Trial Design and Endpoint Considerations Hematologic Malignancies

BINDU KANAPURU
DIVISION OF HEMATOLOGIC MALIGNANCIES II
OFFICE OF ONCOLOGIC DISEASES
FOOD AND DRUG ADMINISTRATION

Disclosure

No disclosures

Topics

- FDA and Oncology Center of Excellence
- Oncology Product Development
- Endpoints
- Clinical trial design

Role of the FDA

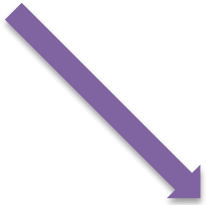
The Food and Drug Administration is responsible for protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices; and by ensuring the safety of our nation's food supply, cosmetics, and products that emit radiation.

FDA Approval Standards and Regulatory Considerations

- Substantial evidence
- Safe and Effective
- FDA **does not** take into account pricing.
- FDA **does not** regulate “practice of medicine”.

Approval Pathways

Substantial Evidence of Effectiveness from Adequate and Well Controlled Investigation(s)
Favorable Benefit Risk Assessment



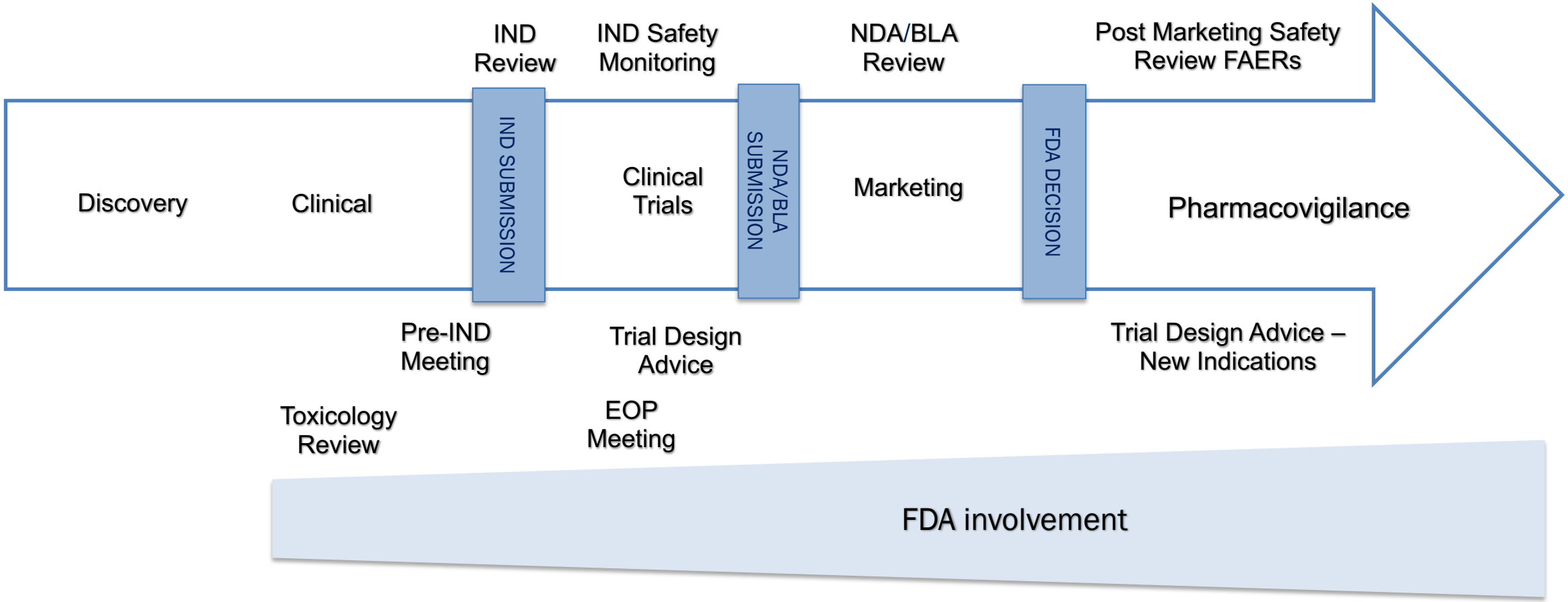
Regular Approval

- No Comparative Effectiveness Standard
- Endpoint with direct evidence of clinical benefit or established surrogate

Accelerated Approval

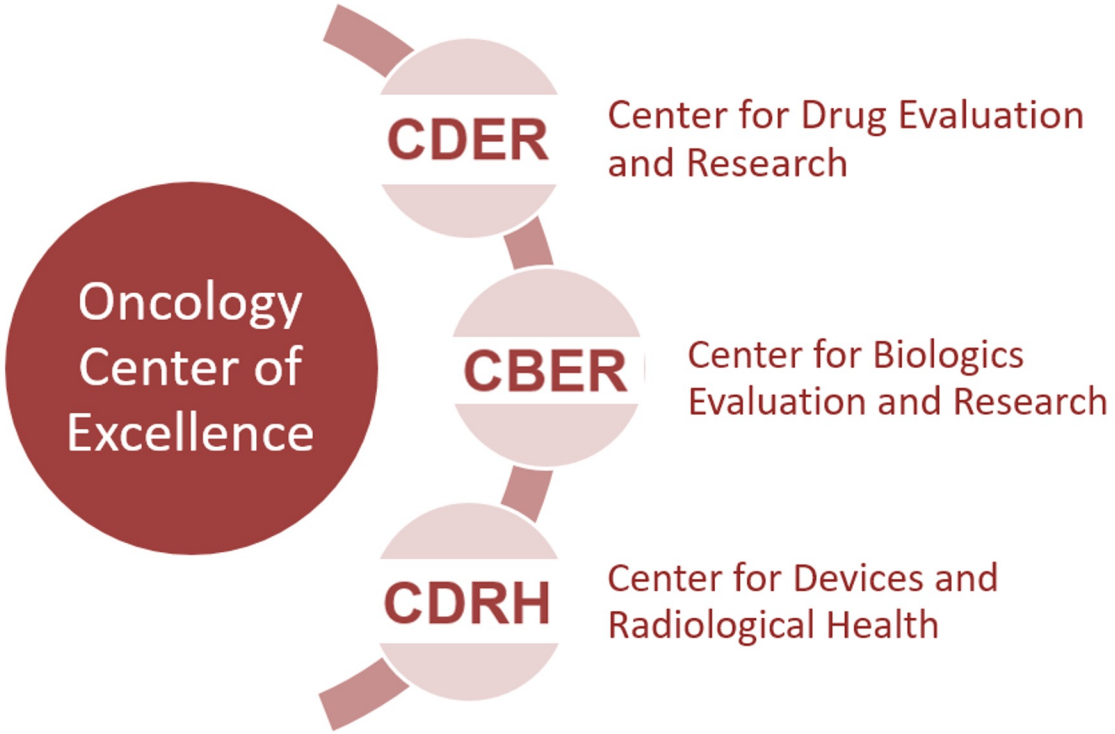
- Serious and life-threatening disease
- Benefit assessed in the context of available therapy
- Intermediate or surrogate endpoint reasonably likely to predict benefit
- Confirmation of clinical benefit

