FDA-AACR Public Workshop On

OPTIMIZING DOSAGES FOR ONCOLOGY DRUG PRODUCTS: QUANTITATIVE APPROACHES TO SELECT DOSAGES FOR CLINICAL TRIALS

February 15 and 16, 2024 I Washington, DC

Session 2B: Novel Trial Designs to Enhance Dose-Selection Decision Making

Moderator Introduction

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The University of Texas MD Anderson Cancer Center

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Disclosure information

- **Employee of:** University of Texas MD Anderson Cancer Center, where I am Vice President, Head of Clinical Development in the Therapeutics Discovery Division, which has a commercial interest in DDR and other inhibitors (IACS30380/ART0380 was licensed to Artios)
- **Consultant for:** AbbVie, Acrivon, Adagene, Almac, Aduro, Amphista, Artios, Astex, AstraZeneca, Athena, Atrin, Avenzo, Avoro, Axiom, Baptist Health Systems, Bayer, Beigene, BioCity Pharma, Blueprint, Boxer, Bristol Myers Squibb, C4 Therapeutics, Calithera, Cancer Research UK, Carrick Therapeutics, Circle Pharma, Clovis, Cybrexa, Daiichi Sankyo, Dark Blue Therapeutics, Diffusion, Duke Street Bio, 858 Therapeutics, EcoR1 Capital, Ellipses Pharma, EMD Serono, Entos, F-Star, Genesis Therapeutics, Genmab, Glenmark, GLG, Globe Life Sciences, GSK, Guidepoint, Ideaya Biosciences, Idience, Ignyta, I-Mab, ImmuneSensor, Impact Therapeutics, Institut Gustave Roussy, Intellisphere, Jansen, Kyn, MEI pharma, Mereo, Merck, Merit, Monte Rosa Therapeutics, Natera, Nested Therapeutics, Nexys, Nimbus, Novocure, Odyssey, OHSU, OncoSec, Ono Pharma, Onxeo, PanAngium Therapeutics, Pegascy, PER, Pfizer, Piper-Sandler, Pliant Therapeutics, Prolynx, Radiopharma Theranostics, Repare, resTORbio, Roche, Ryvu Therapeutics, SAKK, Sanofi, Schrodinger, Servier, Synnovation, Synthis Therapeutics, Tango, TCG Crossover, TD2, Terremoto Biosciences, Tessellate Bio, Theragnostics, Terns Pharmaceuticals, Tolremo, Tome, Thryv Therapeutics, Trevarx Biomedical, Varian, Veeva, Versant, Vibliome, Voronoi Inc, Xinthera, Zai Labs and ZielBio
- **Grant/Research support from:** Acrivon, Artios, AstraZeneca, Bayer, Beigene, BioNTech, Blueprint, BMS, Boundless Bio, Clovis, Constellation, Cyteir, Eli Lilly, EMD Serono, Forbius, F-Star, GlaxoSmithKline, Genentech, Haihe, Ideaya ImmuneSensor, Insilico Medicine, Ionis, Ipsen, Jounce, Karyopharm, KSQ, Kyowa, Merck, Mirati, Novartis, Pfizer, Ribon Therapeutics, Regeneron, Repare, Rubius, Sanofi, Scholar Rock, Seattle Genetics, Tango, Tesaro, Vivace and Zenith
- **Stockholder in:** Seagen

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Clinical perspective: Key biomarkers and trial design for successful dose optimization

3:05 PM Using Novel Activity and Safety Endpoints in Clinical Trials to Support Dosage Selection: Anthony “Nino” Sireci, MD, MS (Eli Lilly)

Translational perspective: Incorporating ctDNA and other biomarkers for dose optimization

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Statistical perspective: Randomization (or not) and backfills for dose optimization

Definitions of a biomarker

"A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention"

Biomarkers Definitions Working Group, Clin Pharmacol Ther 2001

Functional Definitions

Biomarker type	Definition	Example
Predictive	Used to identify individuals who are more likely to respond to a therapy	*BRCA1/2* mutations (PARP inhibitors)
Pharmacodynamic (PD) [with pharmacokinetic (PK)]	Used to determine "how much" and "how long" target and pathway are modulated	γH2AX induction (PARP inhibitors)
Pharmacogenomic	Used to understand how variations within the genome influence drug response and toxicity	DPYD variants (Capecitabine)
Intermediate endpoint (surrogate)	Used as an intermediate readout of treatment effect at a point in time earlier than the clinical endpoint of interest	Tumor shrinkage (for overall survival)
Prognostic	Used to identify likelihood of a clinical event, disease recurrence or progression	PSA (Prostate cancer)

Definitions of a biomarker

"A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention"

Biomarkers Definitions Working Group, Clin Pharmacol Ther 2001

Regulatory Definitions

Biomarker type	Definition	Example
Integral	Biomarkers performed to define eligibility, stratification, disease monitoring or study endpoints. Inherent to the design of the trial and measured in real time.	*BRCA1/2* mutations
Integrated	Associated with a scientific question or a statistically testable hypothesis based on preexisting data. Ideally, the assay should already have been tested in human subjects with the disease in question and demonstrated reproducible analytic qualities.	WES and RNAseq
Exploratory	Other biomarkers, often analyzed retrospectively and not collected for all patients	ctDNA

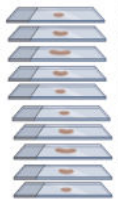
Potential tissue for biomarkers

Tumor Tissue

Cell characterization

Fresh
Flow Cytometry

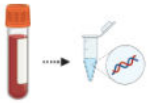
Fresh Frozen
Next Generation Sequencing
Gene expression signatures
TCR & BCR sequencing



FFPE
H&E stain: pathology analysis
IHC markers
Multiplex IF Analysis
Low-input gene expression signatures

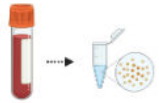
Blood (PBMCS, T-cells)

Systemic response characterization



PBMCs, Plasma/Serum
Next Generation Sequencing (gDNA)
TCR & BCR sequencing

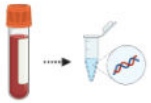
Functional T-cell assays
Flow Cytometry



Cytokines/chemokines

Liquid biopsy (ctDNA, CTC)

Tumor Burden Monitoring



Plasma/Serum
Circulating tumor DNA (ctDNA)
Circulating Tumor Cells (CTC)
Droplet digital PCR (ddPCR)
Next Generation Sequencing

Exosomes

Other biospecimens

Host factors

CSF
Next Generation Sequencing
TCR sequencing
Flow cytometry
Cytokines/chemokines

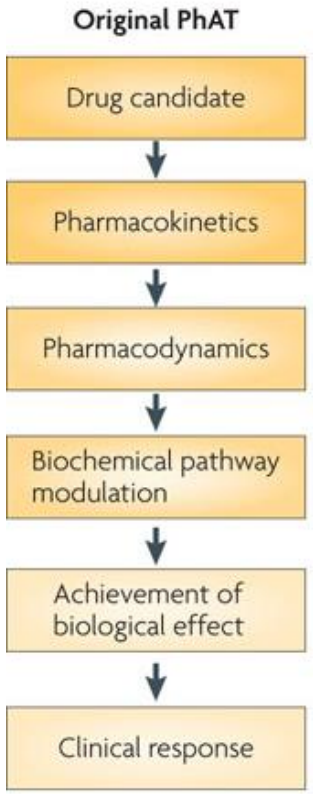
Stool & Urine
Microbiome
Metabiome

Biomarkers should be associated with a specific question/hypothesis and analysis plan

The PhAT

The Pharmacological Audit Trail

"A framework linking biomarkers for go/no-go drug development decisions"



Workman P, Curr. Pharm. Des. 2003

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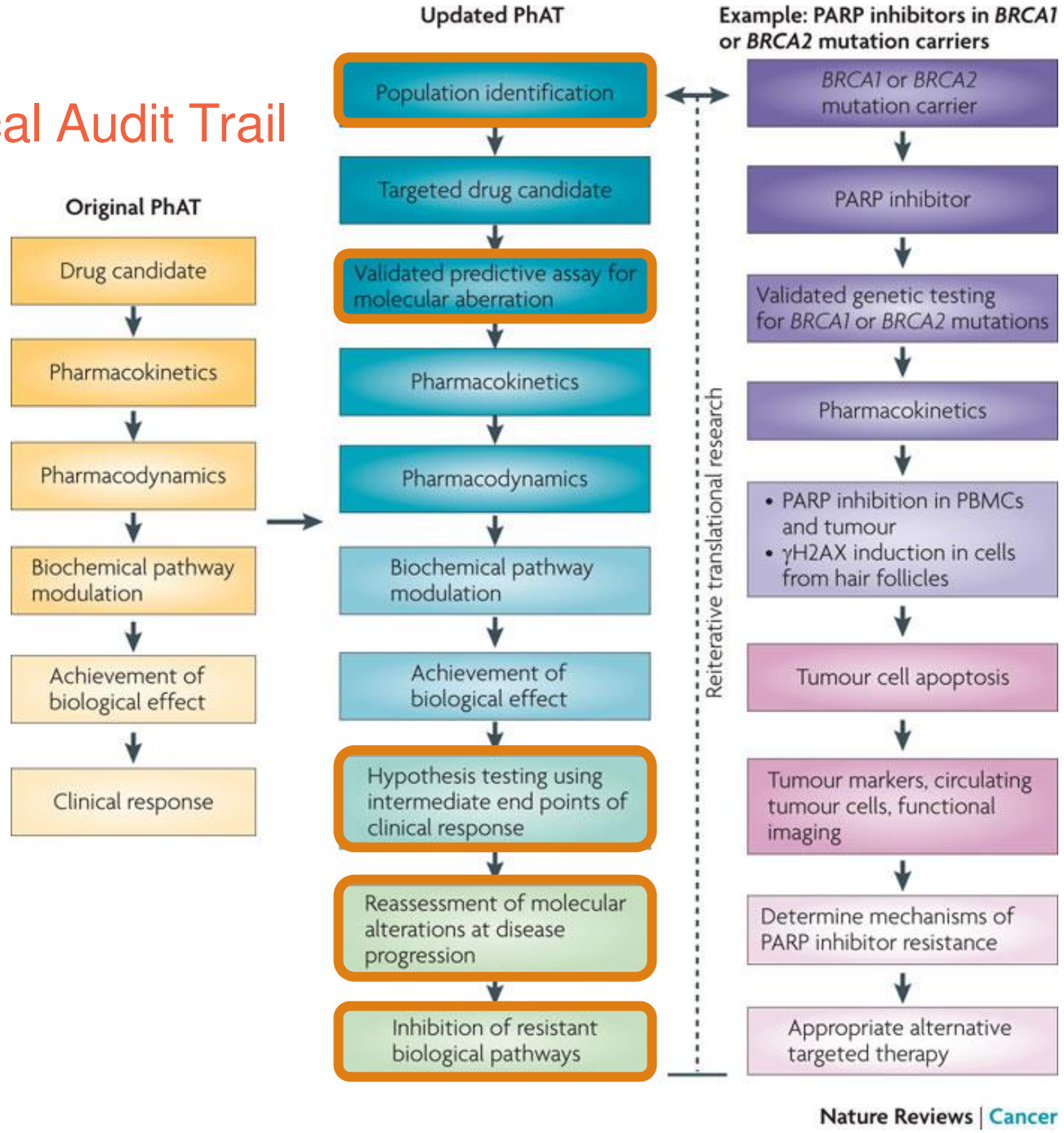
The PhAT

