Person-centeredness in Early Phase Clinical Cancer Research

Dr. Shivaani Kummar
Associate CEO, Knight Cancer Institute
Margaret and Lester DeArmond Chair of Molecular Oncology
Professor & Head, Division of Hematology & Medical Oncology
Co-Director, Center for Experimental Therapeutics
Oregon Health and Science University (OHSU)

OHSU

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Disclosure Information

Shivaani Kummar

I have the following relevant financial relationships to disclose:

- Consultant/Advisory board: Springworks Therapeutics, SeaGen, Bayer, Genome & Company, HarbourBiomed, BPGbio Therapeutics, Oxford Biotherapeutics, Mundibiopharma, BPGbio, Inc., Gilead, Mirati; Fortress Biotech, Inc, GI Innovation Inc, XYone Therapeutics, Genome Insight, Aadi Biosciences, MOMA Therapeutics.

- PATHOMIQ (co-founder); Sift Biosciences (equity)

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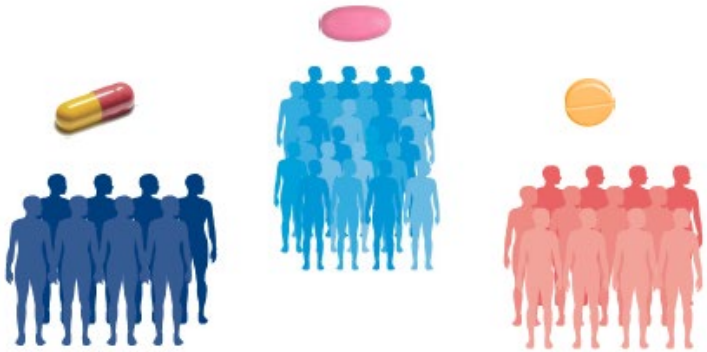
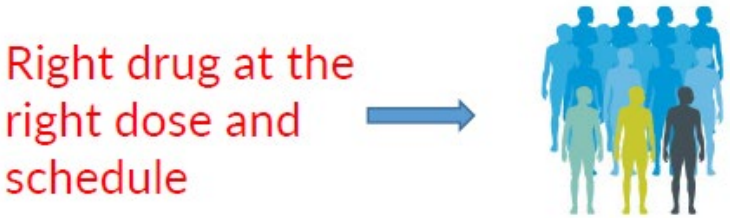
Evolution of Phase I trials

