Innovations in the Design of Clinical Trials in Oncology

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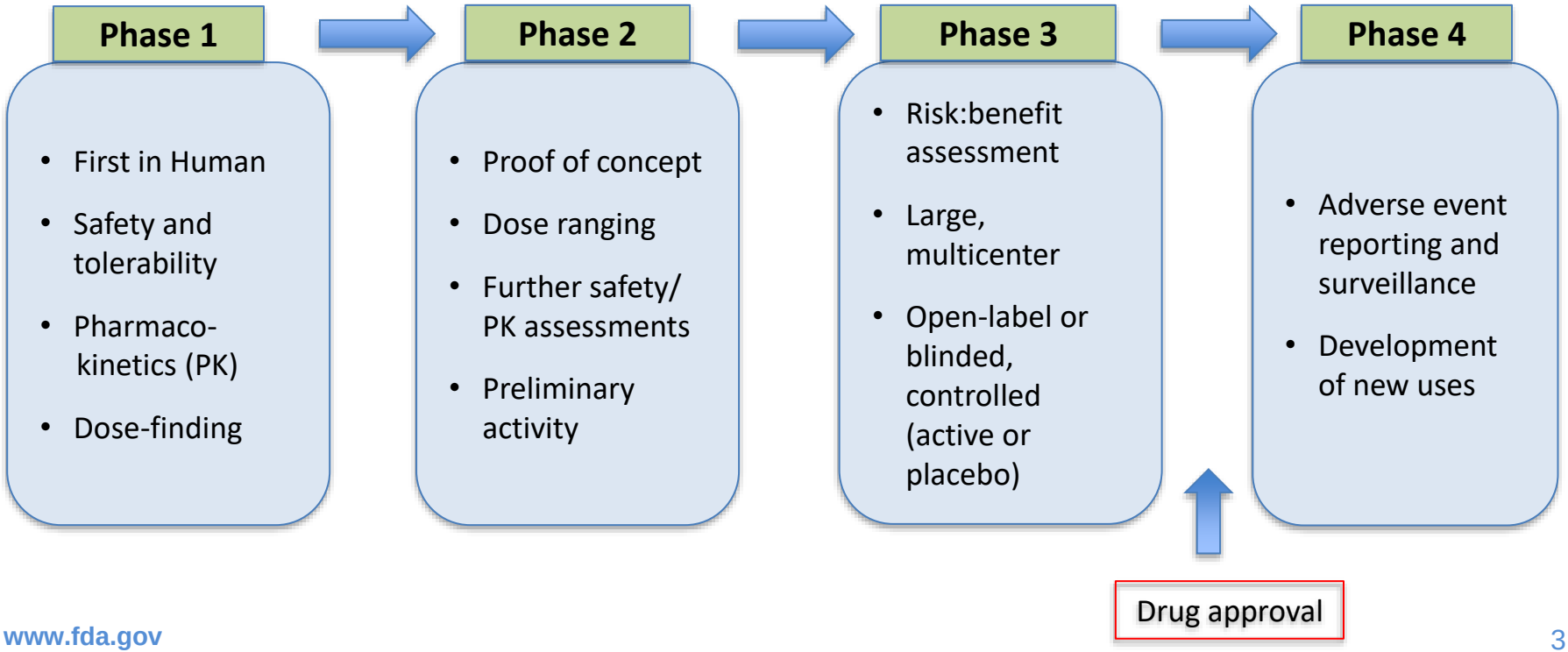
Disclosure information

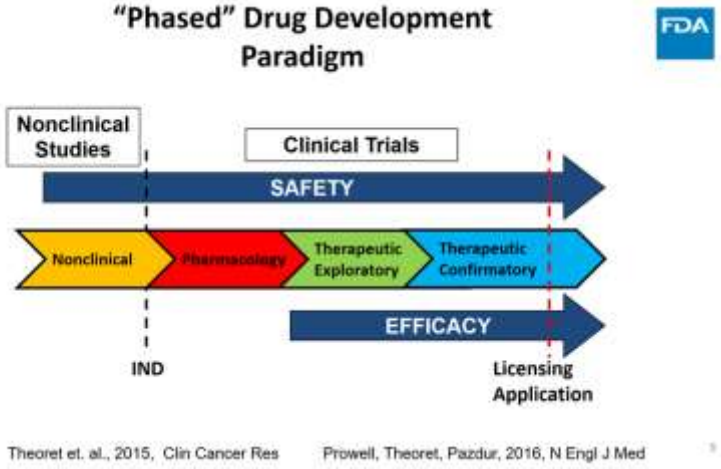
- This talk reflects the views of the author and should not be construed to represent FDA's views or policies.

- No conflicts of interest to disclose.

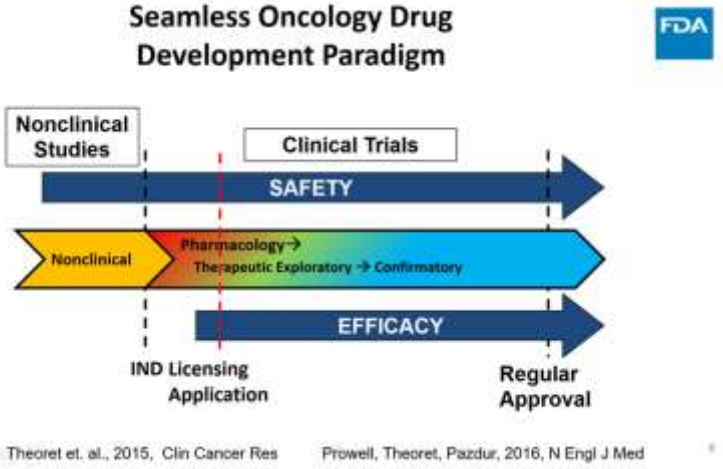
Objectives of clinical trials: traditional approach



