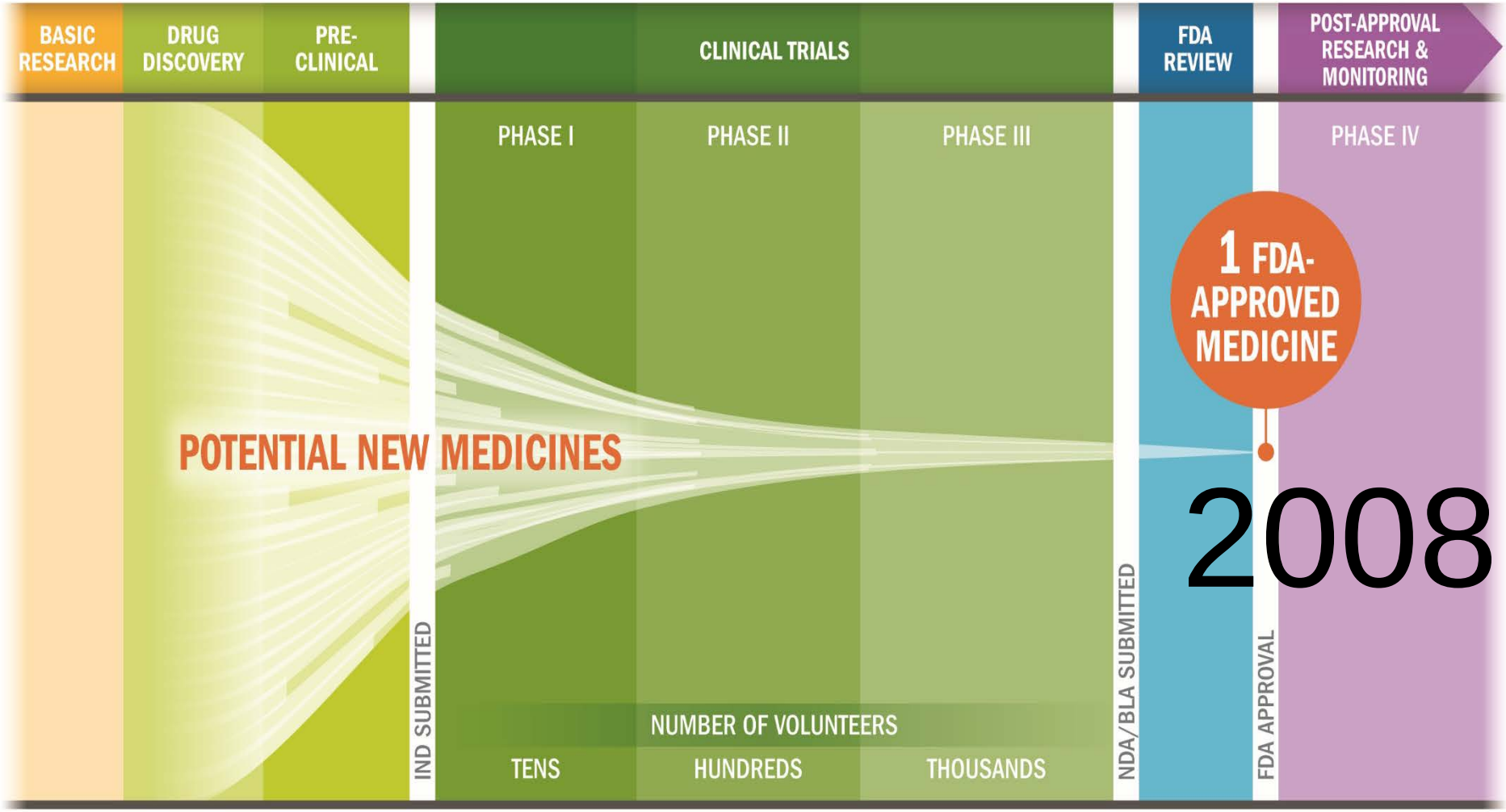
Study designs/approaches to early phase therapeutic development – pharmacology perspective

Michael Maitland, MD, PhD
Professor, Dept of Medicine, University of Virginia
Medical Oncologist, Inova Schar Cancer Institute
January 22, 2021

UNIVERSITY of VIRGINIA
SCHOOL OF MEDICINE

INOVA
Join the future of health.

