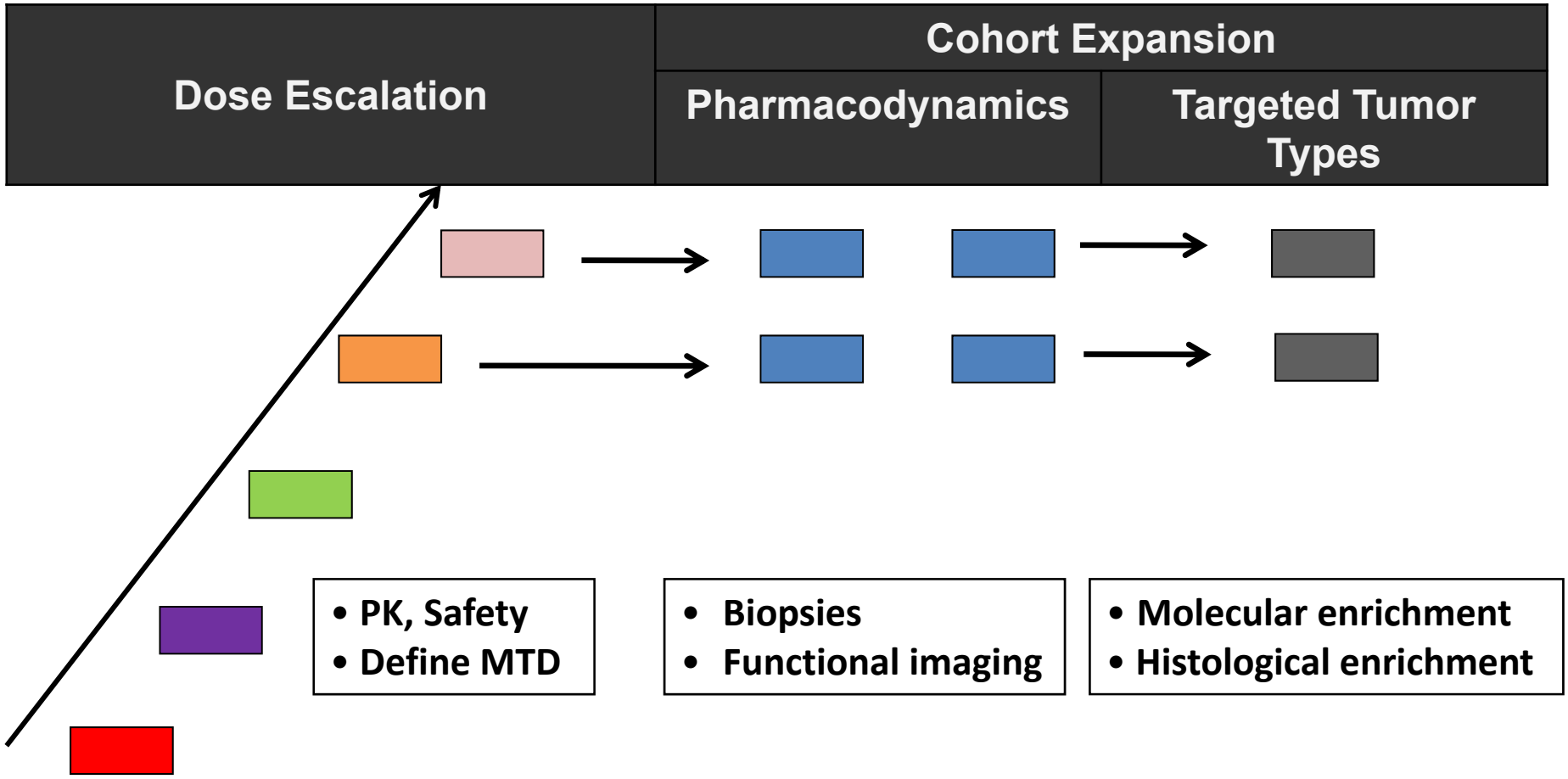
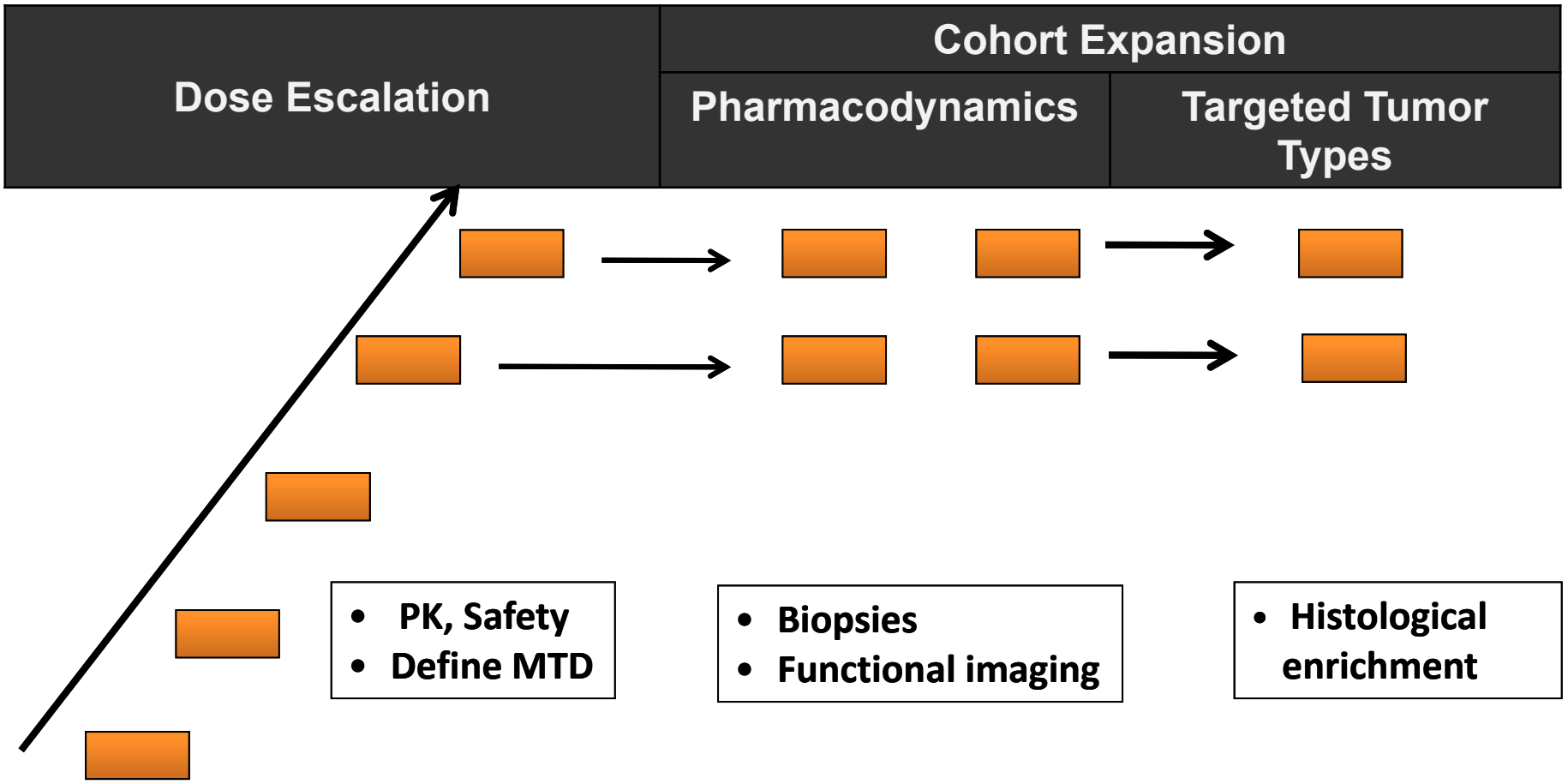
Phase I Study Design – Unselected Patients in Dose Escalation followed by Specific Expansion Cohorts

