Keynote lecture: The need for dose optimization in early drug development

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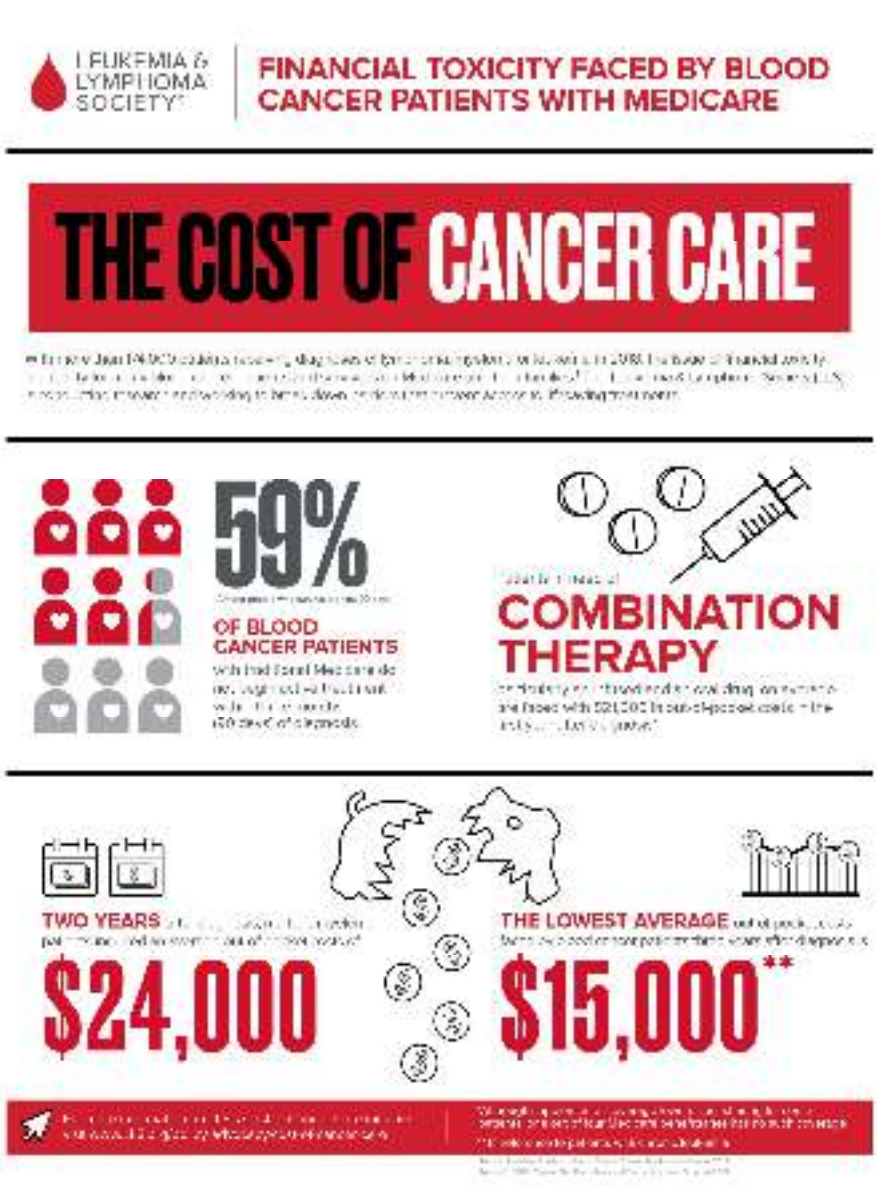
The University of Chicago
April 3, 2023

Mark J. Ratain, MD
Declaration of Relevant Interests

- **Treasurer and Co-Founder, Optimal Cancer Care Alliance (uncompensated)**
- **Patent litigation consulting and expert testimony on behalf of multiple generic companies regarding optimal dosing of anticancer drugs**