Drug development paradigms

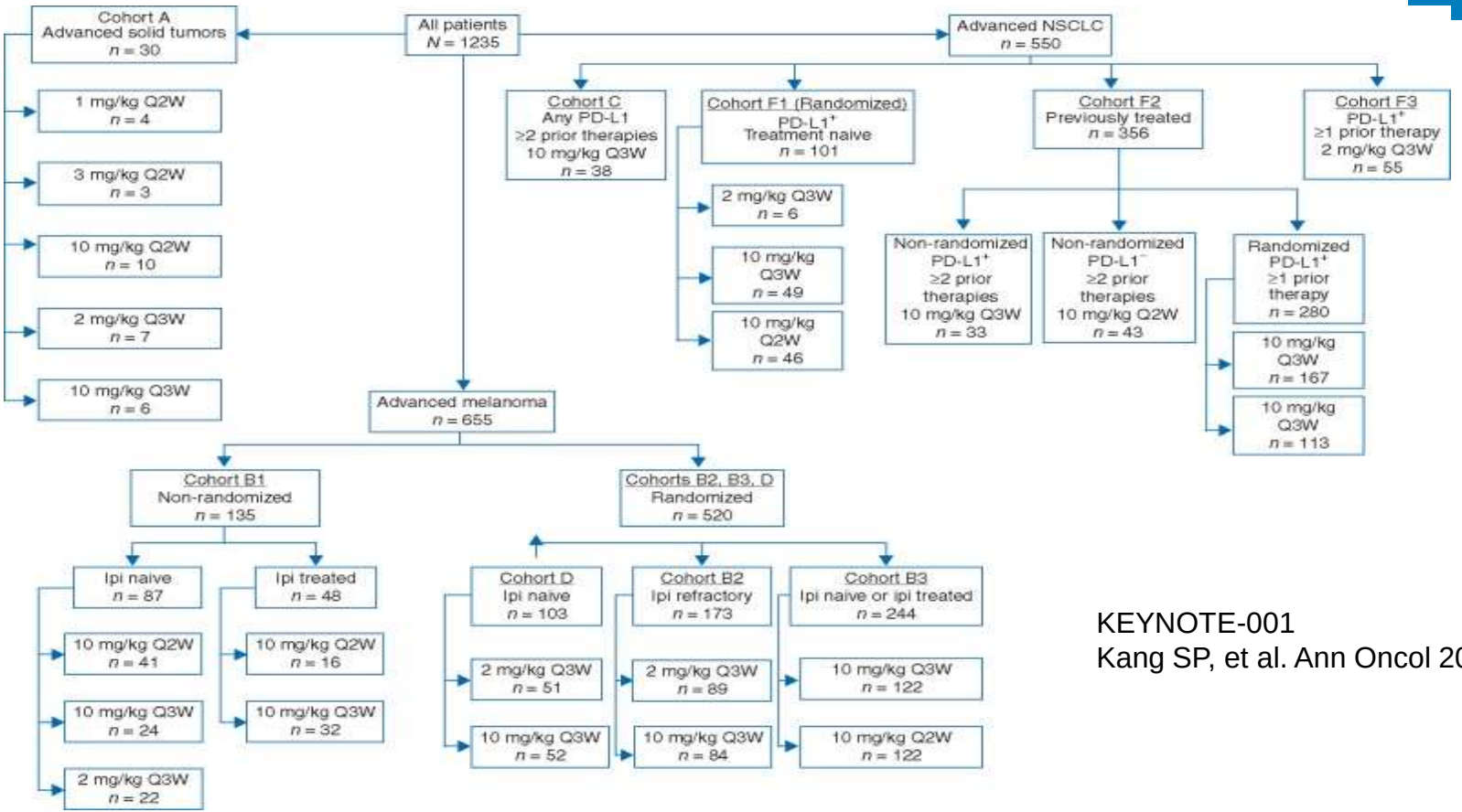


Theoret et. al., 2015, Clin Cancer Res Prowell, Theoret, Pazdur, 2016, N Engl J Med



Theoret et. al., 2015, Clin Cancer Res Prowell, Theoret, Pazdur, 2016, N Engl J Med

“Phase”: an outdated concept?



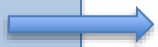
KEYNOTE-001
Kang SP, et al. Ann Oncol 2017

Establishing a dose – assessment of safety and preliminary signs of activity

- Most oncology studies have a dose-finding portion and an expansion cohort
- In general, the dose-finding portion has two competing goals:
  - Identify the highest tolerable dose possible: paradigm applicable to most chemotherapies
  - Identify the optimal dose: paradigm applicable to molecularly targeted therapy (target inhibition, receptor occupancy) or drugs that will be chronically administered
  - Expose as few patients to dose-limiting toxicities (DLTs) as possible
- Can assess the safety and preliminary signs of activity of a single drug or drugs in combination

Dose-finding designs: algorithmic designs

- Traditional 3+3 and variants
- Accelerated titration
- Up and down designs
- PK guided-dose escalation



- Simple to implement
- Generally, poor ability to identify the MTD/RP2D
- More patients may be treated at sub therapeutic doses
- Requires real-time PK data

Dose-finding designs: model-based designs

- Continuous reassessment model (CRM)
- Bayesian logistic regression model (BLRM)
- Escalation with overdose control (EWOC)
- Modified toxicity probability interval (mTPI)
- Bayesian optimal Design (BOIN)

- Generally superior to 3+3 in identification of MTD/RP2D
- More rapid dose escalation
- Use available information in all patients and may use late-onset toxicities
- More difficult to implement - need biostatistical support for decisions
- Need to have a prior guess of toxicity
- Can be aggressive (doses may be skipped)
- If no overdose control may treat more patients with toxic dose

Acceleration of development

Traditional approach

- Phase 2 trial: activity estimation (proof of concept)
  - Single arm
  - Randomized
- A trial for each disease
- Second dose finding study for combinations may be needed

Innovative strategies

- Multiple dose finding combination cohorts
- Expansion cohorts
- Master protocols
  - Basket trials
  - Umbrella trials
  - Platform trials
- Adaptive designs
- Tissue-agnostic

FIH expansion cohorts

Single protocol with an **initial dose-escalation phase** that also contains additional cohorts with cohort specific objectives

- Anti-tumor activity in specific cancer types
- Assessment of subpopulations: pediatric or elderly or pts with organ impairment, impact of food, DDI
- Evaluation of alternative doses or schedules
- Establishment of dose/schedule in combination with another drug
- Evaluation of predictive value of potential biomarker

Adaptive design

Clinical trial design that allows for prospectively planned modifications to one or more aspects of the design based on accumulating data from subjects in the trial.