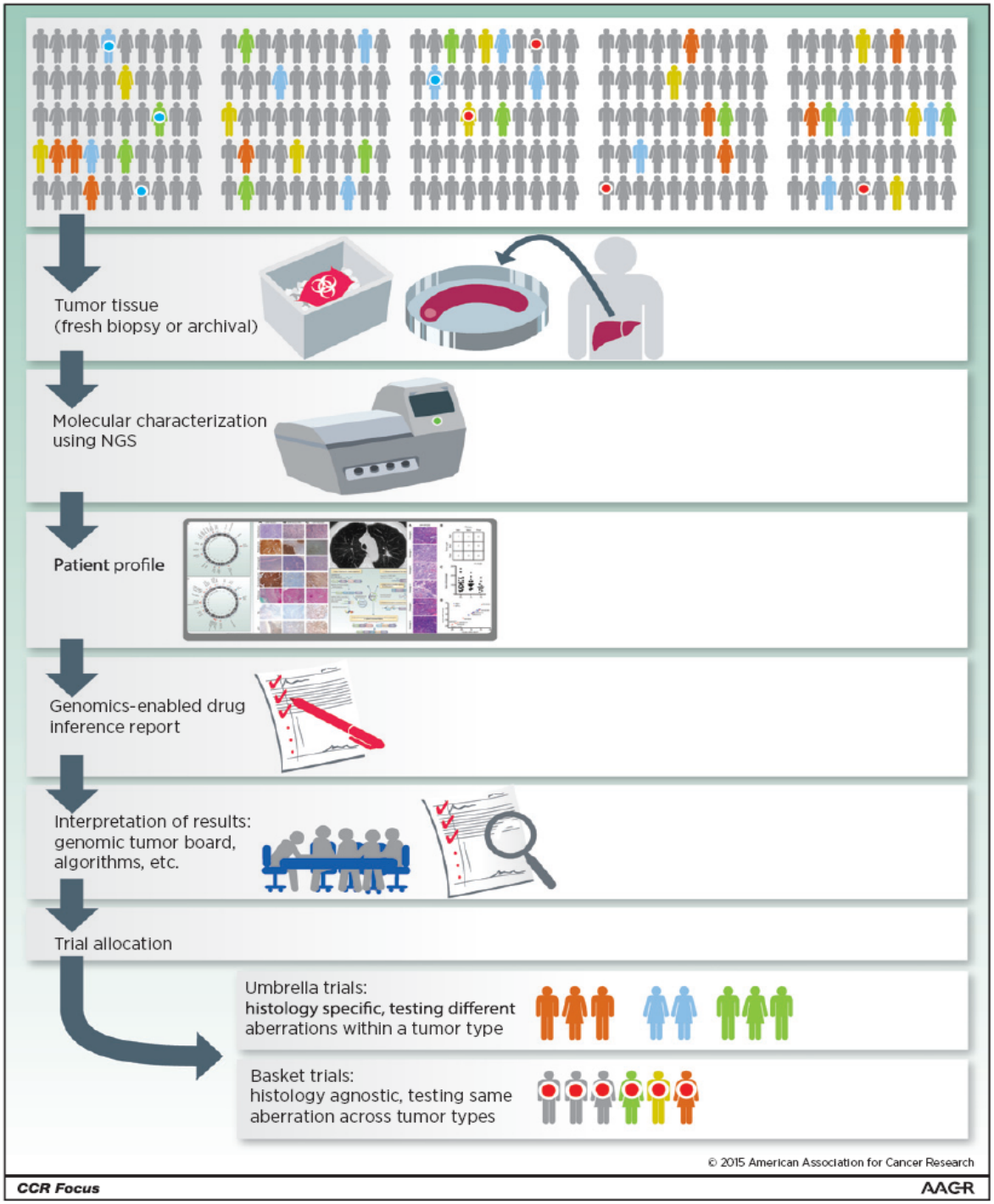


Phase I Study Design – Only Molecularly Enriched Patients



Enrichment and Patient Selection in Phase I Trials

Element	Challenges	Potential Solution
Molecular selection	**Central Screening:** ▪ Archived tumor tissues requested by multiple sponsors, leading to exhaustion of tissues ▪ Turnaround time variable ▪ Return of molecular information may lack sufficient annotation **Local Screening:** ▪ Local screening typically not reimbursed ▪ Assay may not have been validated in CLIA lab	▪ Local laboratory testing using validated multiplexed assay (funding remains an issue)
Identification of rare subsets of patients	▪ ↑screening costs while number of eligible patients ↓, leading to a financial challenge to keep many trials open with few patients recruited per trial	▪ Support for screening ▪ Multiplexed screening ▪ Umbrella or Basket protocols