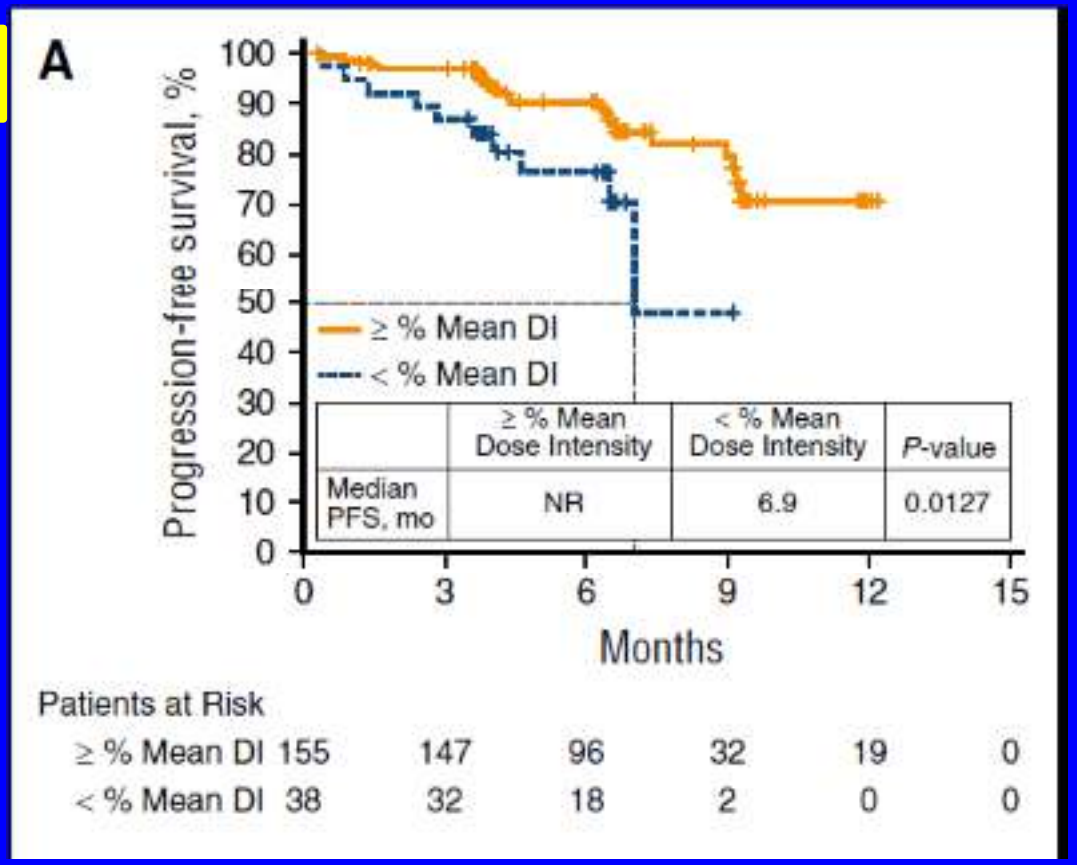
LACK OF DOSE OPTIMIZATION RESULTS IN UNNECESSARY MEDICAL AND FINANCIAL TOXICITIES



Lack of dose optimization of ibrutinib results in avoidable treatment interruptions and reduced efficacy

Barr, Blood, 2017

"Seventy-nine patients had dose holds for adverse events (AEs), 73 (92%) of whom restarted therapy at 420 mg consistent with United States Prescribing Information and European Union labels; 5 patients restarted at a lower dose, and 1 did not restart therapy prior to data cutoff."