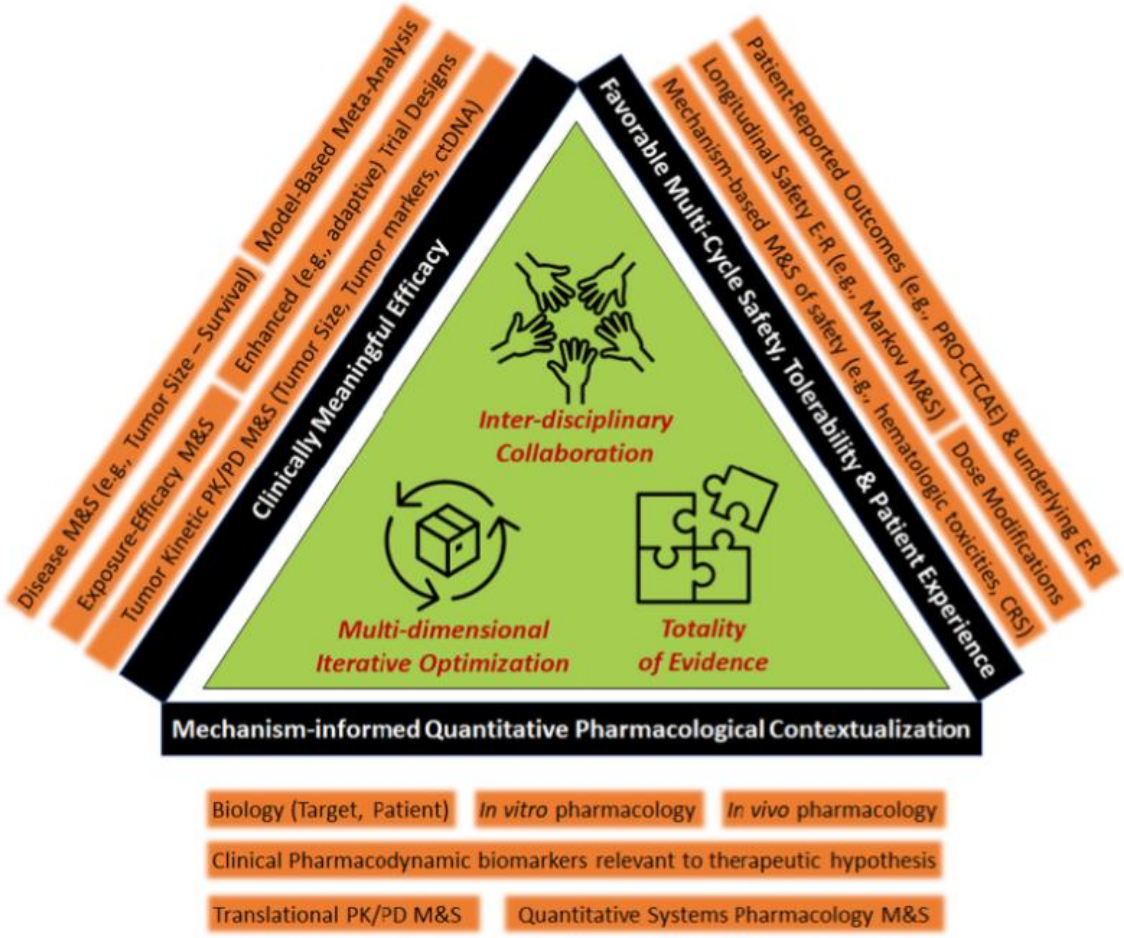
The Pharmacological Audit Trail



Workman P, Curr. Pharm. Des. 2003

Yap et al, Nature Reviews Cancer 2010

Totality of data needed for dose optimization
What are the key ingredients for success?



Drug	• Drug class • MOA
Patient Population	• Histology selection • Molecular biomarker selection
Toxicity	• DLT • Chronic toxicity requiring dose interruptions/reductions
Pharmacokinetics (PK)	• Dose-PK effect relationships • Biologically relevant concentration
Pharmacodynamics (PD)	• Target and pathway modulation • Proof-of-mechanism
Clinical Activity	• Objective responses • Supporting evidence, e.g. tumor markers, ctDNA molecular responses

Venkatakrishnan, K. & van der Graaf P. H, Clinical Pharmacology & Therapeutics, 2022

Table courtesy of Lillian Siu

Need totality of orthogonal data to make informed go/no-go decisions to increase odd of success in drug development

Incorporating predictive biomarkers into phase I trials

How? Use NGS and other assays where available and appropriate for the question you are asking (done on case-by-case basis depending on robust preclinical data)

Enrich dose escalation population with predictive biomarker

- Incorporate *a priori* provisions in protocol to add on patients of interest in each cohort
- Include "backfill" cohorts for biomarker studies
- Try and make every patient count and make the drug count in every patient!
- Need to consider ease/speed of accrual and how validated predictive biomarker is

Mandate expansion cohorts with molecularly-driven tumors

- Phase I expansions are the 'new' single arm Phase II trials for early antitumor signal searching

Advantages?

- Allow early clinical testing/validation of biomarker assays
- Permit early hypothesis-testing/generating studies
- Optimize chance of early antitumor signals and decrease number of patients receiving ineffective treatments (and avoid "drug development fatigue" for drug)
- May avoid late drug attrition and reduce costs

Caveat: combinations may still be needed to optimize antitumor activity

Incorporating predictive biomarkers into phase I trials

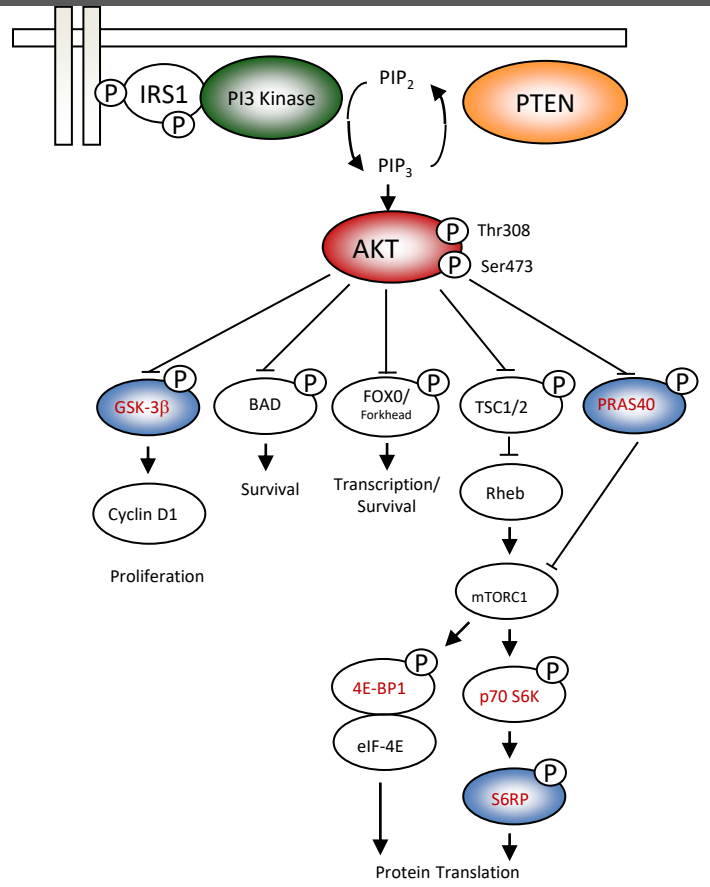
The issues

- No analytically validated and clinically qualified predictive biomarker
- Multiple aberrations:
  - Druggable and/or actionable aberrations?
  - Drivers vs passengers?
  - Lack of functional studies to confirm significance of aberrations
  - Context dependency between tumor types and subtypes
- Exclude patients who may benefit (e.g. PD-L1 negative patients in NSCLC)
- Biomarker costs and logistics
- Quality of tissue processing and tumor content
- Archival tumor may not reflect current day biology
  - Clonal evolution
  - Intratumoral heterogeneity
- Poor molecular matching rates between biomarker positive patients and trials
  - Genomic decision support important for: (1) variant annotation; (2) matching patients with trials

Incorporating pharmacodynamic biomarkers into phase I trials

PD biomarkers: Confirm proof-of-mechanism and define biologically effective dose (BED) range

1. Pick biomarkers
e.g. AKT inhibitor phase I trial



2. Pick tissue

- Tumor biopsies
  - E.g. ELISA for phospho and total AKT, GSK3β, p70S6K and PRAS40
  - Paired pre/on-treatment biopsies; keep optional during dose escalation (start from BED) and mandate during backfill cohorts and/or expansion cohorts
- Blood sampling – e.g. PBMCs or Platelet Rich Plasma (PRP)
  - E.g. ELISA for phospho and total AKT, GSK3β, p70S6K and PRAS40
  - Longitudinal sampling: multiple timepoints (similar timepoints as PK sampling); all patients
- Other normal tissue may also be considered
- ctDNA is an indirect PD biomarker and has other uses

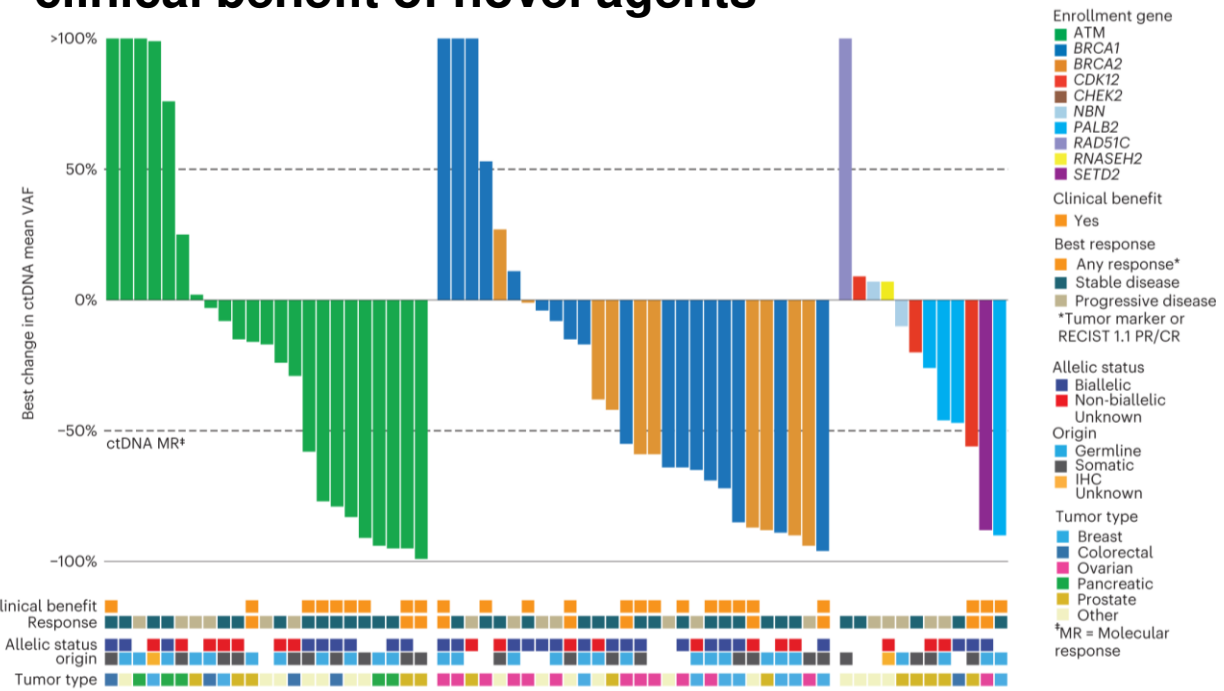
Normal tissue PD data from all patients will support tumor PD data from paired biopsies from selected patients

