Optimizing Drug Development Designs for Precision Medicine Considerations

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Supporters of Kamala Harris turned out this week to hear Michelle Obama, who has been anchoring campaign rallies for the vice president. CHENEY ORR/REUTERS

ELECTION 2024

Harris Bets on Big Turnout Among Women to Push Her Over Finish Line

The vice president and surrogates, including Michelle Obama, are making emotional appeals to women about abortion and health

By Catherine Lucey
Nov. 1, 2024 at 9:00 pm ET

DJIA -0.90% ▼	S&P 500 -1.86% ▼	NASDAQ -2.76% ▼	RUSS

Foreign Adversaries Target Specific Demographics in Attempt to Sway U.S. Election

Russia and Iran have sought to peddle content to influence Spanish-language voters and other groups, officials and researchers say.

⊙ 6 min read   🎧 🔖 ↗

ELECTION 2024   + Follow

Young Men Could Boost Trump to Victory—if They Show Up

Former president courts key group with macho rhetoric and podcast appearances, but in the process risks alienating women

GOP presidential candidate Donald Trump at a rally Friday in Milwaukee. (PHOTO: MUSTAFA HUSSAIN FOR WSJ)

By Andrew Restuccia   + Follow   *in Washington and Michelle Hackman*
+ Follow   *in Milwaukee*
Updated Nov 03, 2024 12:00 a.m. ET

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Donald Trump is pinning his political future on winning the votes of disaffected young

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Early voting at the Metropolitan Library in Atlanta. DUSTIN CHAMBERS FOR WSJ

ELECTIONS   Follow

The Elusive Voters Who Could Make or Break the Election

Harris, Trump campaigns race to find and turn out people who haven't decided whether to vote

Questions

- What is the optimal dose?
- What is the optimal population?
- What is the optimal biomarker to define the population?
- What is the most efficient development plan with the desired probability of success

Overview of Drug Development Process

- Traditional goals: target engagement, proof of concept, dose response, confirmatory
- Precision medicine: tailoring treatments or combinations to specific patient subgroups or biologic features.
- 2023 FDA approvals
  - 8 out of 55 (15%) with precision medicine: AUGTYROTM (repotrectinib), TRUQAP™ (capivasertib) , FRUZAQLA™ (fruquintinib), ZILBRYSQ (zilucoplan), VANFLYTA® (quizartinib) , RYSTIGGO® (rozanolixizumab-noli), QALSODY (tofersen), ORSERDU™ (elacestrant)

Shifts to Precision Medicine

- Why?
  - Patients need greater efficacy or healing and medicines have not been optimized for individuals for optimal efficacy and safety
  - Science has progressed to open the door to targeted medicine
- How?
  - Increases in technology, drug discovery and AI open the door to targeted treatments and population understanding
- When?
  - Now and increasing

Steps to define the precision medicine group

- Define the precision medicine subgroup or anatomical site
  - Ordinal, Nominal or Continuous
  - Relevancy …. Right biomarker for patients, physicians, regulators, health system and company
  - Sources of data - in vitro, in vivo, external data: competitor or real world
- Determine the role of biomarkers and diagnostic devices
  - Different mutations/rearrangements/fusions/biomarkers or collections of them
  - level of expression
  - location

Companion Diagnostics

Definition and Importance of Companion Diagnostics

- Relationship between therapeutic interventions and diagnostics
  - Diagnosis or Safety Consideration
  - Safety or Efficacy Response
  - Cost of Goods
- Regulatory and clinical implications
  - Key regulatory requirements
  - Clinical actions and complexity

Companion Diagnostics …

Evaluation of Companion Diagnostics

- When and how to integrate companion diagnostics in the development plan…. Beginning or End?
- Statistical challenges and solutions…efficacy/safety tradeoffs and cutpoints
- Development program and team?

Statistical Considerations for Precision Medicine Designs

- **Design and Analysis Challenges**
  - Small sample sizes and subgroup analyses.
  - Multiplicity and control of type I error.
- **Methodologies for Addressing Challenges**
  - Bayesian approaches.
  - Adaptive trial designs.
  - Use of historical and real-world data.
- **Phase-specific Considerations**
  - Tailoring design strategies to each phase of development (Phase 1, 2, and 3).
  - Balancing early and late phase questions in precision medicine.