Historical Oncology Drug Dosing Paradigm
(Based on the Inaccurate Assumption that More is Better)

1. Determine the maximal acceptable starting dose for a population of patients.
2. Reduce doses in individual patients based on adverse events.
3. Optimize "dose-intensity", rather than therapeutic index, or even efficacy.
   - If efficacy is impacted by dose interruptions for adverse events, then "less is more."

precision DEFINITIONS AND SYNONYMS

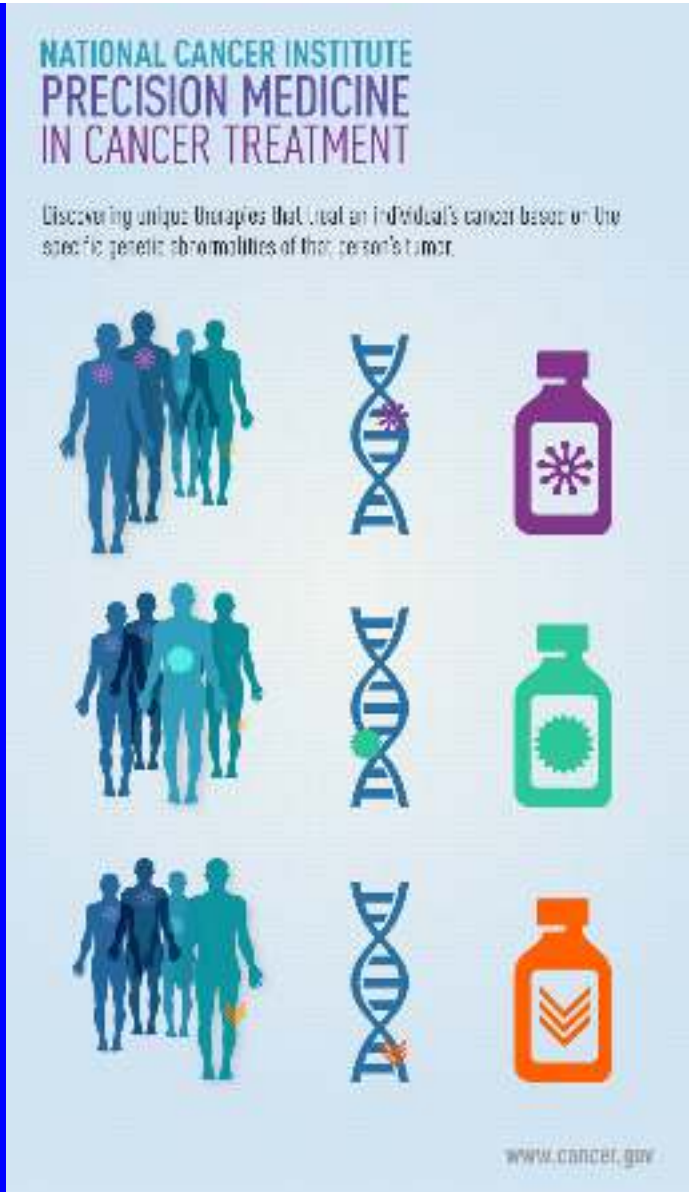
ADJECTIVE US /prɪˈsɪʒ(ə)n/

DEFINITIONS 1

1 very exact and accurate

precision machinery

https://www.macmillandictionary.com/us/dictionary/american/precision_2



Irish Examiner

Precision

November 30, 2018

Cutting edge: Why robotic surgery is the future

Robots are playing a greater role in Irish hospitals, delivering precision operations, with minimal blood loss and shorter recovery times for patients, says **Áilín Quinlan.**

FRI, 30 NOV, 2018 - 00:00

Irish Examiner

Precision ≠ Accuracy

December 11, 2020

Surgeons operate on the wrong body part 63 times in Irish hospitals

file image

MON, 21 DEC, 2020 - 09:10

Precise – but not Accurate

Table 1 XELODA Dose Calculation According to Body Surface Area

Dose Level 1250 mg/m^2 Twice a Day		Number of Tablets to be Taken at Each Dose (Morning and Evening)	
Surface Area (m^2)	Total Daily Dose* (mg)	150 mg	500 mg
≤ 1.25	3000	0	3
1.26-1.37	3300	1	3
1.38-1.51	3600	2	3
1.52-1.65	4000	0	4
1.66-1.77	4300	1	4
1.78-1.91	4600	2	4
1.92-2.05	5000	0	5
2.06-2.17	5300	1	5
≥ 2.18	5600	2	5

*Total Daily Dose divided by 2 to allow equal morning and evening doses

From 2015 label

https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020896s037lbl.pdf

Accurate – but not Precise

2.2 Recommended Dosage for Breast Cancer

Advanced or Metastatic Breast Cancer

Single Agent

The recommended dosage of XELODA is 1,000 mg/m^2 or 1,250 mg/m^2 orally twice daily for the first 14 days of a 21-day cycle until disease progression or unacceptable toxicity. Individualize the dose and dosing schedule of XELODA based on patient risk factors and adverse reactions.