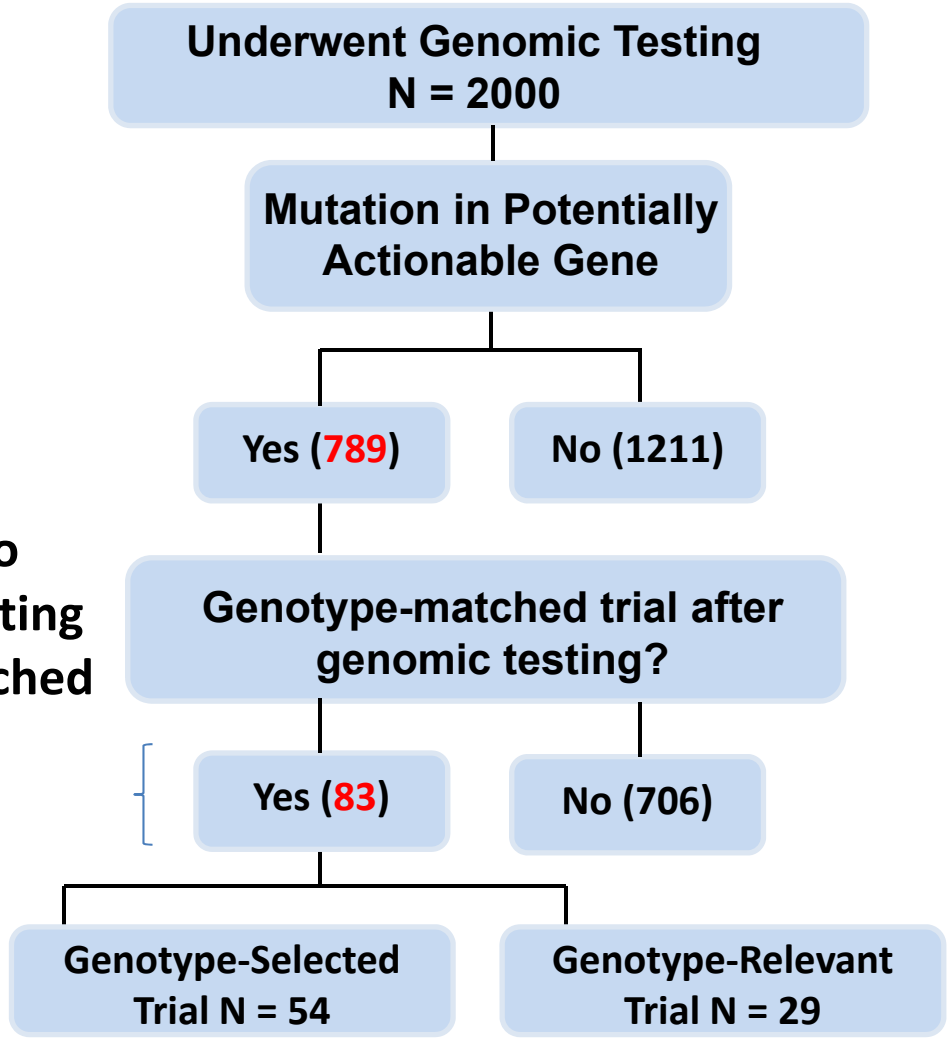


Clinical Application of Next Generation Sequencing to Find Matching Treatment

Siu, Conley, Boerner, Lorusso et al. CCR Focus, In Press

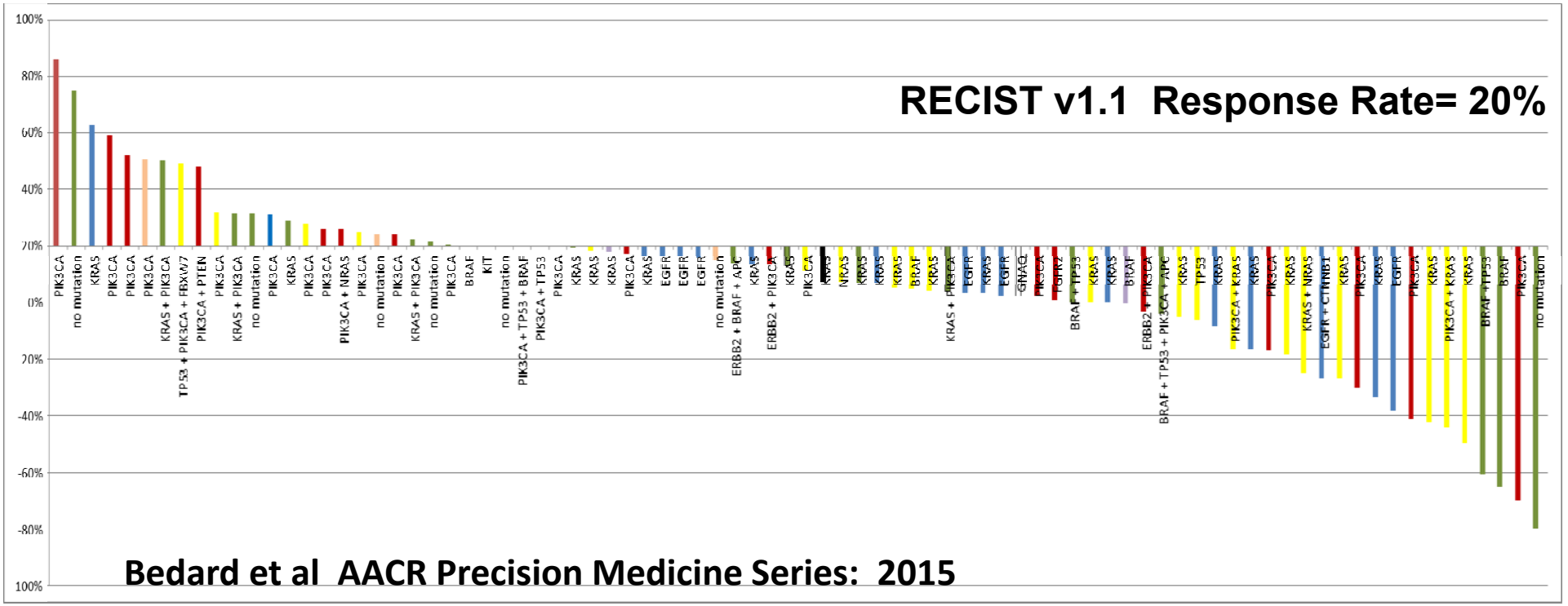
MDACC: Enrollment on Genotype-Matched Trials

54/2000 (3%) of pts who underwent genomic testing received genotype-matched treatment



Meric-Bernstam F et al JCO 2015

Best Tumor Shrinkage of Patients Enrolled in Genotype-Matched Trials



Disease Sites	Genotype Matched Trials	Most Common Mutations
Breast	22	PIK3CA (18)
Colorectal	18	BRAF (8), KRAS (5)
Lung	21	KRAS (11), EGFR (8)
Gynecological	22	KRAS (12), PIK3CA (6)

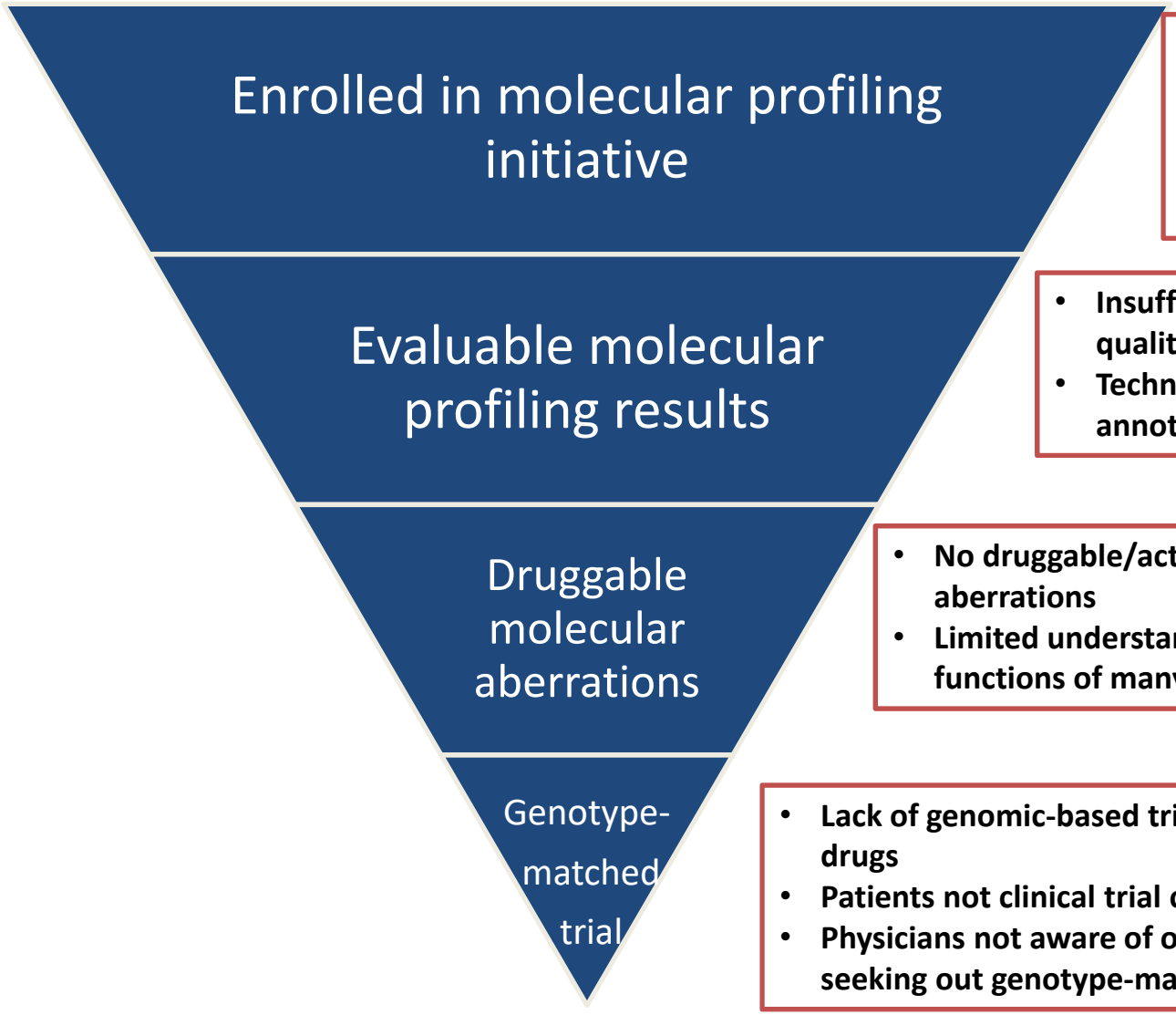
Breast
Colorectal
Lung
Gynecological
Genitourinary
Pancreatobiliary
Upper Aerodigestive
Other