Incorporating longitudinal sampling of ctDNA in early phase trials

Multiple applications

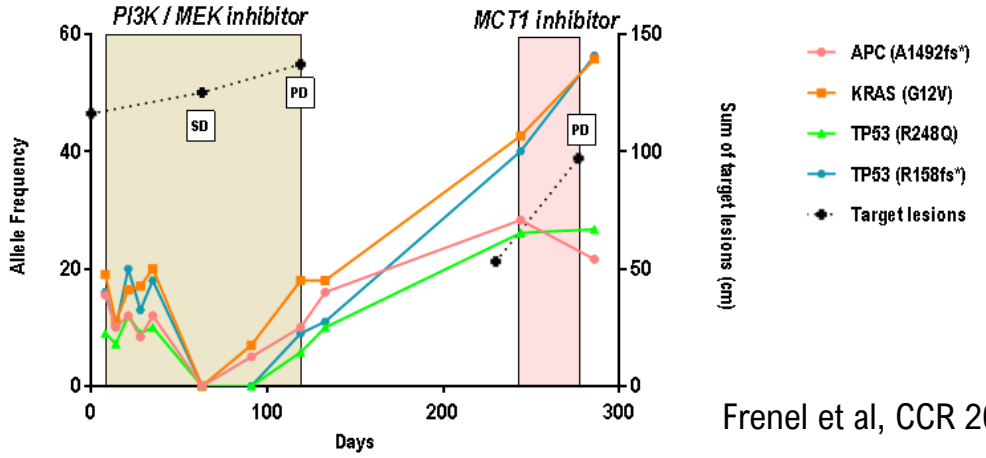
- 'Real-time' molecular characterisation (predictive biomarkers of response or resistance)
- Understanding heterogeneity of response
- Determine mechanisms of resistance
- Early detection of progression (before RECIST)
- Guide early change of treatment
- Suggest potential combinations

Molecular responses with ctDNA may support clinical benefit of novel agents



Monitoring of tumor clone dynamics

Metastatic colorectal cancer with *KRAS*, *TP53* and *APC* mutations



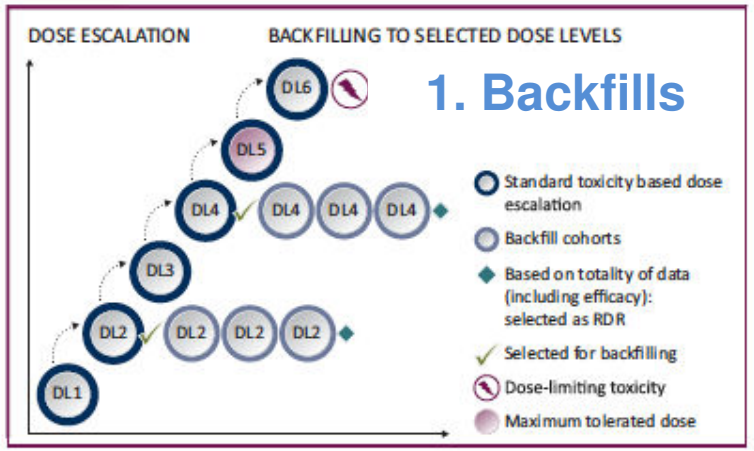
Frenel et al, CCR 2015

E.g. ATR inhibitor camonsertib trial ctDNA studies

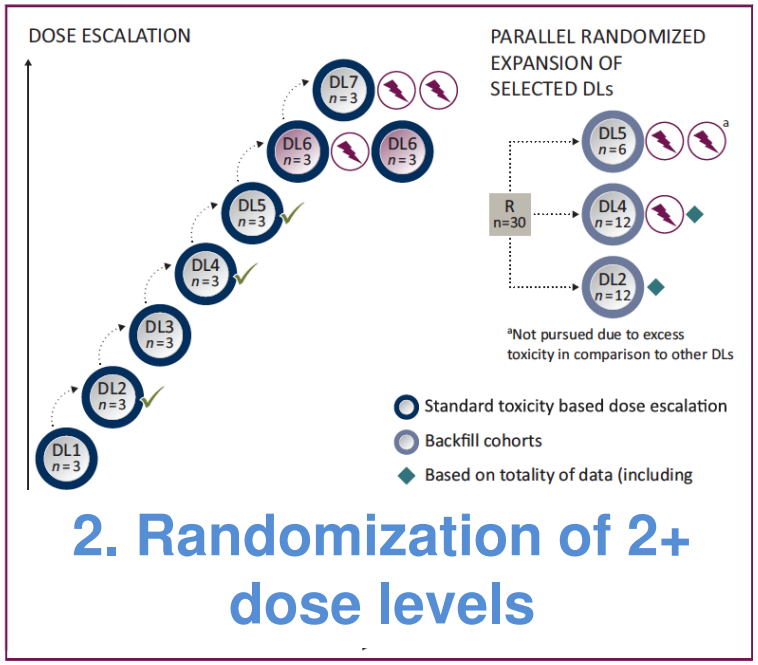
- Longitudinal ctDNA studies incorporated into Phase I ATR inhibitor camonsertib trial (Repare Therapeutics)
- Patients with clinical benefit (CR/PR/durable SD) showed early reductions (at least -50%) in ctDNA mVAF
- Median time to molecular response 3.3 weeks
- Potential utility as early treatment response biomarker

Yap et al, Nature Medicine 2023

Summary:
My ideal phase I trial design



1. Backfills



2. Randomization of 2+ dose levels

1. BOIN Phase I trial design (not 3+3)
2. Molecularly select all patients prospectively for putative predictive biomarkers of response (if supported by preclinical/clinical data)
3. Assess PK/PD in all patients in blood (or other normal tissue for PD)
4. Optional pre/on-treatment tumor biopsies during escalation
5. Mandatory pre/on-treatment tumor biopsies during selected backfill/expansion cohorts
6. Collect streck tubes at multiple timepoints for ctDNA studies in all patients; retrospective analysis at selected timepoints
7. Gain safety/PK/PD/efficacy experience through backfill cohorts during dose escalation (triggered at active dose levels based on safety/ PK/ PD/ efficacy)
8. Backfill cohorts are crucial for selecting dose/schedules and patient populations to use for dose optimization per Project Optimus
9. Compare dose levels with non-overlapping PK in similar patient populations for dose optimization

Remember – if the drug doesn't work, it will never work no matter how good the trial design, but a good design will discontinue such drugs early to minimize exposing more patients to toxic/ ineffective drugs and longer-term fiscal toxicities

Dose optimization biomarker strategies: Final thoughts

- Biomarkers are key to enhancing success in drug development
- Use Pharmacological Audit Trail as a biomarker framework
- Evaluate totality of all orthogonal dose-effect analyses for dose optimization: Safety (acute and chronic), Pharmacokinetics, Pharmacodynamics (define biologically effective dose range), Antitumor Activity (predictive biomarkers)
- Plan and analytically validate predictive and pharmacodynamic biomarker assays early and in parallel to drug discovery and development

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Using Biomarkers in Dose Optimization

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Disclosure Information

Anthony N. Sireci, MD, MSc

I have the following relevant financial relationships to disclose:

Employee of: Eli Lilly and Co

Consultant for: Biocartis, Aster Insights

Stockholder in: Eli Lilly and Co

Executive Summary

- Biomarker data may be useful in making more rapid dose selection decisions in oncology drug development

- We share our experience using tissue-based biomarkers and circulating biomarkers in our early phase development programs

- In conjunction with the totality of the available data (e.g., efficacy, PK and tolerability), biomarker data can support dose selection decisions. Use of biomarker data alone for these decisions is unlikely at this time

Problem and potential solution

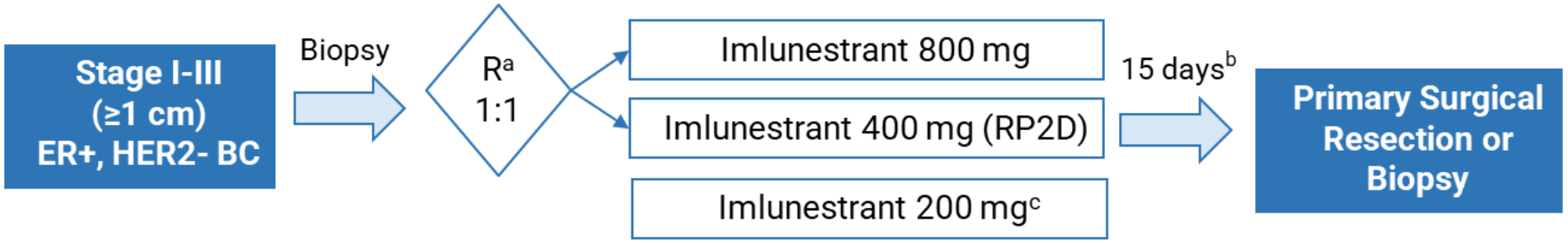
- Previous approaches to dose selection (i.e., MTD) are giving way to more rigorous optimization approaches
- Efficacy and long-term safety readouts, while gold standard, take time and resources
- Use of the correctly chosen biomarker surrogate may help add to the data used in dose selection

Biomarkers and dose selection

- What we've done at Loxo@Lilly
  - Tissue/tumor markers of target engagement
    - Change in target
    - Downstream markers of engagement
  - Circulating markers
    - ctDNA
- Other matrices I'll touch on
    - PBMC, platelets, CTC, circulating metabolites, etc

Tissue-based biomarkers: Pre-operative window of opportunity study (EMBER-2)

- EMBER-2, a pre-operative window of opportunity (WOO) trial assessed PD, PK, biological effect and safety of multiple doses of imlunestrant in patients with ER+, untreated EBC. These data were used, in combination with results of EMBER trial to determine RP2D for two large P3 trials
- Primary objective: determine change in ER expression
- Secondary objectives: determine change in PR expression, Ki67 and % cell cycle arrest
- Key Inclusion criteria:
  - Post-menopausal women with stage I–III (≥1 cm), ER+ (>50% or Allred score >5), HER2-, operable and untreated EBC



[a] Stratified by tumor histology (invasive ductal carcinoma [IDC] vs. invasive lobular carcinoma [ILC] vs. other)
[b] Treatment window was -2 to +7 days up to date of surgery/repeat biopsy
[c] 200 mg cohort was added in a protocol amendment, and opened after enrolment to the randomized cohorts was completed

Neven et al, ESMO, 2023

EMBER-2: results support dose selection

Figure 2. Relative reduction of ER, PR, and Ki-67 at week 2

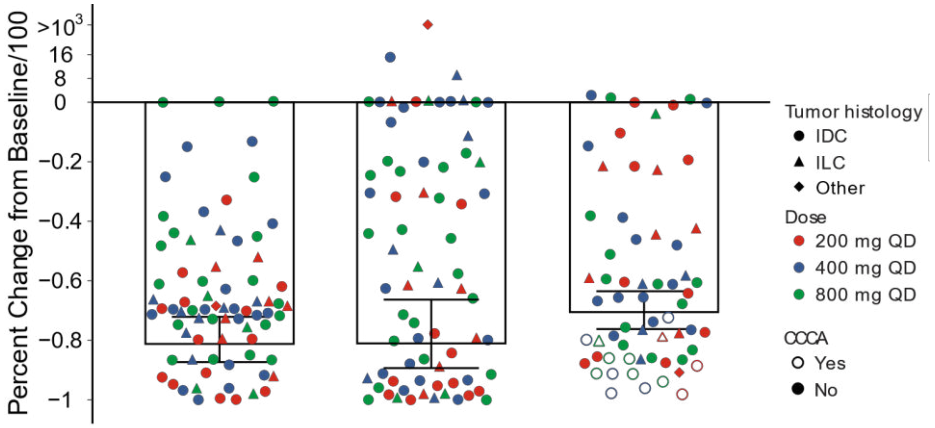
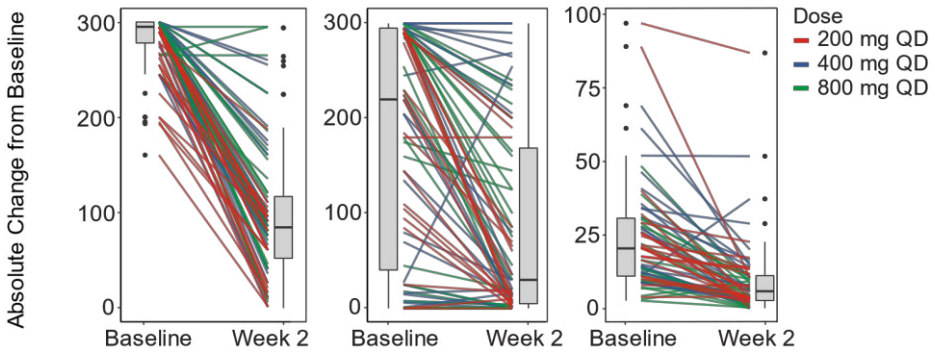