From current label, revised December 2022

https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/020896s044s045s046s047s048s049s050s051lbl.pdf

Potential Benefits of Using an Accurate Lower Dose

- Reduction in the frequency and/or severity of adverse events
- Improvement in efficacy
  - Reduced treatment interruption for adverse events
  - Better patient adherence
- Reduction in costs
  - Indirect cost of adverse events
  - Direct cost of drugs (in post-marketing setting only)

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

DOSE-RESPONSE INFORMATION TO SUPPORT DRUG REGISTRATION

E4

Current *Step 4* version

dated 10 March 1994

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

DOSE-RESPONSE INFORMATION TO SUPPORT DRUG REGISTRATION

E4

Current *Step 4* version

dated 10 March 1994

8 months later

MONDAY, NOVEMBER 14, 1994 PAGE 6

THE NEW YORK TIMES **INTERNATIONAL** MONDAY, NOVEMB

Swedes Vote in Referendum To Join the European Union

From ICH E4, 1994

Dose-Response Assessment Should Be an Integral Part of Drug Development

Assessment of dose-response should be an integral component of drug development with studies designed to assess dose-response an inherent part of establishing the safety and effectiveness of the drug. If development of dose-response information is built into the development process it can usually be accomplished with no loss of time and minimal extra effort compared to development plans that ignore dose-response.

Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact Mirat Shah at 301-796-8547 or Stacy Shord at 301-796-6261.

U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
January 2023
Clinical/Medical

Atkins, JCO, 2004

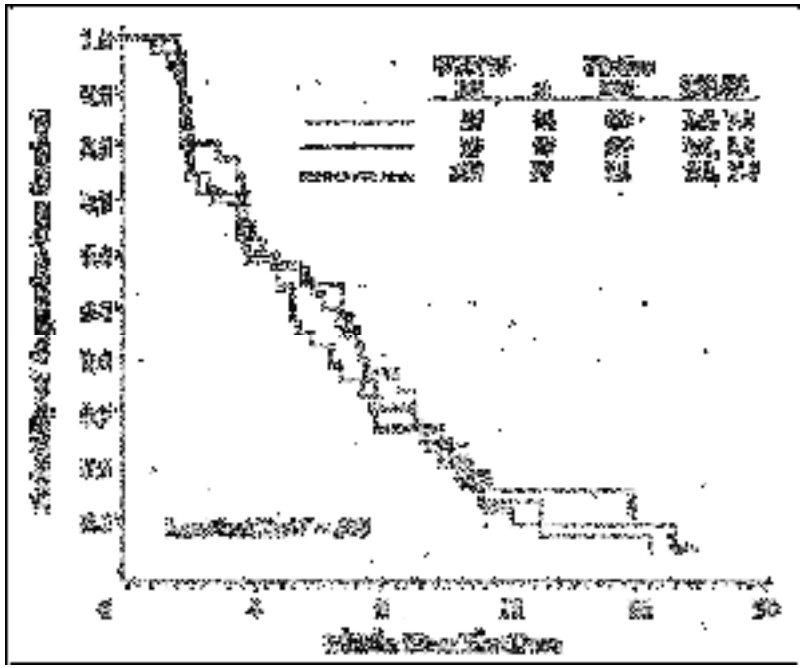


Fig 1. Time to tumor progression for renal cell carcinoma patients in the 25-, 75-, and 250-mg CCI-779 dose groups. mos, months.