Precision Medicine Timing

Joint optimization of dose and precision medicine group and order of selection
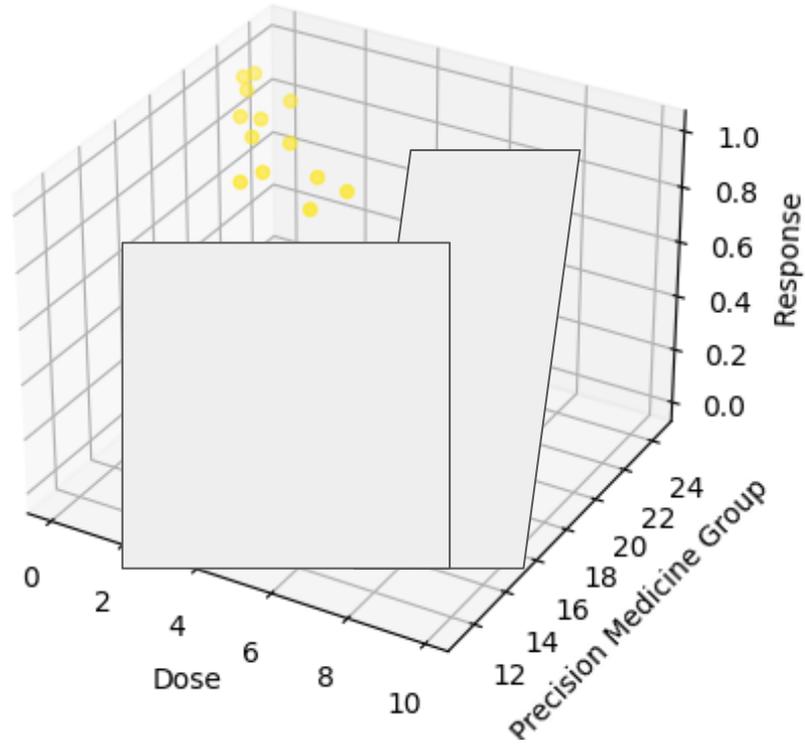- Phase 1 based on target engagement/proof of mechanism
- Phase 2 based on proof of principle/proof of concept
  - Traditional subgroup approaches are not enough
- Phase 3 based on any new data and protect all likely scenarios through alpha control

Other considerations ….

- Interim analyses? Adaptive designs? Response adaptive? Decentralized components? Companion diagnostic? Master protocol? RWD/E?
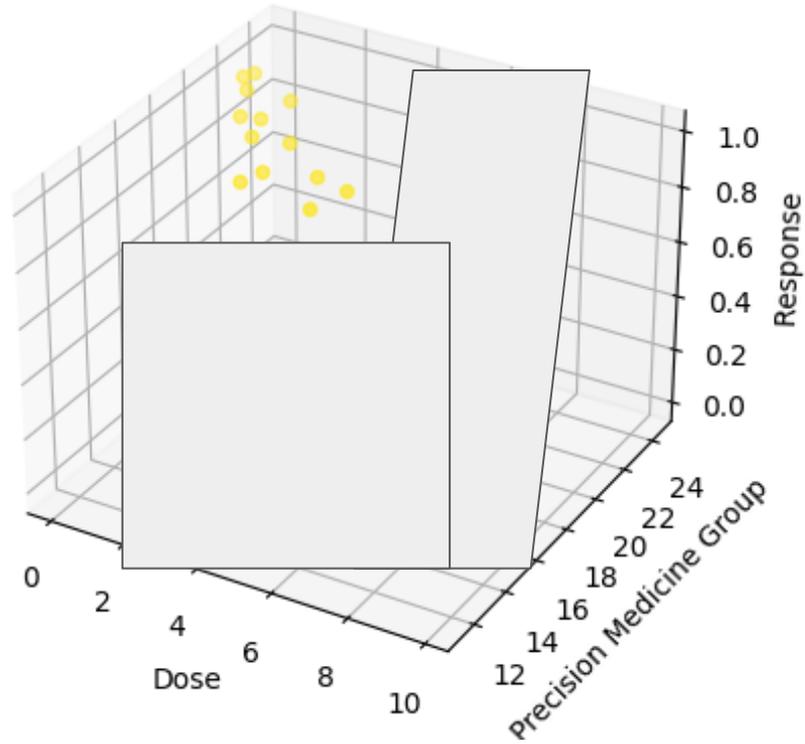
Low Dose and high biomarker --- Proceed?

