



**CDDF SPRING
CONFERENCE 2021**

08 - 10 February 2021

Virtual Conference

Current and future challenges
of innovative oncology drug
development



Tumor Agnostic Drug Development and Re-Use of Registered Drugs

Cancer Drug Development Forum
Spring Conference 2021

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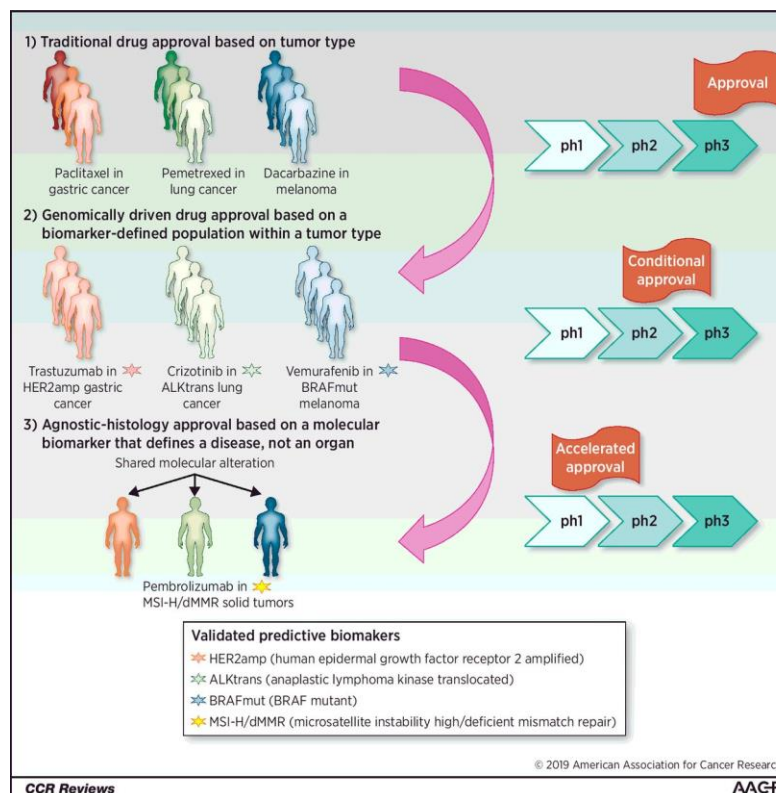


Financial Disclosure

- 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
 - Boehringer-Ingelheim
 - Bristol Myers Squibb
 - Eli Lilly and Co.
 - Genentech
 - Merck
 - Pfizer
- I will discuss the off label use of approved drugs

