The TAPUR Study: Learning from precision medicine in practice

30th Annual Cancer Progress Conference
May 7, 2019

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Financial Disclosure

- I am an employee of the American Society of Clinical Oncology
- ASCO receives grants from the following pharmaceutical companies to support the TAPUR study:
  - Astra-Zeneca
  - Bayer
  - Bristol Myers Squibb
  - Eli Lilly and Co.
  - Genentech
  - Merck
  - Pfizer
- I will discuss the off label use of approved drugs

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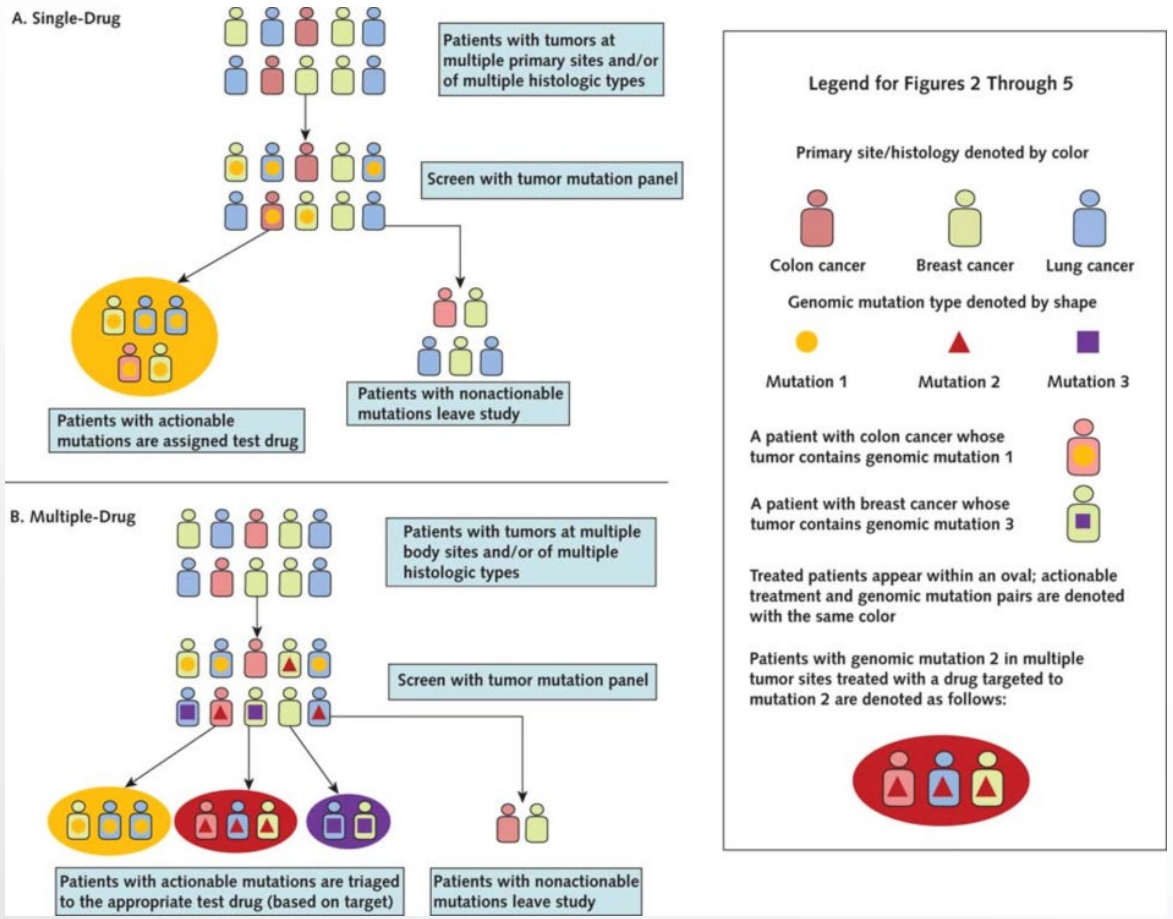
Nonrandomized Basket Designs



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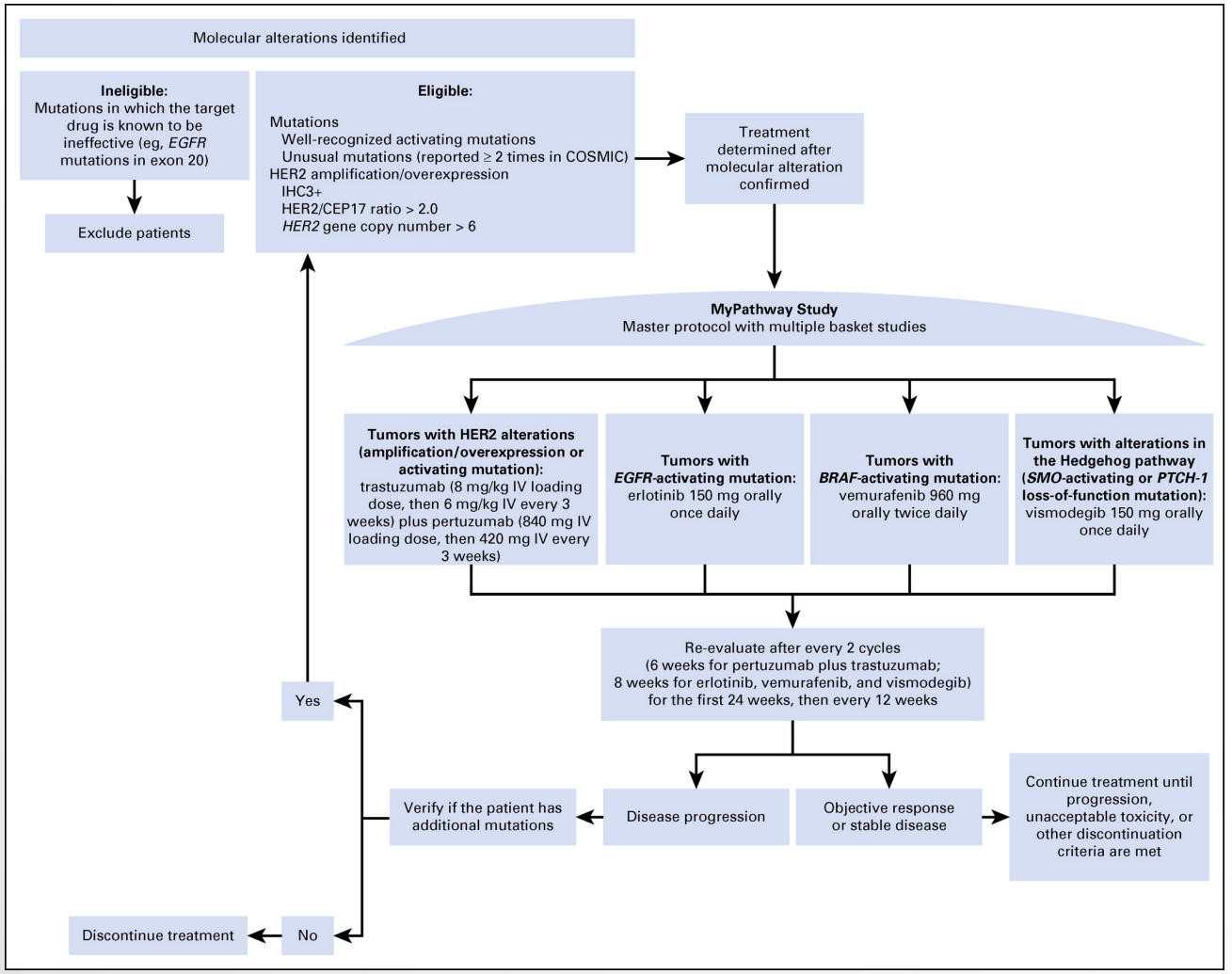
Ann Intern Med. 2016;165(4):270-278. doi:10.7326/M15-2413