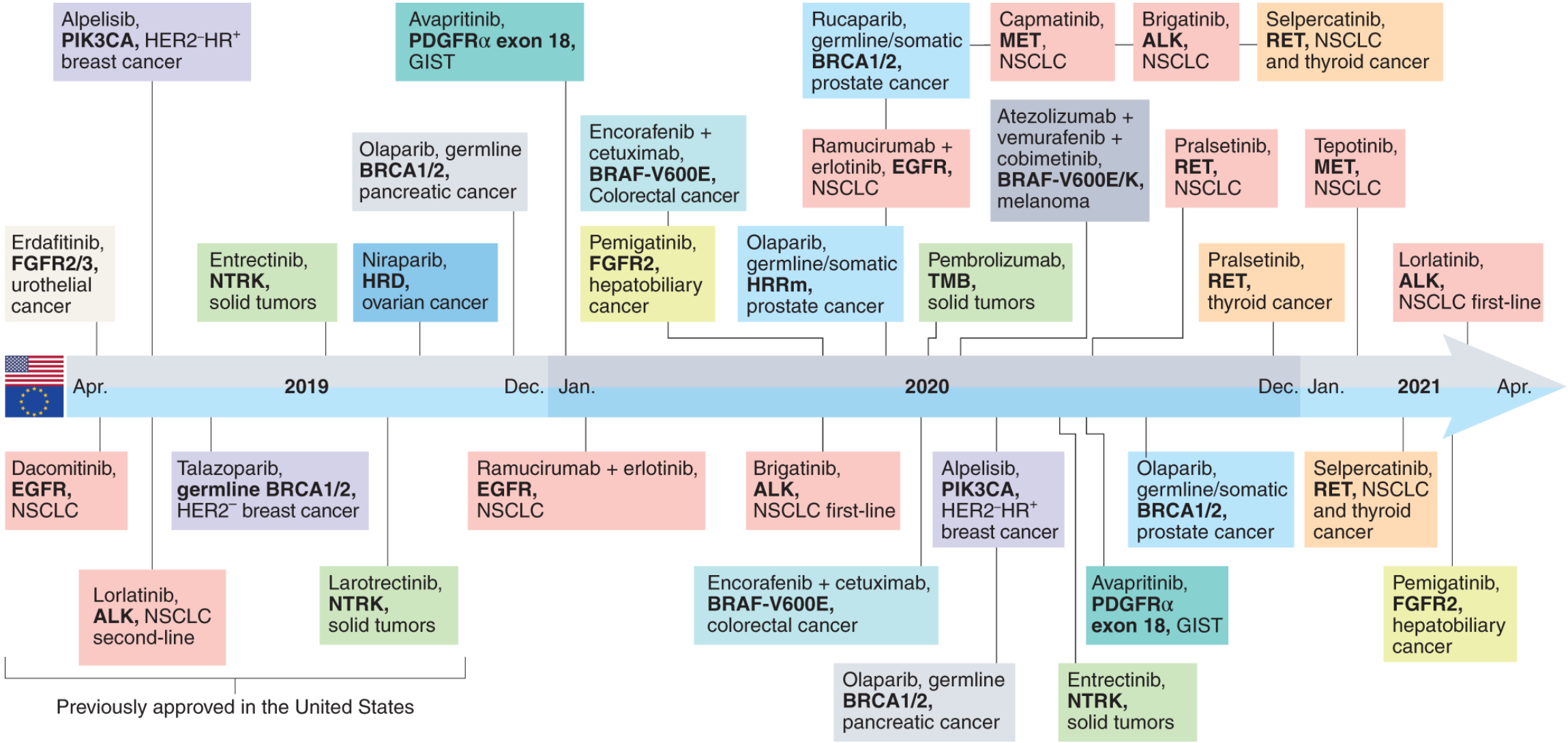


The right treatment for the right person at the right time



The goal is to better identify patients likely to derive clinical benefit; higher efficacy and/or lower toxicity

- Safety, tolerability
- Biomarker based patient selection
  - Within a given histology
  - Across histologies
- Proof of mechanism, assessment of biomarkers
- Evidence of efficacy
- Dose optimization



Recent biomarker-specific solid tumor approvals relevant to comprehensive genomics profiling tests in the United States (Food and Drug Administration) (top half) and EU (EMA) (bottom half) between April 2019 and April 2021, as examples of the rapid advance in the number of available biomarker-driven treatment indications. Approvals related to other means of biomarker testing, such as immunohistochemistry assays, are not included.. *Nature Medicine* **volume 28**, pages658–665 (2022)

Eligibility Criteria

‘Requirements that must be met for a person to be included in a trial.’- NCI glossary of terms

Pros	Cons
Safety Prevent enrollment of patients likely to be at higher risk of developing toxicities	Overall limits enrollment
Identify patient population likely to benefit Exclude patients not likely to derive benefit	Once written these are inflexible rules. Patient excluded for being 1 or 2 points outside the range
Allow cross-trial comparisons	Excessively restrictive, taken from other trials so can become quite a list Lack of generalizability to the wider patient population for a given tumor type
	Restricting eligibility too quickly excludes patients with rare tumors

Eligibility Criteria

- 326 consecutively diagnosed NSCLC patients at Kaiser Permanente Northern California-KPNC were retrospectively evaluated by chart review to determine eligibility for 2 trials evaluating chemo +/- antiangiogenic therapy.
  - Only 34% of the patients were eligible based on RCT criteria and favored those who were younger with less co-morbidities. (ASCO 2009 abstract. J Clin Oncology Volume 27, Number 15_suppl)

- Multiple efforts are ongoing to modify eligibility criteria
  - For one of the phase I trials: 25 criteria with a few including multiple lab-based parameters to be met.