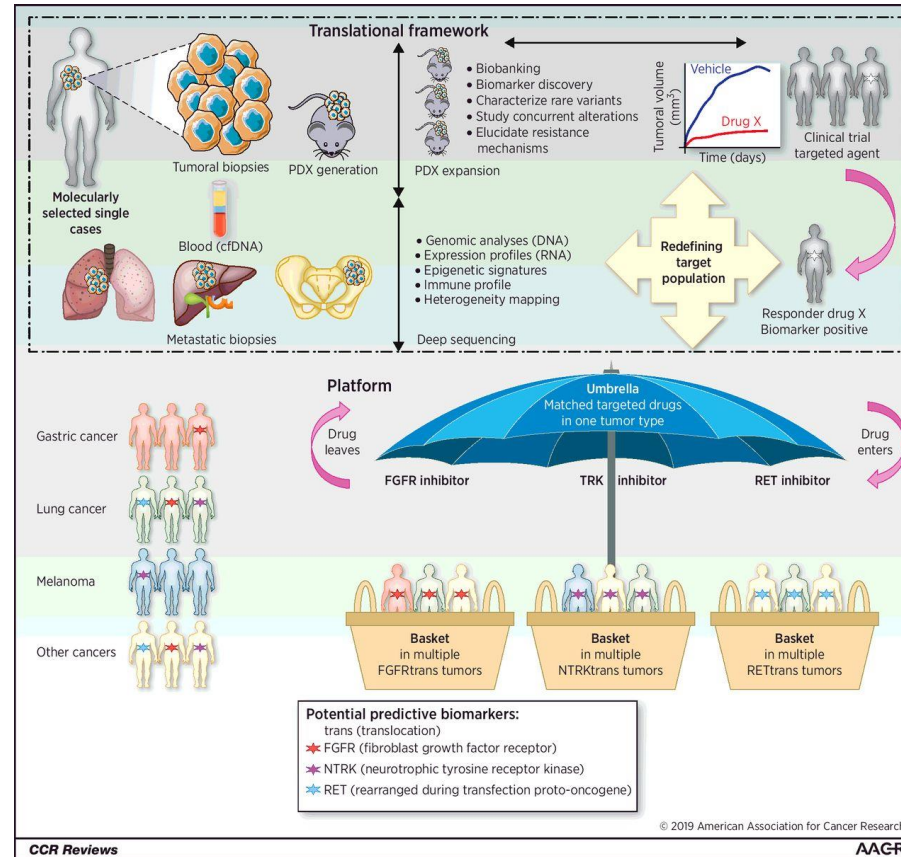


Evolving Framework of Clinical Trials to Support Oncology Drug Approval





Precision Medicine Drug Development





The NEW ENGLAND JOURNAL *of* MEDICINE

Perspective

OCTOBER 12, 2017

First FDA Approval Agnostic of Cancer Site — When a Biomarker Defines the Indication

Steven Lemery, M.D., M.H.S., Patricia Keegan, M.D., and Richard Pazdur, M.D.

Disease indications for drugs have conventionally been defined by pathologic processes, signs or symptoms, or histologic findings in affected organs. Oncology has defined subtypes

nearly 30% for endometrial cancer, 20% for colon or gastric cancer, and less than 5% for most other tumor types.² The incidence of MSI-H or dMMR in these types of tumors has largely been deter-



FDA Tissue Agnostic Approvals

Drug	Indication*	Efficacy ORR (95% CI)	Post Approval Studies?	Device?
2017: Pembrolizumab N=149	MSI-H; dMMR ¹	40% (32, 48)	Yes	No
2018: Larotrectinib N=55	NTRK-fusions	75% (61, 85)	Yes	No
2019: Entrectinib N=54	NTRK-fusions	57.4% (43, 77)	Yes	No
2020: Pembrolizumab N=102	TMB-H ¹	29% (21, 39)	Yes	Yes

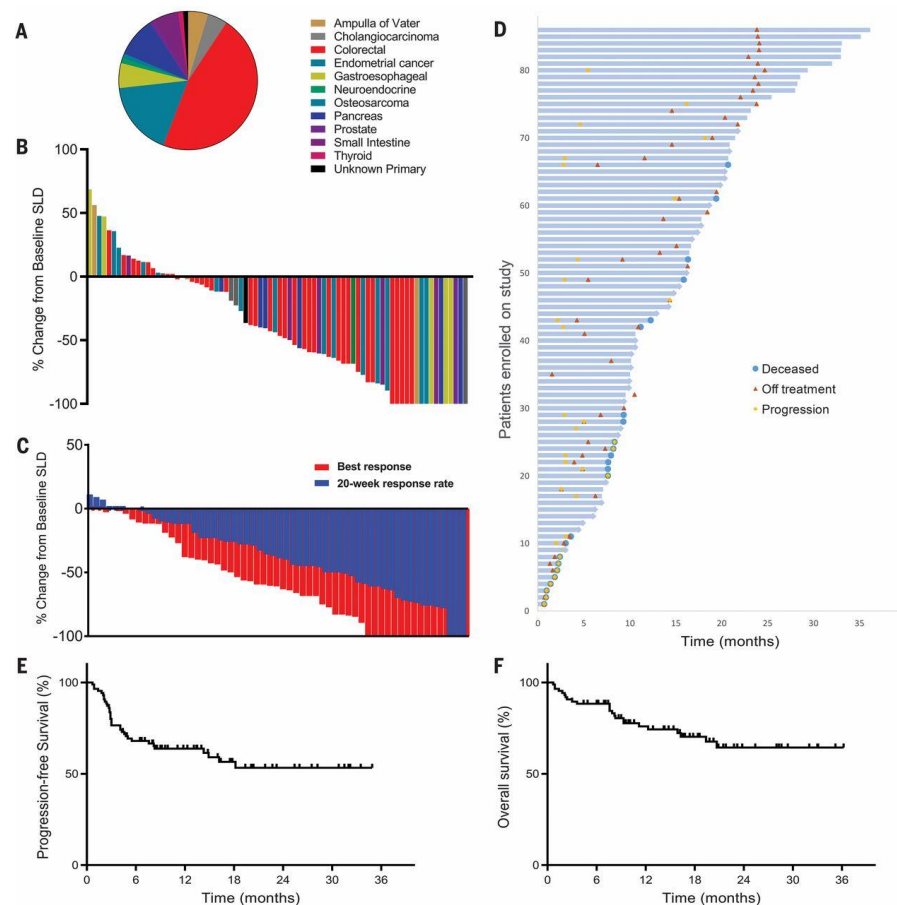
*Approved for adult and pediatric patients