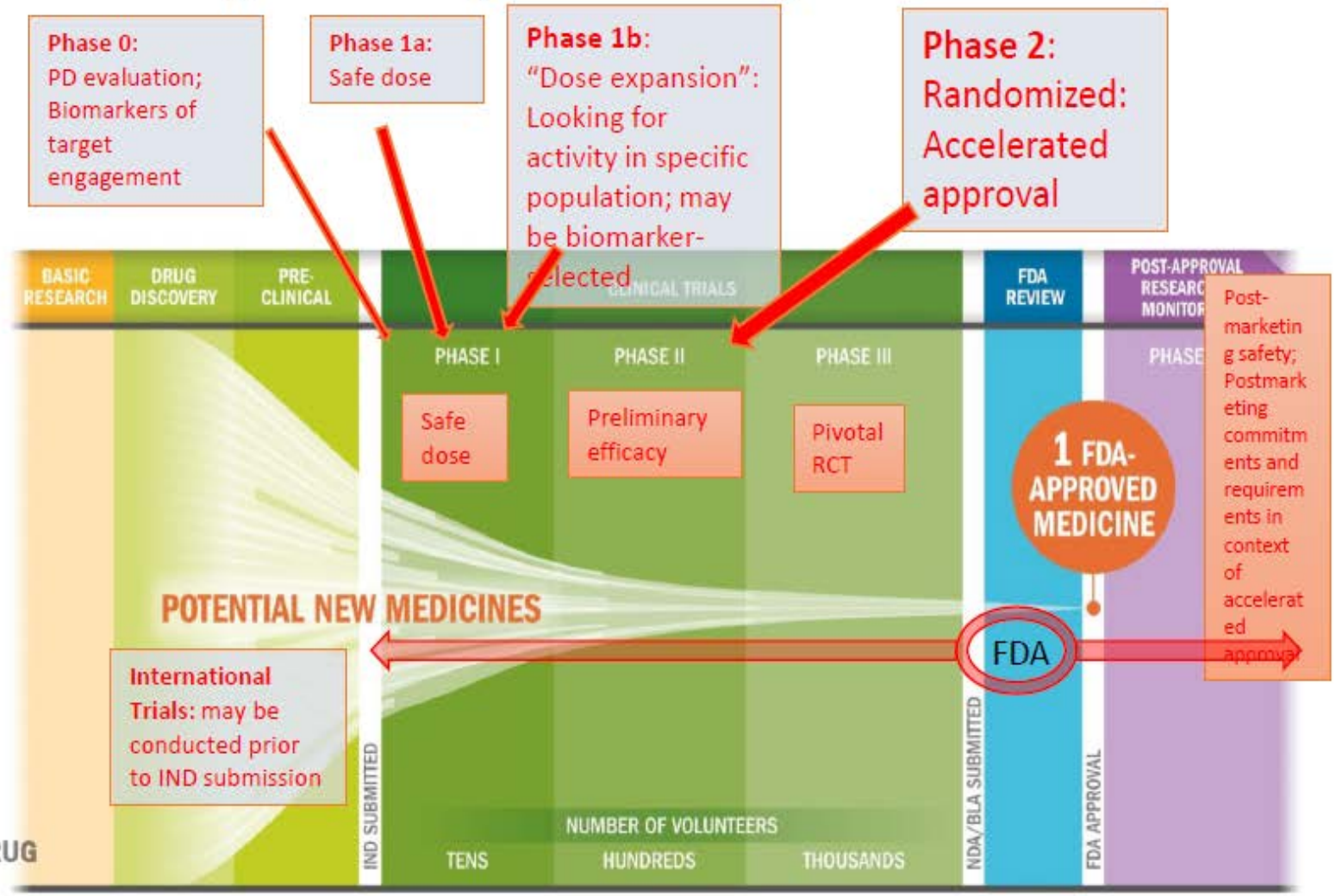
THE BIOPHARMACEUTICAL RESEARCH AND DEVELOPMENT PROCESS



2018, courtesy of Tina Annunziata, NCI

INOVA
Join the future of health.