Figure 3. Absolute change in ER and PR H-score and Ki-67 % stained nuclei at week 2



Geometric mean (90% CI) in PD biomarkers	200 mg N=22	400 mg N=27	800 mg N=26	Total N=75
ER[a]	-89% (-96%, -72%)	-82% (-91%, -60%)	-70% (-78%, -59%)	-81% (-87%, -72%)
PR[a]	-85% (-97%, -37%)	-76% (-90%, -38%)	-82% (-92%, -60%)	-81% (-89%, -66%)
Ki-67[a]	-69% (-79%, -54%)	-71% (-80%, -57%)	-72% (-81%, -59%)	-70% (-76%, -63%)
CCCA[b] (%)	3/20 (15%)	5/22 (23%)	6/17 (35%)	14/59 (24%)

[a] See Figure 1 for PD evaluable (mITT) population for each biomarker; [b] CCCA (complete cell cycle arrest among patients (n=59) with baseline Ki-67 ≥5%

- **Confirms proof of mechanism on key biological targets (ER, PR, Ki-67) in ER+, HER2- EBC**
- **Evidence of robust target engagement and PD biomarker modulation across all dose levels**
- **RP2D of 400mg selected based on efficacy, PK and safety and supported by PD**
- **ER gene module consisted of 11 genes transcriptionally regulated by ER: *PGR, GREB1, PDZK1, TFF1, RASGRP1, AREG, WISP2, GATA3, XBP1, STON1, NBEA—to be published***

Neven et al, ESMO, 2023

Limitations of a tissue approach

- Heterogeneity in sampling
- Preanalytical variables
- Testing on boney lesions or other difficult-to-access lesions
- Patient enrollment/ethics

Circulating biomarkers: ctDNA

- Multiple use cases for ctDNA in drug development
  - Patient selection
  - Response analysis
  - Resistance monitoring
  - Biomarker discovery
- Why may ctDNA be useful in dose optimization?
  - Dynamics correlate to clinical response
  - Operationally feasible/part of standard collection process
  - Differential response by dose?

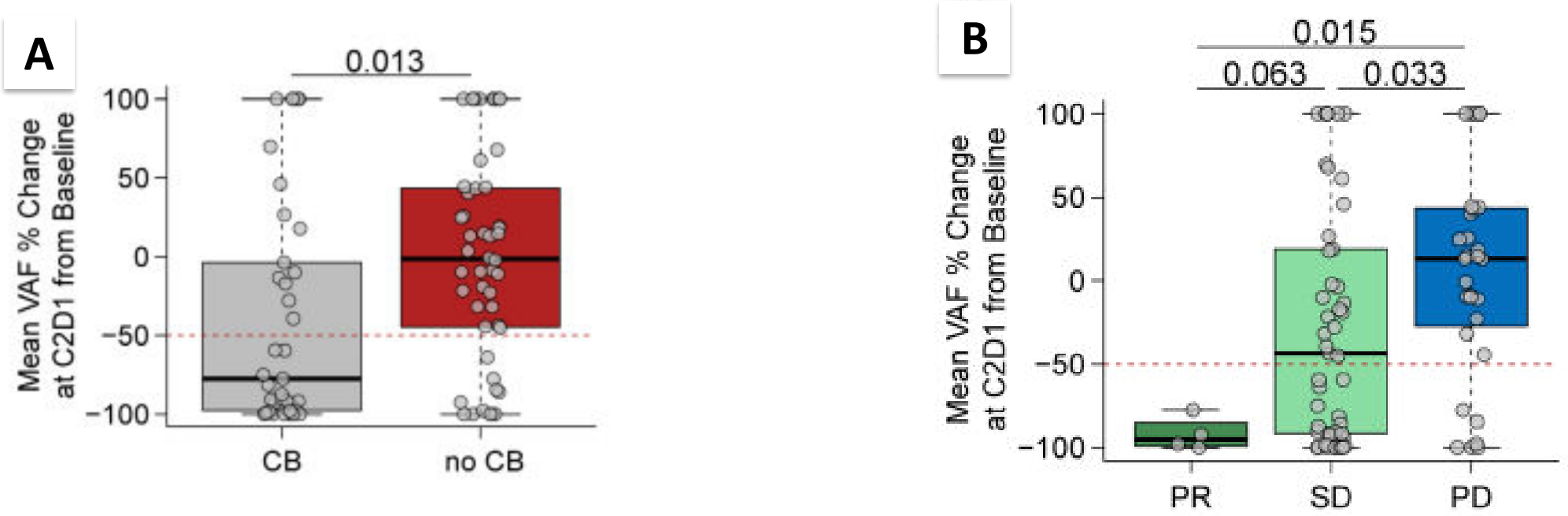
ctDNA dynamics defined

- ctDNA dynamics assessed by measuring ctDNA at baseline and comparing to longitudinal timepoint(s)
  - Level of target engagement and inhibition (by dose)
  - Correlation to response and outcome
- Methods of molecular response measurement:
  - Detection or quantitative levels of ctDNA (positive vs negative, ctDNA parts/mL)
  - Mutation-based dynamics utilizing changes in variant allele frequencies (all vs oncogenic vs specific biomarker of interest)

Ratio of max VAFs[4] R(maxVAF)	Ratio of mean VAFs[8,10] R(mVAF)	Mean of VAF ratios[11] m(rVAF)
$\frac{\text{Max (VAF Treatment)}}{\text{Max (VAF Baseline)}}$	$\frac{\text{Mean (VAF Treatment)}}{\text{Mean (VAF Baseline)}}$	$\text{mean}\left[\frac{\text{VAF}^{1...x}\ \text{Treatment}}{\text{VAF}^{1...x}\ \text{Baseline}}\right]$

ctDNA dynamics correlate to RECIST and Clinical benefit—EMBER

- EMBER is a global first-in-human ph1a/b, open label study of imlunestrant in monotherapy in ABC
- Plasma samples collected at baseline and C2D1 or C3D1

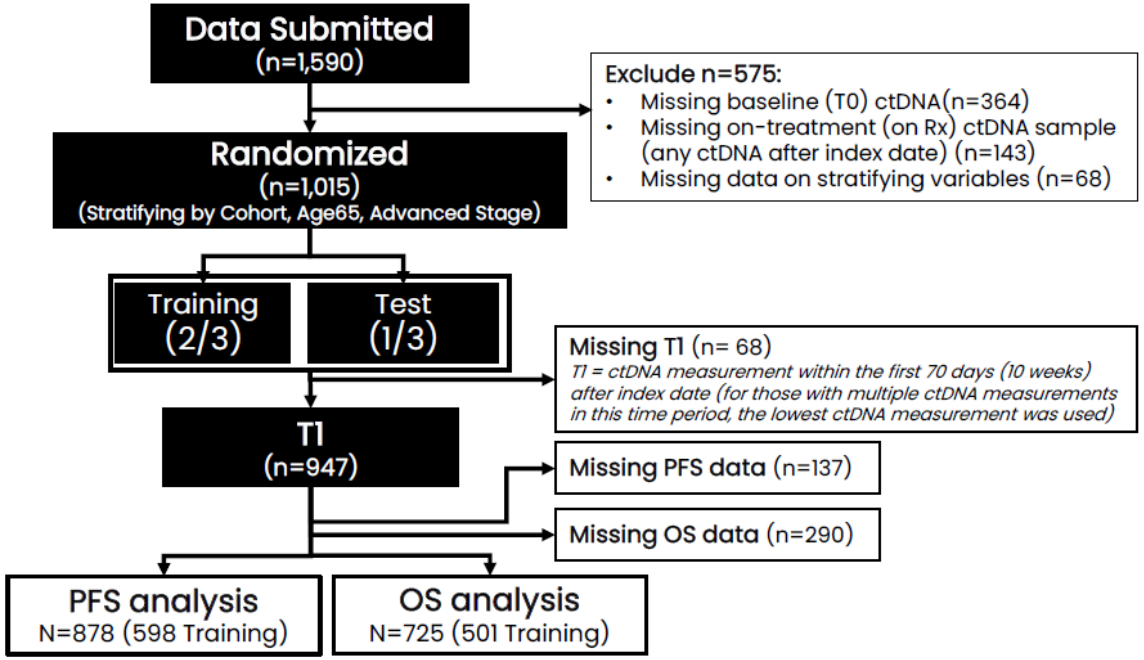


- In ABC patients with serial ctDNA (N=85), clinical benefit (CB) and objective response were associated with deep early declines in overall ctDNA (all oncogenic somatic)

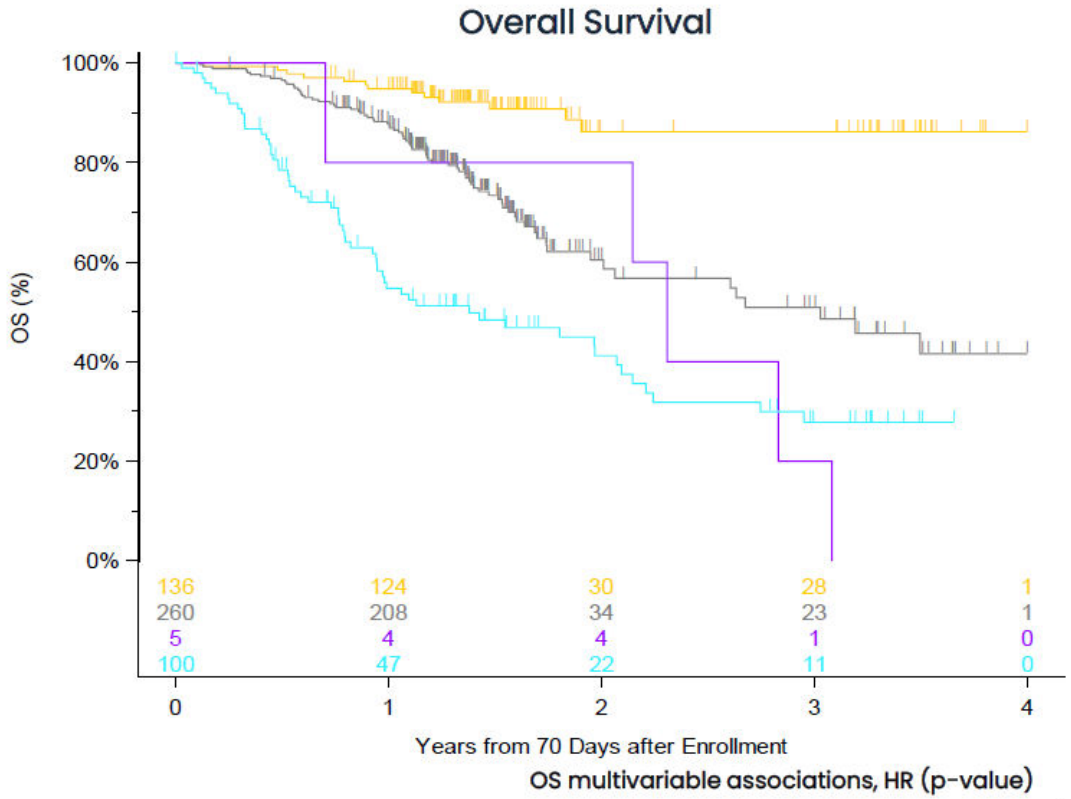
Jhaveri et al. ASCO. 2022

A semiquantitative approach in aNSCLC: ctMonitor study

CONSORT Diagram & Patient/Assay Characteristics



- Analysis across 8 trials of targeted therapies in NSCLC shows association of semi quantitative ctDNA analysis to OS