Study Procedures	Screening	Cycle 1-2										Cycle 3+				End of Study Intervention	Safety Follow-up	Long-term Follow-up
	Day -21 to -1	Day 1	Day 2	Day 5	Day 6	Day 8	Day 13	Day 15	Day 16	Day 21	Day 22	Day 1	Day 8	Day 15	Day 22	Within 7 Days	28 Days After Last Dose	Every 3 Months After Last Dose
Read and sign this form; review your eligibility to participate; questions about your cancer and cancer treatments, demographics, health, medicines you have taken; measure your weight and height	X																	
Assign the drug you will take (Cycle 1 only)		X																
Physical examination; your ability to perform simple daily activities and ECOG	X*	X*				X*		X*			X*	X*				X*	X*	X*
ECGs	X	X	X	X (Cycle 1 only)	X (Cycle 1 Only)	X		X	X		X	X		X		X	X	
Blood and urine for safety tests; questions about other medicines you are taking	X*	X*	X	X	X	X*	X	X*	X	X	X	X*	X*	X*	X	X*	X*	
Pregnancy test for women who can have children	X*	X*										X*				X*	X*	
Receive study drug (on 28-day Regimen C [D1/D15 every 4 weeks])		X						X				X		X				
Receive paclitaxel		X				X		X				X	X	X				
Blood sample to measure the amount of the study drug in your blood				X				X	X									
Liquid biopsy (blood sample for future research)	X											X				X		
Tumor assessments	X*													X*		X*		
Questions about how you are feeling	X	X				X		X		X		X	X	X	X	X	X	
Questions about your status and any new anti-cancer therapies																		X
Approximate Time	3-4 hours	11-12 hours	1 hour	1 hour	1 hour	4-5 hours	1 hour	11-12 hours	1 hour	1 hour	1 hour	5-6 hours	4-5 hours	5-6 hours	1 hour	2-3 hours	2-3 hours	0.5 hours

Types of Research Biopsies	
Integral biopsies (biopsies with potential participant benefit)	*Nonintegral biopsies (biopsies without potential participant benefit)*
Biopsies to define eligibility	Biopsies testing a hypothesis (integrated biopsies for secondary outcomes)
Biopsies to direct interventions within a clinical trial (a drug, surgery, etc.)	Biopsies for exploratory correlative science
	Biopsies for future unspecified research (biobanking)

ASCO Research Statement. J Clin Oncol 2019; 37 (26)

Application of ASCO's Ethical Framework for Mandatory Research Biopsies*

Biopsy risk to participant	*Utility to society*		
	Unknown (exploratory end point/ outcome)	*Potential (secondary end point/ outcome)*	*Expected (primary end point/ outcome)*
Low (with the expected rate of major complications being less than 0.5%) (on a protocol-by-protocol basis)	Acceptable	Acceptable	Acceptable
Moderate (with the expected rate of major complications being 0.5% to 1.5%) (on a protocol-by-protocol basis)	Not acceptable	Acceptable	Acceptable
High (with the expected rate of major complications being greater than 1.5%) (on a protocol-by-protocol basis)	Not acceptable	Not acceptable	Acceptable

* This table is adapted from Levit, L. A., et al., "Ethical Framework for Including Research Biopsies in Oncology Clinical Trials: American Society of Clinical Oncology Research Statement," *Journal of Clinical Oncology* 37, no. 26 (2019): 2368-77, and is reprinted with the permission of the *Journal of Clinical Oncology*.