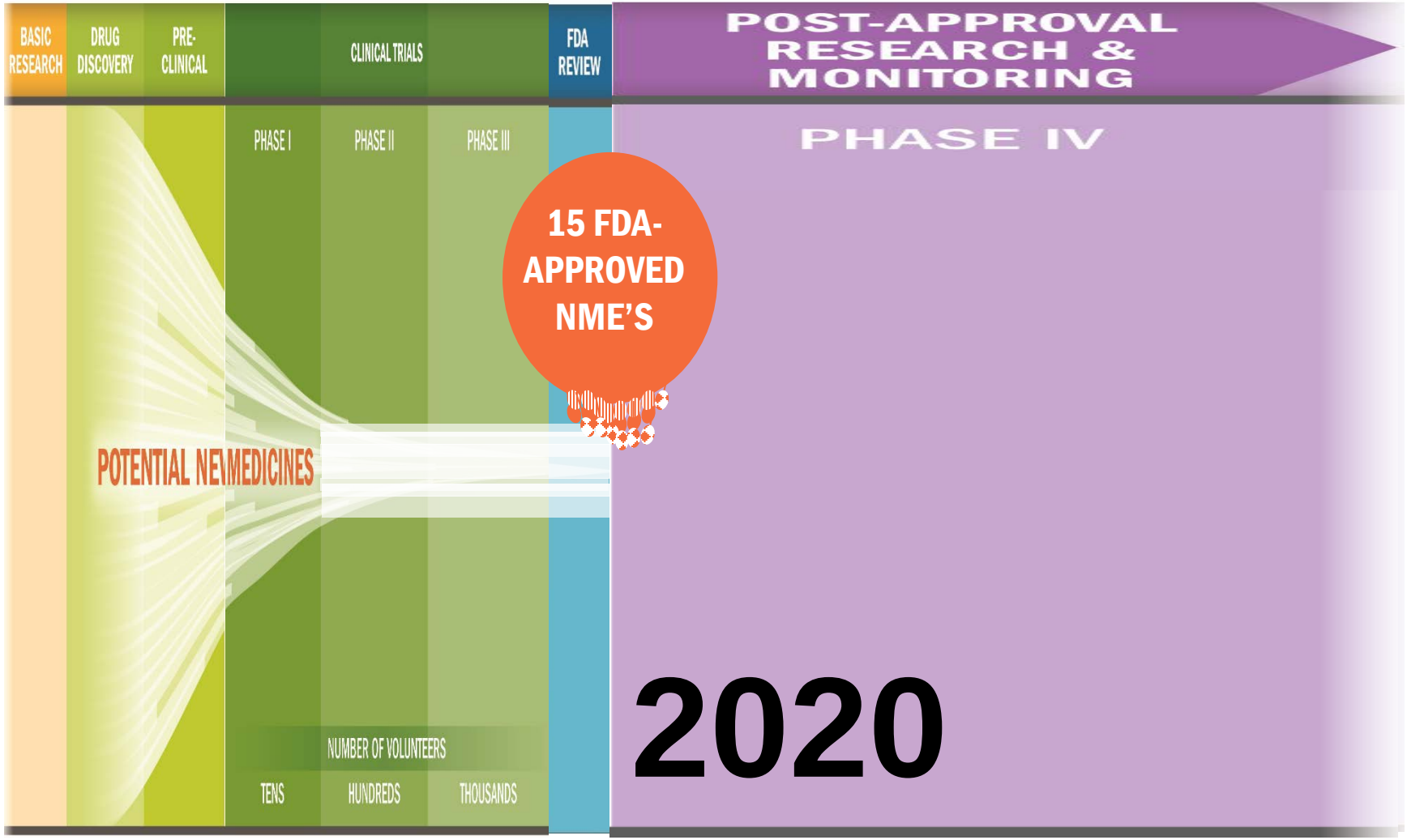
Clinical Regulatory Pathway: Now



FDA U.S. FOOD & DRUG ADMINISTRATION

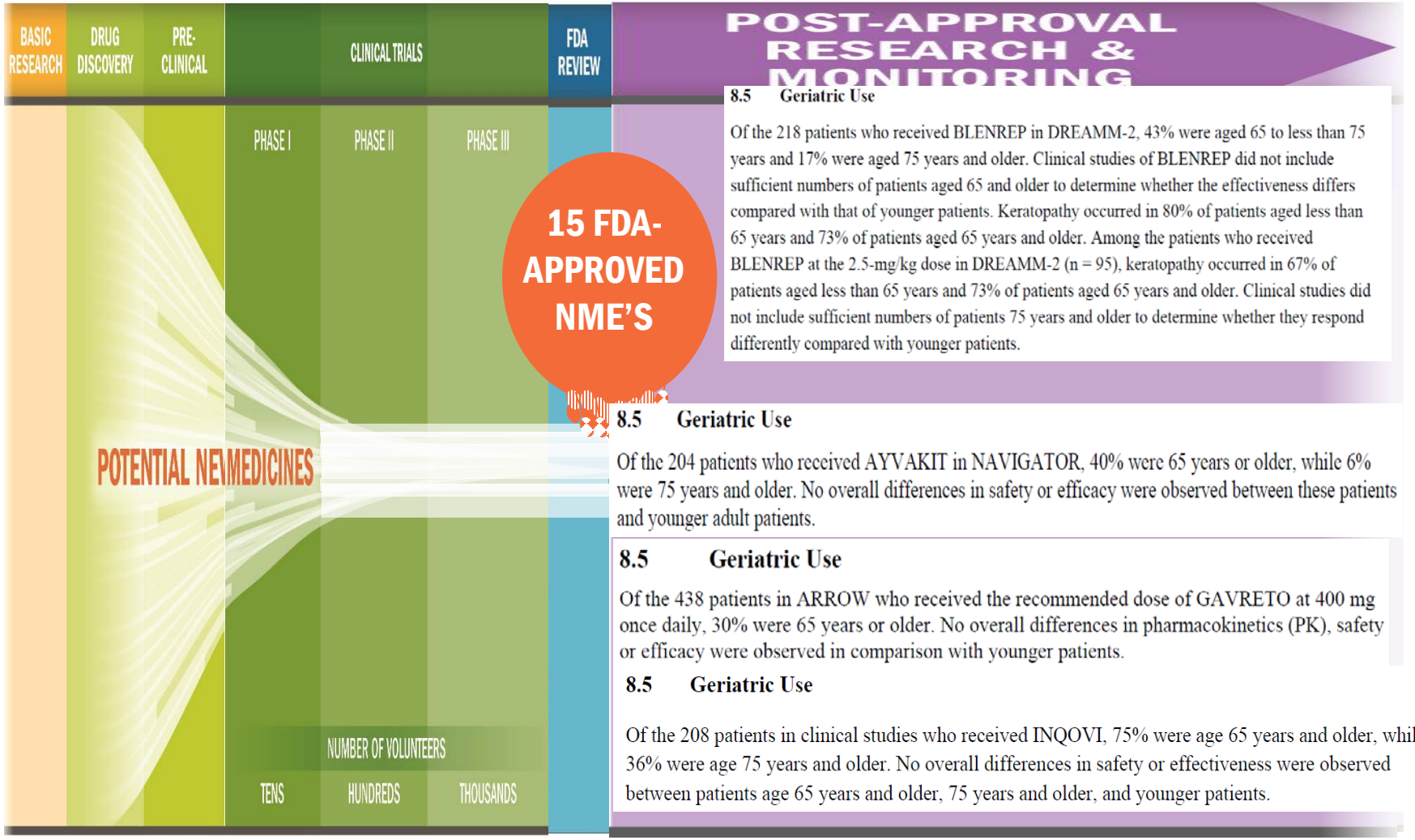
Current state of cancer therapeutics

INOVA
Join the future of health.



Current state of geriatric pop info

INOVA
Join the future of health.