OS multivariable associations, HR (p-value)

	Events / N	Median Years (Range)	1-Yr Estimate % (IQR)
ND/ND	13/136	NR	95% (91, 99)
D/ND	78/260	3 (2, .)	88% (84, 92)
ND/D	5/5	2.3 (0.7, .)	80% (45, 100)
D/D	58/100	1.4 (0.9, 2.1)	55% (44, 65)

		Reference			
		ND/ND	D/ND	ND/D	D/D
Comparator	ND/ND				
	D/ND	3.03 (0.002)			
	ND/D	9.63 (<0.001)	3.28 (0.026)		
	D/D	6.88 (<0.001)	2.27 (<0.001)	0.69 (0.512)	

Stiles et al, ASCO, 2023

Libretto-001: ctDNA dynamics across doses

- Libretto-001: the registrational trial of the RET inhibitor, selpercatinib in fusion-positive NSCLC and TC and RET mutant MTC
- ctDNA dynamics at C1D15 showed nearly universal response across dose levels and clinical responses (change in VAF of RET alteration)
- Unpublished data from our phase 1 trial of KRAS G12C inhibitor shows similar evidence of response across dose levels

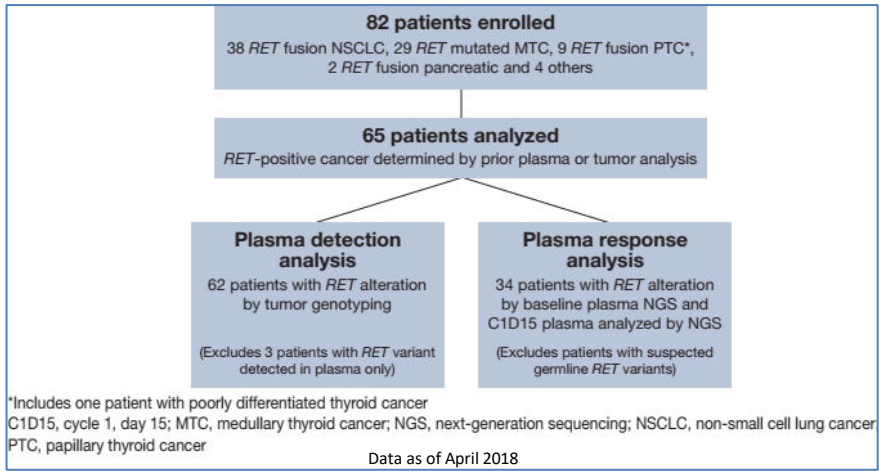
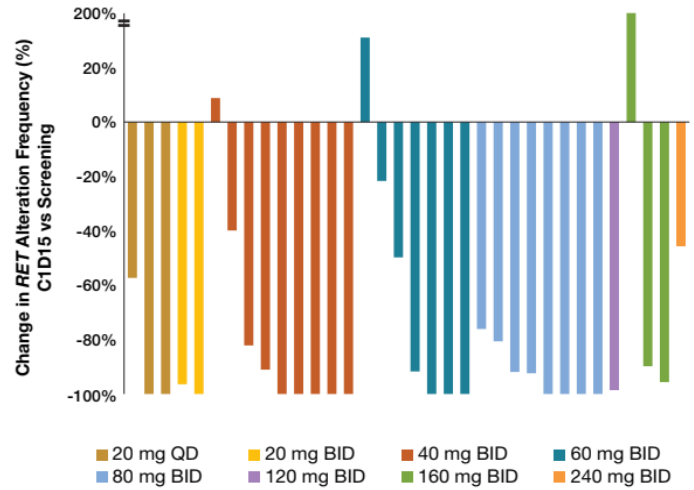
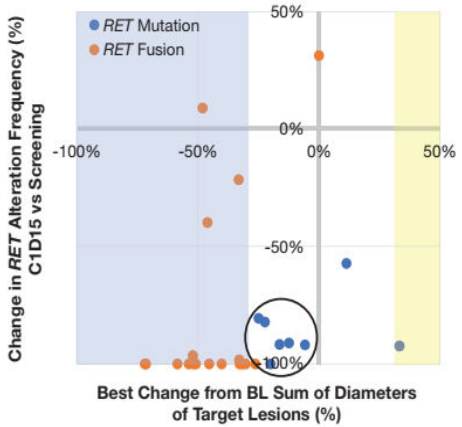


Figure 5. Plasma response analysis: by starting dose



C1D15, cycle 1, day 15

Figure 6. Imaging (RECIST) vs cfDNA



ne case outside of the plot range (8% tumor decrease, 191% plasma increase) is not shown.
L, baseline; RECIST, Response Evaluation Criteria In Solid Tumors.

Remaining questions from analyses:

- When is the best time for landmark assessment?
- Landmark vs multiple time points?
- Which variants do we follow?

Oxnard, ASCO, 2018

Limitations of ctDNA

- Variable ctDNA shed from tumors
- Very sensitive assays may be required to discriminate effect—Expensive
- Tissue required to create bespoke panels (MRD)
- Can be unstable compared to FFPE (Collection/pre-analytics)

Other technologies

- Improvement on existing blood-based technology
  - Platelets
  - PBMC
  - **Flow cytometry**
  - **CTC analysis**
  - **Metabolomics**
  - Methylation
  - ctRNA expression
  - **DNA fragmentation**
- **Urine**
- Multimodal technologies synthesizing multiple approaches

Conclusions

- Tissue and circulating biomarkers can provide evidence of target engagement and correlate to response
- Changes in biomarkers may be too sensitive to use in dose selection given decreases at early landmark timepoints
- Future studies using a variety of novel biomarkers, methodologies and timepoints may improve utility of this analysis
- For now, biomarker data should be used as part of the totality of clinical response, PK and tolerability data to support dose selection

FDA-AACR Public Workshop On
OPTIMIZING DOSAGES FOR ONCOLOGY DRUG PRODUCTS: QUANTITATIVE APPROACHES TO SELECT DOSAGES FOR CLINICAL TRIALS
February 15 and 16, 2024 I Washington, DC

Utilizing Randomization, Backfill and Expansion Cohorts to Gain Greater Understanding of Dose- and Exposure-Response Relationships

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Disclosure Information

Alexia Iasonos

I have the following relevant financial relationships to disclose:

Employee of: Memorial Sloan Kettering Cancer Center

My additional financial relationship disclosures are:

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•Intelligencia Inc.
Professional Services and Activities

•Journal of Clinical Oncology
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Objectives

1. How do we define a successful trial?

2. What are the ethical constraints in early phase trials?

3. What is the optimal design?

A successful trial

(1) Scientifically rigorous - no information wasted, timely design, efficiency

(2) Obtain as much information as possible via **expansions, randomization** to better guide later studies

(3) Patients included in the early phase trial must be treated in accordance with established ethical principles

- **can not under or over-dose, or**
- **expose too many patients to futile drugs**

Research or state of the art, best treatment care?

"……. something is either research or standard care; it cannot be both"
(Miller and Rosenstein, NEJM 348: 2003)

Versus

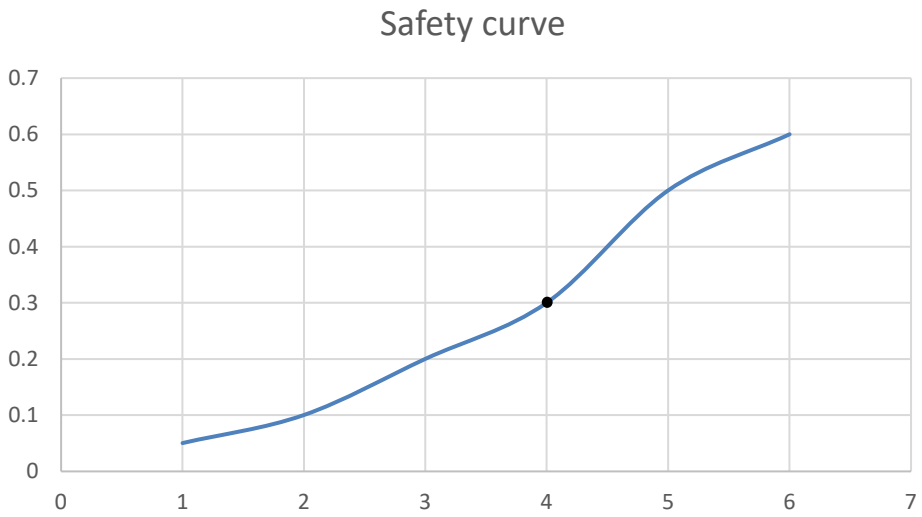
"Enrollment on an investigational study is state-of-the-art care for many patients in oncology today" (ASCO, NCCN, advocacy organizations, etc.)

Much of the treatment-related research we do is performed in a care-delivery context with characteristics of both care and research.

New therapies – new ways of dosing

Chemotherapy

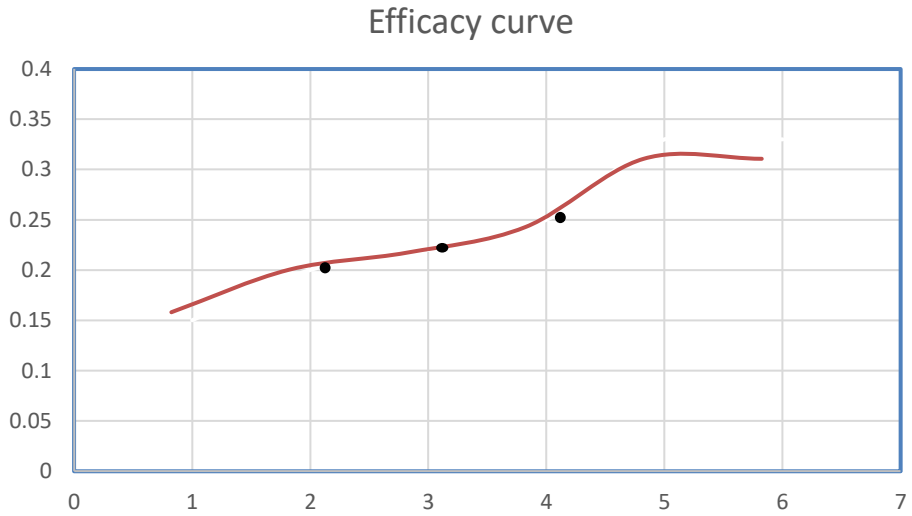
More is better



Dose escalation
Dose elimination
Find a Single dose MTD

New mechanisms of action

Less is more



Dose ranging
Dose exploration
More than 1 dose

Controlled backfill, Hakim Dehbi et al 2022, 2023

When we start thinking of a trial

Whom to treat?	Patient population
When to treat?	Eligibility
How are we going to treat?	Treatment

How do we measure success? Objective

- Measurable endpoint
- Design

Design 1 Simple dose escalation	Design 2 Dose escalation + dose expansion (DEC)	Design 3 Dose escalation +DEC + randomization
1. Identify the MTD and establish the safety profile in a heterogenous patient population (safety only)	1. Identify the MTD in a heterogenous patient population (dose escalation; safety)	1. Identify the MTD in a heterogenous patient population (dose escalation)
	2. Identify whether the drug shows promising efficacy and in which disease groups (DEC)	2. Identify whether the drug shows promising efficacy and in which disease groups (DEC; efficacy)
	3. Identify the appropriate patient population for drug development (DEC and dose escalation)	3. Assess whether the drug works uniformly or whether there are differences in response within subgroups (disease heterogeneity and drug activity)
		4. Identify patient populations, dose and treatment schedule
		5. Identify which drugs need to be eliminated early because they are ineffective and which drugs to take forward because of promising activity (DEC and dose escalation)