Advantages

- Statistical efficiency
- Enrichment strategies
- Re-estimation of sample size
- Seamless designs

Limitations

- Specific analytical methods
- Logistical challenges
- Results before and after adaptation may be different: challenge to interpretability of the study

Master protocols

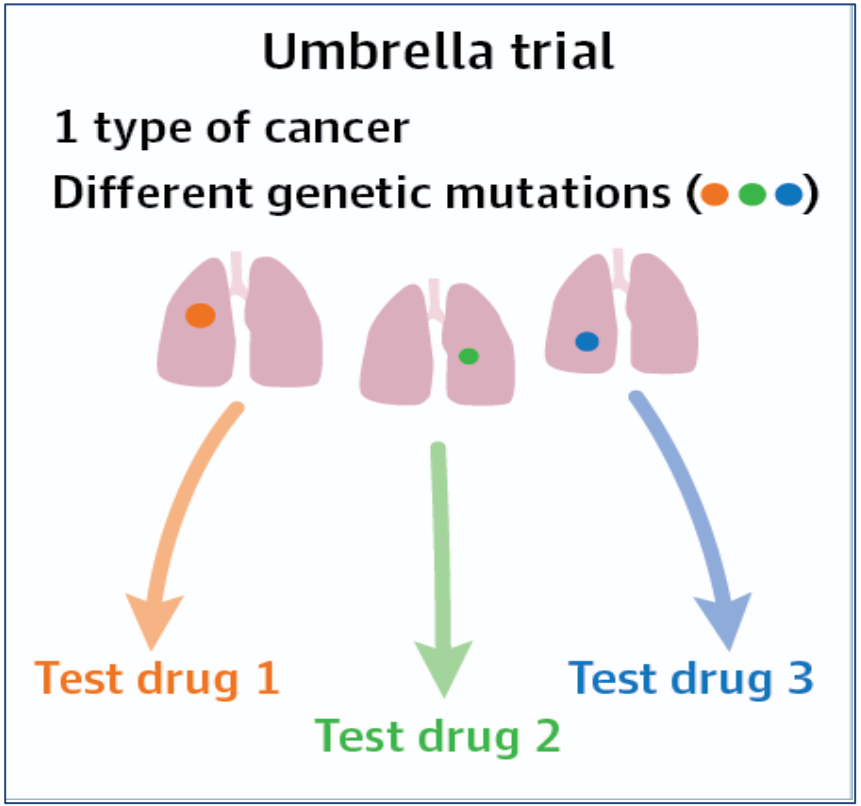
- A protocol designed with multiple substudies
  - May have different objectives
  - May evaluate one or more investigational drugs
  - May evaluate one or more disease subtypes
- Used for exploratory purposes or to support a marketing application
- Ideally, the recommended dose has been established in prior studies

Opportunity: Efficiency

- Centralized governance structure –central IRB, standing DMC, central labs with QA oversight
- Infrastructure advantages: streamlined enrollment, central electronic data capture system, common case report form, etc.
- Arms can be closed upon early analysis and new arms can be easily incorporated.
- Potential for data sharing: useful in future design of trials –Bayesian priors, historical/external control, etc.