Dose-Response Relationship and Precision Medicine Group
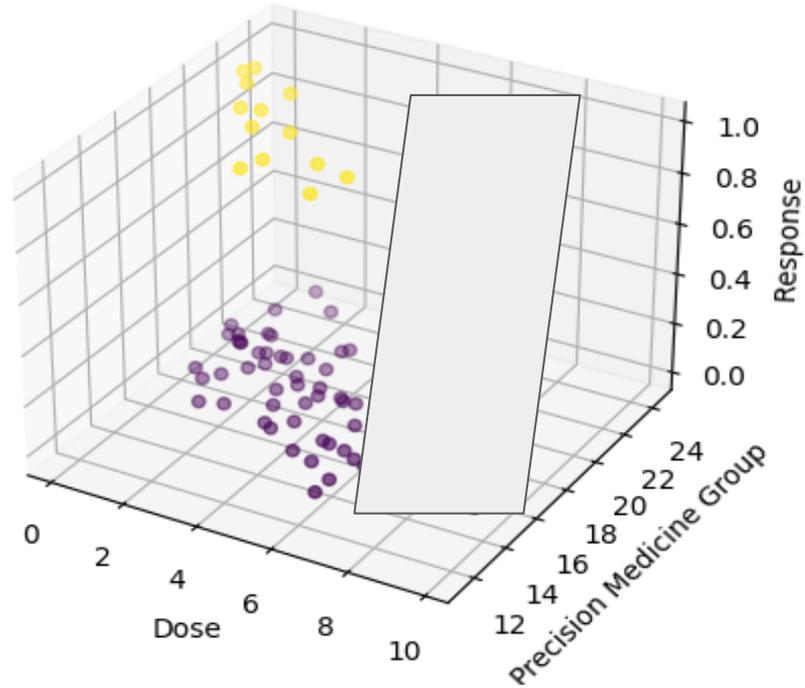
Low Dose and high biomarker --- Proceed?

Maybe?

Benefit/Risk?

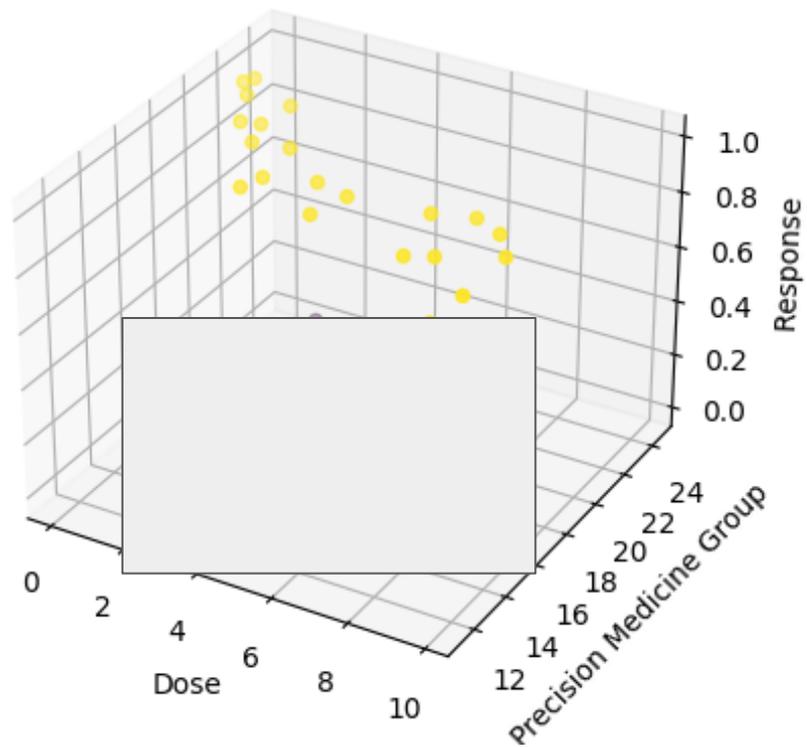Dose-Response Relationship and Precision Medicine Group

What about lower biomarker groups?