Randomized expansion cohort

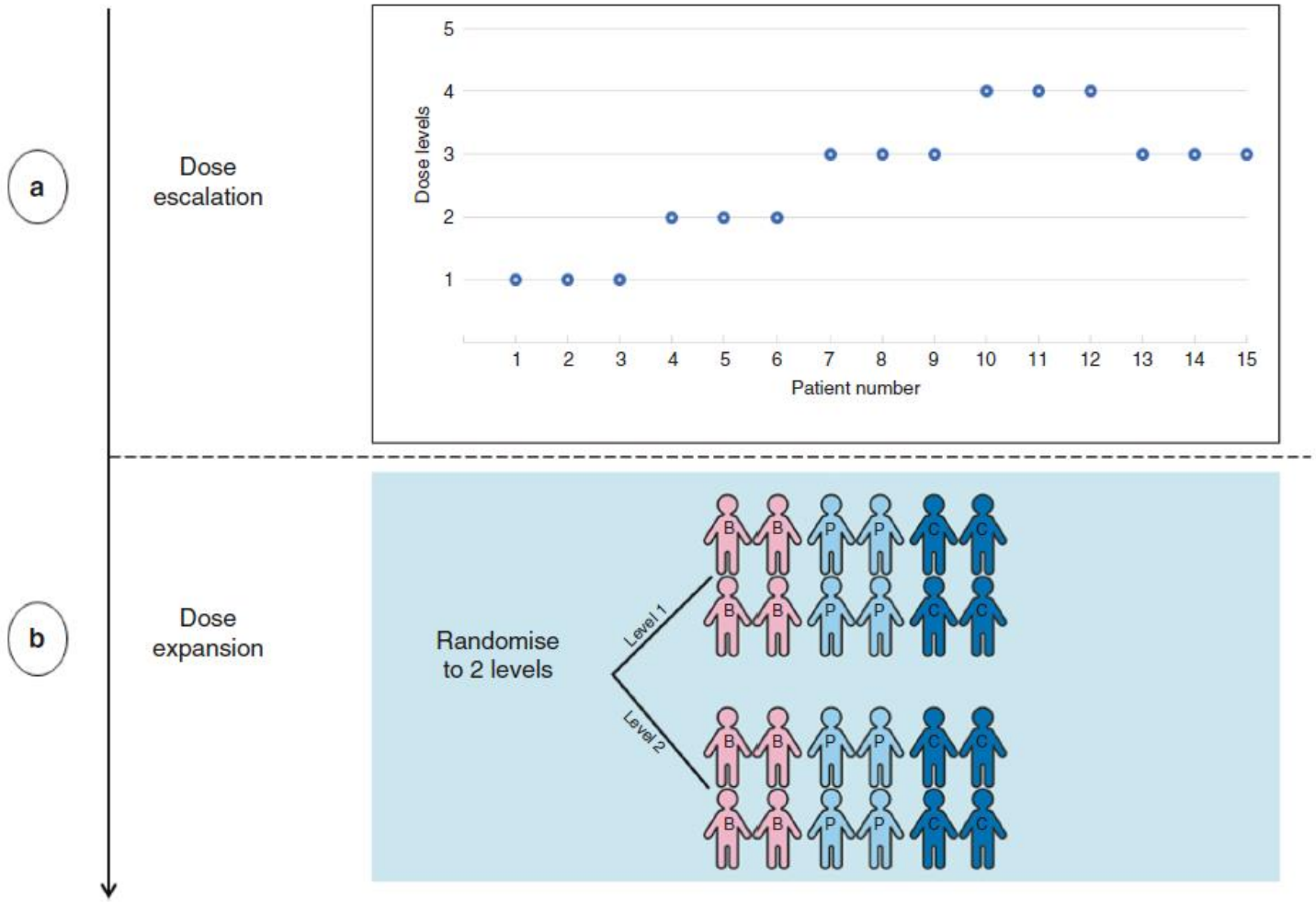


Fig. 1 **Dose escalation (carried out in cohorts of 3 patients) followed sequentially by dose expansion after the maximum-tolerated dose (MTD) has been determined.** Dose expansion randomises subjects equally to two dose levels in molecular- or disease-specific patient populations (denoted by B: breast, P: prostate and C: colon cancer). **a** shows the dose escalation. **b** shows the dose expansion.

- 2-step approach
  - Dose escalation first
  - Dose expansion via randomization afterwards
- Limitation: focus on 2 dose levels chosen in escalation phase/part

Iasonos, A., O'Quigley, J. Randomised Phase 1 clinical trials in oncology. *Br J Cancer* **125,** 920–926 (2021).

Backfill cohorts

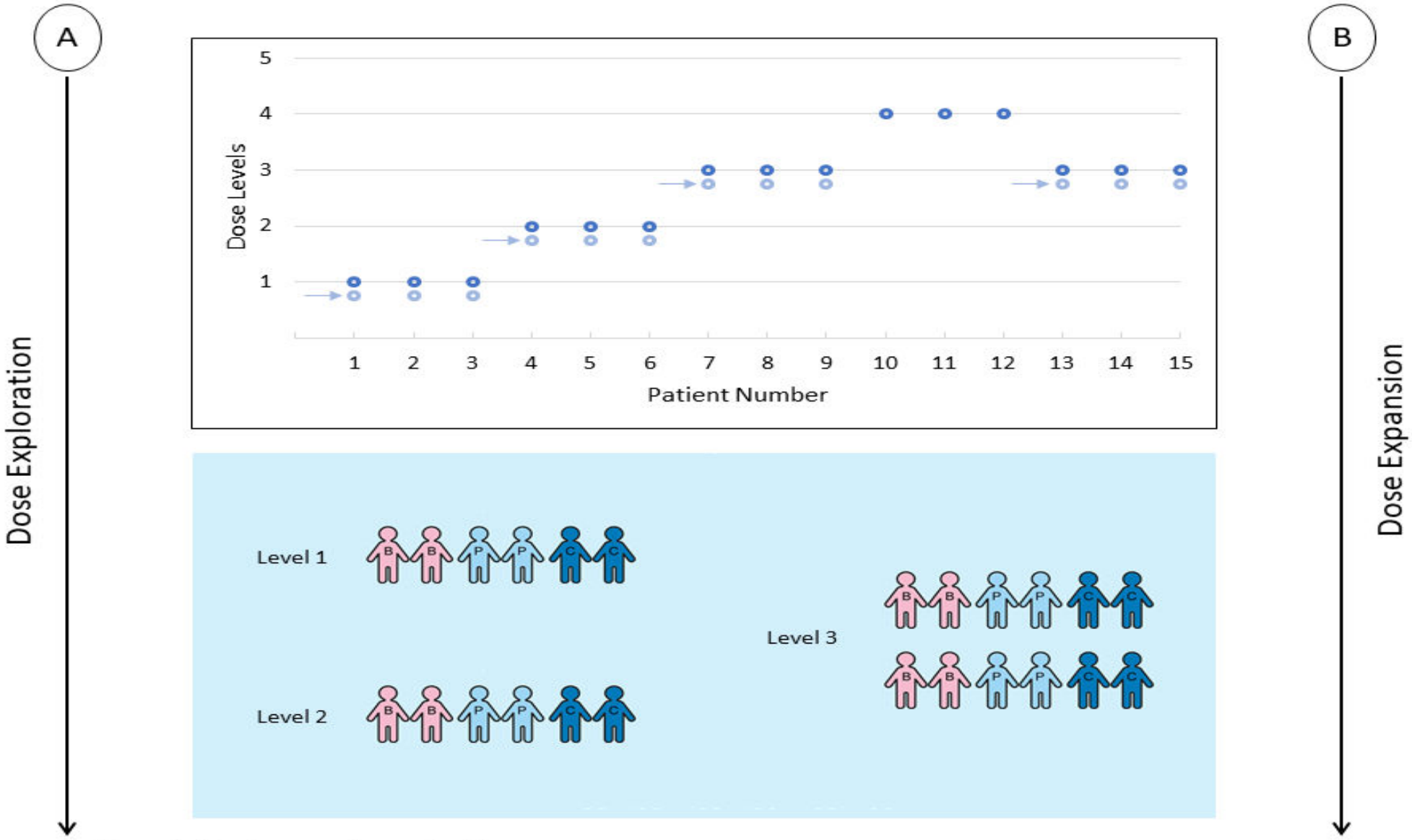


Figure 2. Simultaneous dose exploration

How many patients?

- How many dose levels? How many patients per dose level?
- Patient heterogeneity:
  - Disease (e.g. melanoma, gynecological, breast) – dose escalation
  - Dose (3 levels) - backfill in heterogenous groups
  - Efficacy: disease specific or marker specific cohorts (dose expansion)
- Subgroups become small very fast 18 subgroups times 20 pts = 360;
- How do we determine the total sample size given that, per dose level *n* is still underpowered to address the question(s) of interest?

Patient heterogeneity and sample size

- The answer is on the number of questions being addressed
- Hierarchy in the questions
  - Primary
  - Secondary
  - Exploratory
- Collect rigorous data to understand why it failed, where it is working, where it is not going to work (inform next study), move the field forward.
- Eliminate systematic biases (randomization)

Role of randomization in phase I trials

- To balance the patient population with respect to confounders such as
  - Comorbidities
  - Prior treatment
  - Advanced disease
  - Factors not controlled by eligibility criteria

- Eligibility criteria define the patient population only up to **known risk factors**
  - Risk factors that remain unknown
  - Patient population may be different due to these unknown factors
  - At the conclusion of the study, a higher efficacy in one cohort could be
    - a function of the treatment or the differences in patient populations?

Randomize or not

Pros:

- With a randomized design have a concurrent comparison group
- Uniform evaluation criteria - controlled eligibility criteria
- Risk factors (known and unknown) tend to be balanced between treatment groups
- Can be used to evaluate additional questions: e.g. biomarkers, PK/PD comparisons

Cons

- Are there sufficient resources?
- What is the anticipated accrual/ duration?
- Does it increase the total sample size?

Constrained resources

- What information do we want to get?
- How can we maximize the information?
- Feasibility -we cannot get answers in 5-10 years
- Rare cancers or subgroup of patient population (mutation)

- Small dose escalation phase I designs still have an important role
- Can inform subsequent studies or hypotheses

Rare patient population

- In rare patient populations, a long-term drug development process that studies the drug in distinct phases of three clinical trials including a comparative follow-up study might not be feasible.
- Thus, results from early phase trials, in terms of dose, treatment schedule and patient population, will inform registrational studies.
- Although the sequential entry of patients eliminates some biases, randomisation will enhance our chances of avoiding imbalances in patients from specific categories being treated at particular doses or schedules.
- Eliminating the chance of patients receiving an ineffective or unsafe dose

Drug optimization

- Answer the question(s) using the minimum number of patients,
- Stop a futile drug early or
- Expand a safe/active drug to more patients if feasible.