Drug development lifecycle

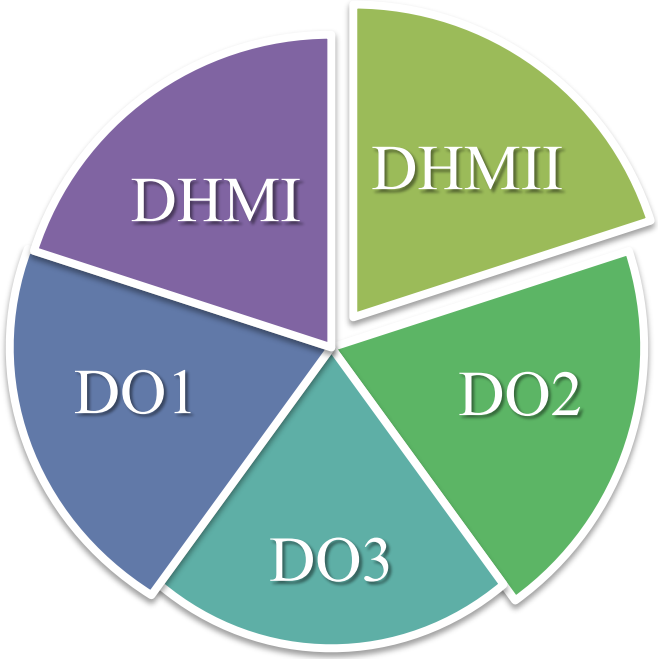


IND: Investigational New Drug Application, **NDA**: New Drug Application, **BLA**: Biologics License Application, **FAERs**: FDA Adverse Event Reporting System

OCE/ OOD



Division of Heme Malignancies II: **Lymphoma, MM**

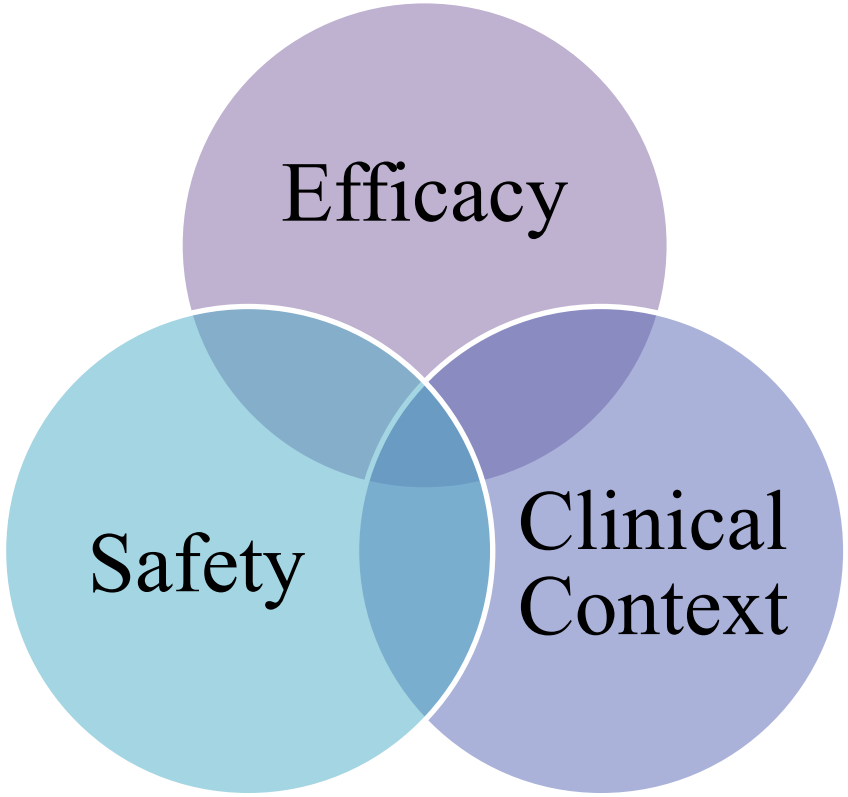


Division of Oncology 1: **Breast, GYN, GU**
Division of Oncology 2**:Thoracic, H&N, Neuro, Peds, Rare cancers**
Division of Oncology 3:GI, Cutaneous, Melanoma, Sarcoma
DHMI: Acute and Chronic Leukemia, MDS, Transplant

Considerations in Oncology Product Development

Life-threatening nature of diseases--patient access *vs* necessary data for approval

- Drugs multiple action modes; combinations
- Risk/benefit ratio--different perspective on serious adverse events compared to non-cancer diseases
- Product label and off-label uses



Evaluating Efficacy

- Design of the trial—specification of endpoint, statistical analysis plan
- Quality of data ensured
- Demonstration of statistical significance
- Interpretation of the “clinical significance of the finding”
  - Includes an assessment of safety magnitude of benefit

How is Clinical Significance evaluated?