- The recommended dose of TORISEL is 25 mg administered as an intravenous infusion over a 30-60 minute period once a week. Treat until disease progression or unacceptable toxicity. (2.1)

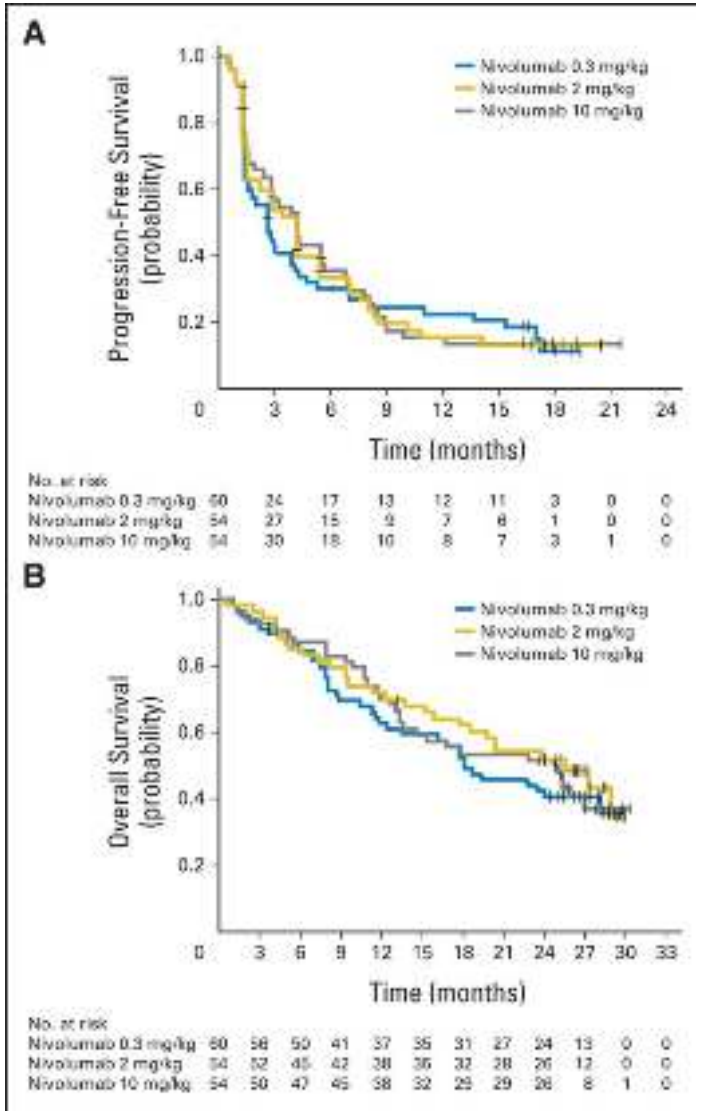
Motzer, JCO, 2015

Nivolumab for metastatic renal cell carcinoma: results of a randomized phase II trial

Flat dose-response over range of 0.3-10 mg/kg q3w

DOSAGE AND ADMINISTRATION

Administer 3 mg/kg as an intravenous infusion over 60 minutes every 2 weeks. (2.1)