Characteristics of Therapeutic Trial Patients

	All	Genotype Matched	Genotype Unmatched	p-value
Median Prior Therapies	4	4	4	p=NS
Range Prior Therapies	1-18	1-18	1-15	
Genotyping Platform				
Sequenom	176	63	113	
Illumina TruSeq	101	29	72	p=0.23
Ion Ampliseq	0	0	0	
≥1 mutation(s)	168	84	84	
no actionable mutation	109	8	101	
Trial Phase				
Phase I	158	74	84	
Phase II	67	9	58	p<0.001
Phase III	50	8	42	
Investigational Agent(s)				
Targeted Monotherapy	112	23	89	
Targeted Drug Combination	86	61	25	p<0.001
Targeted Drug + Chemotherapy	43	7	36	
Immunotherapy	34	1	33	

Bedard et al AACR Precision Medicine Series: 2015

Attrition in Molecular Profiling and Genotype-Drug Matching



- **Limitation of resources and personnel to perform profiling**
- **Screening/eligibility criteria e.g. ECOG, organ functions**

- **Insufficient tissue or poor DNA quality/quantity**
- **Technical, operational or annotation issues**

- **No druggable/actionable molecular aberrations**
- **Limited understanding in biological functions of many variants**

- **Lack of genomic-based trials or approved drugs**
- **Patients not clinical trial candidates**
- **Physicians not aware of or not actively seeking out genotype-matching trials**

Selected Molecular Profiling Initiatives and Genotype-Matching to Clinical Trials

Group	Sample Size	Platform	Fresh Biopsy vs FFPE	Germ-line Control	Number and % of Patients in Genotype-Matched Clinical Trials
Gustave Roussy	708	30-75 gene panels (Life) + CGH (Agilent)	Fresh biopsy	Yes	140/708 = 19%
Institut Curie	741	46 gene panel (Life) + CNA (Affymetrix) +IHC	Fresh biopsy	No	195 randomized/741 = 26%
BCCA	100	Whole genome	Fresh biopsy	Yes	1/100 = 1%
MD Anderson	2,000	11-50 gene panels (Life)	FFPE	No	83/2000 = 4%
Princess Margaret	1,640	23-48 gene panels (Ilumina, Life)	FFPE	Yes	92/1640 = 5.6%

CNA = Copy number alterations; IHC = Immunohistochemistry

Ferte et al. TAT 2015; LeTourneau et al. Lancet Oncol 2015; Laskin J, et al. Cold Spring Harb Mol Stud 2015; Meric-Bernstam et al. J Clin Oncol 2015; Bedard P, et al. AACR Precision Medicine Series 2015.

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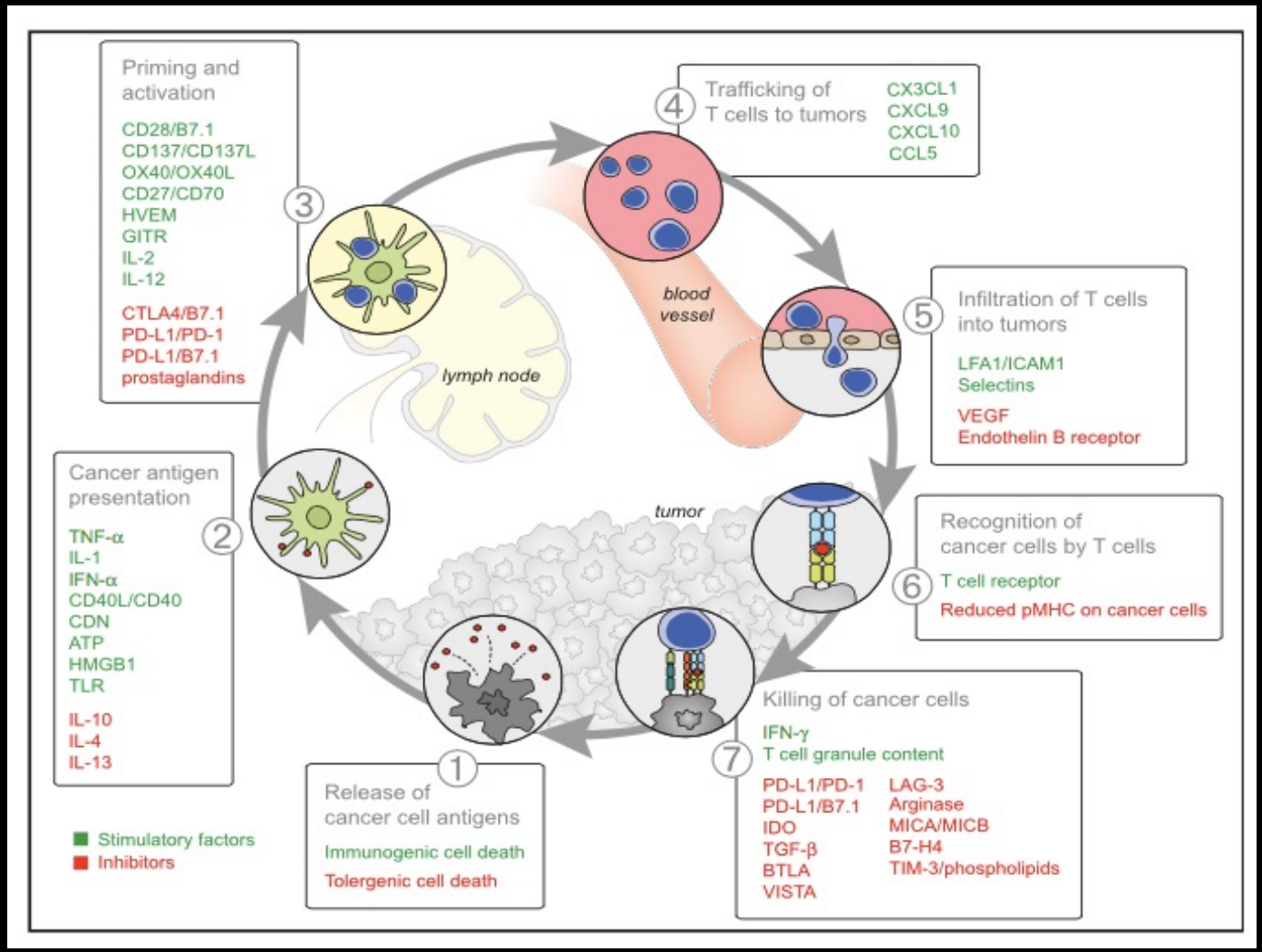
Requirements for Spontaneous or Therapeutic Immune Response



Chen and Mellman, Immunity 2013 39, 1-10DOI: (10.1016/j.immuni.2013.07.012)

Exhibit 25: Heat map of Immuno-oncology development progress by IO class and company (in-house assets)

IO class \ Company	Bristol-Myers	Merck & Co.	Roche	AstraZeneca	Pfizer	Novartis	GlaxoSmithKline	Sanofi
PD-1								
PD-L1								PC
CTLA-4								
Chemo combo				TBD				
IDO	PC	PC						
4-1BB/ CD137								
OX40								
LAG3								PC
GITR								PC
CSF-1R								
KIR								

Legend

Approved monotherapy	Appproved combo
Phase 3 monotherapy	Phase 3 combo
Phase 2 monotherapy	Phase 2 combo
Phase 1 monotherapy	Phase 1 combo
PC: preclinical	
TBD: AZN has announced plans to initiate a Phase 3 study for durvalumab with chemo combo	