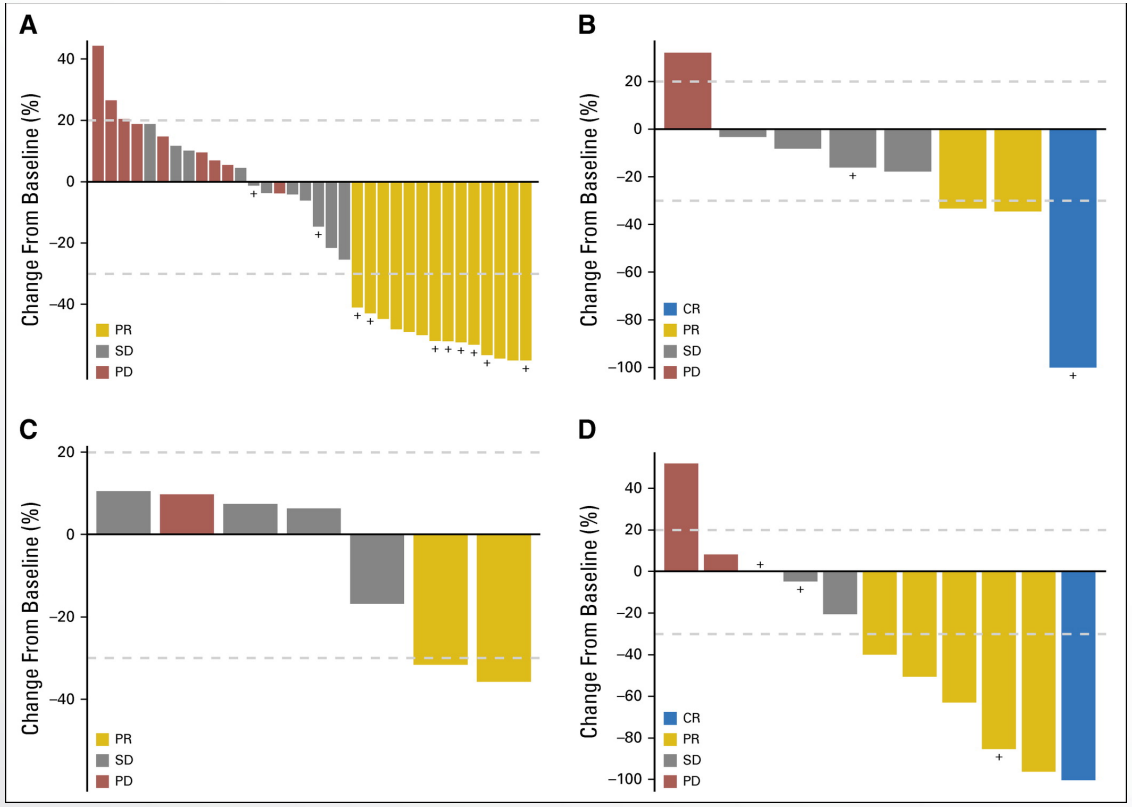
Multi-Basket MyPathway Study



Published in: John D. Hainsworth; Funda Meric-Bernstam; Charles Swanton; Herbert Hurwitz; David R. Spigel; Christopher Sweeney; Howard Burris; Ron Bose; Bongin Yoo; Alisha Stein; Mary Beattie; Razelle Kurzrock; *Journal of Clinical Oncology* **2018,** 36, 536-542.
DOI: 10.1200/JCO.2017.75.3780

Results of MyPathway Study

HER2-amplified CRC (A), Bladder (B), Biliary Cancer (C); BRAF mutant NSCLC (D)



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DOI: 10.1200/JCO.2017.75.3780