8.5 Geriatric Use

Of the 218 patients who received BLENREP in DREAMM-2, 43% were aged 65 to less than 75 years and 17% were aged 75 years and older. Clinical studies of BLENREP did not include sufficient numbers of patients aged 65 and older to determine whether the effectiveness differs compared with that of younger patients. Keratopathy occurred in 80% of patients aged less than 65 years and 73% of patients aged 65 years and older. Among the patients who received BLENREP at the 2.5-mg/kg dose in DREAMM-2 (n = 95), keratopathy occurred in 67% of patients aged less than 65 years and 73% of patients aged 65 years and older. Clinical studies did not include sufficient numbers of patients 75 years and older to determine whether they respond differently compared with younger patients.

8.5 Geriatric Use

Of the 204 patients who received AYVAKIT in NAVIGATOR, 40% were 65 years or older, while 6% were 75 years and older. No overall differences in safety or efficacy were observed between these patients and younger adult patients.

8.5 Geriatric Use

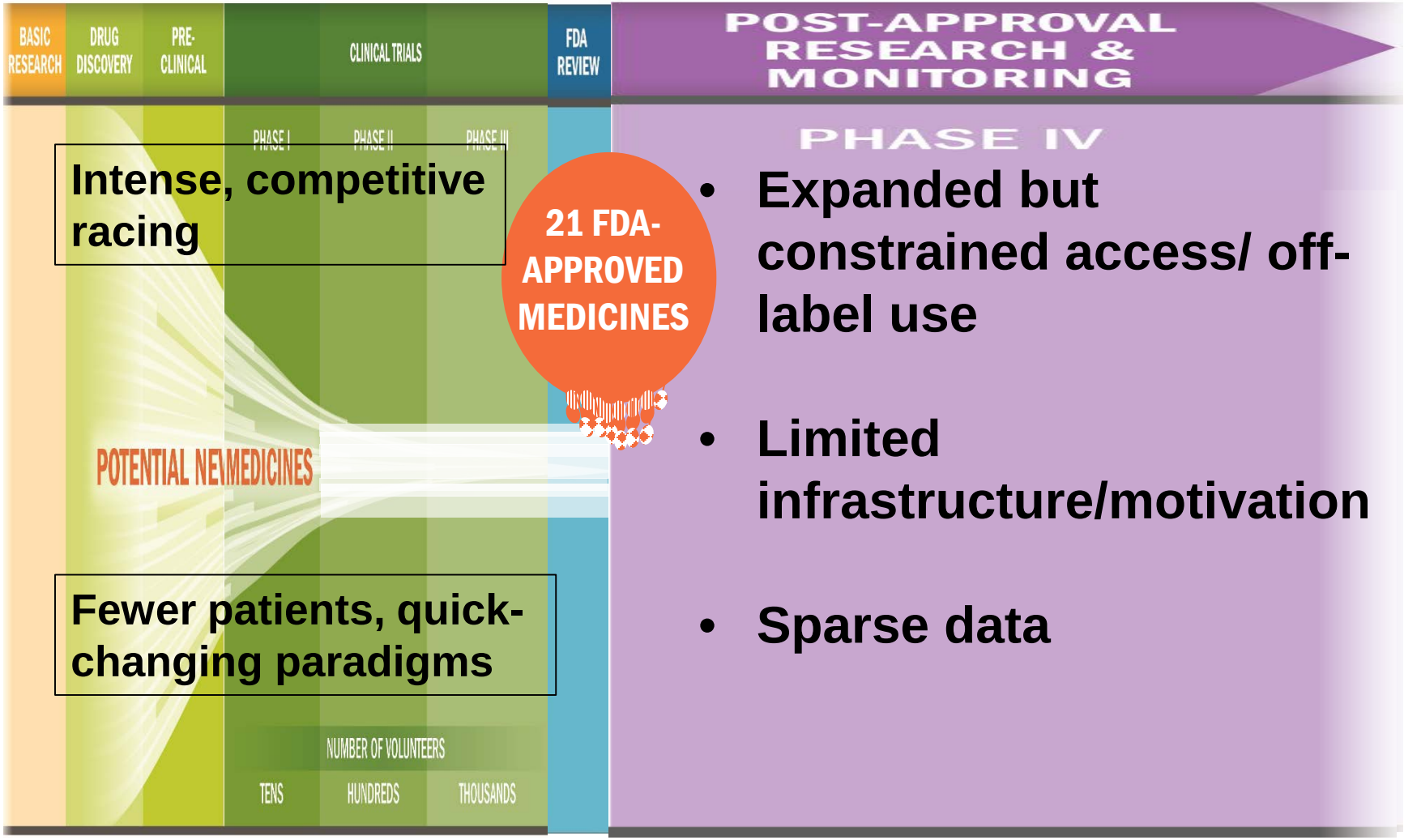
Of the 438 patients in ARROW who received the recommended dose of GAVRETO at 400 mg once daily, 30% were 65 years or older. No overall differences in pharmacokinetics (PK), safety or efficacy were observed in comparison with younger patients.