- **What** is being measured? **(endpoint selection)**
  - Direct benefit (feels/functions/survives) considered more meaningful
- **How** accurately is it being measured? **(measurement characteristics)**
  - Accuracy of the measure
  - Susceptibility to bias
  - Accuracy of the timing of the event
- **How much** effect on the endpoint is observed? **(magnitude of effect)**

Endpoints

Direct Endpoint: A *direct* measure of how a patient feels, functions, or survives

- Examples: overall survival (OS), clinical outcome assessments (e.g. patient reported outcomes)

Indirect Endpoint: An *intermediate* measure which can be evaluated earlier, before irreversible morbidity or mortality

- Examples: objective response rate (ORR)

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Strengths and Weaknesses of Endpoints

	Clinical Benefit	Low Risk of Bias	Practicality
Progression-Free Survival	− / +	− / +	+
Overall Survival	+	+	− / +

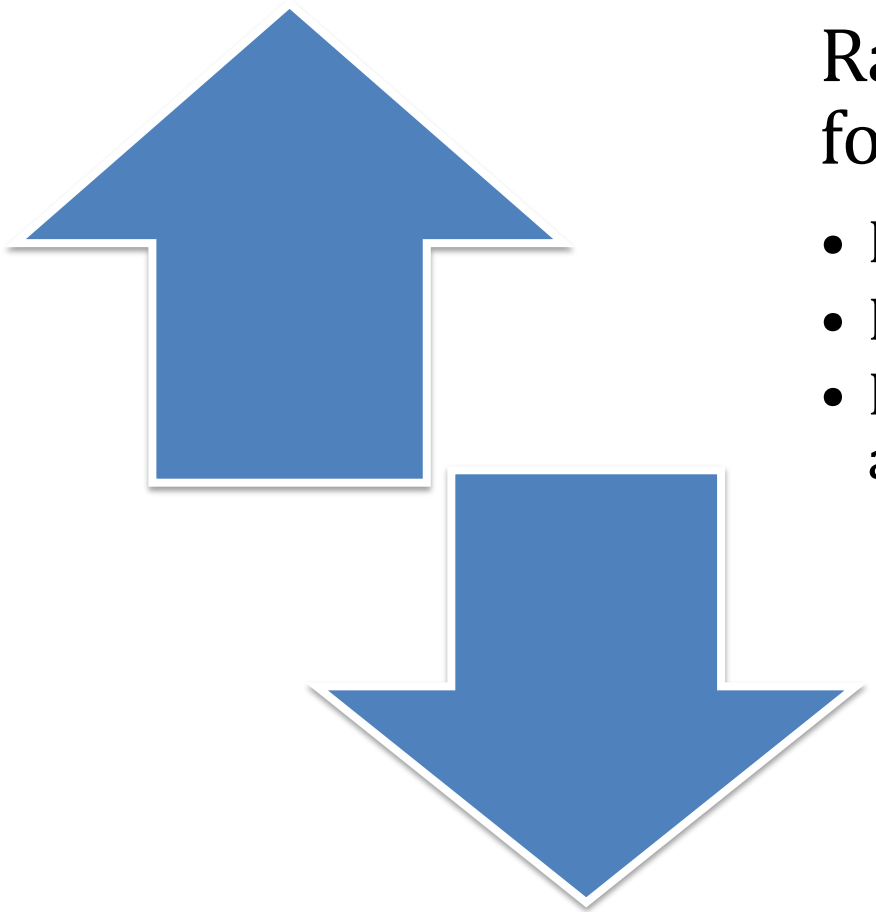
Most interpretable in cross-trial comparisons

Strengths and Weaknesses of Endpoints

	Clinical Benefit	Low Risk of Bias	Practicality
Progression-Free Survival	− / +	− / +	+
Overall Survival	+	+	− / +
Response Rate	+	− / +	+

Most interpretable in cross-trial comparisons

Randomized Clinical Trials



Randomized trials still gold standard for effectiveness and safety

- Minimize sources of potential bias
- Randomization accounts for unknown factors
- Enables reliable characterization of efficacy and safety

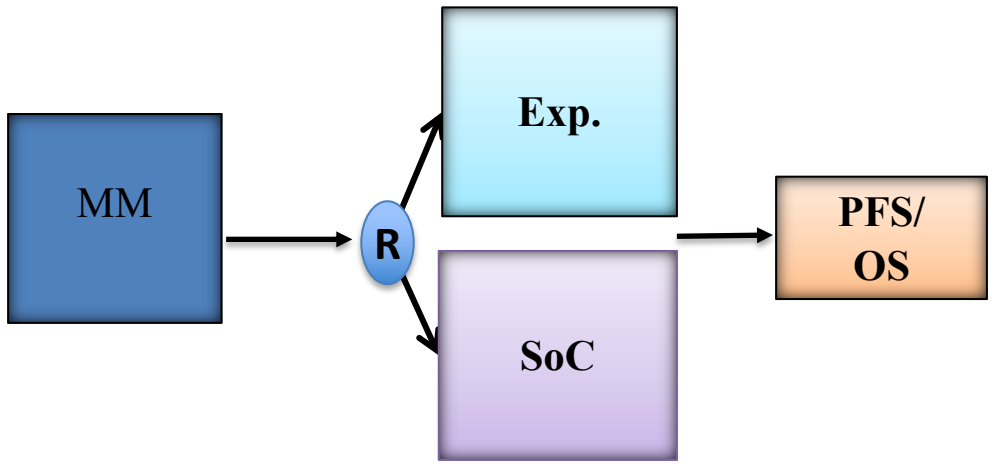
Caveats

Defining appropriate control in refractory population

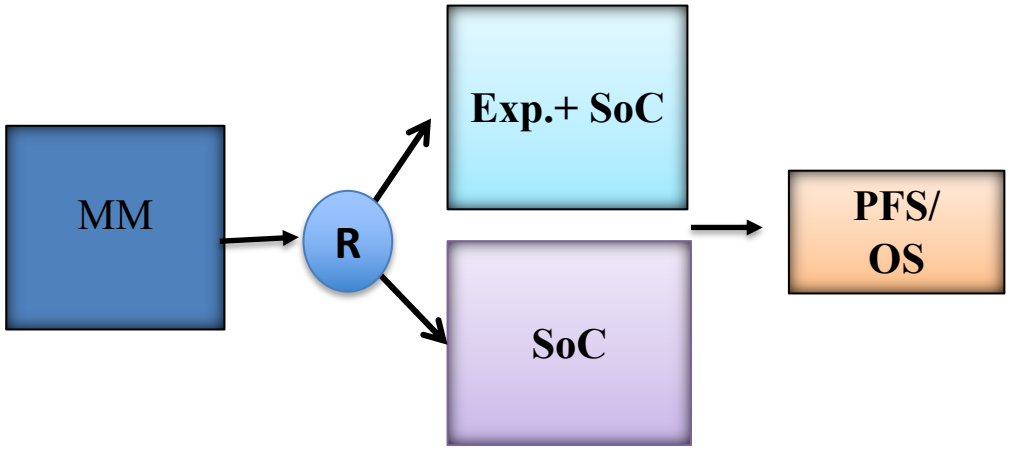
Placebo-controlled trials may be unethical due to high risk of progression