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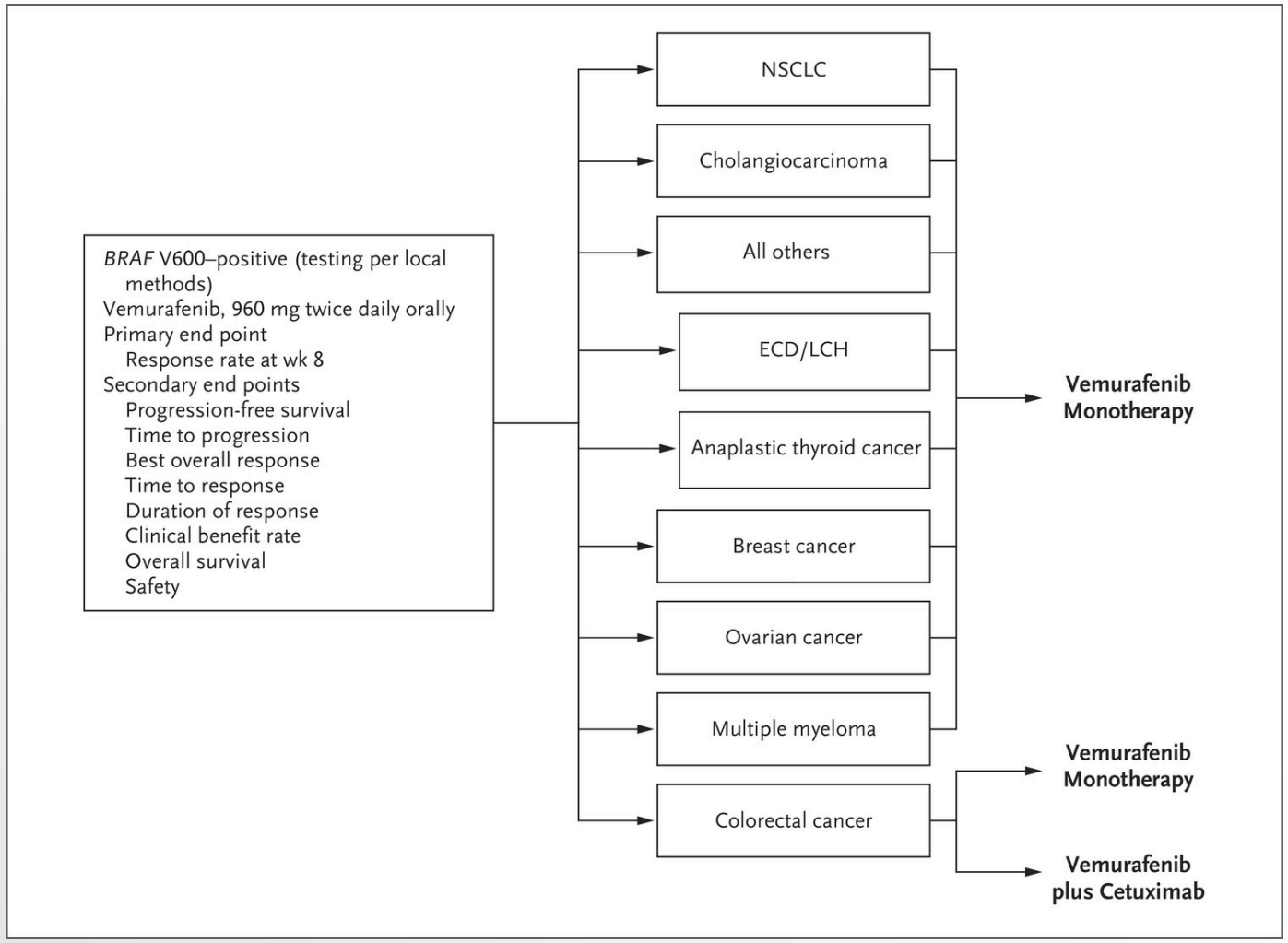
BRAF Basket Study



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Hyman DM et al. N Engl J Med 2015;373:726-736.

Common Features of These Trials

- Master protocol with multiple arms
- Rely on a genomic screen to direct patients to different treatment options
- Optimize use of rare patient resources
- Enable patient populations and treatments to move in/out of trial using a single protocol
- Include general and drug-specific inclusion/exclusion criteria
- Include a futility analysis
- Most are signal-finding; not all arms perform equally well

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Why TAPUR?

- Patient with advanced cancer; no standard Rx options
- Genomic profile test performed
- Potentially actionable variant detected
- How to get the drug?
- How to learn from the treatment?

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TAPUR Study Primary Objective

- To describe the anti-tumor activity and toxicity of commercially available, targeted anti-cancer drugs prescribed for treatment of patients with advanced solid tumors, B cell NHL or MM with a genomic variant known to be a drug target or to predict sensitivity to a drug.

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TAPUR Eligibility

- Patients with advanced solid tumors, B cell NHL and multiple myeloma for whom no standard treatment options exist
- Adequate organ function; PS 0-2
- Results available from a genomic test (FISH, PCR, NGS, WES, IHC for gene expression) performed in a CLIA certified, CAP accredited lab. Labs located or offering services to residents of NY must also have NY State accreditation. Tests registered with NIH Genetic Test Registry preferred.
- Treatment specific inclusion/exclusion criteria