¹Extrapolation from adults to pediatrics

ORR= Overall response rate by RECIST 1.1



Response to Pembrolizumab across Different Tumor Types with dMMR





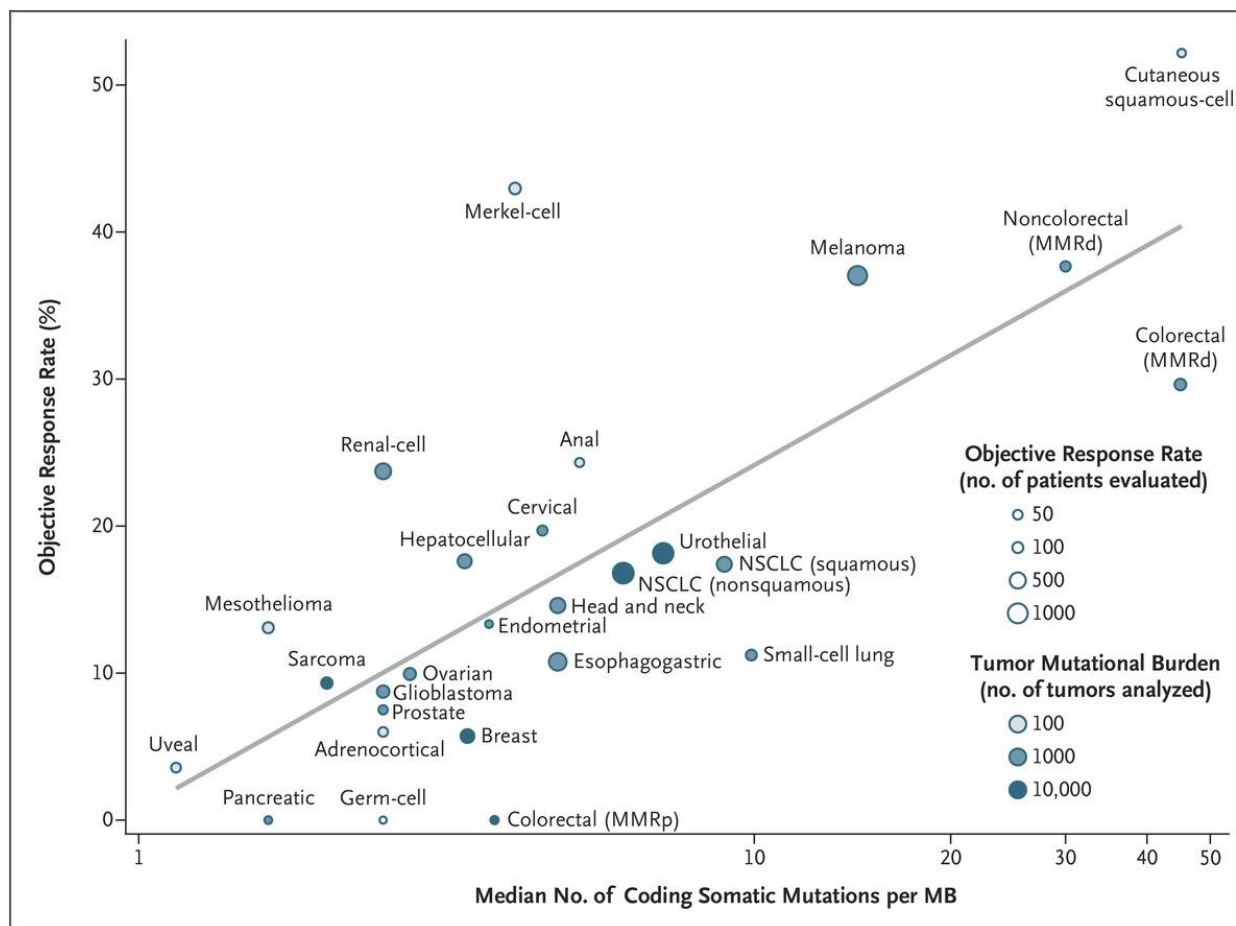
Pembrolizumab Response Rate by Tumor Type

Pembrolizumab Response Rate by Tumor Type.*			
Tumor Type	No. of Tumors	Patients with a Response <i>no. (%)</i>	Range of Response Duration <i>mo</i>
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.