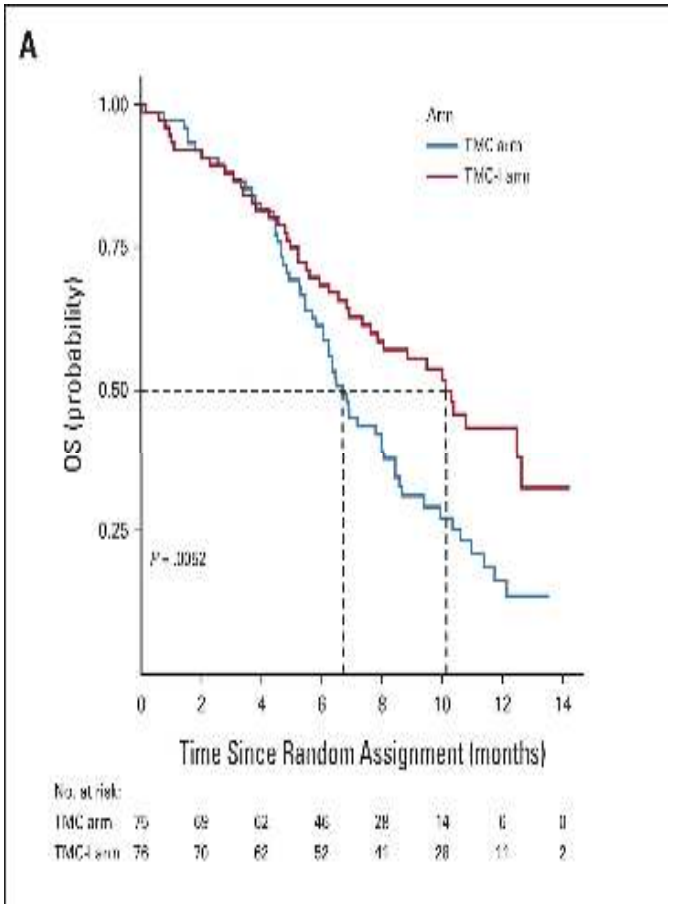
Patil, JCO, 2022

Low-dose (20 mg q3w) nivolumab for advanced head and neck cancer, combination with chemotherapy (TMC)

Original sample size 184 patients; study stopped early based on interim analysis.

No difference in grade 3-4 adverse events (50%, TMC; 46% TMC-I)

FIG 2. (A) OS graph. The P value shown is from the log-rank test.



OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC MEMO

Application Number	NDA 205552
Submission Number (Date)	Original-2 (06/28/2013)
Compound	Ibrutinib
Dosing regimen	420 mg QD (Chronic Lymphocytic Leukemia)
Clinical Division	DHP
Primary PM Reviewer	Bahru A Habtemariam, Pharm.D.
Clinical Pharmacology Team Leader	Julie M. Bullock, Pharm. D.
Secondary PM Reviewer	Anshu Marathe, Ph.D.

Is the proposed dose of 420 mg QD in CLL patients appropriate?

However, the proposed dose is 2.4-fold higher than the lowest dose that resulted in maximum BTK occupancy and maximum clinical response. Dose-response relationship for ORR and BTK occupancy from Phase 1 study suggested that maximum ORR and maximum occupancy was achieved at doses of ≥ 2.5 mg/kg (≥ 175 mg for average weight of 70 kg) [see Pharmacometrics review in DARRTS dated 11/01/2013. The sponsor should thus consider exploring lower doses in future development programs.

p. 4 of 2014 Office of Clinical Pharmacology Pharmacometric Memo

Redefining the Phase 1-2 Strategy

1. Primary objective of "phase 1" is to determine a range of doses for a randomized dose-ranging "phase 2" study.
2. Upper bound constrained by toxicity.
3. Lower bound ideally identified based on tumor-related biomarkers (*e.g.*, radiographic size, ctDNA, serum biomarkers).
4. Optimal dose based on global assessment of dose/exposure-efficacy/toxicity relationships in randomized dose-ranging studies, with a focus on accuracy rather than precision.