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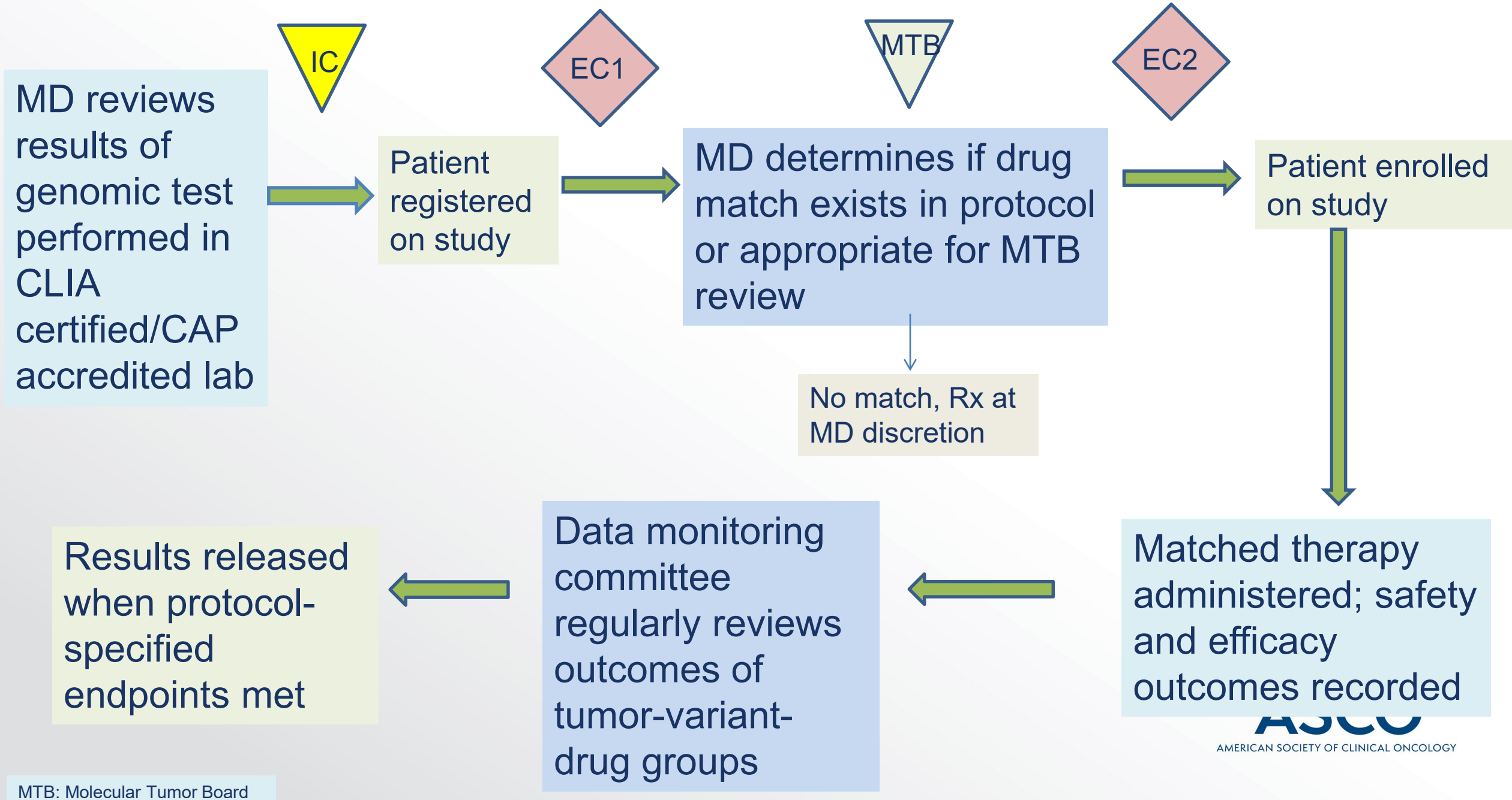

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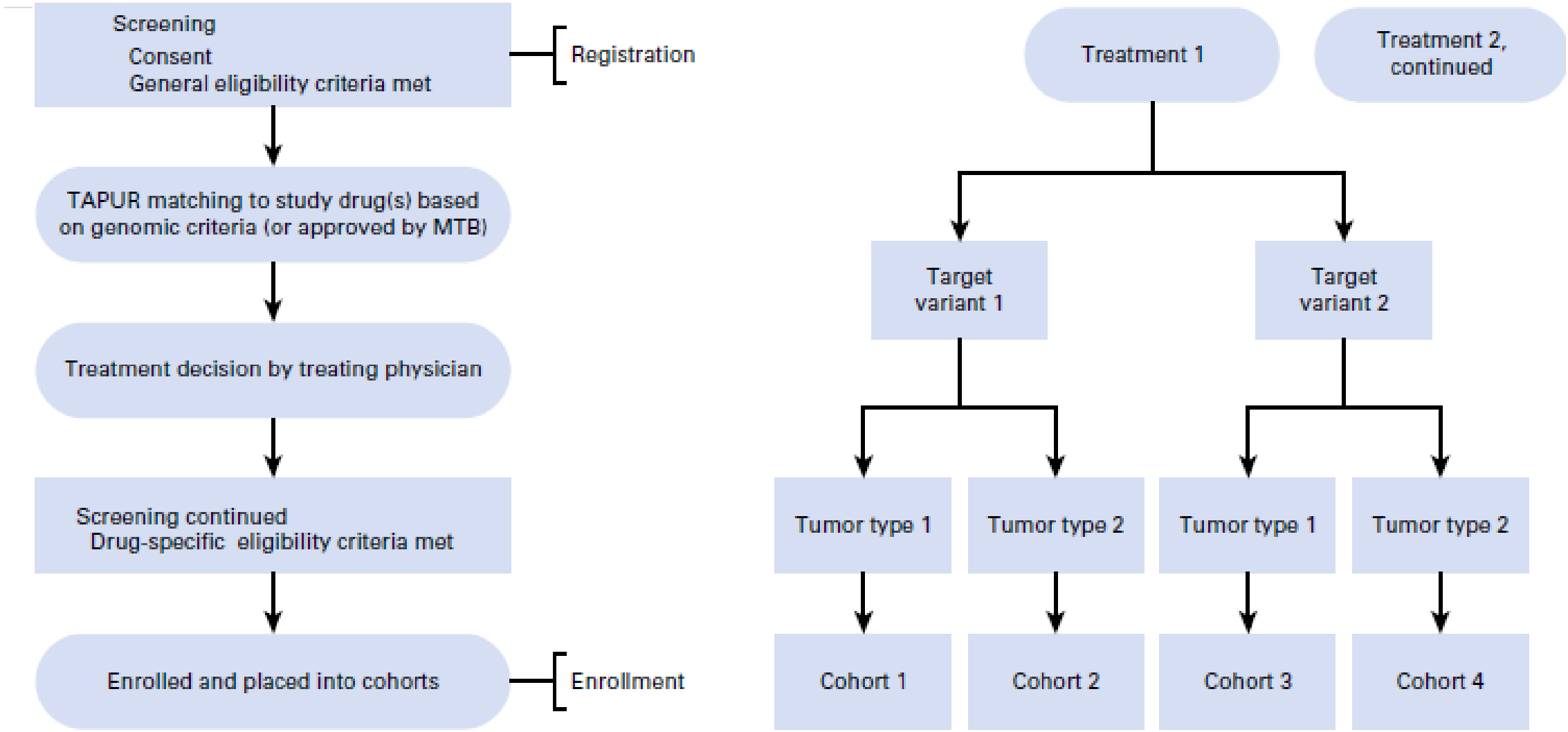
MTB: Molecular Tumor Board