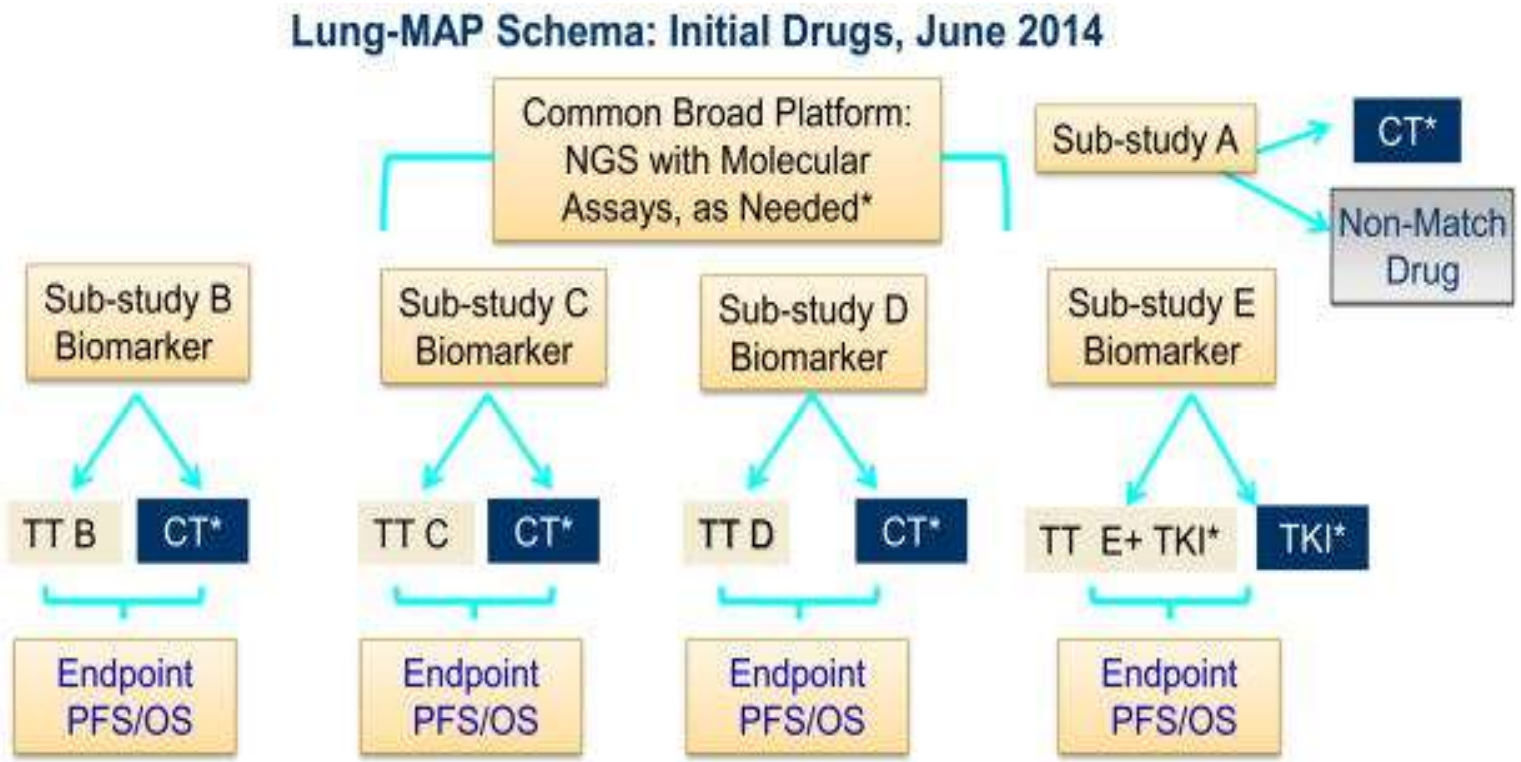
Master protocols: umbrella trials

- Single cancer type or subtype
- Evaluate multiple drugs administered as single drugs or drug combinations
- Matched to cohorts, e.g., based on biomarker
- Examples:
  - LUNG-Map
  - I-SPY-2
  - NCI-MATCH



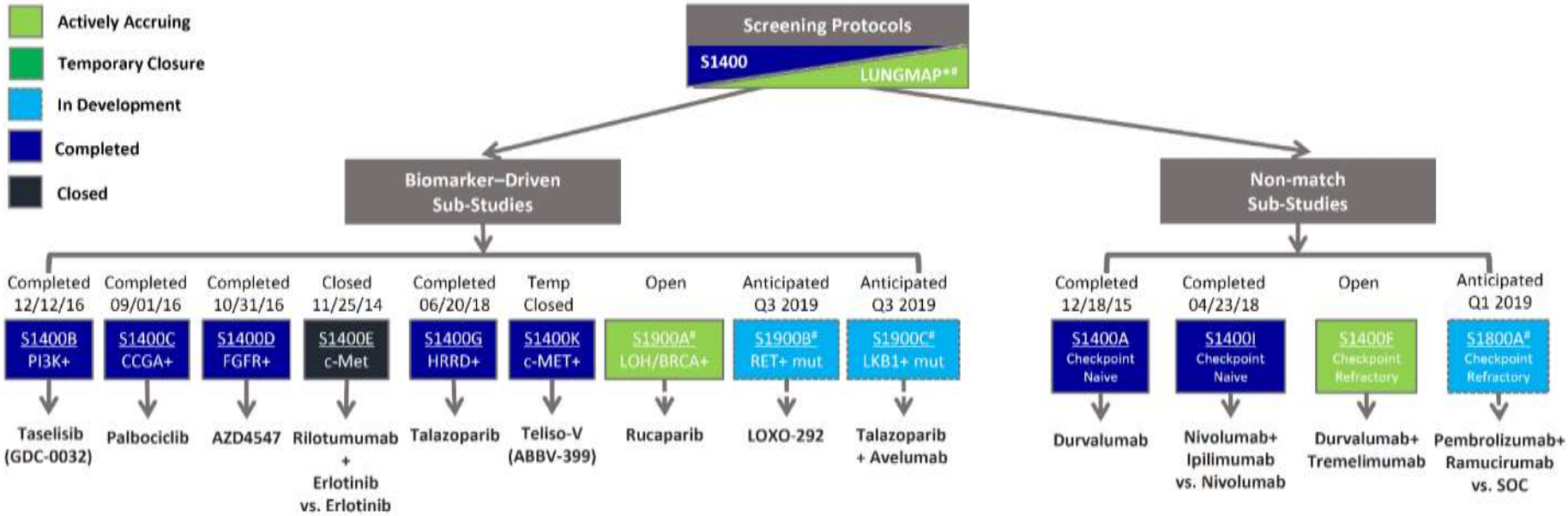
West H, JAMA Oncol 2017

Umbrella trial example: LUNGMAP (2014)



Herbst R. et al, CCR 2015

Umbrella Trial Example: LUNGMAP (2019)