Source: Company data, clinicaltrials.gov, Jefferies LLC

From @SheffStation

Immunotherapy at Princess Margaret

Approx. 400 patients/ year receive immunotherapy at PM and growing

	Phase I trials: Drug targets	Patient No.		Phase I trials: Drug targets	Patient No.
1	PD-1	80	*15*	TIM3+/-PD-1	5
2	PD-1	34	*16*	CSF1R+PD-1	5
3	PD-L1	32	*17*	PD-1	4
4	GITR+/-PD-1	21	*18*	PD-1+CTLA-4	3
5	PD-1	19	*19*	PD-1	3
6	PD-L1+OX40	16	*20*	PD-L1+CD40	2
7	OX40	13	*21*	PD-1	2
8	LAG+/-PD-1	12	*22*	CD40+ANG2	2
9	PD-L1+CTLA-4	9	*23*	4-1BB+PD-L1	2
10	PD-1+VEGF	9	*24*	CD73+PD-1	2
11	PD-1+CTLA-4 or VEGF	8	*25*	PD-L1 + MEK	1
12	PD-L1	8	*26*	TIGIT+PD-L1	1
13	IDO+PD-1	7	*27*	GITR+PD-L1	1
14	PD-L1	5	*28*	ICOS+PD-1	1
				Total	**307**

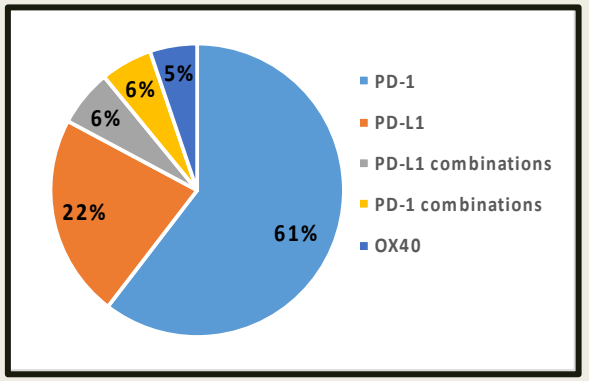
Development of the Princess Margaret Immune Oncology Prognostic Index (PM-IPI): A novel prognostic score for patients treated in immune oncology phase I trials

Results

Baseline patient characteristics

	No. of patients	%
Sex		
Male	107	56%
Female	85	44%
Age	median 57.5 (range 20.4-84.8)	
ECOG PS		
ECOG PS 0	76	40%
ECOG PS 1	116	60%
Primary tumor site		
Melanoma	52	27%
Thoracic	41	21%
Genitourinary	22	11%
Head and neck	20	10%
Sarcoma	14	7%
Gynecologic	13	7%
Gastrointestinal	18	8%
Breast	8	4%
Other	6	3%
No. of prior systemic therapies	median 2 (range 0-8)	
No. of metastatic sites	median 3 (range 0-7)	
≤2 sites	86	45%
>2 sites	106	55%
Sites of metastasis		
Lung	123	64%
Liver	74	39%
Bone	52	27%
Brain	23	12%

PI IO trials: Drug targets



Patient outcomes (n=192)

- Median PFS: 13.4 weeks
- Median OS: 73.6 weeks
- 90DM: 16%
- ORR: 20% by RECIST 1.1/ irRECIST

Dai et al. ASCO 2016

Results

- Multivariate analysis: Independent prognostic factors
  - *ECOG PS ≥1 (HR 3.2, p < 0.001)*
  - *No. of metastatic sites > 2 (HR 2.0, p = 0.003)*
  - *Albumin < lower limit of normal (HR 1.8, p = 0.007)*

PM-IPI

- Patients with a score of 2-3 compared to patients with a score of 0-1:
  - *Shorter OS (HR 3.4, p < 0.001)*
  - *Shorter PFS (HR 2.3, p < 0.001)*
  - *Higher 90DM (OR 8.1, p < 0.001)*
  - *Lower ORR (OR 0.4, p = 0.019)*

- Comparison of PM-IPI with previously published P1 prognostic scores

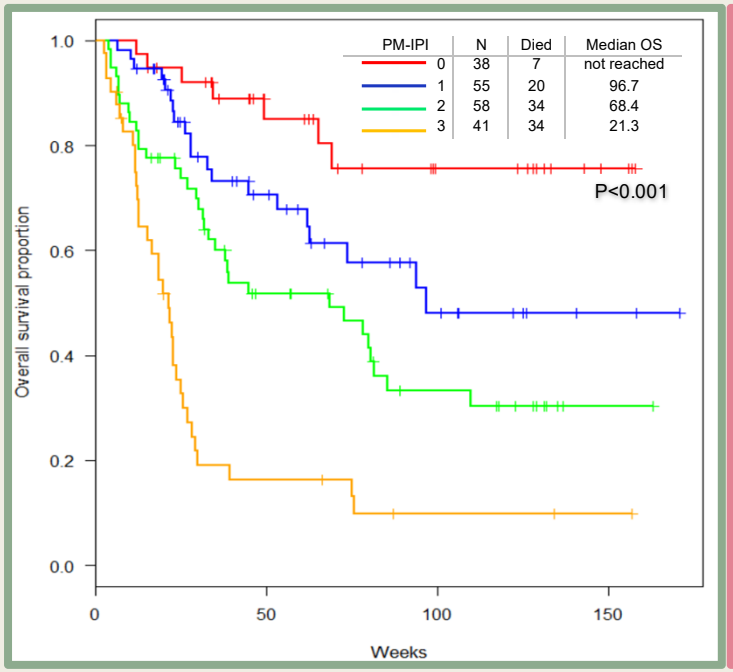
		PM-IPI	RMI	PMHI	NS	HS
OS	(C-index)	**0.71**	0.65	0.69	0.59	0.59
PFS	(C-index)	**0.66**	0.63	0.63	0.58	0.58
90DM	(AUC)	**0.75**	0.69	0.73	0.68	0.70
ORR	(AUC)	**0.64**	0.59	0.64	0.58	0.56

RMI: Royal Marsden Index; PMHI: Princess Margaret Hospital Index; NS: Nijmegen Score; HS: Hammersmith Score; AUC: Area under the curve

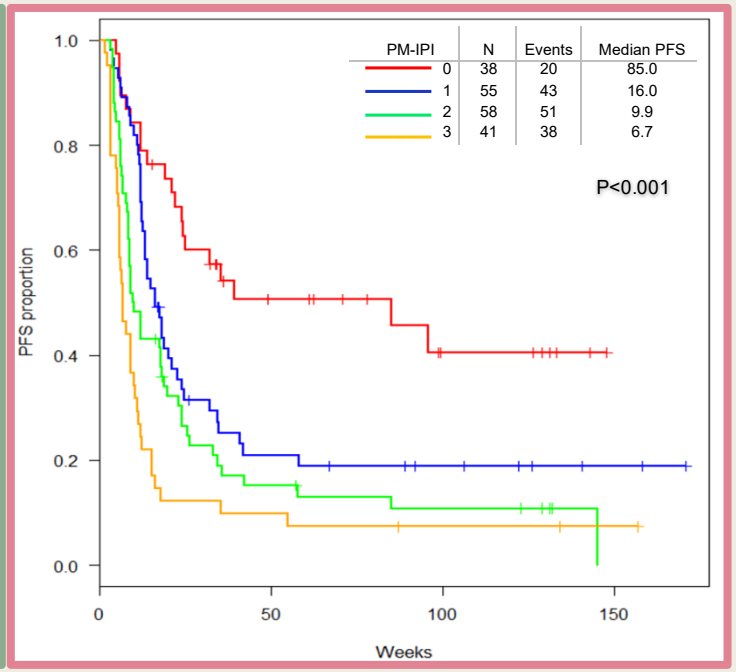
0.5 = no discriminative ability; 1.0 = perfect discriminative ability

Results

OS



PFS



Optimization of Phase I Referral Process

Developing an App to Assist with Trial Allocation

Tumor Types (e.g. Breast Cancer)