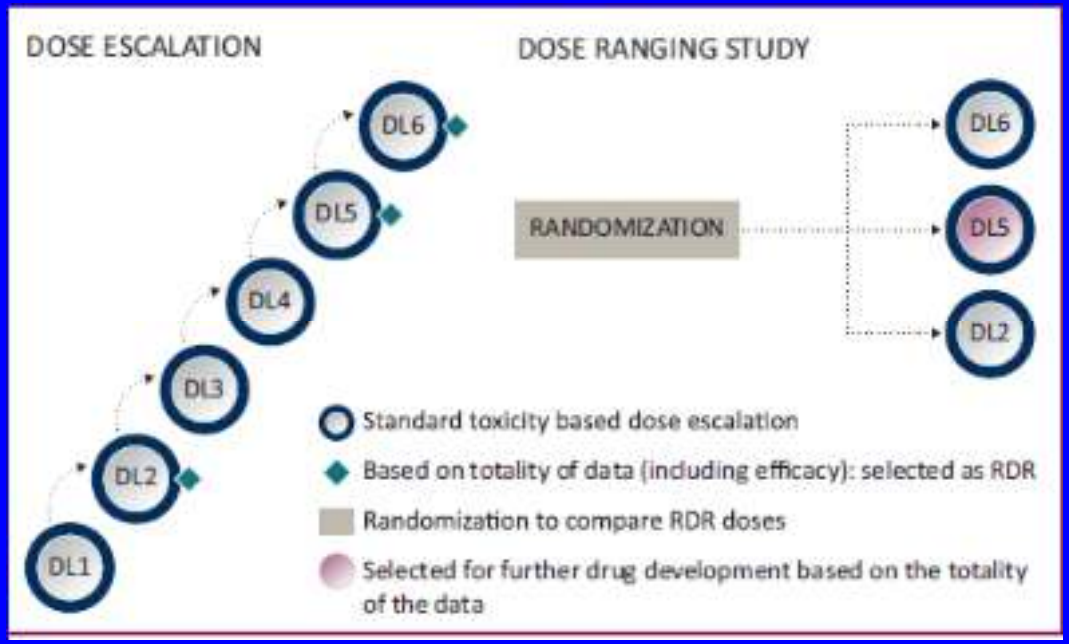
ESMO

ANNALS OF ONCOLOGY

REVIEW

Oncology phase I trial design and conduct: time for a change - MDICT Guidelines 2022

D. Araujo[1], A. Greystoke[2], S. Bates[3], A. Beyle[4], E. Calvo[5], L. Castelo-Branco[6], J. de Bono[7,8], A. Drilon[9], E. Garralda[10], P. Ivy[11], O. Kholmanskikh[12,13], I. Melero[14], G. Penthenoudakis[15], J. Petrie[16], R. Plummer[2], S. Ponce[4], S. Postel-Vinay[4], L. Siu[16], A. Spreafico[16], A. Stathis[17], N. Steeghs[18], C. Yap[7], T. A. Yap[19], M. Retain[20] & L. Seymour[1,*]



EXPLANATORY STATEMENT FOR AGRICULTURE, RURAL DEVELOPMENT, FOOD AND DRUG ADMINISTRATION, AND RELATED AGENCIES APPROPRIATIONS BILL, 2023

OVERVIEW AND SUMMARY OF THE BILL

RELEASED 7/28/2022

TITLE VI

RELATED AGENCY AND FOOD AND DRUG ADMINISTRATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

Dosing Optimization Studies.—The Committee is concerned about the escalating cost of specialty cancer drugs and biologics. One issue is the common approach for sponsors to pursue labels at the maximum tolerated dose, despite the high cost, and which often results in significant side effects. The Committee notes that several studies have demonstrated cost savings from alternate dosing strategies for oncology medications, without impacting the efficacy of the treatment. The Committee acknowledges FDA's recent premarket dose selection efforts under Project Optimus, led by the Oncology Center of Excellence [OCE]. The Committee strongly encourages FDA to organize clinical trials, in collaboration with academic medical centers and other Federal agencies, of marketed cancer drugs and biologics to assess whether dosing and frequency adjustments may decrease the cost of care and/or toxicities of treatment without compromising efficacy.