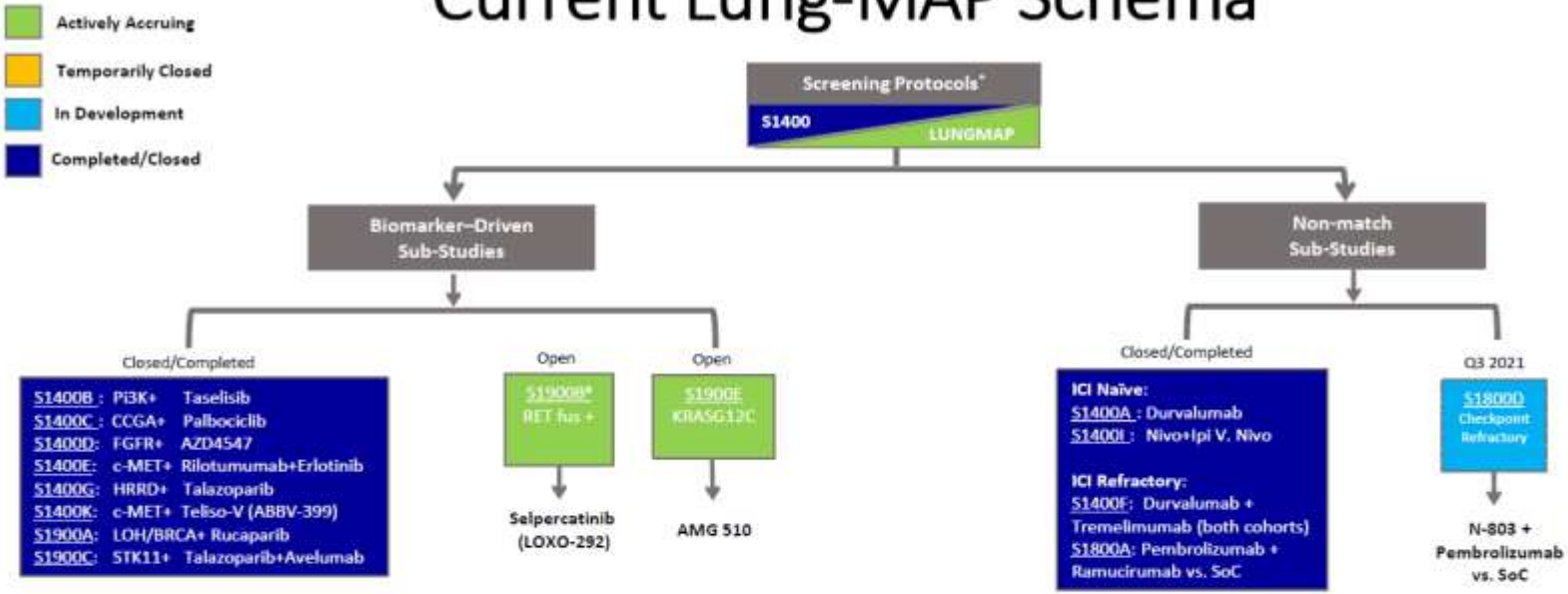
*The new umbrella screening protocol will be referred to as **LUNGMAP**. It is a major revision to allow Lung-MAP to expand to include all NSCLC histologies and include more patients.

#Only new sub-studies will be open to all NSCLC histologies. The rest of the current sub-studies are for patients only with squamous cell carcinoma.

January 2019 – Post LUNGMAP activation

https://www.lung-map.org/sites/default/files/Lung-MAP_Schema.pdf

Current Lung-MAP Schema



*LUNGMAP screening protocol (activated 1/28/19) allows all histologic types of NSCLC. S1400, the original screening/umbrella protocol included only squamous lung cancer. S1400 accrued patients between 6/16/2014 and 1/28/2019. While S1400 is closed to accrual, patients enrolled to S1400 may participate in sub-studies they are eligible for.

TRIAL POINTS OF INTEREST:

- Each of sub-study operates independently of the others
- Prescreening can be performed while the patient is on any line of therapy for stage IV disease
- Repeat or fresh biopsy necessary for tissue screening is paid by the trial
- **#Biomarker-driven sub-studies may progress to Phase III if study meets endpoint and Phase III is feasible, at which point the standard of care arm will be determined.**

https://www.lung-map.org/sites/default/files/Lung-MAP_Schema.pdf

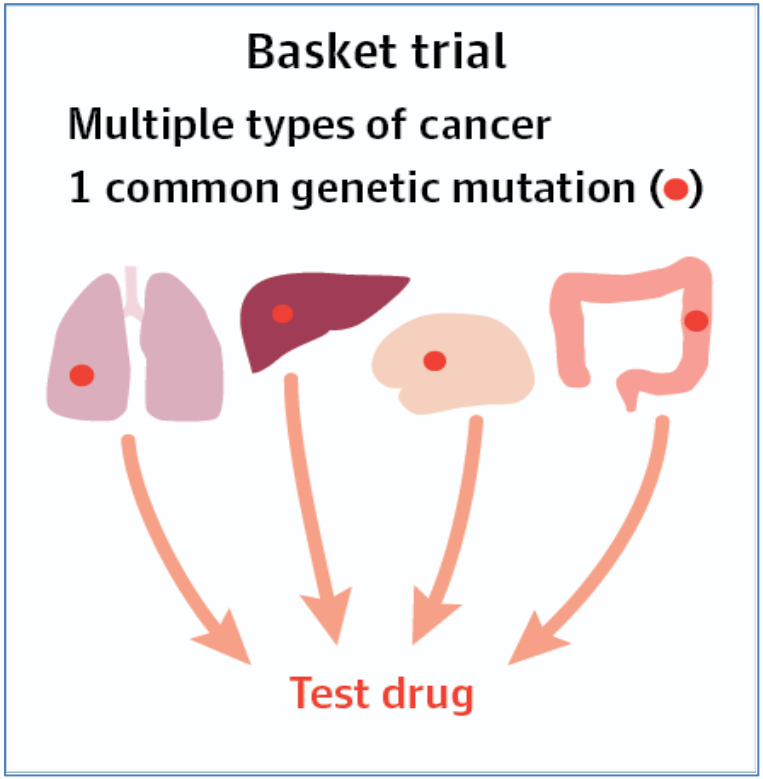
Master protocols: basket trials

<u>Biomarker-driven approach</u>:

Patients across many different tumor types into discreet, biomarker defined baskets