8.5 Geriatric Use

Of the 208 patients in clinical studies who received INQOVI, 75% were age 65 years and older, while 36% were age 75 years and older. No overall differences in safety or effectiveness were observed between patients age 65 years and older, 75 years and older, and younger patients.

WHEN/HOW to STUDY OLDER PTS?

INOVA
Join the future of health.



- Expanded but constrained access/ off-label use
- Limited infrastructure/motivation
- Sparse data

What do we need to know?

- appropriate initial dose for this patient
- how soon will intended effect start
- how long will it last
- will tolerance/resistance develop
- what happens if patient misses some doses
- chances that initial dose will have to be altered
- what do I follow to see if dose needs to be altered
- how do I alter it: how long do I wait to re-evaluate, what increments are suggested

Sheiner, “Learning vs. confirming in clinical drug development” *Clin Pharmacol Ther* ’97

Lyauk, “Dose Finding in the Clinical Development of 60 US Food and Drug Administration-Approved Drugs Compared With Learning vs. Confirming Recommendations.” *Clin Transl Sci* ‘19

Move beyond age to predictors

INOVA
Join the future of health.

Table 1. Prediction Model and Scoring Algorithm for Chemotherapy Toxicity

Variable	Value/Response	Score
Age of patient	≥ 72 years	2
	< 72 years	0
Cancer type	GI or GU cancer	2
	Other cancer types	0
Planned chemotherapy dose	Standard dose	2
	Dose reduced upfront	0
Planned No. of chemotherapy drugs	Polychemotherapy	2
	Monochemotherapy	0
Hemoglobin	< 11 g/dL (male), < 10 g/dL (female)	3
	≥ 11 g/dL (male), ≥ 10 g/dL (female)	0
Creatinine clearance (Jeliffe, ideal weight)	< 34 mL/min	3
	≥ 34 mL/min	0
How is your hearing (with a hearing aid, if needed)?	Fair, poor, or totally deaf	2
	Excellent or good	0
No. of falls in the past 6 months	≥ 1	3
	None	0
Can you take your own medicine?	With some help/unable	1
	Without help	0
Does your health limit you in walking one block?	Somewhat limited/limited a lot	2
	Not limited at all	0
During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc)?	Limited some of the time, most of the time, or all of the time	1
	Limited none of the time or a little of the time	0

Hurria, Mohile, et al *J Clin Oncol*'16

Age

Disease type

Intensity/complexity of planned treatment

Bone marrow reserve/ nutritional status

Kidney function

Hearing

Balance/coordination

Functional independence

Endurance/fitness

Overall social/physical well-being self-assessment

Innovative design 1

PHASE I, II, or I/II
LETTER OF INTENT
Submission Form v6.0

National Cancer Institute
Division of Cancer Treatment and Diagnosis
Cancer Therapy Evaluation Program

To complete the form electronically, use the mouse pointer or the Tab key to navigate. Select and enter text for each text field.