Common Trial Designs

Head to Head Design

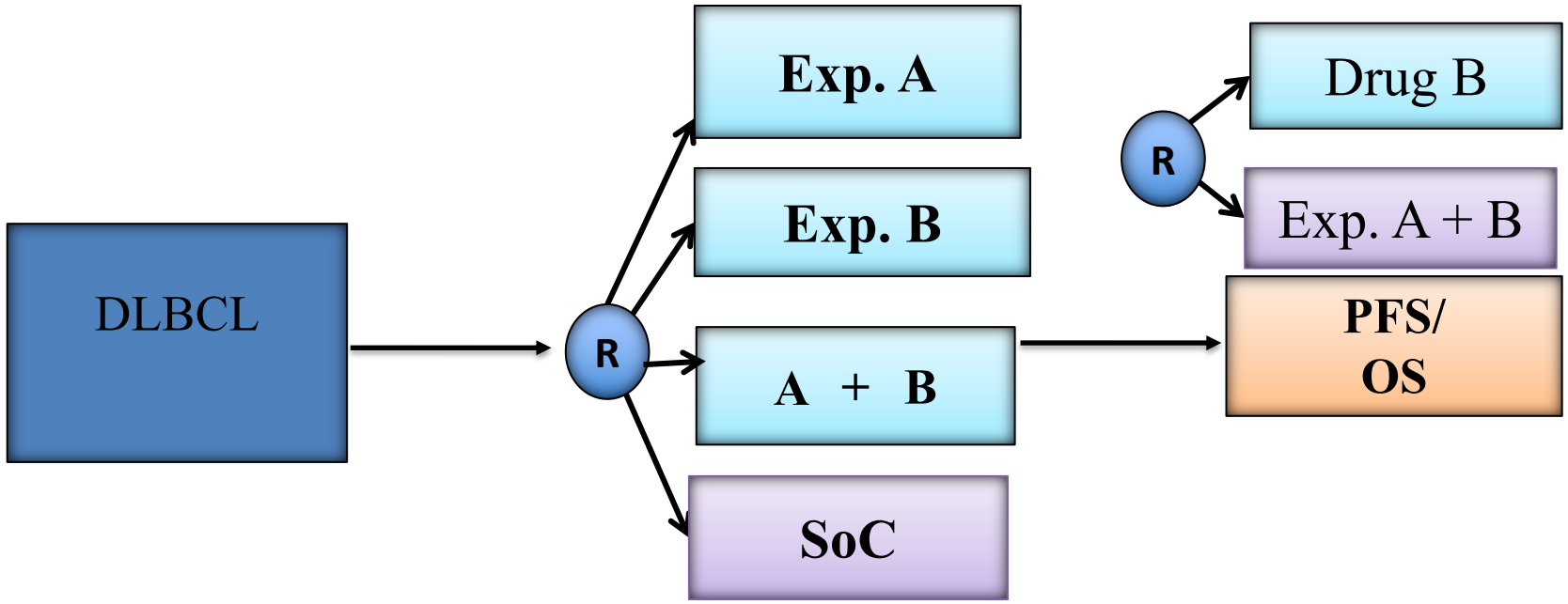


Add-on Design



SoC: Standard of Care, MM- Multiple Myeloma

Common Trial Designs- Combinations



- Isolation of effect key component
  - monotherapy arm(s) in the combination design with early stopping
  - Additional trial(s)

SoC: Standard of Care, DLBCL- Diffuse large B cell lymphoma, PFS-Progression-Free Survival, OS-Overall Survival