Dose-Response Relationship and Precision Medicine Group
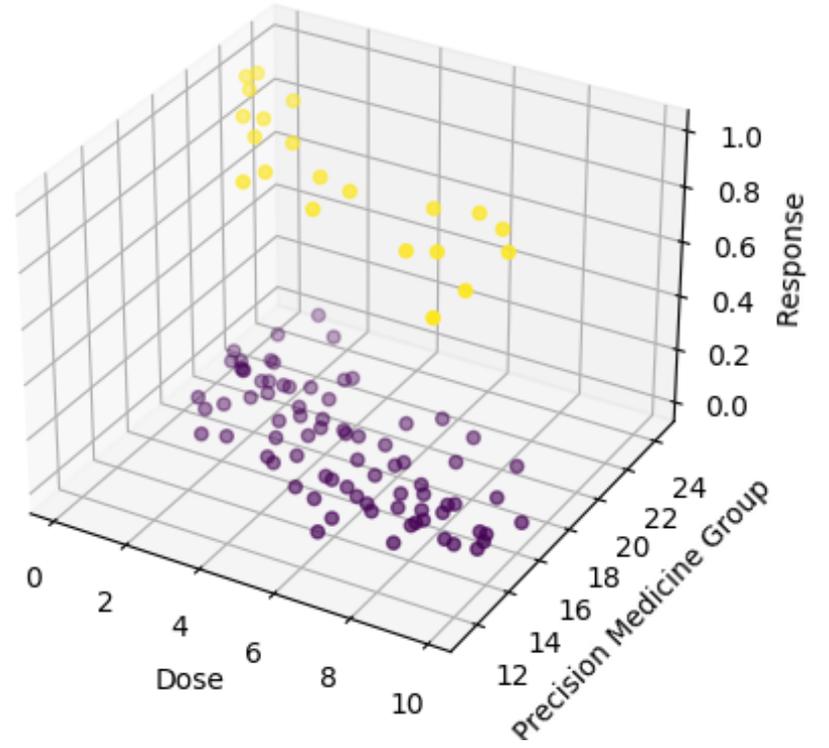
What about higher doses for the precision medicine group?

Dose-Response Relationship and Precision Medicine Group

When to start phase 3?

When to modify phase 3?

When to complete phase 2?