Response Rate to Anti-PD1or Anti-PD-L1 Therapy vs. TMB

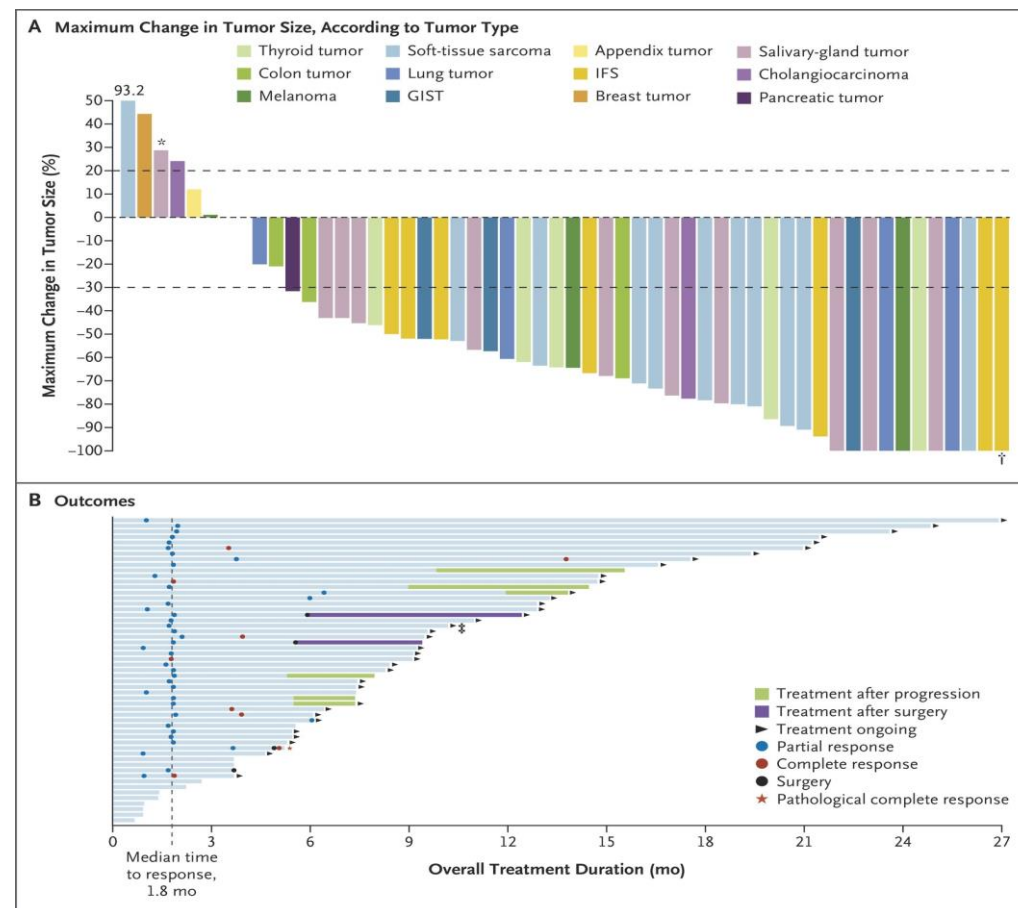


Response to Pembrolizumab in Tumors with ≥ 10 Muts/Mb

Tumor Types	Number	Objective Response Rate N (%) (95% CI)	Duration of Response Range (months)
Overall	102	30 (29) (21,39)	2.2+, 34.8+
Small cell lung	34	10 (29) (15,47)	4.1, 32.5+
Cervical	16	5 (31) (11,59)	3.7+, 34.8+
Endometrial	15	7 (47) (21,73)	8.4+, 33.9+
Anal	14	1 (7) (0.2,34)	18.8+
Vulvar	12	2 (17) (2,48)	8.8, 11
Neuroendocrine	5	2 (40) (5,85)	2.2+, 32.6+
Salivary	3	PR, SD, PD	31.3
Thyroid	2	CR, CR	8.2, 33.2+
Mesothelioma	1	PD	