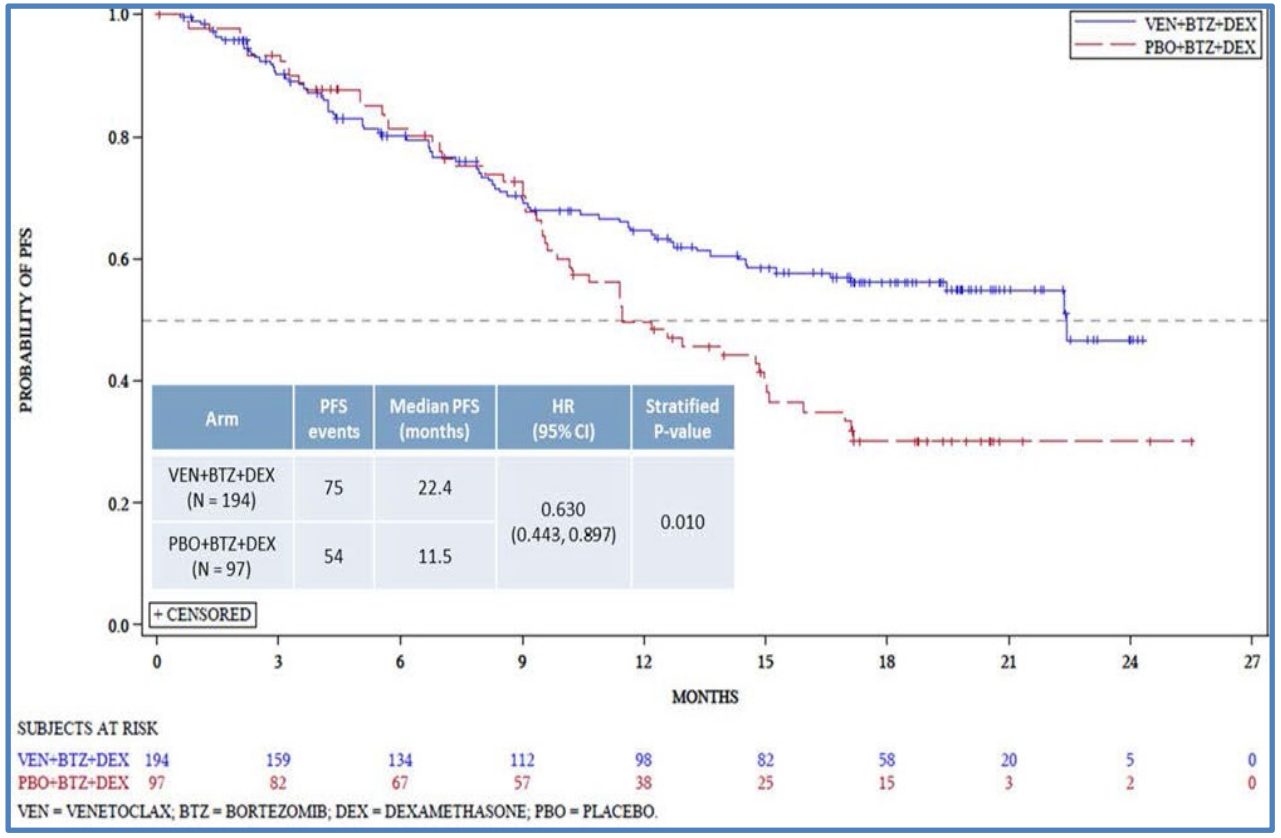
Common Trial Designs: Single Arm Design

Useful for drugs that show overwhelming superior efficacy

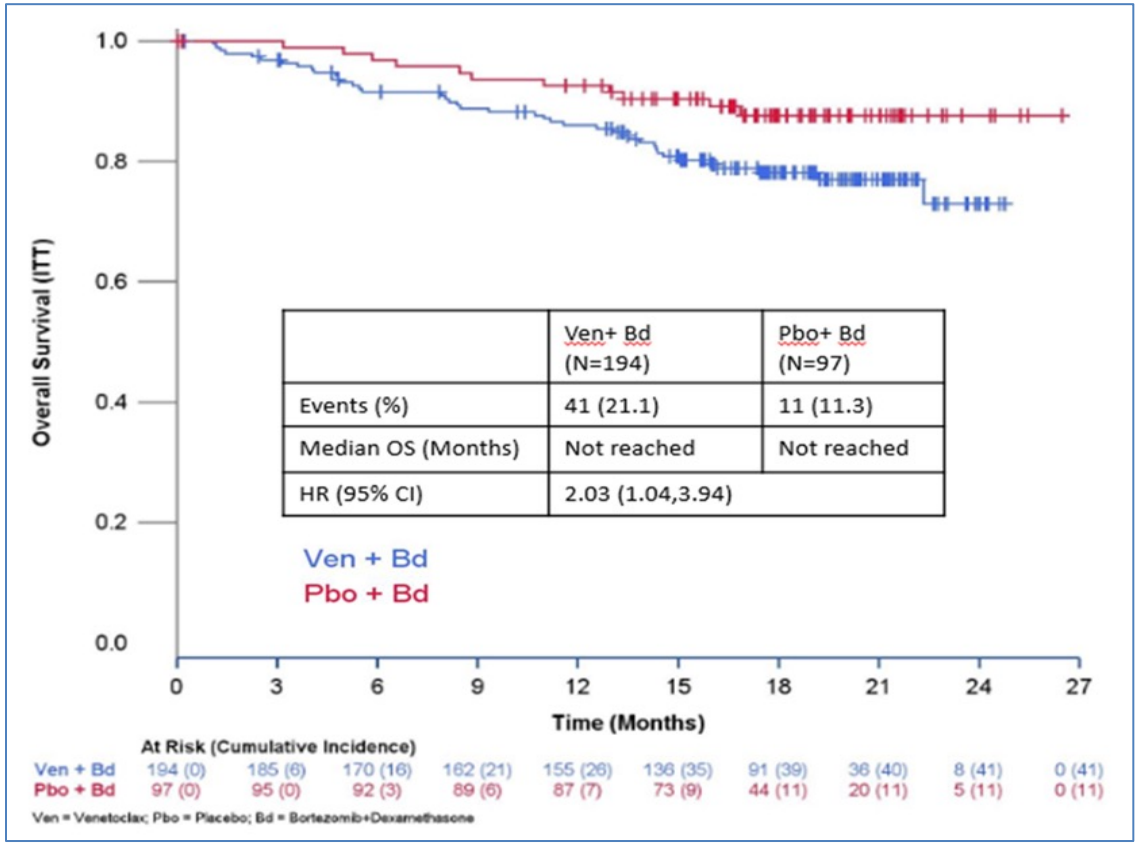
- Single-arm most appropriate for monotherapy
- Time to event endpoints cannot be interpreted in single arm trial
- Similarly assessment of safety can be challenging