Optimization with respect to sample size/ trial duration

Probabilistic statements in clinical trials

- Probabilistic estimates of getting the correct answer
  - Phase III setting: getting the right drug (power)
  - Phase I setting: getting the right dose or dose levels (or schedule)
- Stopping rules decrease the total N

- Even if savings seem small (3-6 patients), it allows allocating resources elsewhere:
  - Ending the trial one year earlier or expanding another dose level; comparing PK/PD in another cohort of 6 patients

Dynamic Stopping Rules

1. **Posterior Probability;** Iasonos and O'Quigley (2016)
2. **Tree-based evaluation;** O'Quigley and Reiner (1998)
3. **Allocation;** Goodman et al (1995)

Original Research Article

SMMR
STATISTICAL METHODS IN MEDICAL RESEARCH

Stopping rules for phase I clinical trials with dose expansion cohorts

Sean M Devlin[1], Alexia Iasonos[1], and John O'Quigley[2]

Statistical Methods in Medical Research
1–13

DOI: 10.1177/09622802211064996
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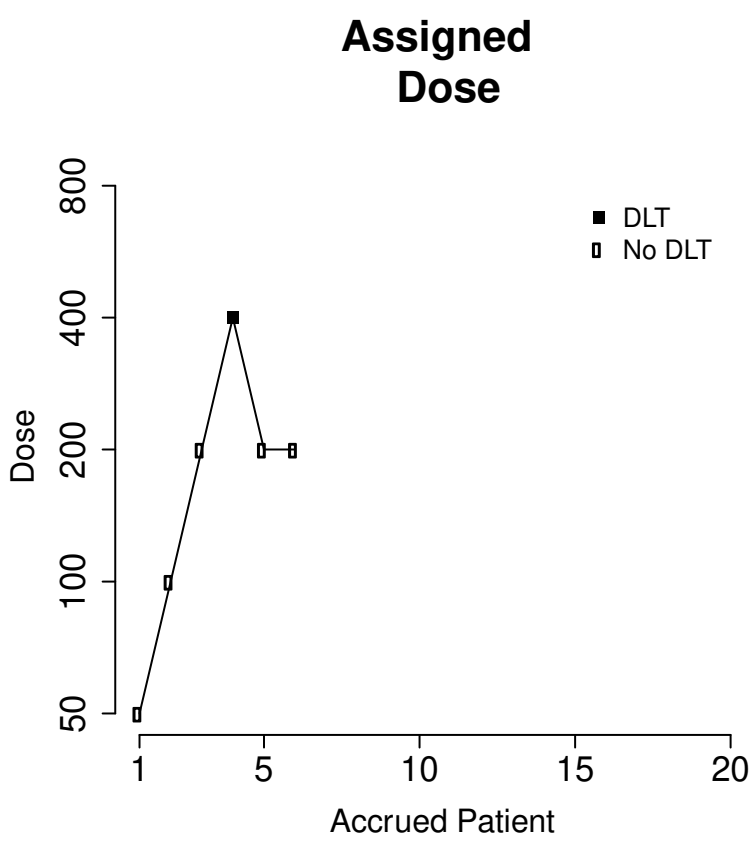
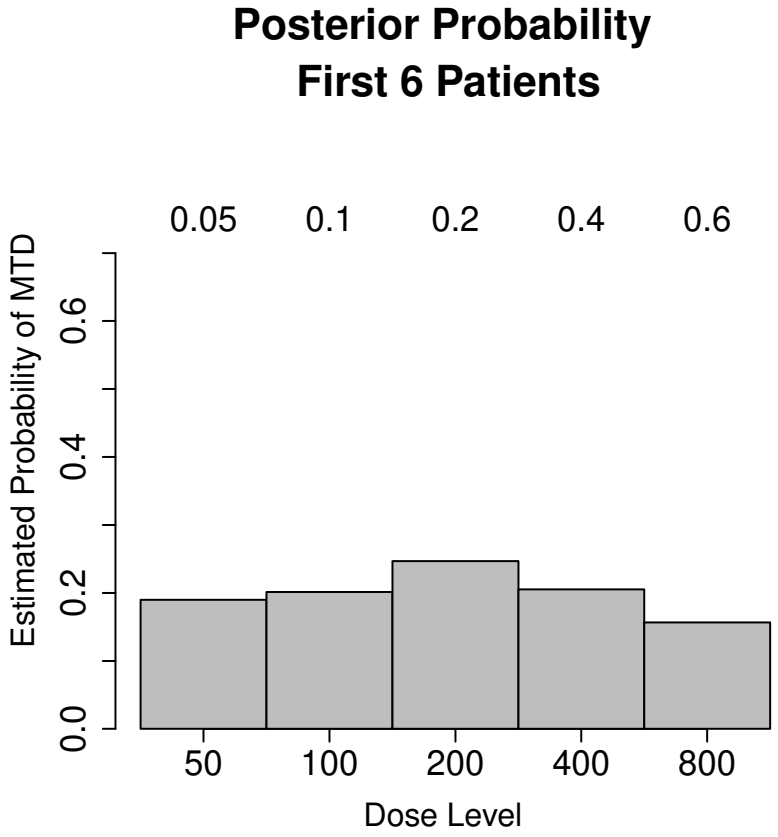
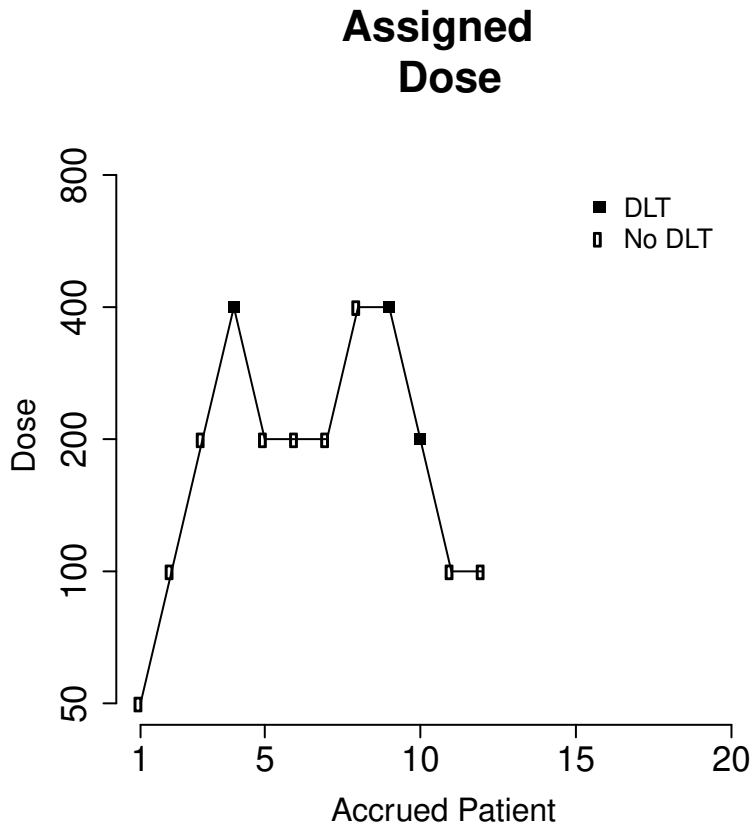
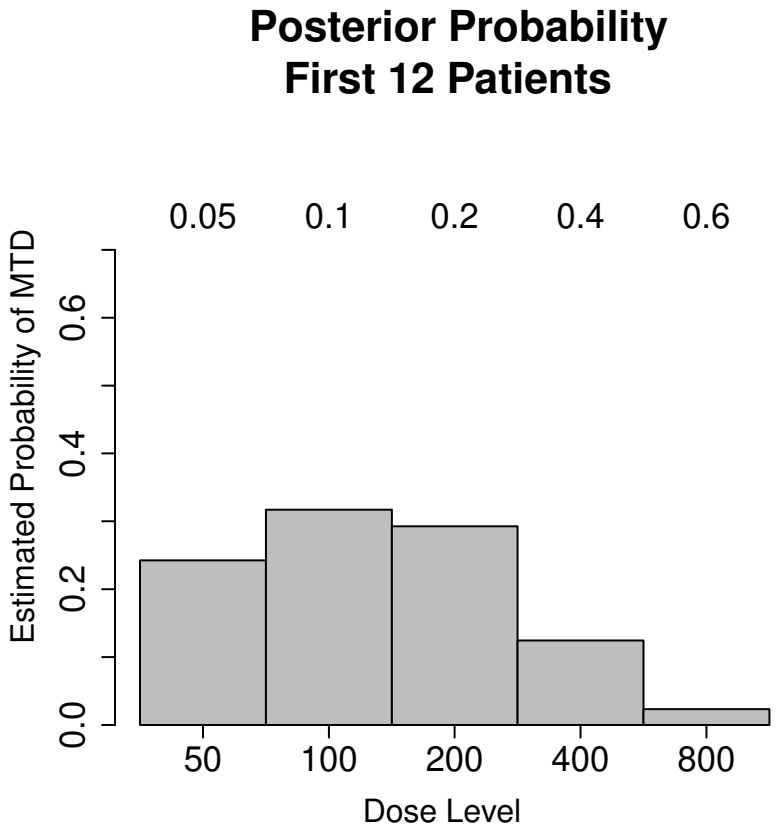
Posterior Probability Rules