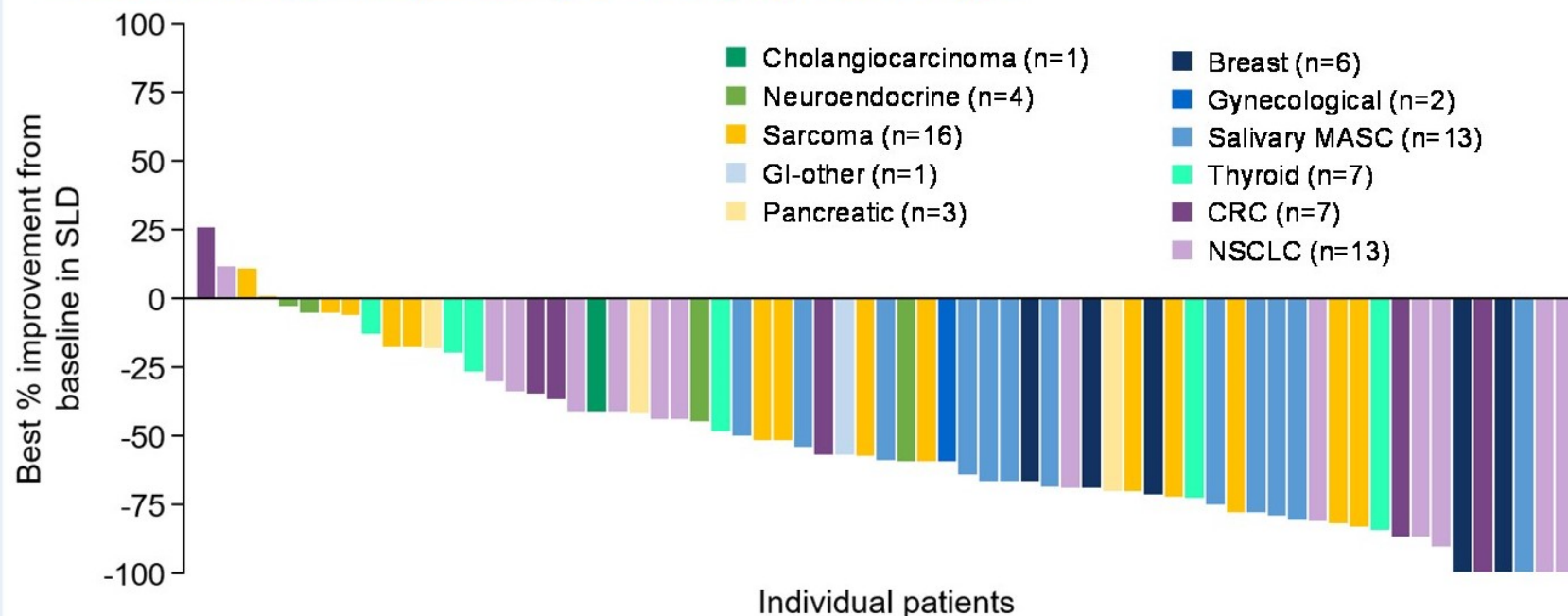
Efficacy of Larotrectinib in Tumors with *NTRK* Fusions





Efficacy of Entrectinib in Tumors with *NTRK* Fusions

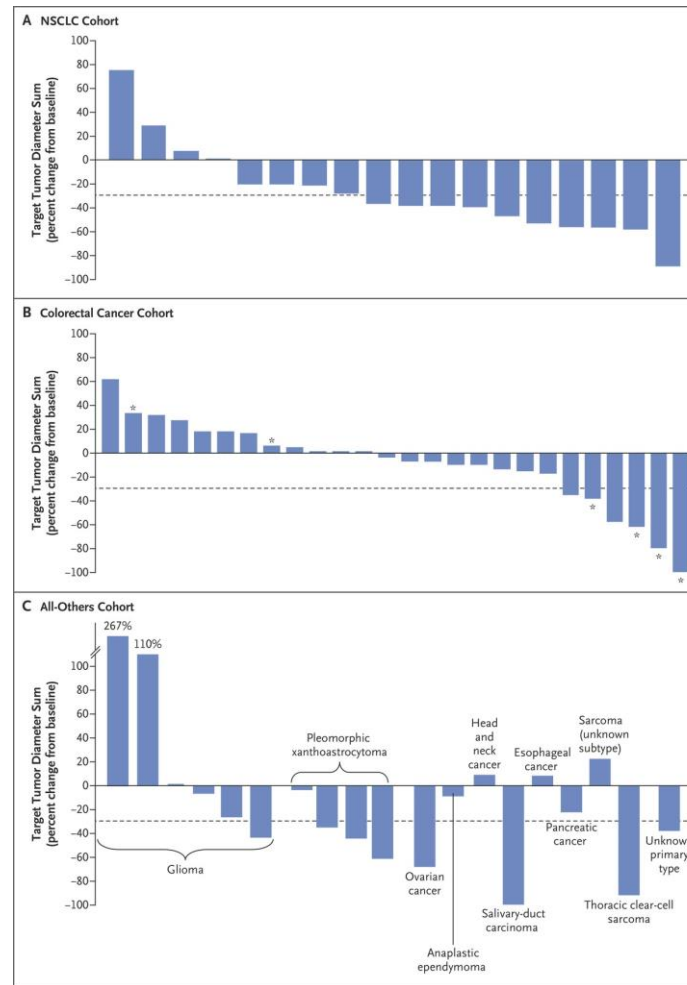
Best individual response per BICR, by tumor type



Patients with missing SLD percent change are excluded from the plot. SLD, sum of longest diameters. GI, gastrointestinal. CRC, colorectal cancer. NSCLC, non-small-cell lung cancer. MASC, mammary analogue secretory carcinoma.