Dose-Response Relationship and Precision Medicine Group

3D Dose-Response Relationship: Two Precision Medicine Populations

Not always so clear …
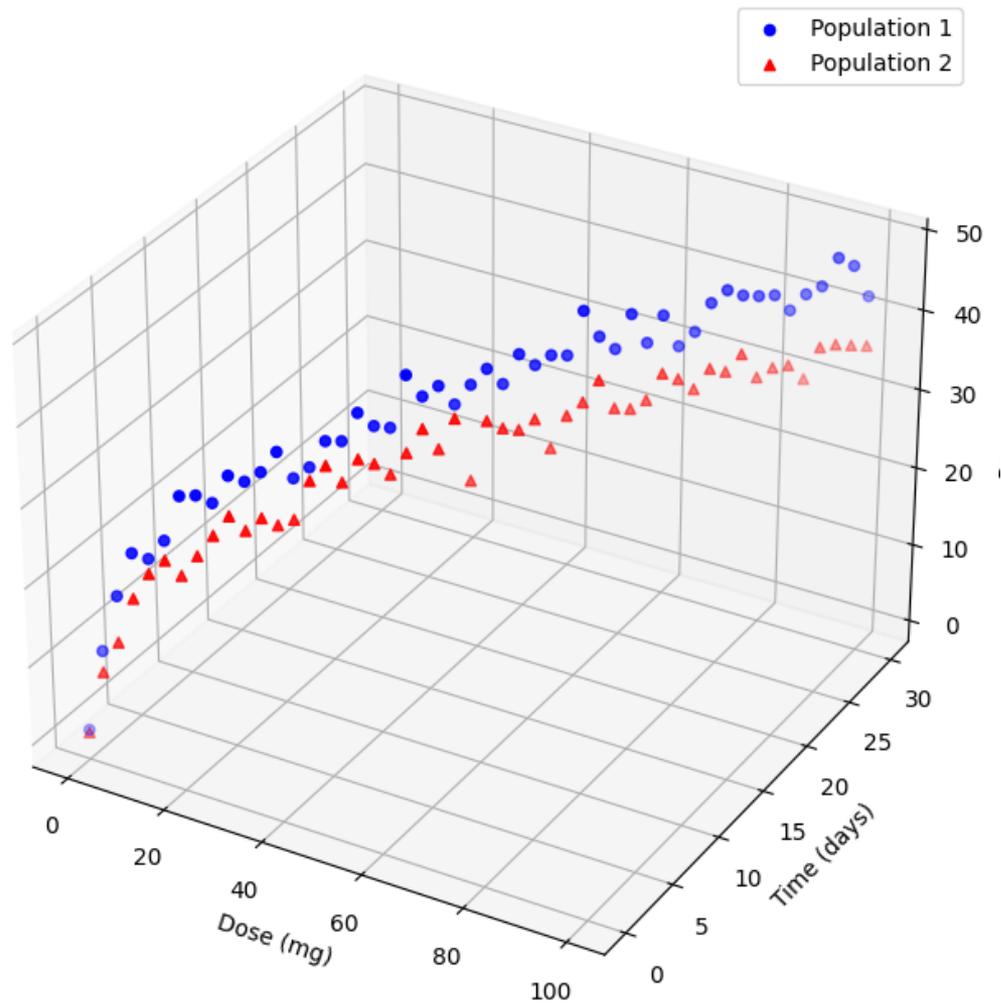
RARP – Response Adaptive Randomization & Population

- Start with the full parameter range for dose and population

- Adapt the dose randomization ratio and population refinement based on **predefined operating characteristics**

- Start with a joint model to characterize dose and population response

- Update based on the data using parametric or Bayesian approaches

…Predefined operating characteristics

- Go - No Go
- P-value
- Lower limit of confidence interval
- Which variables…surrogates, linked efficacy and safety

Changing Biomarkers for target group

- Start with one identified preclinically
- Adapt and change as needed
- Repeat development plan?... Store samples to mitigate changes

Examples

Healthy Normal and In Vitro Investigations and First in Human - Target Engagement

- Biomarker present in healthy normals,e.g. CRP
- Initial study in patients, oncology
- Samples from patients and medicine applied to samples
- Disease biomarker applied to samples from healthy normal phase 1 study