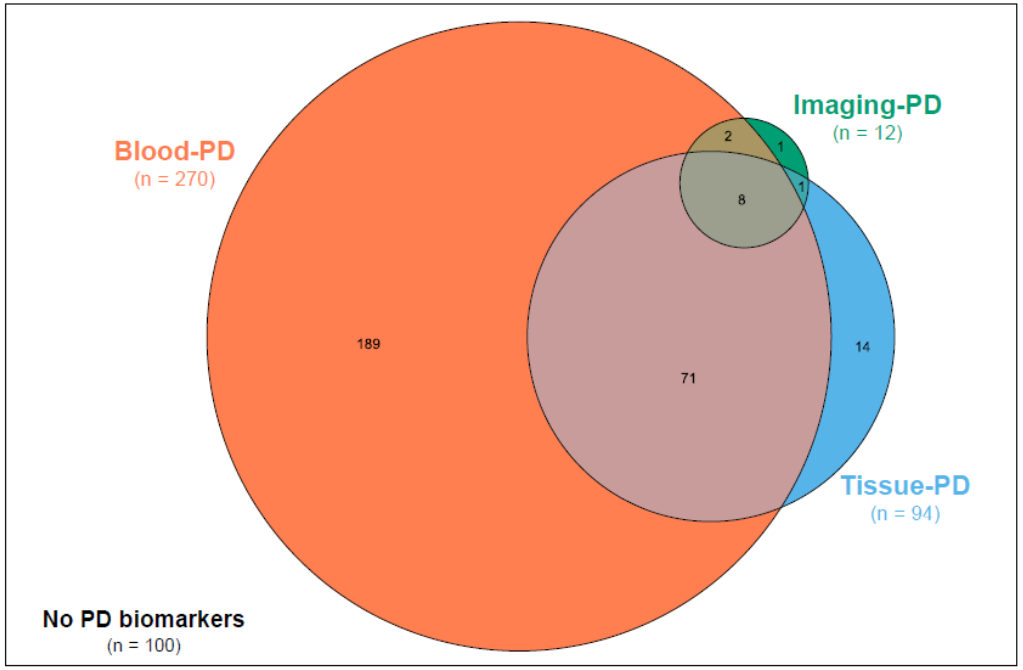
Unknown utility = The biopsy or biomarker test is included for exploratory or descriptive analyses or for tissue biobanking. Its potential for advancing scientific knowledge is unknown.

Potential utility = The biopsy or biomarker test is embedded in a trial that includes clear scientific plans to generate knowledge based on analyses of the biopsied tissue.

Expected utility = The biopsy or biomarker test is a primary end point of the trial, supported by a strong hypothesis and adequate statistical power, or is used to determine trial eligibility or stratification. It is expected to contribute to generalizable knowledge.

Pharmacodynamic biomarker assessment in Phase I trials

- Phase I trial between 1/2014-12/2020:
  - Total 386
  - Included vaccines (32%), PD-(L)1 (25%)
  - Tissue, blood and imaging-based biomarkers
  - Results from 22 (8%) of trials were referenced in subsequent publications



Phase 1 IO studies reporting pharmacodynamic biomarkers by sample type.

	Total number of Phase 1 studies	Studies with mandatory PD assessment *n (%)*	Total sample size	Patients involved in PD assessments *n (%)*
Tissue biomarkers	94	29 (31)	3,492	1,272 (36)
Blood biomarkers	270	241 (89)	7,227	6,165 (85)
Imaging biomarker	12	5 (42)	422	198 (47)