Cohort Creation



Treatments Studied in TAPUR

Pharmaceutical Company (Number of Drugs)	**Drug(s) Provided for TAPUR Study**
AstraZeneca (1)	**Olaparib**
Bayer (1)	**Regorafenib**
Bristol-Meyers Squibb (3)	**Dasatinib*, Nivolumab + Ipilimumab**
Eli Lilly (1)	**Cetuximab**
Genentech (6)	**Trastuzumab + Pertuzumab, Vemurafenib + Cobimetinib, Erlotinib*, Vismodegib***
Merck (1)	**Pembrolizumab**
Pfizer (6)	**Axitinib*, Bosutinib*, Crizotinib*, Palbociclib, Sunitinib, Temsirolimus**

*Study drug no longer enrolling

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TAPUR Matching Rules

- Specific genomic inclusion and exclusion criteria for each drug
- Matching at variant level if possible
- Automated rules engine approves/rejects match proposed by treating MD
- If no match proposed or match rejected or multiple matches identified, treating MD may consult TAPUR MTB
- MTB identifies TAPUR drugs or other options based on tumor genomics
- Thus far, approximately 70% of cases matched by rules engine. Of those sent to MTB, 50% enrolled on a TAPUR study drug

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Study Endpoints

- Primary endpoint: Objective response rate per standard response criteria or SD at 16+ weeks
- Other endpoints:
  - Overall survival
  - Progression-free survival
  - Time on treatment
  - Grade 3-5 AEs per CTCAE
  - SAEs

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Statistical Design

- Simon's two-stage design
- Each tumor type-gene-drug is a "cohort"
- Null Hypothesis: ORR<15% vs. Alternative Hypothesis: ORR ≥ 35%
- Enroll 10 patients/cohort
  - If 0-1 response, stop
  - If 2 or more responses, enroll additional 18 pts
- Reject null hypothesis if 7 or more responses/28
- 85% power and one-sided Type 1 error rate of 0.10

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TAPUR is a Pragmatic Trial

- Broad eligibility criteria
- Physician discretion on genomic testing, drug dosing, dose modifications
- Minimum necessary data collection
- Investigator assessment of response
- Data validation procedures but no auditing/monitoring
- IND exempt per FDA
- However, specific inclusion/exclusion criteria, genomic matching rules and standard response criteria, required evaluations and data submission

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Current Status of TAPUR

- 2002 patients registered (04/30/19)
- 1437 patients enrolled (04/30/19)
- 120 participating sites (22 states)

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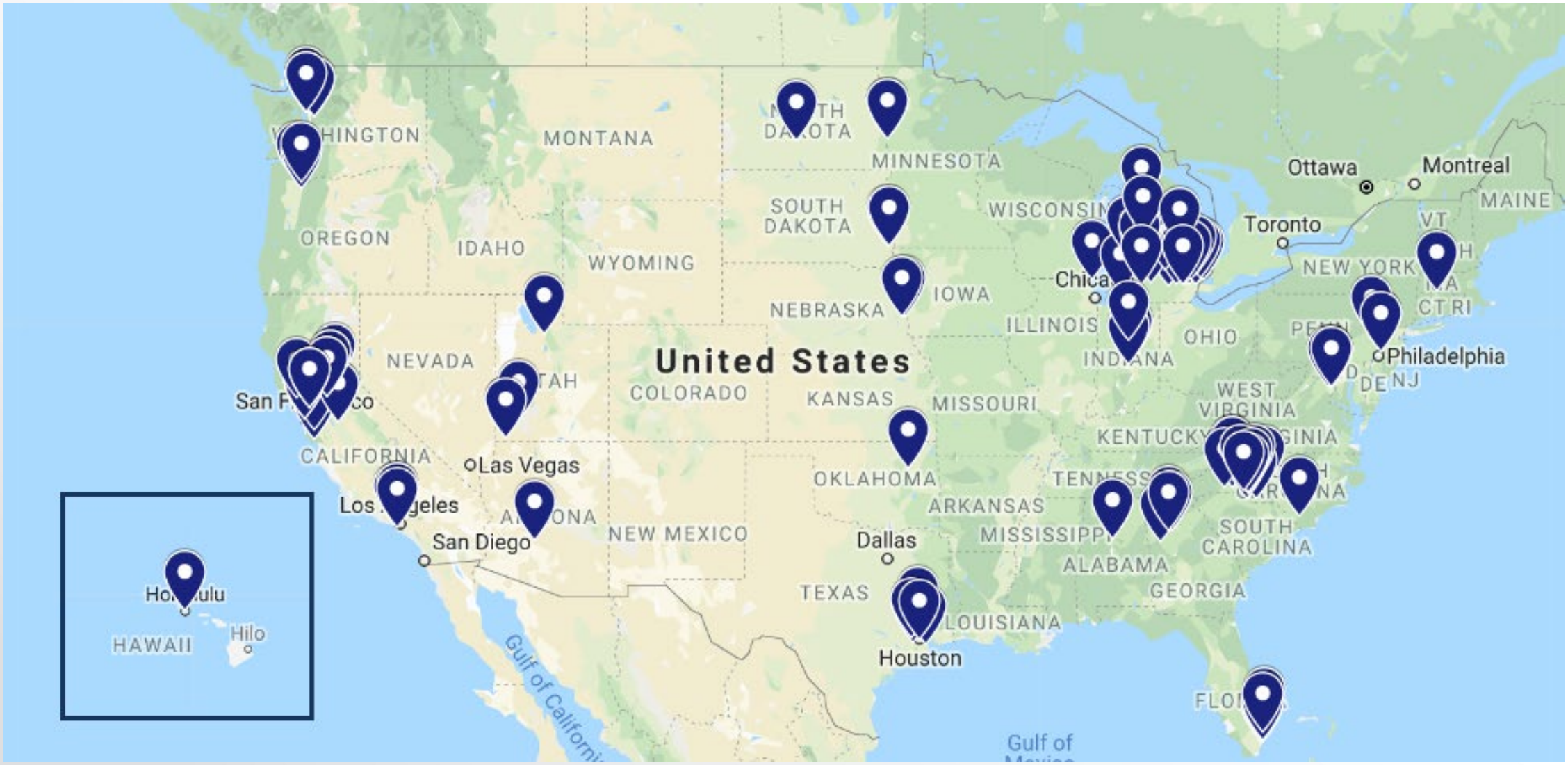
TAPUR Clinical Sites: 120 locations, 22 states