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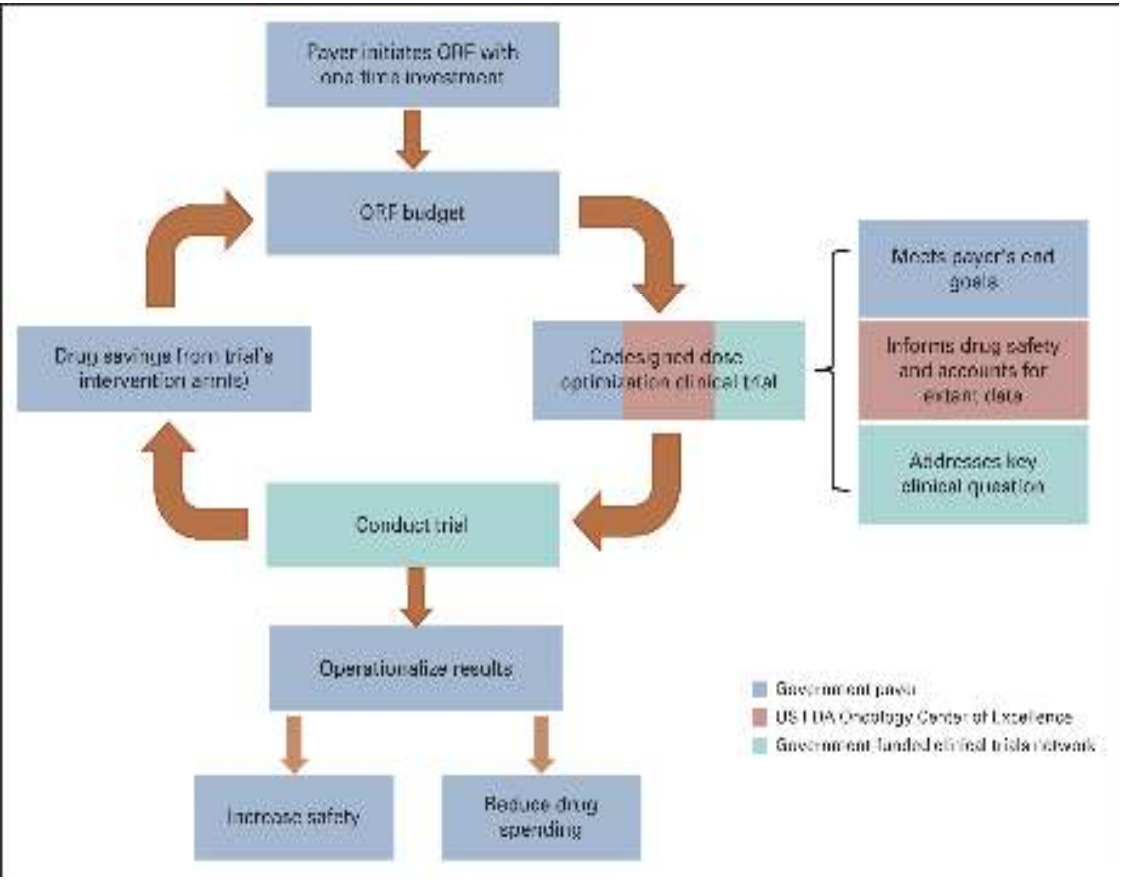
US Government Payer–Funded Trials to Address Oncology's Drug-Dosing Conundrum: A Congressional Call to Action?

Strohbehn, JCO, 2023



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ANNALS OF ONCOLOGY

EDITORIAL

A revolving research fund to study efficient use of expensive drugs: big wheels keep on turning

van Ommen-Nijhof, Ann Oncol, 2021

POLITICS

STAT+

Califf criticizes insurers for doing too little on drug research

By John Wilkerson March 16, 2023

Reprints

FDA Commissioner Robert Califf wants insurers to help with drug research. It's a new request for an old initiative to find new ways to test drugs.

MANUEL BALCE CENETA/AP

WASHINGTON — FDA Commissioner Robert Califf wants private insurers to chip in on doing post-approval clinical research on drugs. It's a new request from the agency chief, who's long pushed to find new ways to test drugs.

Summary

1. Toxicity-based dosing regimens are inappropriate for most modern oncology drugs.
2. Precise dosing of most oncology drugs is unimportant.
3. Randomized dose-ranging trials with reproducible biomarker endpoints (e.g., tumor size) are required to determine the optimal dose.
4. Post-marketing dose optimization studies could be funded by payers, since such trials have no (or even a negative) net cost.


R.I.P.
STUPID
MTD
I'M WITH
STUPID
BSA