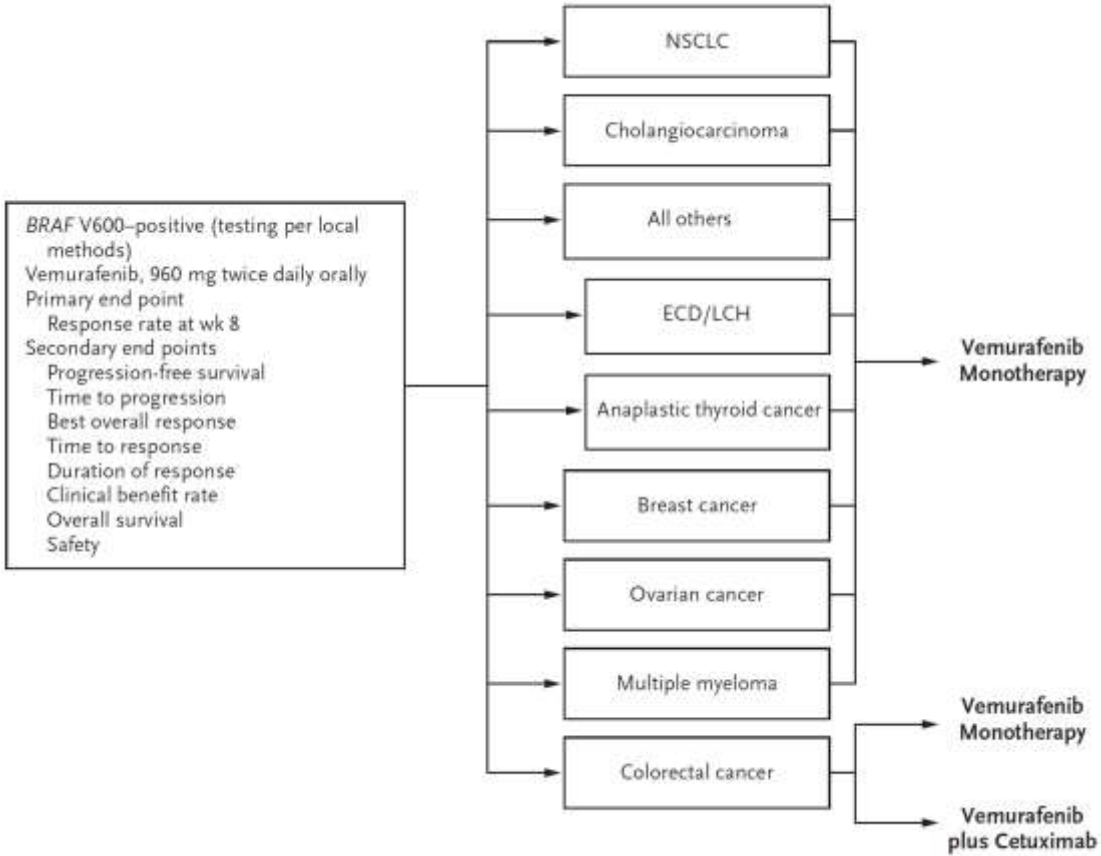
Examples:

- B2225 (imatinib)
- Vemurafenib (MO28072)
- NCI-MATCH



West H, JAMA Oncol 2017

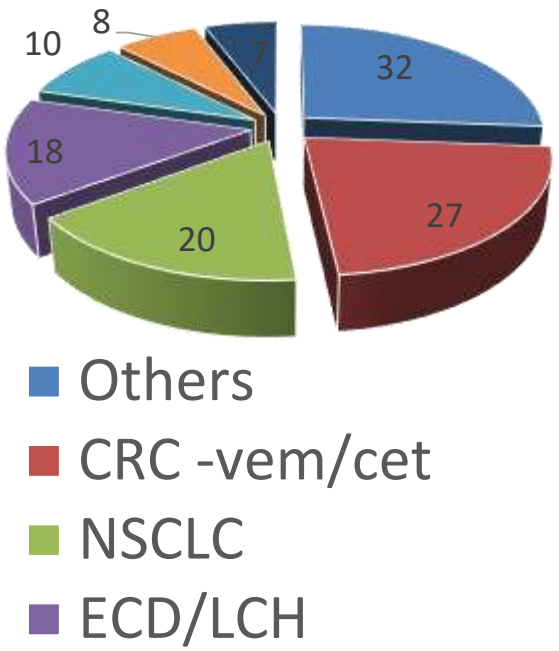
Basket Trial Example: Vemurafenib in BRAF V600-mutated non-melanoma cancers



- Simon 2-stage design
- Deemed efficacious if ORR >15%
- Recruitment into any cohort/indication could be expanded up to 70 patients

Hyman DM et al., 2015, N Engl J Med

Basket Trial Example: Vemurafenib in BRAF V600-mutated non-melanoma cancers



- n=122 patients enrolled
- Insufficient accrual into several cohorts for stage 1 analysis: patients included in the “all others” cohort
- Erdheim-Chester Disease cohort
  - FDA approval 11/2017 (n=22) ORR 54.5% with median follow-up of 26.6 months and duration of response that was not reached

Drugs@fda

Hyman DM et al., 2015, N Engl J Med

Some considerations

- **For non-randomized, activity-estimating design**
  - Use of a design that would limit exposure of large number of patients to ineffective drug (e.g. Simon 2 stage)
- **For randomized activity-estimating protocols**
  - Umbrella design: use of common control arm Type-I error rate only for the comparison between one experimental drug vs. control
  - Avoid formal comparison between experimental drugs (unless specified)
- **Need for independent oversight**: IDMC, safety committee
- **If biomarker based:**
  - Definition for maker positivity prior to initiation for each biomarker
  - Pre-specified plan for allocations of patients: eligible for ≥ 1 substudy

Tissue agnostic: paradigm change

- Traditional paradigm: cancers defined by histology and tumor location

However,

- Advances in molecular biology show that cancers arise from common somatic genetic building blocks,

but

- genetic changes are complex and often heterogeneous and concomitant genetic alterations (or epigenetic changes) may mediate resistance to targeted therapy.
- Can cancer be a biomarker-defined, tissue-agnostic disease?