ORR-Overall Response Rate, DOR-Duration of response, , FL- Follicular lymphoma

BELLINI Trial

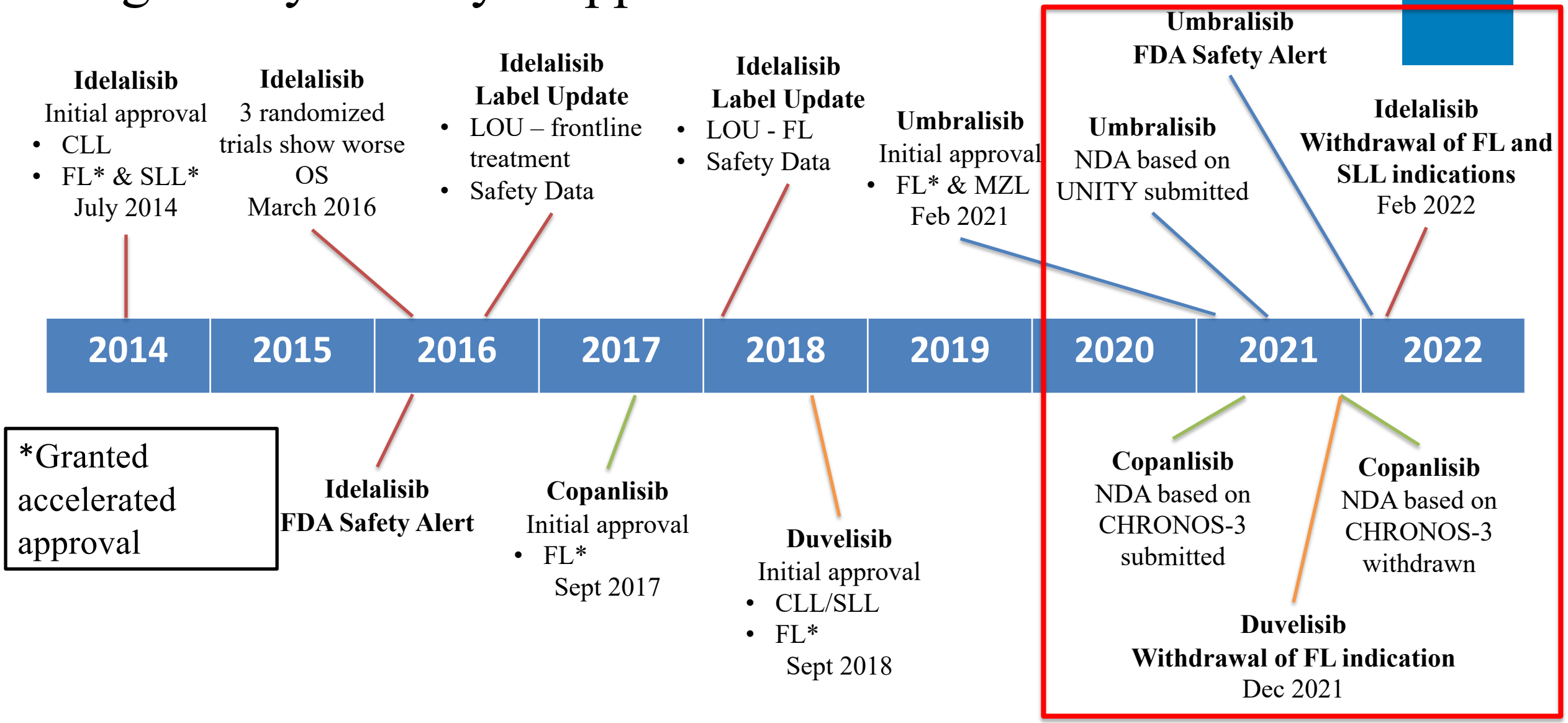


Arm	PFS events	Median PFS (months)	HR (95% CI)	Stratified P-value
VEN+BTZ+DEX (N = 194)	75	22.4	0.630 (0.443, 0.897)	0.010
PBO+BTZ+DEX (N = 97)	54	11.5		



	Ven+ Bd (N=194)	Pbo+ Bd (N=97)
Events (%)	41 (21.1)	11 (11.3)
Median OS (Months)	Not reached	Not reached
HR (95% CI)	2.03 (1.04,3.94)	

Regulatory History - Approved PI3K Inhibitors



Abbreviations: CLL, chronic lymphocytic leukemia, FL, follicular lymphoma, LOU, limitation of use, MZL, marginal zone lymphoma, NDA, new drug application, OS, overall survival, SLL, small lymphocytic lymphoma Slide courtesy: Nicholas Richardson, PI3K inhibitors ODAC

PI3K Inhibitor ODAC

- On April 21, 2022, an ODAC was convened to discuss key issues related to the PI3K inhibitor class:
  - Concerning trends in OS across multiple RCTs
  - Toxicities of the class
  - Inadequate dose optimization
  - Limitations of single-arm trials

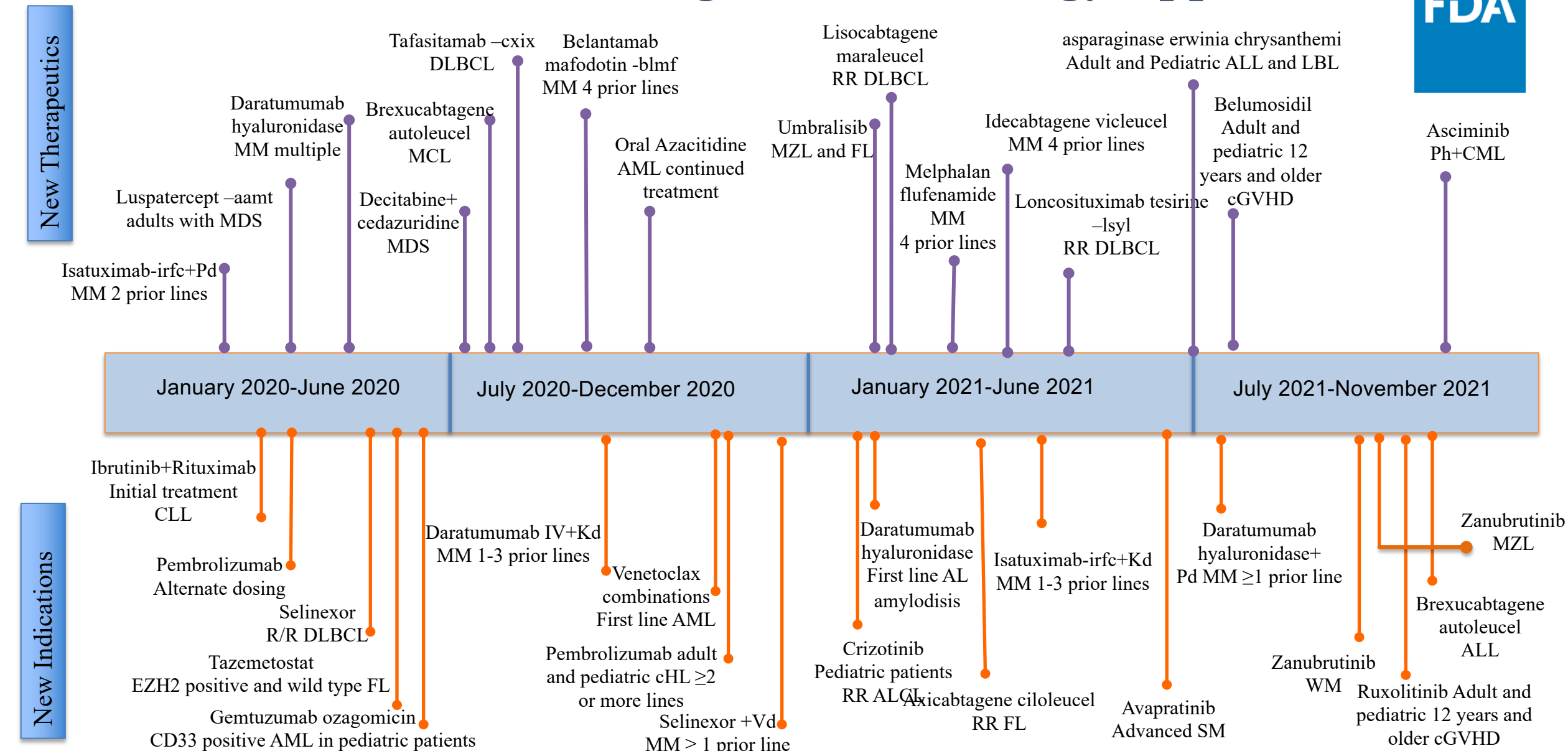
Voting Question

Given the observed toxicities with this class, previous randomized trials with a potential detriment in OS, and a narrow range between effective and toxic doses, **should future approvals of PI3K inhibitors be supported by randomized data?**