Lead Group/Institution:	University of Chicago
Lead Group/Institution Code[1]:	IL057
Other Trial Team Sites[1]:	City of Hope Comprehensive Cancer Center University of North Carolina Lineberger Comprehensive Cancer Center
Title of LOI :	Geriatric Assessment and Pharmacokinetics (GAP) Study of Eribulin in Elderly Cancer Patients- LOI 9961
LOI Version Submission Date:	**April 24, 2015**

AGE	< 70	≥ 70				
Organ function	Nl org function	Nl org function (nl hepatic, nl/ mild renal)	Mild hepatic	Moderate renal	Mild hepatic	Moderate renal
Geriatric As'sment	n/a	Nl risk	Nl risk	Nl risk	Incr'd risk	Incr'd risk
Cycle 0 (initial dose, PK and 14 day observation)	1.1mg/m^2					
C1 D1&8 Dose level 1	1.4mg/^{2}	1.4mg/m^2	1.1mg/m^2	1.1mg/m^2	1.1mg/m^2	1.1mg/m^2

Innovative design 1

PHASE I, II, or I/II
LETTER OF INTENT
Submission Form v6.0

National Cancer Institute
Division of Cancer Treatment and Diagnosis
Cancer Therapy Evaluation Program

To complete the form electronically, use the mouse pointer or the Tab key to navigate. Select and enter text for each text field.

Lead Group/Institution:	University of Chicago
Lead Group/Institution Code[1]:	IL057
Other Trial Team Sites[1]:	City of Hope Comprehensive Cancer Center University of North Carolina Lineberger Comprehensive Cancer Center
Title of LOI :	Geriatric Assessment and Pharmacokinetics (GAP) Study of Eribulin in Elderly Cancer Patients- LOI 9961
LOI Version Submission Date:	**April 24, 2015**

Treatment Plan: *(State the dose, method of administration, and schedule of each drug, and, if phase 1, provide the dose escalation scheme, and definitions of DLTs. State the duration of treatment, the duration of the study, and the duration of follow-up.)*

All patients will undergo geriatric assessment with the patient-administered and health care team-administered standardized assessment tools at http://www.mycarg.org/SelectQuestionnaire. All responses will be recorded and submitted to the investigator team after informed consent, at the time of registration. The registrar will enter the information and require additional information from the study team to compute the Chemotherapy Toxicity Predictive Model Risk Score (at http://www.mycarg.org/Chemo_Toxicity_Calculator) and determine the cohort assignment for the patient.

Mild Hepatic Dysfunction will be defined as: bilirubin >1.5 mg/dL(and $\leq$ 3 mg/dL) and/or serum albumin <3.5 mg/dL(and $\geq$ 2.8 mg/dL)