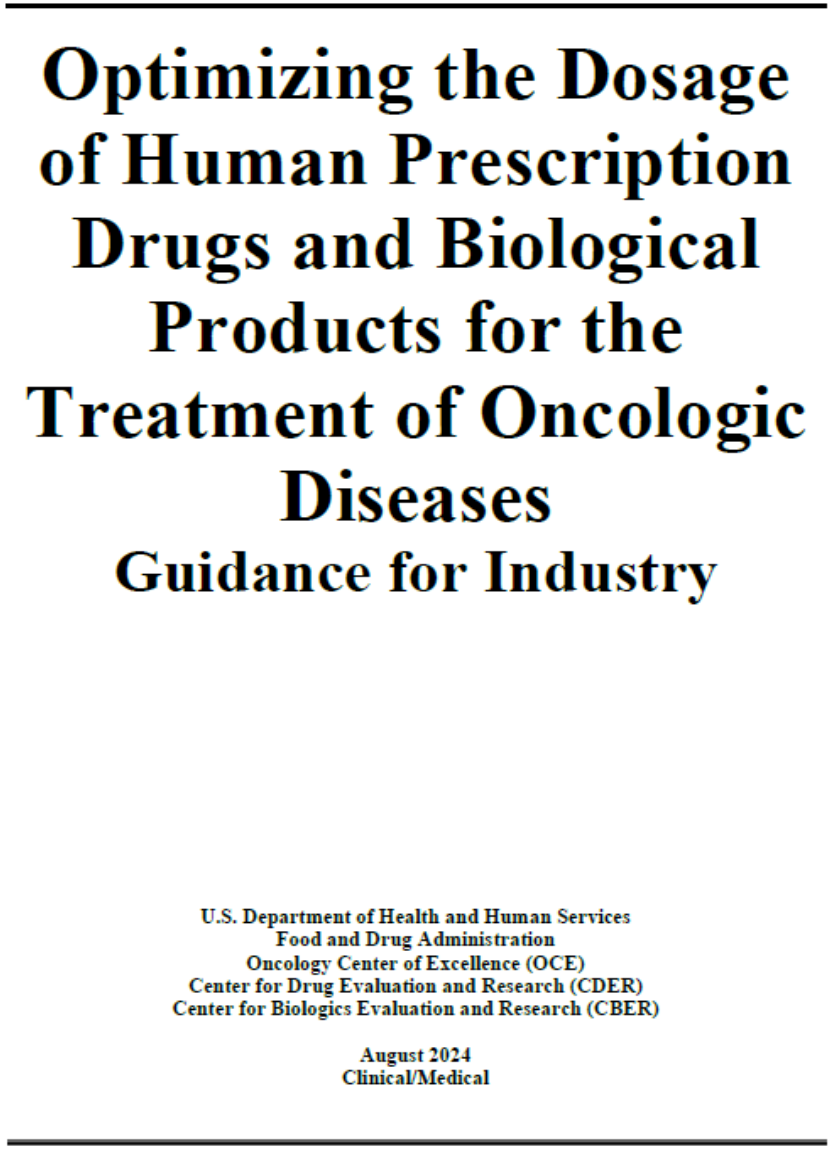
Tissue based biomarkers: genomic (21), transcriptomic (25), immunophenotyping (67), IHC (85)

A. Salawu et al. / European Journal of Cancer 173 (2022) 167–177

Defining the ‘right’ dose

- ‘Dose that is optimally efficacious while being tolerable’
- Maximum tolerated doses are determined under the premise that ‘more is better’
- Efficacy may not be directly related to higher doses
    - Non-dose proportional PKs (e.g. sotorasib 240 mg versus 960 mg, efficacy seen across a dose range)
- Dose may be different for particular subsets of patients (e.g. imatinib at dose of 800 mg for patients with GIST carrying KIT exon 9 mutations)
- Chronic ‘lower’ grade toxicities

Dose Optimization



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

Guidance for Industry

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)

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Clinical/Medical

- Dosage (dose and schedule)
  - Determined by efficacy and overall tolerability
- Preferably a dose range (especially considering future combinations)
  - Based on data from a dose confirmation component of the phase I trial
  - Informed by PK (target drug exposures)
  - Supported by PD data (proof of mechanism, downstream effects, tumor vs surrogate)
- Patient population

Person-centered early phase clinical trials

- Liberalize eligibility for phase I trials: Efforts have focused on initial criteria, consider modifying during the conduct
- Reduce patient burden for repeated visits: modify biomarker sampling schedule based on initial results
- DDIs: con med review. Strong/Moderate CYP3A4, CYP2D6, or CYP2C8 Inhibitor/inducers and Substrates-list includes a number of commonly prescribed medications
- Tumor biopsies: carefully review the need and intended use
- Dose optimization
- All stakeholders- FDA, study sponsors, clinical trialists, patient participants should come together to specifically address this for first-in-human and early phase trials.

I would like to thank the patients and their families, many of whom travel long distances to participate in clinical trials

THANK YOU!

Shivaani Kummar; kummar@ohsu.edu