Enrollment by Study Drug as of 04/30/19

Drug Name	Total participants enrolled on drug
Axitinib (INLYTA)	5
Bosutinib (BOSULIF)	1
Cetuximab (ERBITUX)	114
Cobimetinib (COTELLIC) + Vemurafenib (ZELBORAF)	69
Crizotinib (XALKORI)	21
Dasatinib (SPRYCEL)	15
Erlotinib (TARCEVA)	1
Nivolumab (OPDIVO) + Ipilimumab (YERVOY)	150
Olaparib (LYNPARZA)	215
Palbociclib (IBRANCE)	239
Pembrolizumab (KEYTRUDA)	162
Pertuzumab (PERJETA) + Trastuzumab (HERCEPTIN)	153
Regorafenib (STIVARGA)	54
Sunitinib (SUTENT)	136
Temsirolimus (TORISEL)	97
Vismodegib (ERIVEDGE)	5
Total	1437

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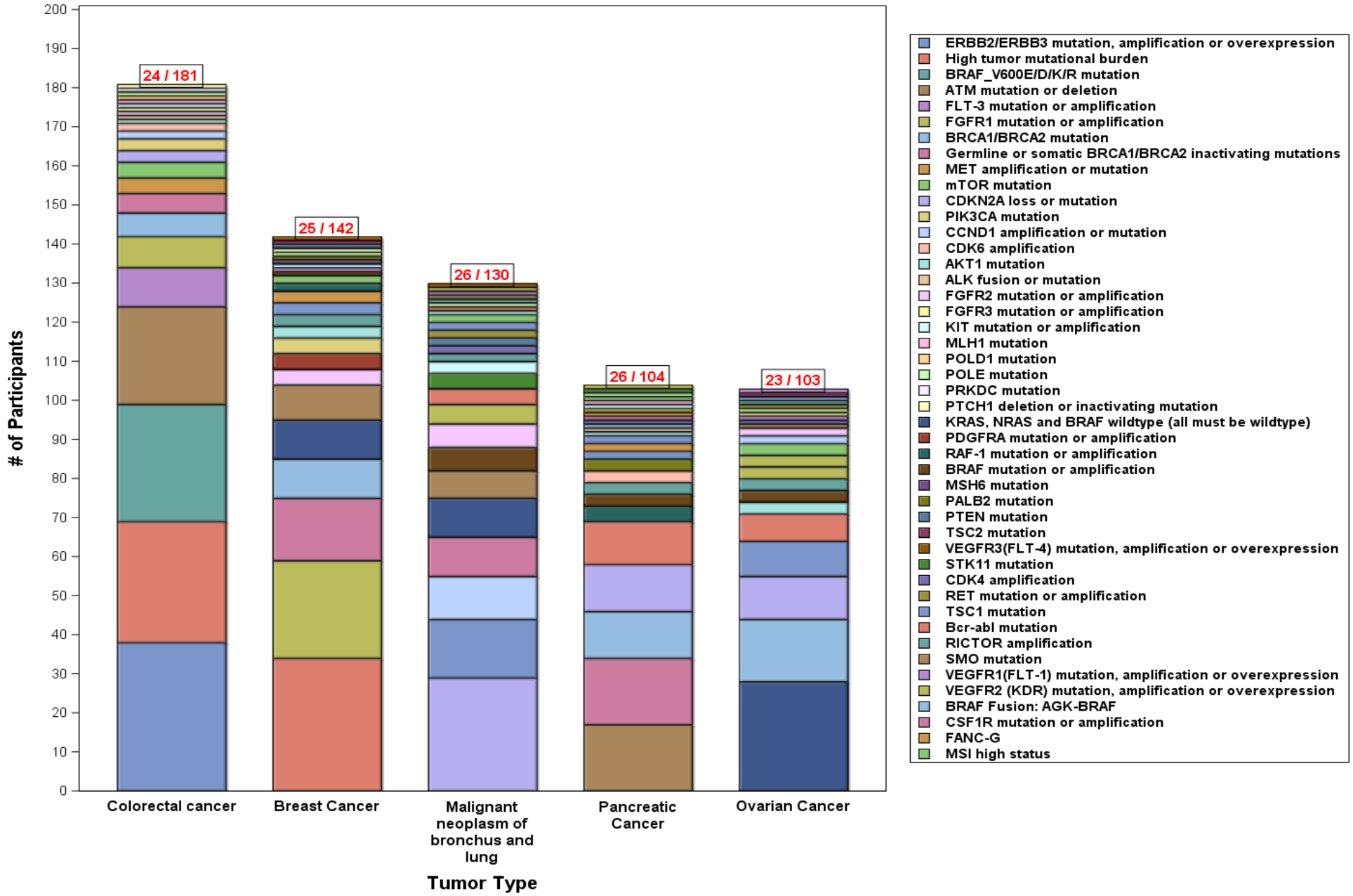
Variation of Genomic Aberrations in 5 Most Frequent Tumor Type
As of Monday, February 25, 2019