Vemurafenib Response in a *BRAF* Basket Trial





Efficacy of HER2-Directed Therapy in *HER2*-Amplified Tumors

Table 3. Efficacy of Treatment With Trastuzumab Plus Pertuzumab in Patients With HER2 Amplification/Overexpression

Primary Site	No. of Patients	Response, No. (%)			ORR, % (95% CI)
		CR	PR	SD > 120 Days	
Colorectal	37	0	14 (38)	4 (11)	38 (23 to 55)
Lung, non-small-cell	16	0	2 (13)	2 (13)	13 (2 to 38)
Bladder	9	1 (11)	2 (22)	2 (22)	33 (8 to 70)
Pancreas	9	0	2 (22)	1 (11)	22 (3 to 60)
Biliary	7	0	2 (29)	3 (38)	29 (4 to 71)
Ovary	8	0	1 (13)	0	13 (0 to 53)
Uterus	7	0	0	0	0
Salivary gland	5	0	4 (80)	0	80 (28 to > 99)
Other (11 sites)*	16	1 (6)	1 (6)	3 (19)	13 (2 to 38)
Total	114	2 (2)	28 (25)	16 (14)	26 (19 to 35)

NOTE. N = 114. Includes 12 patients with amplification/overexpression plus mutation.

Abbreviations: CR, complete response; ORR, objective response rate; PR, partial response; SD, stable disease.

*Responses occurred in patients with adenocarcinomas of the prostate (one) and skin (apocrine; one).

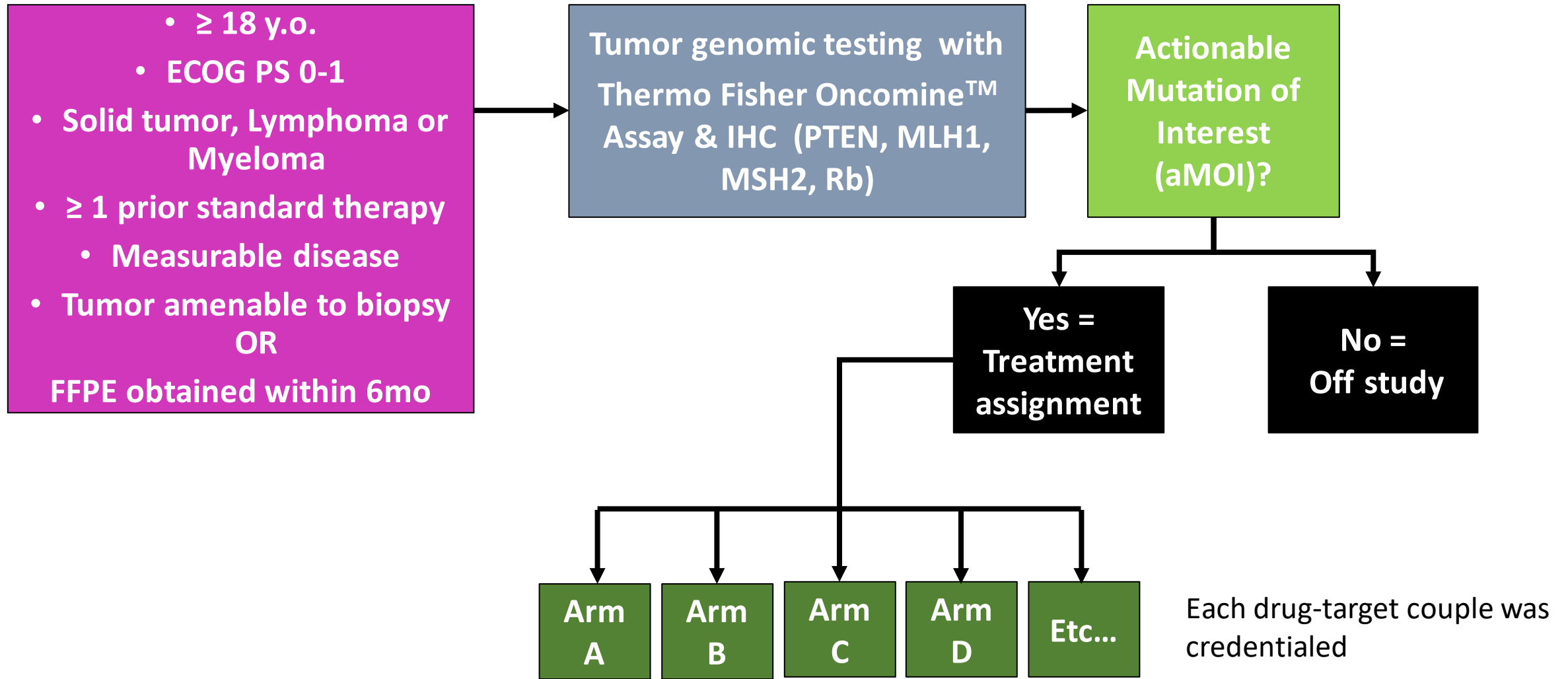


NCI-MATCH Objective

- To determine whether matching certain drugs or drug combinations in adults whose tumors have specific gene abnormalities will effectively treat their cancer, regardless of the cancer type
- This is a signal-finding trial; treatments that show promise can advance to larger, more definitive trials