Abbreviations: ODAC, Oncologic Drugs Advisory Committee; RCT, randomized controlled trial

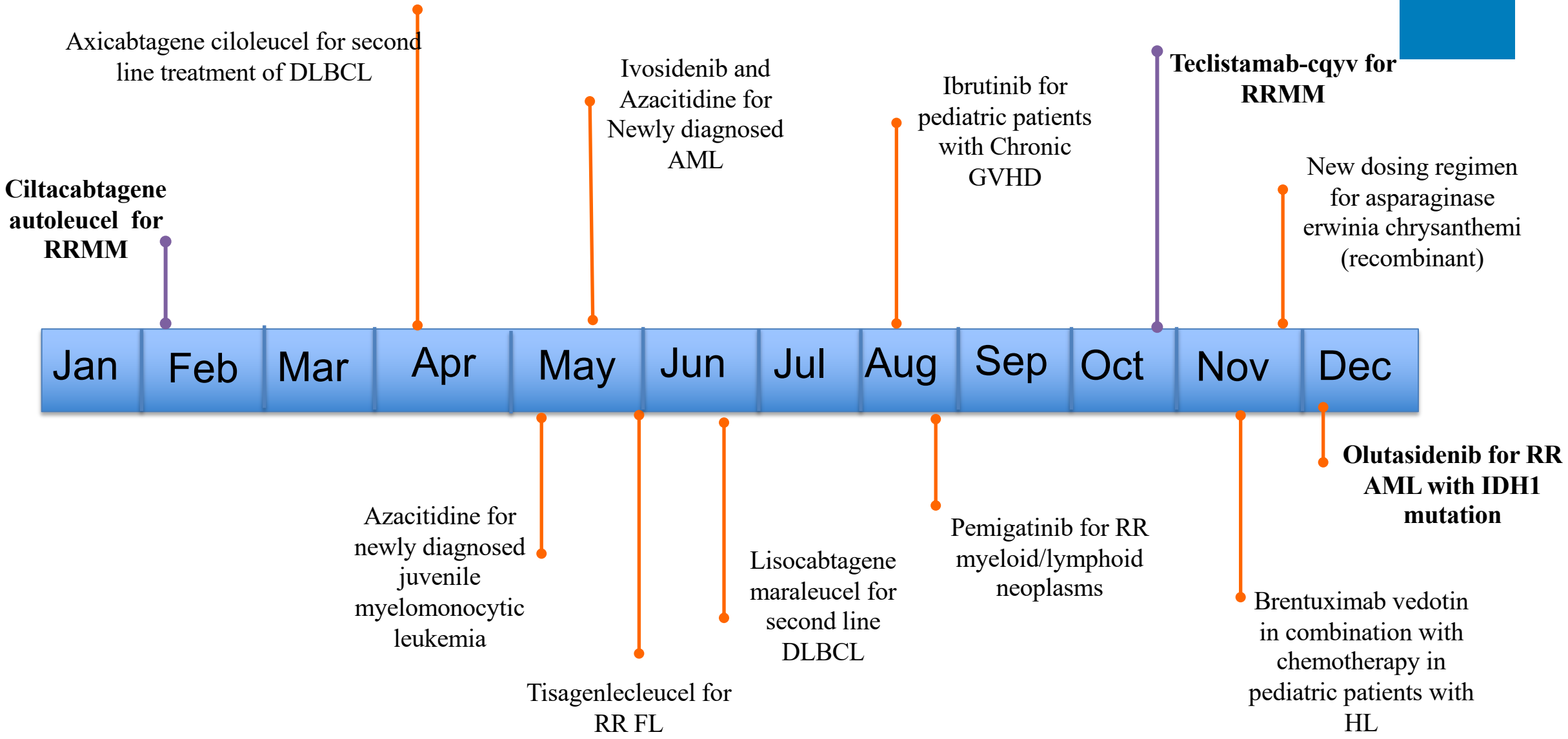
Slide courtesy: Nicholas Richardson, PI3K inhibitors ODAC

2020-2021 FDA Malignant Hematology Approvals*



AML: Acute Myeloid Leukemia, AL-Light chain; CLL: Chronic lymphocytic leukemia, ALCL: Anaplastic large cell lymphoma; ALL: Acute lymphoblastic leukemia; CML- Chronic myeloid leukemia, cGVHD: chronic graft versus host disease, FL: Follicular lymphoma, MM: multiple myeloma, MDS: Myelodysplastic syndrome, MCL: Mantle cell lymphoma; MZL: Marginal zone lymphoma; LBL: Lymphoblastic leukemia; SM: Systemic mastocytosis; WM: Waldenstroms macroglobulinemia, V: bortezomib, C: cyclophosphamide, d: dexamethasone; K: carfilzomib; P: pomalidomide. * See USPI for full indication; https: //www.fda.gov/drugs/resources-information-approved-drugs/oncology-cancer-hematologic-malignancies-approval-notifications

2022 FDA Malignant Hematology Approvals



AML: Acute Myeloid Leukemia, AL-Light chain; CLL: Chronic lymphocytic leukemia, ALL: Acute lymphoblastic leukemia; cGVHD: chronic graft versus host disease, FL: Follicular lymphoma, MM: multiple myeloma MCL: Mantle cell lymphoma; MZL: Marginal zone lymphoma; LBL: Lymphoblastic leukemia; SM: Systemic mastocytosis; WM: Waldenstroms macroglobulinemia, V: bortezomib, C: cyclophosphamide, d: dexamethasone; K: carfilzomib; P: pomalidomide