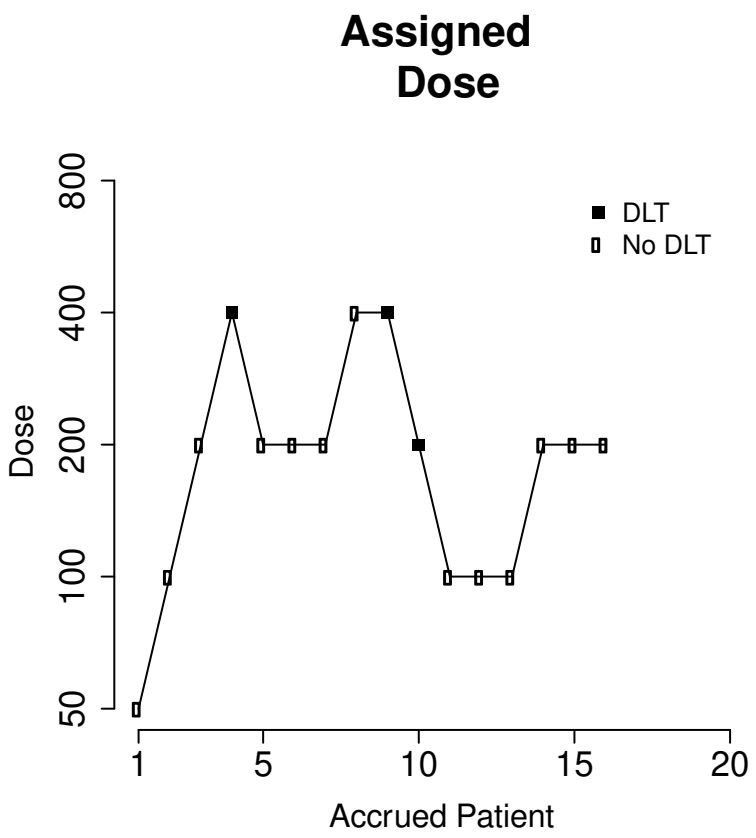


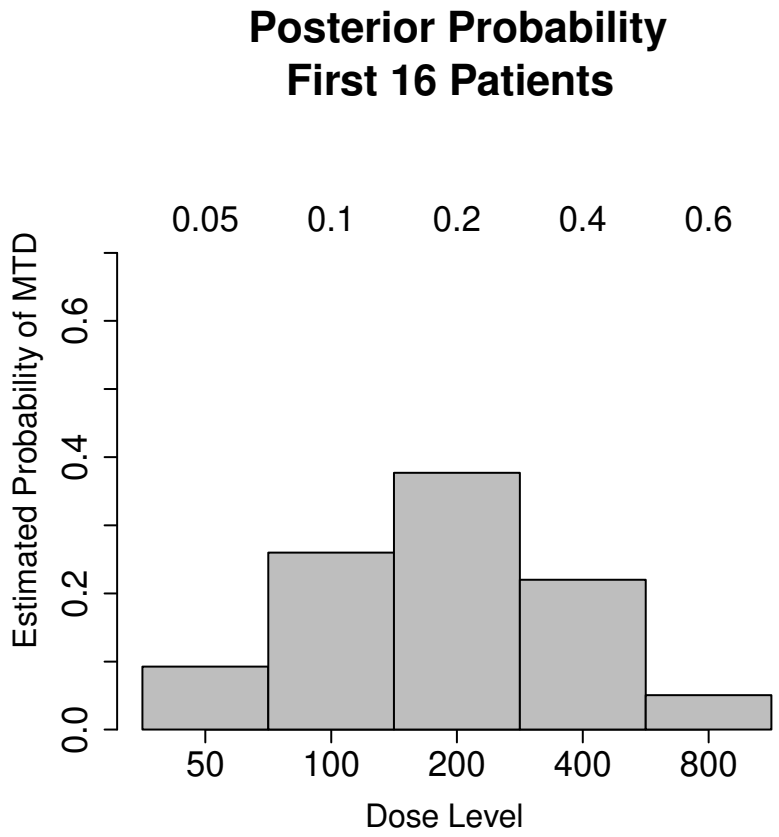
Posterior Probability Rules



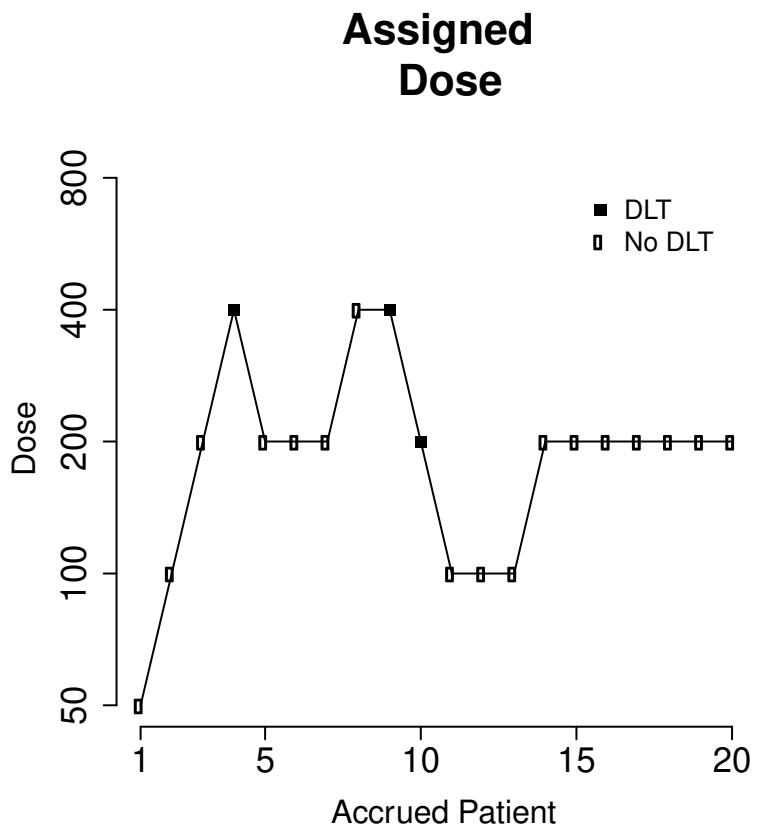


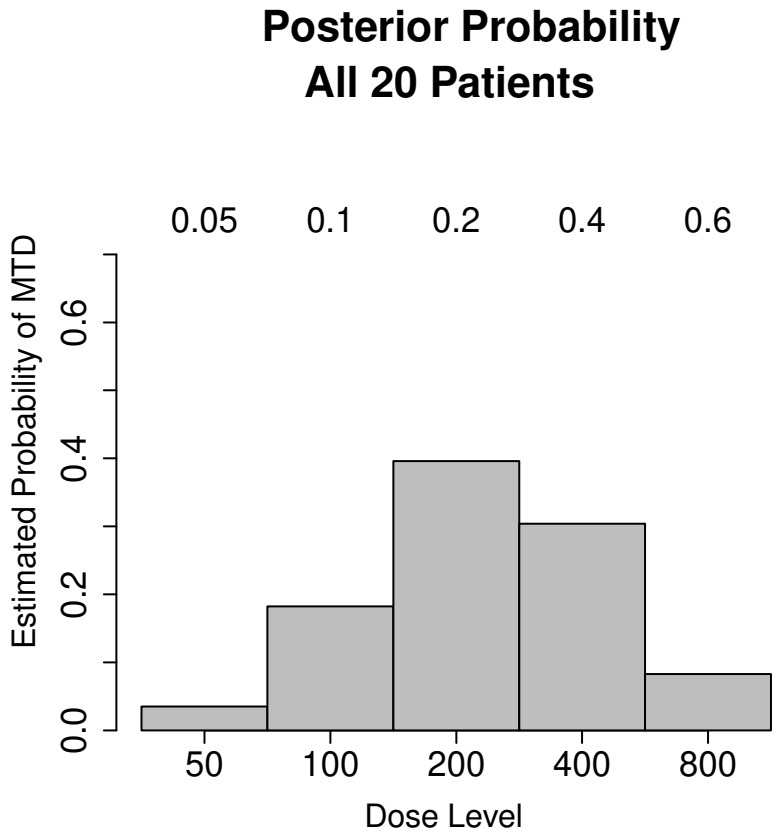
Posterior Probability Rules





Posterior Probability Rules





Concluding remarks

- There is no boilerplate design that can address all the clinical objectives
- The research questions being addressed, and the hierarchy of importance would determine the optimal design
- Each trial has unique elements based on preclinical, clinical and emerging data; patient population and available treatments
- Small, dose escalation phase I designs still have an important role in understanding and improving cancer treatment

Concluding remarks

- Available and well established, studied tools exist and can be used (as is or with modification) to address challenges posed by new therapies
- Randomization is one such tool
- Adaptive, model-based designs provide solutions to the current clinical challenges
- Stopping early: probabilistic estimates of getting to the correct answer

FDA-AACR Public Workshop On

OPTIMIZING DOSAGES FOR ONCOLOGY DRUG PRODUCTS: QUANTITATIVE APPROACHES TO SELECT DOSAGES FOR CLINICAL TRIALS

February 15 and 16, 2024 I Washington, DC

BJC British Journal of Cancer

www.nature.com/bjc

REVIEW ARTICLE

Randomised Phase 1 clinical trials in oncology

Alexia Iasonos[1] and John O'Quigley[2]

The aims of Phase 1 trials in oncology have broadened considerably from simply demonstrating that the agent/regimen of interest is well tolerated in a relatively heterogeneous patient population to addressing multiple objectives under the heading of early-phase trials and, if possible, obtaining reliable evidence regarding clinical activity to lead to drug approvals via the Accelerated Approval approach or Breakthrough Therapy designation in cases where the tumours are rare, prognosis is poor or where there might be an unmet therapeutic need. Constructing a Phase 1 design that can address multiple objectives within the context of a single trial is not simple. Randomisation can play an important role, but carrying out such randomisation according to the principles of equipoise is a significant challenge in the Phase 1 setting. If the emerging data are not sufficient to definitively address the aims early on, then a proper design can reduce biases, enhance interpretability, and maximise information so that the Phase 1 data can be more compelling. This article outlines objectives and design considerations that need to be adhered to in order to respect ethical and scientific principles required for research in human subjects in early phase clinical trials.

British Journal of Cancer (2021) 125:920–926; https://doi.org/10.1038/s41416-021-01412-y

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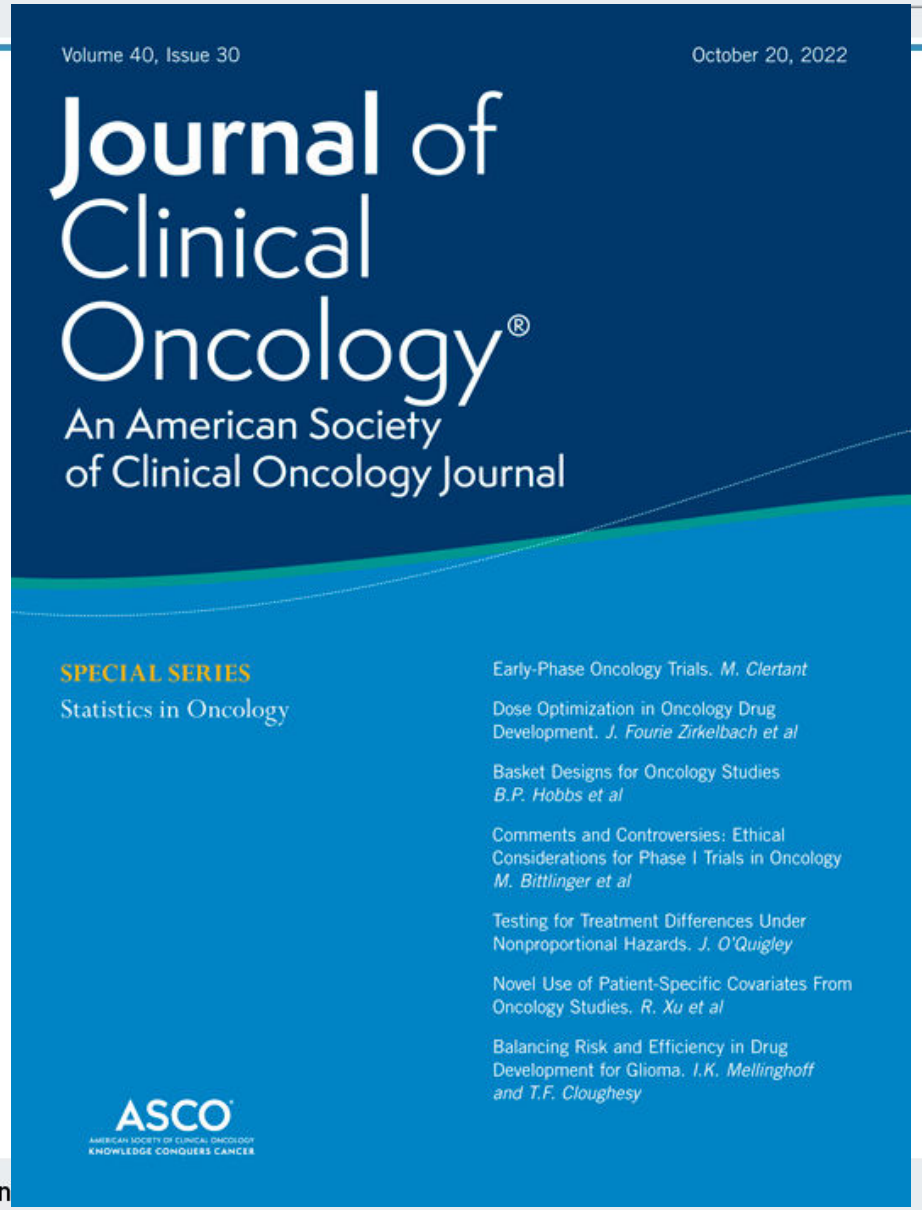
Special Issue: Statistics in Oncology

Guest Editor Dr S. Devlin

- Educational purpose ~75 references
- Audience: an updated review on timely topics
- Discussion: insights where the field is going
  - FDA papers (CAR T approvals)
  - Ethics
  - Immune based treatment - non PH assumption
  - Window of opportunity; basket trials; patient covariates
- iasonosa@mskcc.org



SESSION 2B: NOVEL TRIAL DESIGNS TO ENHANCE DOSE-SELECTION DECISION MAKING

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MODERATOR

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MD Anderson

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INTRODUCTORY SPEAKER

Alexia Iasonos, PhD
Memorial Sloan Kettering Cancer Center

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Mallorie Fiero, PhD
U.S. Food and Drug Administration

Nicole Gormley, MD
U.S. Food and Drug Administration

Vishal Bhatnagar, MD
U.S. Food and Drug Administration

DAY 1 WRAP-UP AND DAY 2 PREVIEW

Raj Madabushi, PhD
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