Screening (Step 0) Overall Design





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NCI-MATCH Treatment Arms with Published Final Results

Arm	Molecular Target	Drug	Overall Response Rate	Citation
Q	HER2 amplifications	T-DM1	5.6%	Jhaveri KL, <i>Annals of Oncology</i> , Nov 2019
Z1D	dMMR status	Nivolumab	36%	Azad NS, <i>J Clin Onc</i> , Dec 2019
R	BRAF Non-V600	Trametinib	3%	Johnson DB, <i>Clin Cancer Res</i> , Jan 2020
W	FGFR	AZD4547	8%	Chae YK, <i>J Clin Onc</i> , May 2020
H	BRAF V600E	Trametinib + dabrafenib	38%	Salama AK, <i>J Clin Onc</i> , xx 2020 (Accepted)

<https://ecog-acrin.org/nci-match-eay131-findings>





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NCI-MATCH Treatment Arms with Presented Preliminary Results (Publications in Development)

Molecular Target	Drug	Arm	Overall Response Rate	First Author and Meeting
AKT	Capivasertib	Y	23%	Kalinsky KM, EORTC-NCI-AACR 2018 Mtg
BRCA1 or BRCA2	AZD1775	Z1I	3.2%	Kummar S, AACR 2019 Annual Mtg
CCND1, 2, or 3	Palbociclib	Z1B	0%	Clark AS, AACR 2019 Annual Mtg
HER2 activating	Afatinib	B	2.7%	Bedard PL, AACR 2019 Annual Mtg
PIK3CA	Taselisib	I	0%	Krop IE, ASCO 2018 Annual Mtg
PTEN	GSK2636771	P N	0% 5%	Janku FM, ESMO 2018 Annual Mtg





Challenges of Histology Agnostic Trials

- Patient identification
- Not all tumor types represented and small sample size for many tumor types.
- Not all tumor types respond or respond equally well; wide CI around response rates and duration
- Biomarker prevalence/predictive value may vary across tumor types
- Molecular diagnostic tests may not be standardized
- Are RCTs necessary/possible? What is appropriate control group? Are synthetic control groups possible?
- How much evidence is sufficient for a histology-agnostic approval? Can approval be withdrawn/modified if post-market data fail to confirm?



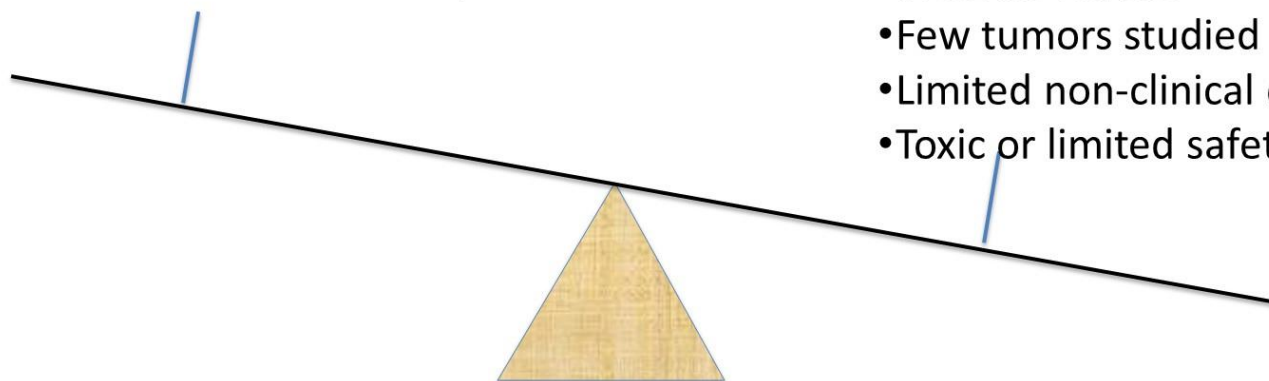
Does the data support approval?