Anatomical Targeting

Tracing technology

Biomarker expression

Crohn's Disease
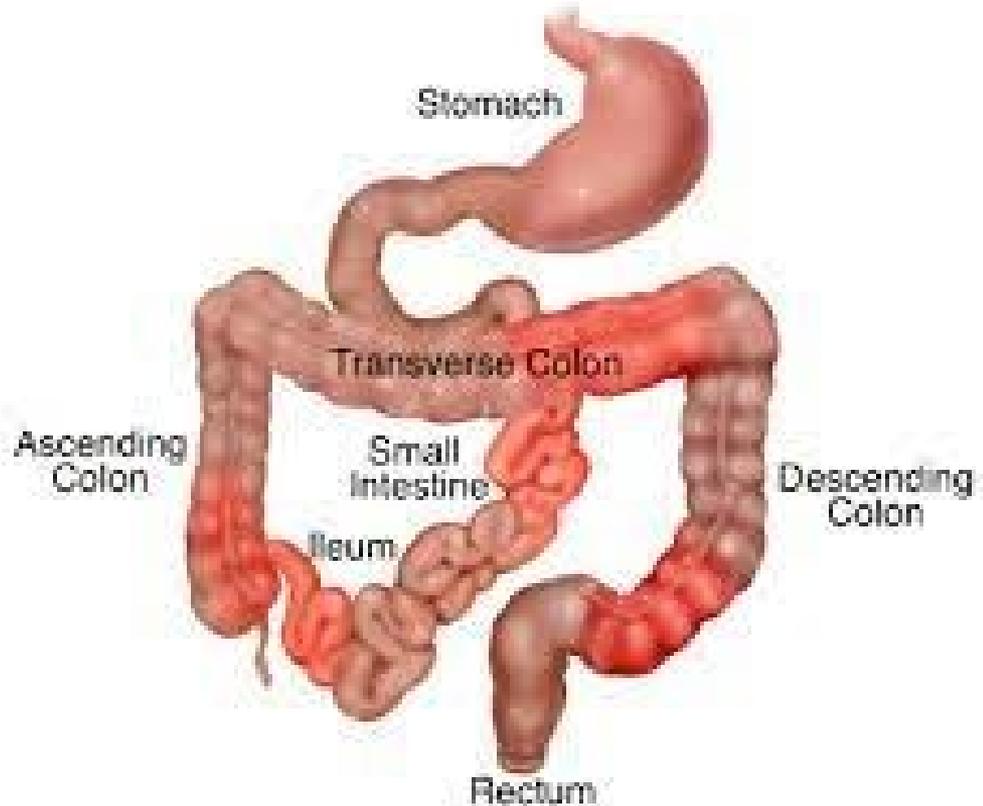
Generic approved

What is the generic profile?

Dose-Response Relationship and Precision Medicine Group

Generic approved

- Include generic medication in studies…maybe just for the target group
- Compare using publications and real world data…sometimes no data for the target group
  - Consider registries
  - Transcelerate
- Create a natural progression group to follow simultaneously

Concurrent Phase 2 and 3 subgroup identification

- Choice to start broad or narrow in phase 2
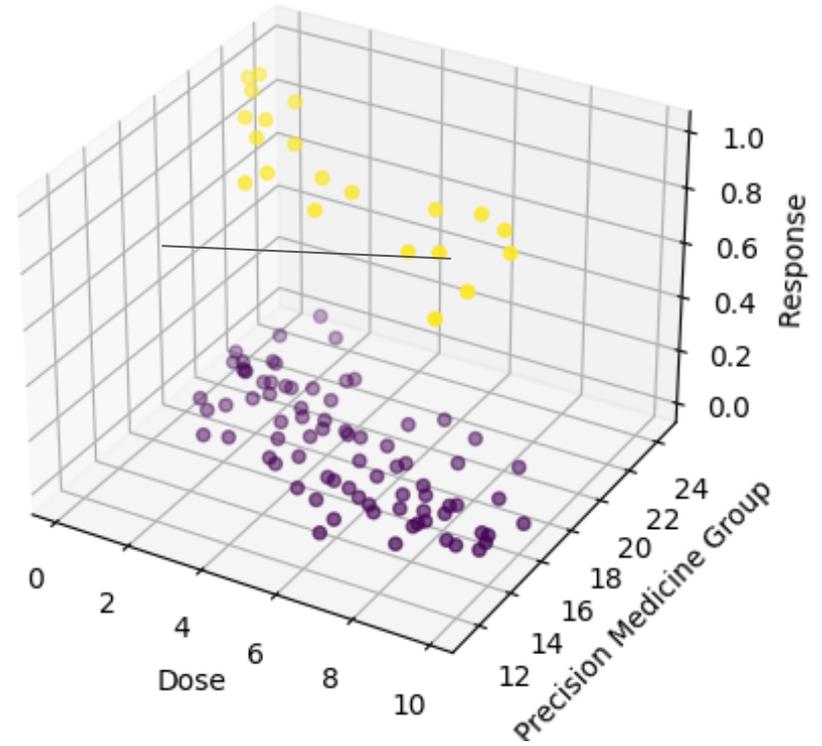 - Drivers …. Cost, Patent life, Competition, Precedent for mechanism, Genetic evidence
- Start phase 2 and define decision points for expansion to phase 3 or declaring futility
  - Outcome based
  - Timing based
- Protocols: Include broad range of doses and populations and plan to select doses and populations to maximize efficacy and safety
- Revise phase 2 randomization and populations as warranted
- Expand or constrict phase 3 doses and population based on phase 2 data with regulatory agreement

Mixing with Platform Studies

- Common in combination studies and similar to utilizing design of experiments
- One example multiple combinations/precision medicine groups and multiple doses under a single protocol with many subprotocols
- Examples: Diabetes and combination studies, oncology, disease/tumor types, multi-devices, etc.