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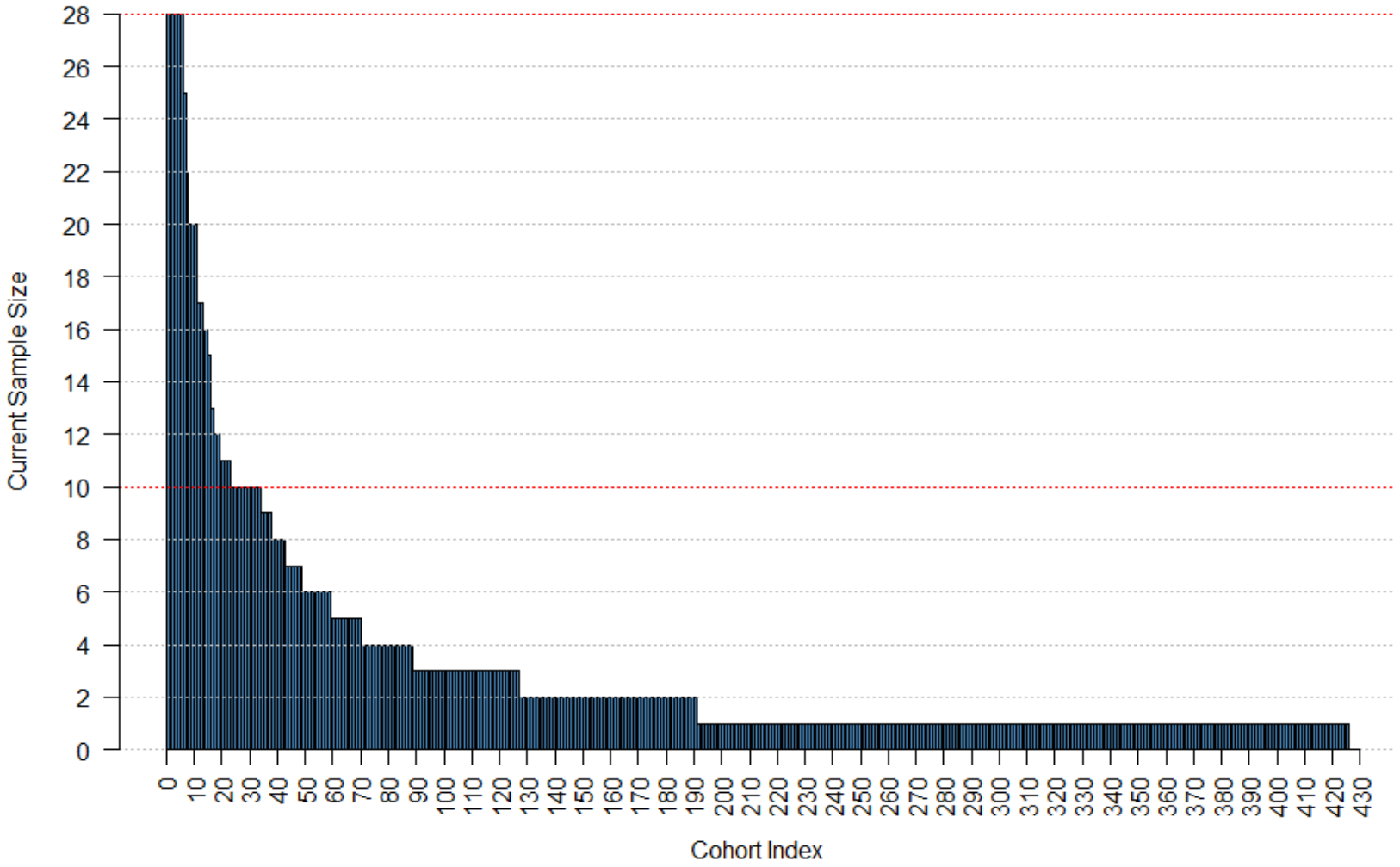
Unique Cohorts in TAPUR Study

- 1400+ patients distributed in 430 cohorts!
- Each cohort requires at least 10 patients for analysis.



Drug	Tumor Type	Variant	Signal
Palbociclib	Gallbladder and Bile Ducts	CDKN2A mutation or loss	
Palbociclib	Pancreatic Cancer	CDKN2A mutation or loss	
Cetuximab	Breast Cancer	KRAS, NRAS and BRAF wildtype	
Cetuximab	NSCLC	KRAS, NRAS and BRAF wildtype	
Sunitinib	Colorectal Cancer	FLT-3 mutation or amplification	
Palbociclib	NSCLC	CDKN2A loss or mutation	
Pembrolizumab	Breast	HTMB	
Pertuzumab + Trastuzumab	Colorectal Cancer	ERBB2 amplification	
Vemurafenib + Cobimetinib	Colorectal Cancer	BRAF_V600E/D/K/R mutation	

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Pembrolizumab	Breast	HTMB	
Pertuzumab + Trastuzumab	Colorectal Cancer	ERBB2 amplification	
Vemurafenib + Cobimetinib	Colorectal Cancer	BRAF_V600E/D/K/R mutation	

Enrolling Stage II Cohorts as of 04/30/2019

Drug	Tumor Type	Variant
Cetuximab	Ovarian Cancer	KRAS, NRAS and BRAF wildtype (all must be wildtype)
Olaparib	Breast Cancer; Prostate Cancer; Pancreatic Cancer; Uterine Cancer; Gallbladder and Bile Duct Cancer, NSCLC	Germline or somatic BRCA1/BRCA2 inactivating mutations
	Colorectal Cancer	ATM mutation or deletion
Palbociclib	Soft Tissue Sarcoma	CDK4 amplification
	Head and Neck Cancer; Ovarian Cancer	CDKN2A loss or mutation
	NSCLC	CCND1 amplification
Sunitinib	Breast Cancer	FGFR1 mutation or amplification
	Gallbladder and Bile Duct Cancer	FGFR2 mutation or amplification
Pembrolizumab	Uterine Cancer	High tumor mutational burden
Pertuzumab + Trastuzumab	Uterine Cancer; Gallbladder and Bile Duct Cancer; NSCLC; Bladder Cancer	ERBB2/ERBB3 mutation, amplification or overexpression
Nivolumab + Ipilimumab	Breast Cancer; Ovarian Cancer	BRCA1/BRCA2 mutation

TAPUR Future Plans

- Primary objective: **Combine an immune checkpoint inhibitor (anti-PD-1 or anti-PD-L1)** with a targeted treatment for patients with advanced solid tumors that have **high microsatellite instability or high tumor mutational burden and a genomic variant** targeted by a TAPUR study drug

- Study population: As per TAPUR except **genomic test must confirm that the tumor has *both* (a) MSI-H status or high tumor mutational burden (b) at least one potentially actionable genomic variant targeted by a TAPUR study drug**

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Genomic alterations in MSI-H/high TMB TAPUR Participants