Tissue agnostic considerations

- Strength of scientific evidence that biomarker identifies a population with common characteristics (e.g., serves as primary oncogenic driver when present) regardless of tumor  BRAFV600 vs. NTRK
- Strength of evidence that drug has the same pharmacologic effects on biomarker across tumor types in nonclinical & clinical studies  HER2
- Ability to reliably identify biomarker across tumor types, where biomarker-defined population is a subset of a specific tumor type

Can the tissue agnostic paradigm be used for tumors with BRAF V600 mutations?

- ~ 50% melanomas have a BRAF V600 mutation
- BRAF inhibition results in an ORR of 50% in these tumors

BRAF V600 in mCRC (10% patients with CRC)

- 21 patients: 1 response (4.7%)
- BRAF inhibition causes rapid feedback activation through EGFR
- Combination with EGFR agents needed
- BEACON: BRAF V600 inhibitor encorafenib + EGFR inhibitor cetuximab – ORR 20%

Kopetz S, 2015 and 2019

Basket trial in non-melanoma tumors with BRAF V600 mutations (Hyman D, 2015)

Disease	N pts	ORR – n (%)
NSCLC	20	8 (42%)
CRC - vemurafenib	10	0
CRC – vemu+cetuximab	27	1 (4%)
Cholangio	8	1 (12%)
ECD	18	6 (43%)

NSCLC: non-small cell lung cancer; CRC: colorectal cancer; ECD: Erdheim-Chester Disease

When tissue agnostic works: FDA approvals

- **Microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR)**
  - Pembrolizumab for the treatment of adult and pediatric patients with unresectable or metastatic MSI-H or dMMR solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options.
- **Tumor mutation burden- high (TMB-H)**
  - Pembrolizumab for the treatment of adult and pediatric patients with unresectable or metastatic TMB-H (≥10 mut/Mb) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options
- **Neurothrophic tyrosine receptor kinase fusions (NTRK)**
  - Larotrectinib and entrectinib are both approved for the treatment of adult and pediatric patients with solid tumors that have an NTRK gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have no satisfactory alternative treatments or that have progressed following treatment.

MSI-H/dMMR

- dMMR: deficiency in proteins responsible for DNA repair when a mismatch occurs in the replication process ⟹ accumulation of mutations and microsatellite instability
- dMMR/MSI-h are potentially immunogenic: tumors have high T-cell infiltration, PD-L1 expression, increased neoantigen formation, and high-mutational burden
- Frequency of MSI-H varies across tumor types and stages within a tumor type. Higher frequency: colon (15-20%), gastric (20%), endometrial cancers (30%)
- MMR predictive biomarker of response to checkpoint inhibitors:
  - dMMR CRC: ORR 57%
  - dMMR non-CRC: 53%
  - Proficient MMR CRC: 0%

(Le T 2016, Diaz L 2016)

Pembrolizumab ORR in MSI-H/dMMR tumors

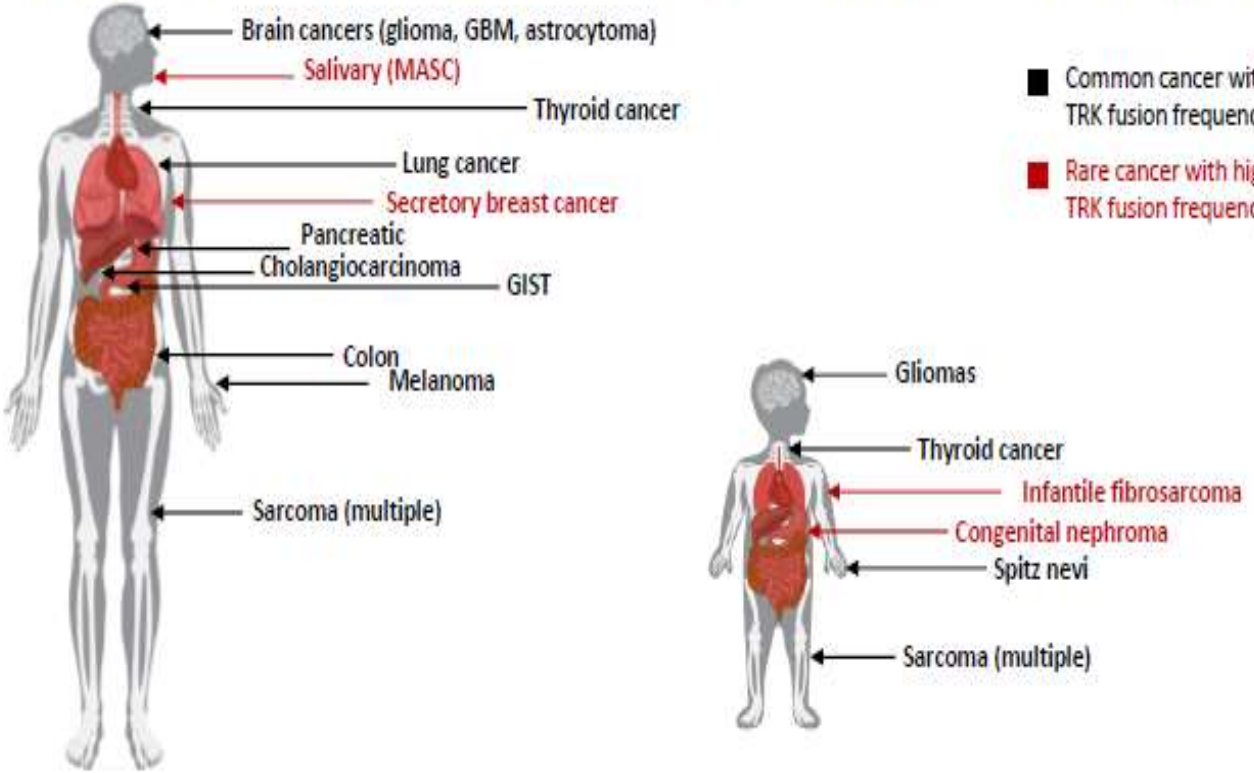
Pembrolizumab Response Rate by Tumor Type.*