↓

Trials: A, C, D, F, G, H, K, L, M, N, S, W

Molecular Selection (e.g. PIK3CA)

↓

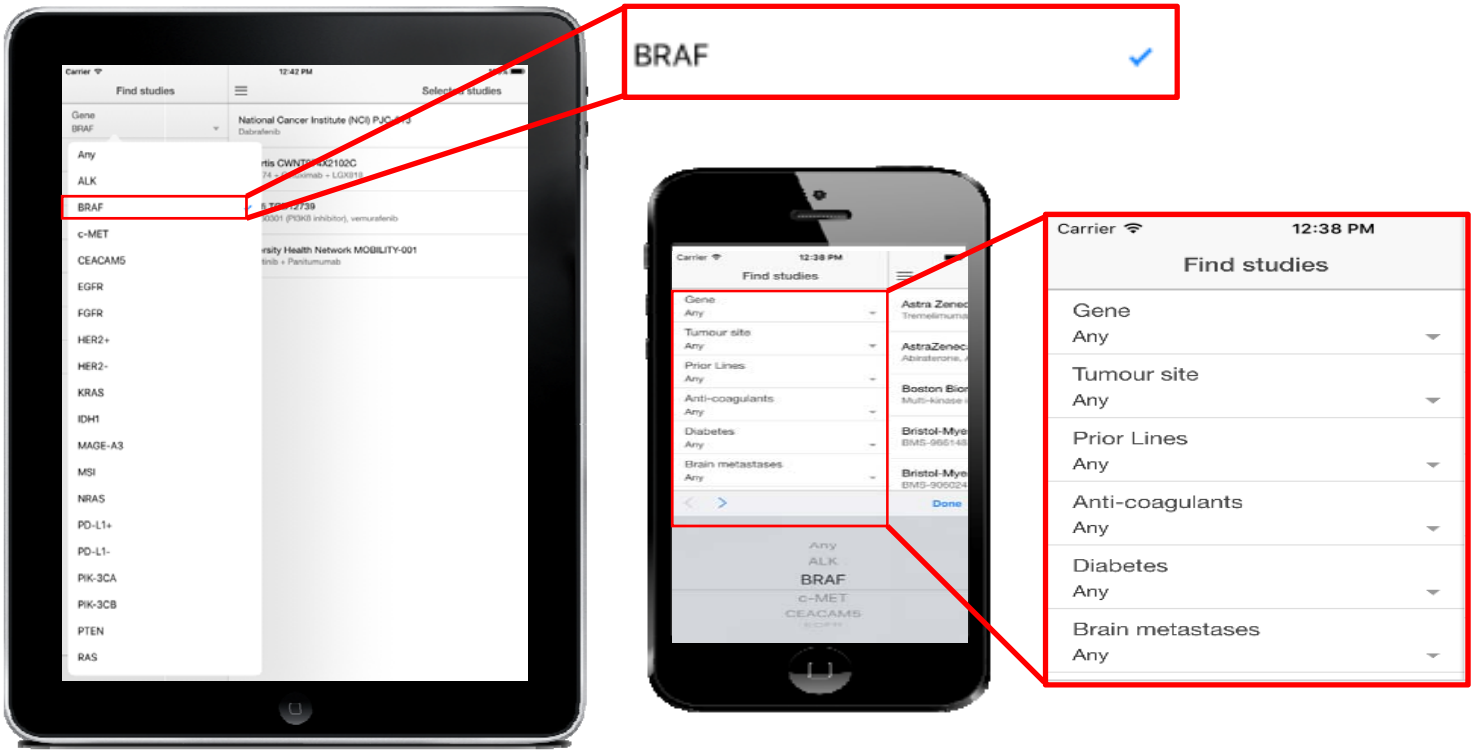
Trials: C, G, K, L, W

No. of Prior Lines (e.g. 4 Lines)

↓

Trials: C, W

Mobile Application



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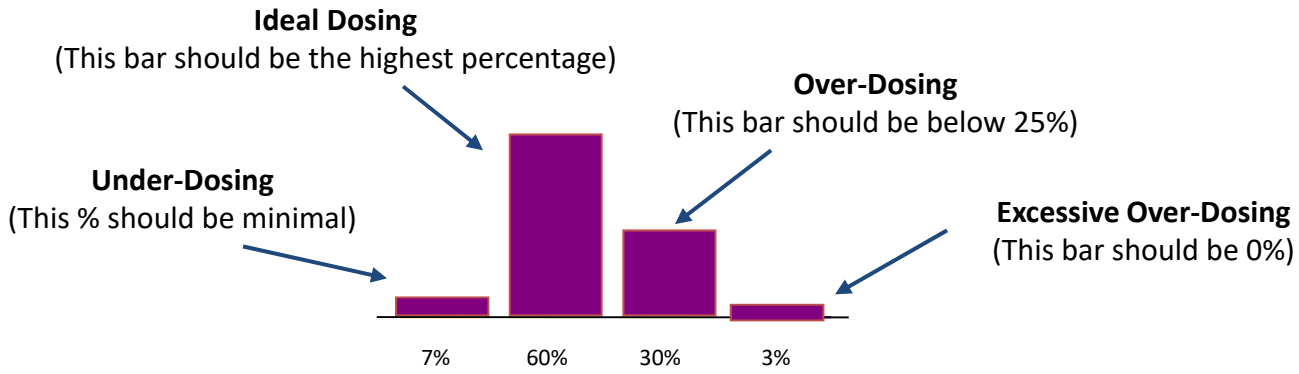
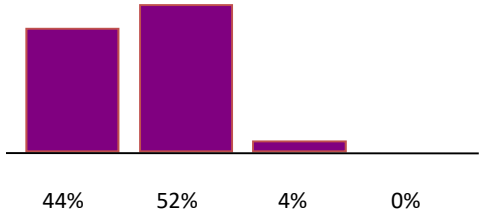
Estimated MTD Based on Bayesian Logistic Method (2-parameter evaluation with over-dose control)

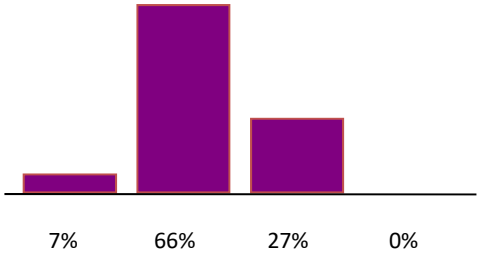
EXAMPLE of Probability of DLTs (Bayesian Design)