Resources

- Oncology Center of Excellence
  - https://www.fda.gov/about-fda/oncology-center-excellence/oce-annual-report
- OCE Programs
  - Project Socrates: https://www.fda.gov/about-fda/oncology-center-excellence/project-socrates-educational-network-oncology-product-development
  - Project Renewal: https://www.fda.gov/about-fda/oncology-center-excellence/project-renewal
  - Project Livin' Label: https://www.aacr.org/professionals/policy-and-advocacy/regulatory-science-and-policy/regulatory-science-and-policy-educational-activities/project-livin-label/
  - Project Orbis: https://www.fda.gov/about-fda/oncology-center-excellence/project-orbis
  - Project Equity: https://www.fda.gov/about-fda/oncology-center-excellence/project-equity
  - Project Community: https://www.fda.gov/about-fda/oncology-center-excellence/project-community
  - OCE Real World Evidence Program: https://www.fda.gov/about-fda/oncology-center-excellence/oncology-real-world-evidence-program
  - Project Facilitate: https://www.fda.gov/about-fda/oncology-center-excellence/project-facilitate
  - Project Confirm: https://www.fda.gov/about-fda/oncology-center-excellence/project-confirm
- Drug labels: https://www.accessdata.fda.gov/scripts/cder/daf/
- IND
  - https://www.fda.gov/drugs/types-applications/investigational-new-drug-ind-application
  - https://www.fda.gov/drugs/investigational-new-drug-ind-application/ind-application-procedures-overview
- NDA/BLA
  - https://www.fda.gov/drugs/types-applications/new-drug-application-nda
  - https://www.fda.gov/drugs/types-applications/therapeutic-biologics-applications-bla
- Expedited Programs
  - https://www.fda.gov/patients/learn-about-drug-and-device-approvals/fast-track-breakthrough-therapy-accelerated-approval-priority-review
- Expanded Access and Project Facilitate
  - https://www.fda.gov/patients/learn-about-drug-and-device-approvals/fast-track-breakthrough-therapy-accelerated-approval-priority-review
  - https://www.fda.gov/about-fda/oncology-center-excellence/project-facilitate

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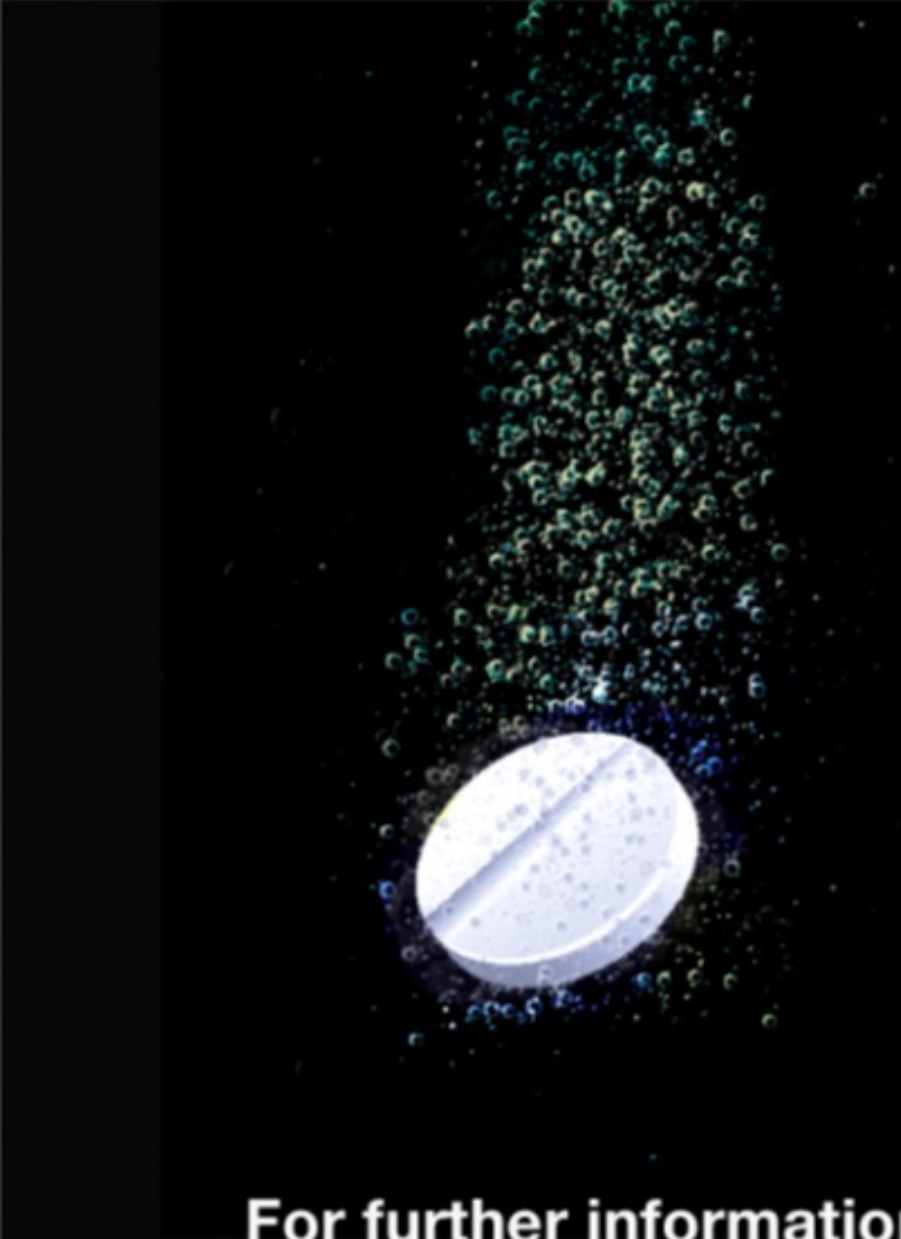
FDA Oncology Team

Patients and Physicians



One Pill. One Life. One Career.

One pill can transform a life.

One life can transform many.

One career can transform that pill,

that life, that many.

Transformative Careers. FDA Oncology.

For further information please email: futureofhemeonc@fda.hhs.gov