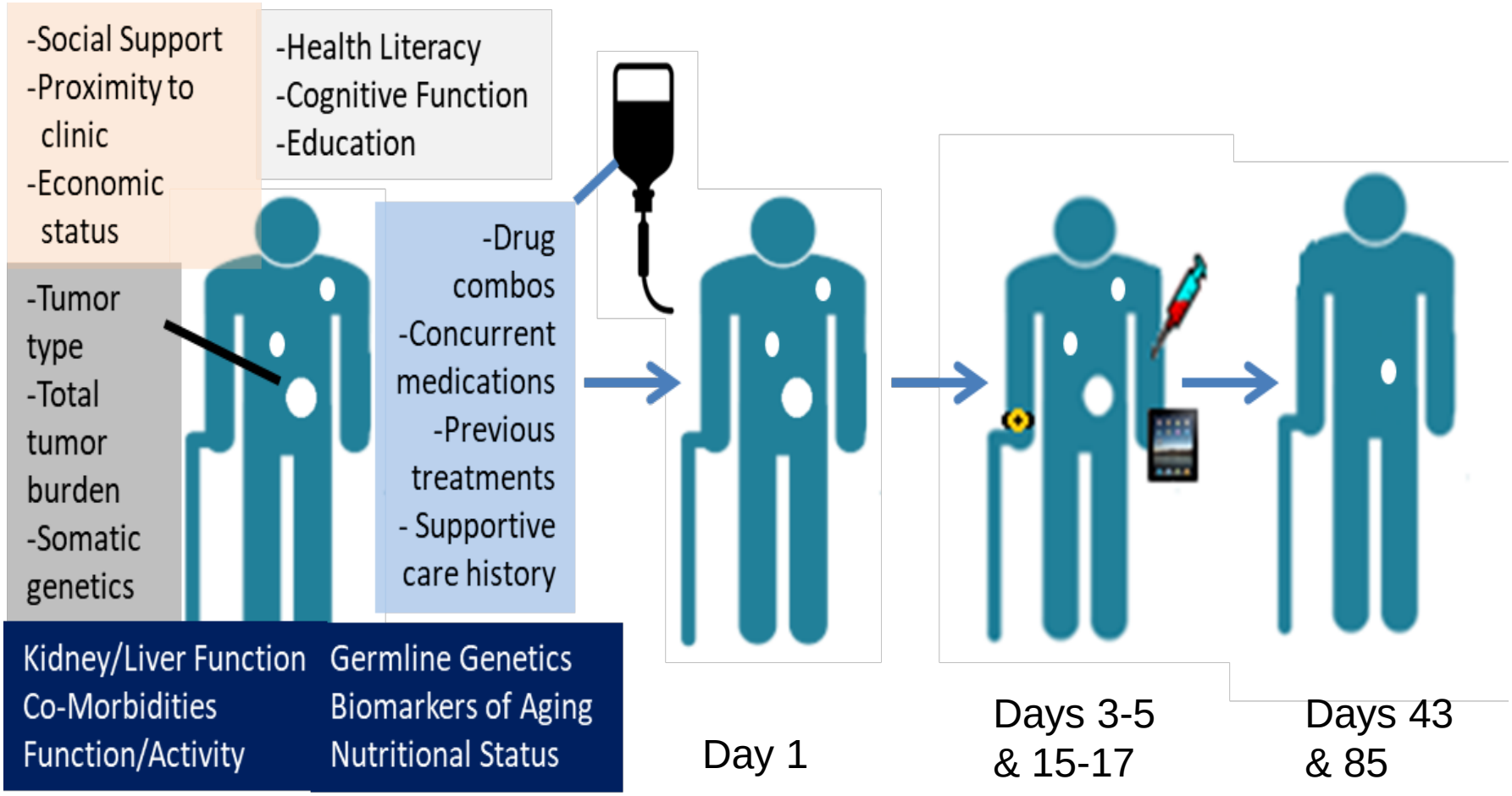
Moderate Renal Dysfunction will be defined as: Cockcroft-Gault calculated GFR 30-50 ml/min without adjustments for BSA

Incr'd risk from Geriatric Assessment will be defined as: Chemotherapy Toxicity Predictive Model (CTPM) score $\geq$ 6

All patients will receive a run-in dose/pharmacokinetics evaluation at an initial dose of 1.1mg/m^2 (Cycle 0). After a 14 day observation period, treatment at the indicated dose will commence (Cycle 1). Patients who complete all screening and pharmacokinetics assessments and either complete Cycle 1 or experience a DLT before completing Cycle 1 will be considered evaluable.

In order to ensure patient safety we will follow a "3+6" design within groups 5 and 6 (elderly, increased risk cohorts), i.e., we will first enroll 3 patients and if 0 or 1 DLTs are observed we will add the remaining 6 patients at the same dose level. However if more than 2 of 3 or more than 3 of 9 (>33%) have DLT, we will consider the dose to be too toxic for that group. An additional expansion group of up to 6 patients will then be tested at the 0.7mg/m^2 dose.

Scientifically personalizing taxane therapy for geriatric cancer patients a UVACC pilot study



Study designs/approaches to early phase therapeutic development – pharmacology perspective

- Clinical Pharmacology!
- The next level- more and better data
- Innovation in interdisciplinary research…

- Not an issue of not enough patients
- Insufficient representative diversity of patients
  - Missing heterogeneity
  - Missing determination of the specific predictors
- Not a scientific challenge
- An engineering/operations/culture challenge
- Need to design proper “learning trials” and intentionally capture the diversity to generate worthwhile and testable hypotheses
- Dedicated academic trials- enhance safety with teamwork among geriatrics and drug development oncology
-