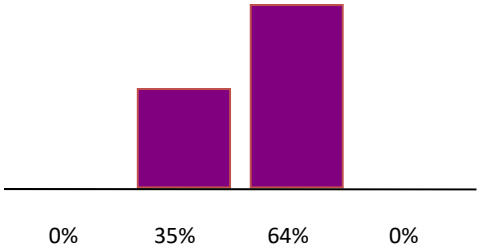
Drug at 0.5mg



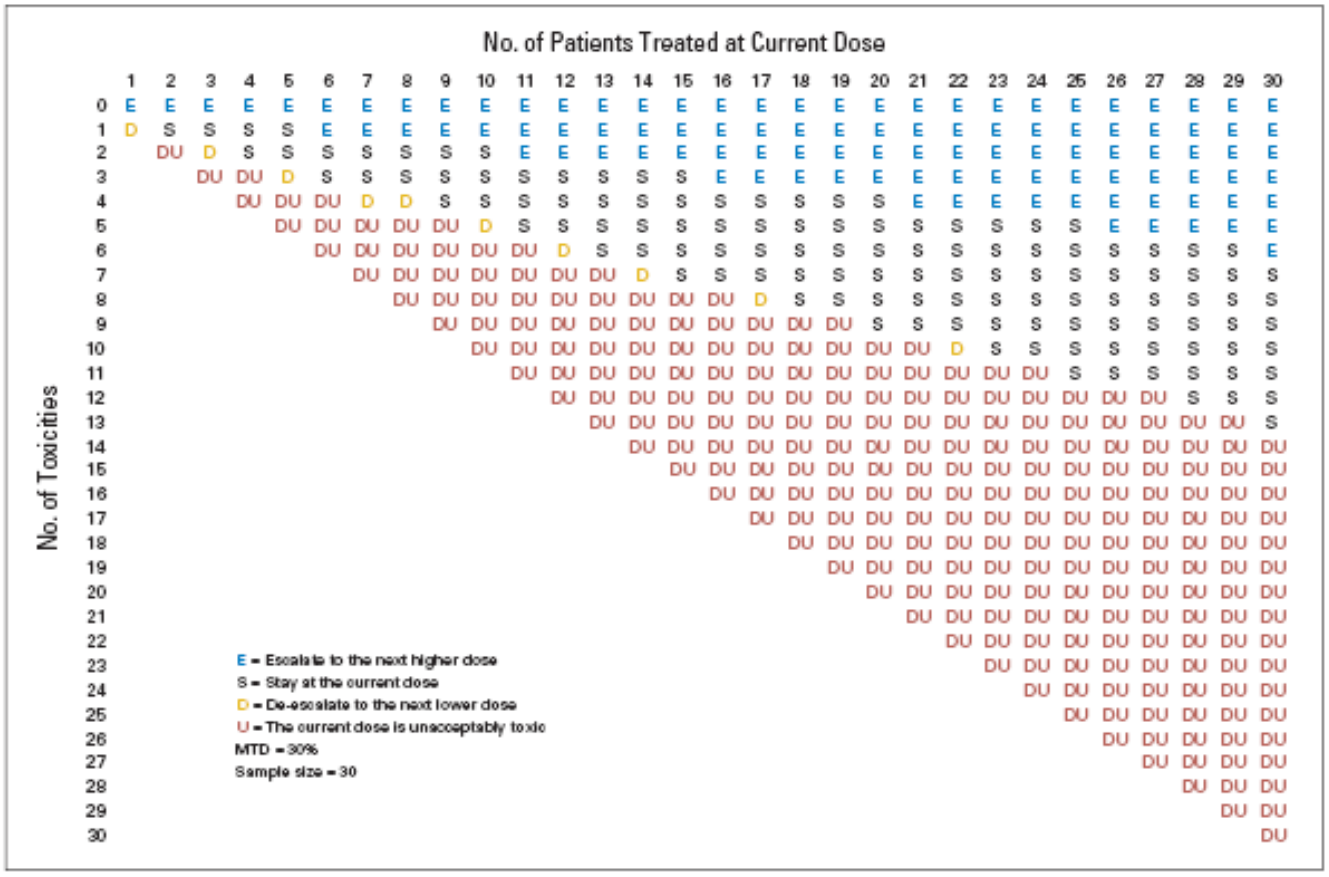
Drug at 0.75 mg



Drug at 1.0 mg



Modified Toxicity Probability Interval (mTPI) Design



Ji Y and Wang S-Y. J Clin Oncol 31: 1785-1791, 2013

In Your Opinion, What is the Most Appropriate Dose Escalation Method for these Examples

Example	Most Appropriate Dose Escalation Method
1. A monoclonal antibody without a valid pharmacodynamic biomarker for optimal biological activity and likely will not have an MTD	
2. Combination of radiation with a new drug with concern for delayed/late toxicity	
3. Combination of radiation with a new drug with minimal concern for interaction or toxicity	
4. A first-in-class new drug with no obvious concerns raised by preclinical data	
5. A first-in-class new drug with likely a narrow therapeutic index	
6. Combination of two drugs each with its own RP2D with unknown risk of interaction	

Purpose of Tumor Biopsies

Diagnostic Tumor Biopsies:

- To establish a clinical diagnosis and to perform validated prognostic or predictive markers for clinical management

Post-Diagnostic Tumor Re-Biopsies:

- To measure a biomarker that can be used to guide clinical management (e.g. integral biomarker – *KRAS* in CRC):
  - Insufficient tumor from archival sample
  - To obtain current tissue due to concern for clonal evolution
- To perform research (e.g. integrated or exploratory biomarkers – ↓phospho-S6 as a measure of PI3K pathway inhibition)

Patient Attitudes Towards Genomic Testing in Cancer (GTC) (n = 98 patients referred for genomic testing or phase I trials)

Item	Yes	No	Unsure
Would you be interested in leaning more about GTC?	76%	6%	17%
Would you be willing to undergo needle biopsy if required for GTC?	66%	13%	19%
Would you be willing to undergo surgical biopsy if required for GTC?	39%	27%	33%
Do you believe GTC would significantly improve your cancer care?	64%	5%	30%
Would you want disclosure of incidental GTC results regarding:			
a) Inherited familial risk of developing cancer	87%	5%	7%
b) Inherited risk of developing diseases other than cancer	79%	7%	13%
Would you consent to biobank your GTC results and tissue sample for future scientific research?	91%	2%	5%

Blanchette et al. Cancer 2014

Patients' Willingness to Undergo Multiple Tests in a Single Trial (n = 61)

	Geometric Mean±SD[a]					
No. of Tests	PET Scan	CT Scan	X-Ray	MRI	Ultrasound	Echocardiogram
1	9.1±1.4	9.5±1.3	9.7±1.4	7.9±1.9	9.7±1.2	9.4±1.4
2	8.2±1.6	8.8±1.5	9.0±1.5	6.6±2.2	9.2±1.4	8.4±1.8
3	7.1±1.9	7.1±2.1	8.1±1.8	5.9±2.3	8.3±1.7	7.8±2.0
4	6.4±2.2	6.7±2.1	7.3±2.1	5.5±2.4	7.9±1.8	7.7±2.0
P test for trend	<.001	<.001	<.001	<.001	.003	.010

	Geometric Mean±SD[a]					
No. of Tests	Skin Biopsy	Tumor Biopsy	Blood Sample	Hair Follicle	Stool Sample	Urine Sample
1	8.1±1.6	7.6±1.9	9.9±1.2	8.6±1.7	9.1±1.3	9.9±1.2
2	6.1±2.2	5.8±2.2	9.6±1.3	7.9±1.9	8.0±1.8	9.9±1.2
3	5.3±2.3	4.6±2.3	9.0±1.5	7.5±2.0	7.4±1.9	9.3±1.6
4	4.6±2.5	4.0±2.4	8.4±1.7	7.2±2.0	7.3±1.9	9.3±1.6
P test for trend	.001	.001	.001	.001	.001	.045

SD indicates standard deviation; PET, positron emission tomography; CT, computed tomography; MRI, magnetic resonance imaging.

[a] Answers were scored on a scale from 1 (not willing) to 11 (very willing). The scale range was recoded from a 0-to-10 scale to a 1-to-11 scale by adding 1 to each score to accommodate calculation of the geometric mean and SD.