Data thru September 4, 2018

Alternative TAPUR Matches	Genomic Targets	N
Cetuximab (ERBITUX)	BRAF, KRAS, and NRAS Wildtype	14
Crizotinib (XALKORI)	MET Amplification	3
Olaparib (LYNPARZA)	**BRCA1/BRCA2 Inactivating Mutation**	**10**
Olaparib (LYNPARZA)	**ATM Mutation or Deletion**	**13**
Palbociclib (IBRANCE)	CDK4 Amplification	1
Palbociclib (IBRANCE)	**CDKN2A Loss or Mutation**	**17**
Palbociclib (IBRANCE)	CCND1 Amplification	3
Pertuzumab (PERJETA) + Trastuzumab (HERCEPTIN)	**ERBB2 Amplification or Mutation**	**15**
Regorafenib (STIVARGA)	BRAF Mutation	2
Regorafenib (STIVARGA)	RAF1 Amplification	1
Regorafenib (STIVARGA)	RET Amplification	1
Regorafenib (STIVARGA)	KIT Mutation or Amplification	2
Sunitinib (SUTENT)	FGFR2 Mutation or Amplification	3
Sunitinib (SUTENT)	FGFR1 Amplification	8
Sunitinib (SUTENT)	FGFR3 Mutation	1
Sunitinib (SUTENT)	FLT3 Amplification or Mutation	6
Sunitinib (SUTENT)	RET Amplification	1
Sunitinib (SUTENT)	CSF1R Mutation	1
Sunitinib (SUTENT)	PDGFRA Amplification	1
Temsirolimus (TORISEL)	TSC2 Mutation	1

Who Benefits if the TAPUR Trial Succeeds?

- **Patients** receive targeted agent matched to tumor genomic profile; drugs at no cost
- **Physicians** receive guidance in interpretation of genomic test results and treatment options, access to drugs, clinical data on off-label use
- **Pharma** receives data on drug use and outcomes to inform R&D plans and life cycle management
- **Payers** receive data on test and drug use and outcomes to inform future coverage decisions
- **Regulators** receive data on extent and outcomes of off label drug and test use and real world safety data

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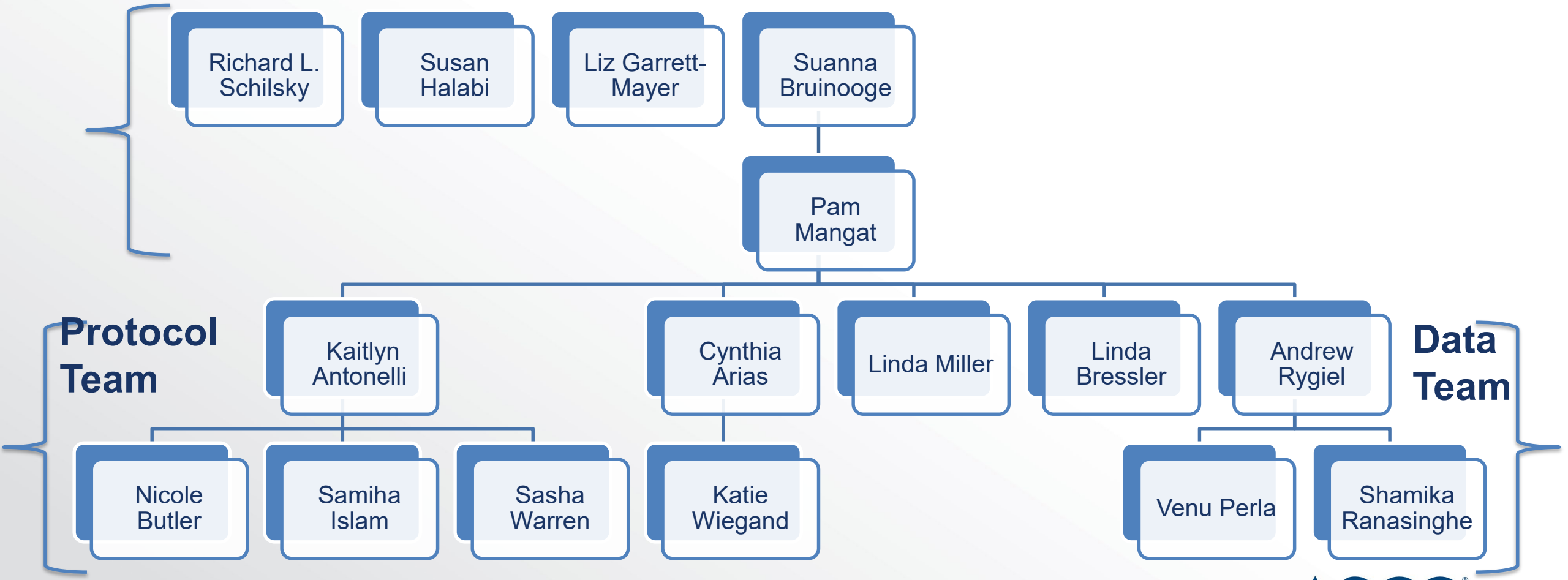
TAPUR Study Team



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TAPUR Clinical Sites and PIs

- Michigan Cancer Research Consortium; Dr. Philip Stella
- Cancer Research Consortium of West Michigan; Dr. Kathleen Yost
- University of Michigan; Dr. Ajjai Alva
- Carolinas HealthCare System's Levine Cancer Institute; Dr. Edward Kim
- Cancer Treatment Centers of America
  - Atlanta; Dr. Ricardo Alvarez
  - Chicago; Dr. Eugene Ahn
  - Philadelphia; Dr. Pamela Crilley
  - Phoenix; Dr. Ashish Sangal
  - Tulsa; Dr. Theodore Pollock
- Sanford Health
  - Sioux Falls; Dr. Steven Powell
  - Fargo; Dr. Anu Gaba
  - Bismarck; Dr. Peter Kurniali
- Intermountain Healthcare – Precision Genomics; Dr. Ramya Thota
- Intermountain Healthcare; Dr. Derrick Haslem
- University of Nebraska Medical Center; Dr. Alissa Marr
- Swedish Cancer Institute; Dr. Thomas Brown
- Providence Health and Services; Dr. Walter Urba
- Inova Schar Cancer Institute; Dr. Timothy Cannon
- The University of Texas MD Anderson Cancer Center; Dr. Funda Meric-Bernstam
- The Angeles Clinic and Research Institute; Dr. Samuel Klempner
- University of Alabama at Birmingham Comprehensive Cancer Center; Dr. Eddy Yang
- Emory University Winship Cancer Institute; Dr. Olatunji Alese
- Fox Chase Cancer Center; Dr. Margaret von Mehren
- University of Miami Sylvester Comprehensive Cancer Center; Dr. Carmen Calfa
- Sutter Cancer Research Consortium; Dr. Stacy D'Andre

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