Repotrectinib

Figure S1. Overview of the Phase 1–2 TRIDENT-1 Study Design

Key Eligibility Criteria	Phase 1 *Dose escalation**	Phase 2 *Expansion cohorts*		Phase 2 Endpoints
Phase 1-2 • Locally advanced or metastatic solid tumors harboring *ROS1* or *NTRK1-3* gene fusions • Treated or untreated asymptomatic CNS metastases and/or leptomeningeal carcinomatosis allowed	Repotrectinib (dose escalation) ↓ RP2D: 160 mg QD × 14 days, then 160 mg BID[†]	*ROS1+ advanced NSCLC cohorts*		**Primary end point:** • cORR by BICR using RECIST v1.1
		EXP-1 ROS1 TKI-naïve[‡] (n = 110)[§]		
		EXP-2 1 ROS1 TKI *and* chemotherapy-pretreated[‡] (n = 60)[§]		**Key secondary end points:** • DOR,[¶] CBR,[¶] TTR[¶] • cORR[¶] in TKI-pretreated patients harboring *ROS1* G2032R • PFS,[¶] OS • icORR by mRECIST v1.1 in patients with measurable brain metastases • Safety, patient-reported outcomes
		EXP-3 2 ROS1 TKI-pretreated *and* chemotherapy-naïve[‡] (n = 40)[§]		
• Primary efficacy population includes patients pooled from phase 1[‖] and 2 who began repotrectinib treatment approximately 14 months prior to the data cutoff date of December 19, 2022		**EXP-4** 1 ROS1 TKI-pretreated *and* chemotherapy-naïve[‡] (n = 60)[§]		

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*Phase 1 primary endpoints: DLT, MTD, RP2D.

[†]Based on tolerability.

[‡]Up to one prior line of chemotherapy or immunotherapy is allowed for EXP-1; must have received one prior line of platinum-based chemotherapy or in combination with immunotherapy before or after a ROS1 inhibitor for EXP-2; no prior lines of chemotherapy or immunotherapy are allowed for EXP-3 and EXP-4.

[§]N's for expansion cohort indicate enrollment targets.

[¶]By RECIST v1.1.

[‖]Patients from phase 1 received 40 mg once daily to 240 mg once daily and 200 mg twice daily.

Mutation or gene profile: 2017 to 2023 --- Repotrectinib for genetic related lung cancer?

- Which genetic profile… *ROS1*, *NTRK*1–3, or *ALK* gene fusions?

- How to confirm the fusions /level of expression? … diagnosis/inclusion

- Which dose?... Max dose with ROS1 signal

- How to progress from phase 1 to phase 2 to phase 3? Plan for a single trial?...single

- When to submit and publish? Data maturity

- Which subgroups to protect operational characteristics? …Mutation and intracranial

- How to handle safety and efficacy? Late agreement for pooling

- RESULT - "AUGTYRO (repotrectinib) is indicated for the treatment of adult patients with locally advanced or metastatic ROS1-positive non-small cell lung cancer (NSCLC) "

Summary

Challenge - Identify dose response and precision medicine population in the most efficient manner…cost, time and precision

- **Exploring Various Development Scenarios**
    - Different strategies based on biomarker discovery and validation.
    - Early vs. late phase incorporation of precision medicine considerations.
    - Companion diagnostics
- **Response Adaptive Precision Medicine Population Identification**
    - Methodologies for integrating precision medicine in adaptive designs.
    - Identify dose response curve and precision medicine population simultaneously

Continue to consider …

- ○ Importance of early and strategic incorporation of precision medicine.
- ○ Statistical methodologies to optimize drug development designs.
- ○ Emerging trends and technologies in precision medicine … ML and AI
- ○ Potential improvements in design methodologies.

References and Further Reading

Key References

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- https://clinicaltrials.gov/study/NCT03093116
- https://www.augtyrohcp.com/

Thank You!