1 (not willing) 11 (very willing)

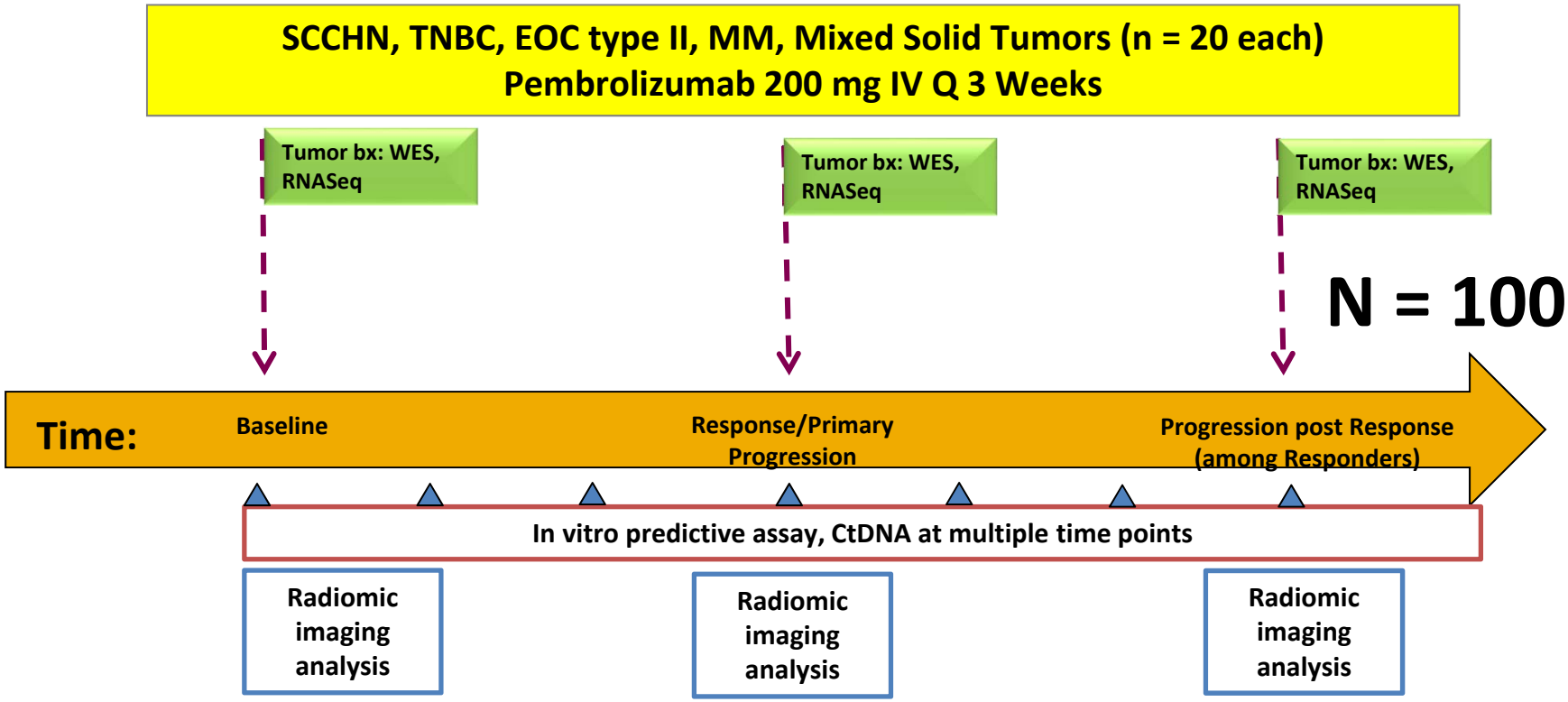
Tibes et al. Cancer 2011

Research Biopsies

- **Identified 22 phase I trials from 2003-2006 which included post-treatment biopsies for PD-biomarkers**
- **9/22 studies (41%) tested >4 PD-biomarkers**
- **Statement on impact on future studies found in 9/22 studies (41%)**
- **None of the PD-biomarkers impacted phase II/III dose or schedule**

Sweis R and Ratain M ASCO 2014

INvestigator-initiated Phase II Study of Pembrolizumab Immunological Response Evaluation (INSPIRE)



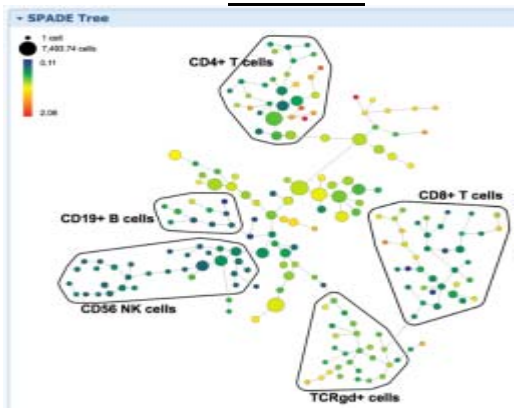
INSPIRE-A-002

Flow Cytometry Panel #1
(T cell analysis)

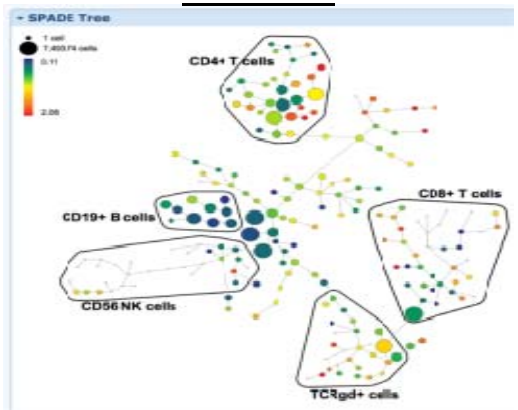
CD3	T cells
CD8	CTL
CD4/ CD19	Helper cells / B cells
CD56	NK cells
TcRγδ	γδ T cells
PD-1	exhaustion
TIGIT	exhaustion
PDL1	exhaustion
CTLA4	exhaustion
4-1BB	co-stimulation

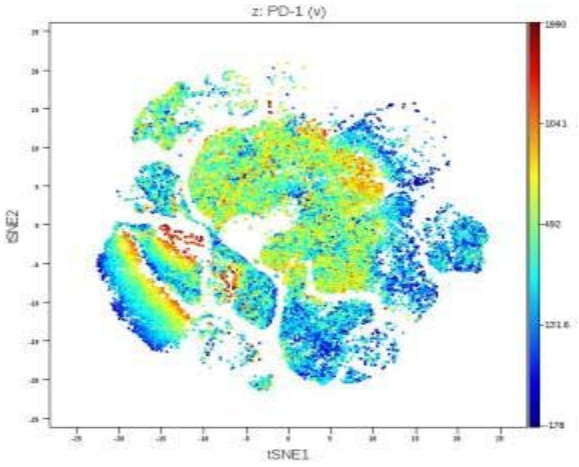
Unpublished data

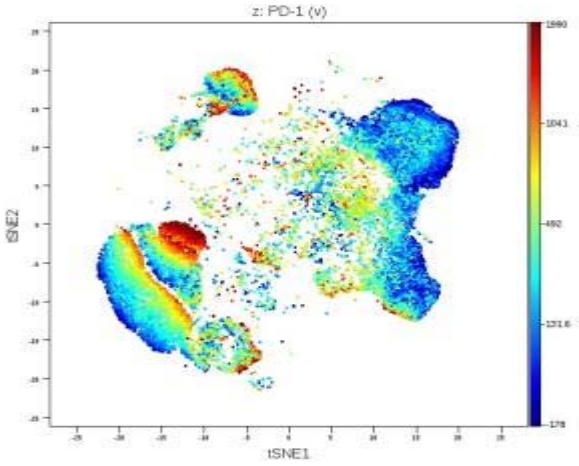
PBMC



Tumor







The Future Drug Development Paradigm?

Histology + Molecular Selection	Proof of Concept
o Safety, tolerability o Functional target selection o Pharmacology o Antitumor activity	o Substantial efficacy in selected pt populations using innovative trial designs and endpoints o Trial design accounting for interpatient and intratumor heterogeneity

Conclusions

- Phase I trials are playing an increasingly critical role for go-no-go in drug development
- Many emerging features have arisen out of the need to find rare molecular patient subsets, expedite drug development, incorporate promising emerging agents (e.g. IO), while preserving safety in our conduct of phase I trials
- We need to keep key stakeholders (patients, IRB members, referring physicians, study team members) informed and engaged as phase I trials evolve in the drug development paradigm

Phase I Team at the Princess Margaret Cancer Centre