Tumor Type	No. of Tumors	Patients with a Response	Range of Response Duration
		no. (%)	*mo*
Colorectal cancer	90	32 (36)	1.6+ to 22.7+
Endometrial cancer	14	5 (36)	4.2+ to 17.3+
Biliary cancer	11	3 (27)	11.6+ to 19.6+
Gastric or gastroesophageal junction	9	5 (56)	5.8+ to 22.1+
Pancreatic cancer	6	5 (83)	2.6+ to 9.2+
Small-intestine cancer	8	3 (38)	1.9+ to 9.1+
Breast cancer	2	2 (100)	7.6 to 15.9
Prostate cancer	2	1 (50)	9.8+
Other cancers	7	3 (43)	7.5+ to 18.2+

* Response was as defined by RECIST. "Other cancers" includes one patient each with the following tumor types: bladder, esophageal, sarcoma, thyroid, retroperitoneal, small-cell lung cancer, and renal cell cancer (includes two patients who could not be evaluated and were considered not to have had a response). A + sign indicates that the response was ongoing at the time of data cutoff.

Lemery S, 2017

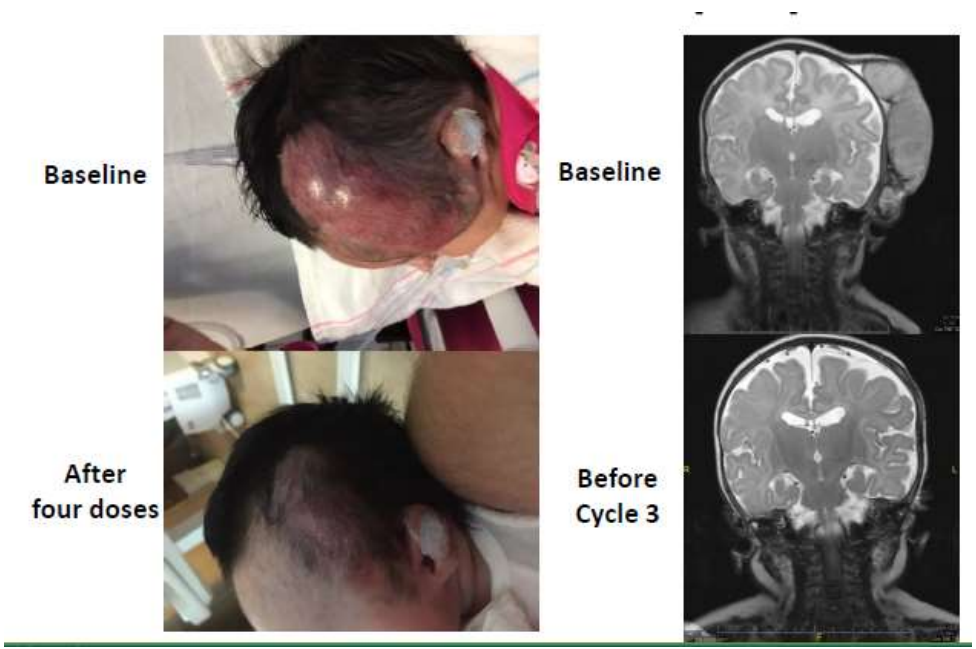
TRK fusions found in diverse cancer histologies



~ 1,500–5,000 pts have new NTRK fusion+ cancers in the U.S. annually

Source: ASCO 2017, David Hyman MD

Larotrectinib in infantile fibrosarcoma (IFS)



Images: AACR Special Conference on Pediatric Cancer Research 2017

- Infants and young children disease
- Locally aggressive, fast growing soft tissue sarcoma
- Surgical treatment, if possible, may result in severe sequelae
- Standard chemotherapy and radiotherapy are not effective
- Larotrectinib: 100% ORR

Larotrectinib ORR (tumors with NTRK fusions)

Efficacy Parameter	VITRAKVI N = 55
Overall response rate (95% CI)	75% (61%, 85%)
Complete response rate	22%
Partial response rate*	53%
Duration of response**	**N = 41**
Range (months)	1.6+, 33.2+
% with duration ≥ 6 months	73%
% with duration ≥ 9 months***	63%
% with duration ≥ 12 months****	39%

+ Denotes ongoing response.

*Includes one pediatric patient with unresectable infantile fibrosarcoma who underwent resection following partial response and who remained disease-free at data cutoff.

**Median duration of response not reached at time of data cutoff.

***3 patients with an ongoing response were followed < 9 months from onset of response.

****10 patients with an ongoing response were followed < 12 months from onset of response.

Tumor Type	Patients (N=55)	ORR		DOR
		%	95% CI	Range (months)
Soft tissue sarcoma	11	91%	(59%, 100%)	3.6, 33.2+
Salivary gland	12	83%	(52%, 98%)	7.7, 27.9+
Infantile fibrosarcoma	7	100%	(59%, 100%)	1.4+, 10.2+
Thyroid	5	100%	(48%, 100%)	3.7, 27.0+
Lung	4	75%	(19%, 99%)	8.2, 20.3+
Melanoma	4	50%	NA	1.9, 17.5+*
Colon	4	25%	NA	5.6*
Gastrointestinal stromal tumor	3	100%	(29%, 100%)	9.5, 17.3
Cholangiocarcinoma	2	SD, NE	NA	NA
Appendix	1	SD	NA	NA
Breast	1	PD	NA	NA
Pancreas	1	SD	NA	NA

Source: Viktrakvi USPI

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Thanks for your attention!


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