Totality of Data / Uncertainty



- High durable ORRs
- Consistent results in many tumors
- RCTs in one or more settings
- Good and well understood toxicity profile

- Low ORRs with no responses in some tumors
- Few tumors studied
- Limited non-clinical data
- Toxic or limited safety data





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Overall Goals of TAPUR

- To learn from the real world practice of prescribing approved, targeted therapies to patients with advanced cancer whose tumor harbors a genomic variant known to be a drug target outside of approved indications
- To educate oncologists about implementation of precision medicine in clinical practice





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, CGH, NGS, WES, IHC for gene expression) performed in a CLIA certified, CAP or NY state accredited lab. Tests registered with NIH Genetic Test Registry preferred.
- Treatment specific inclusion/exclusion criteria



Study Endpoints

- Primary endpoint: Disease control rate (DCR) measured as Objective Response rate per standard response criteria plus SD at 16+ weeks
- Other endpoints:
 - Overall survival
 - Progression-free survival
 - Time on treatment
 - Grade 3-5 AEs per CTCAE
 - SAEs



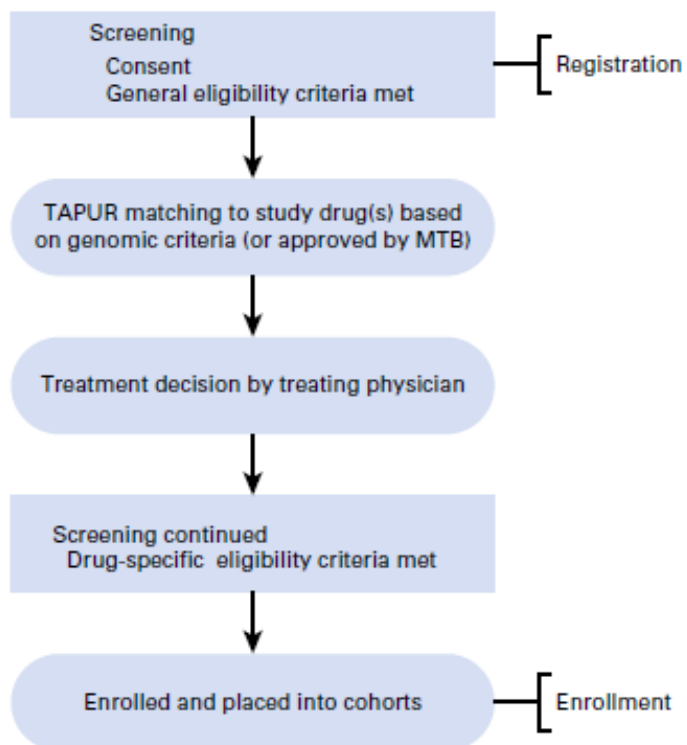
Statistical Design

- Simon's two-stage design
- Each tumor type-gene-drug is a “cohort”
- Null Hypothesis: $DCR < 15\%$ vs. Alternative Hypothesis: $DCR \geq 35\%$
- 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

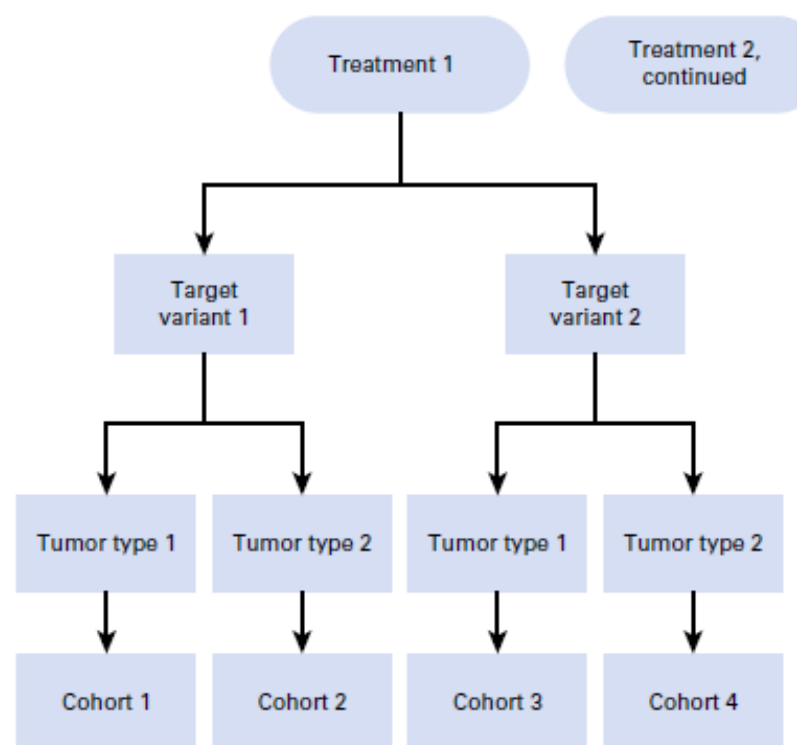


Cohort Creation

A



B



Completed Cohorts



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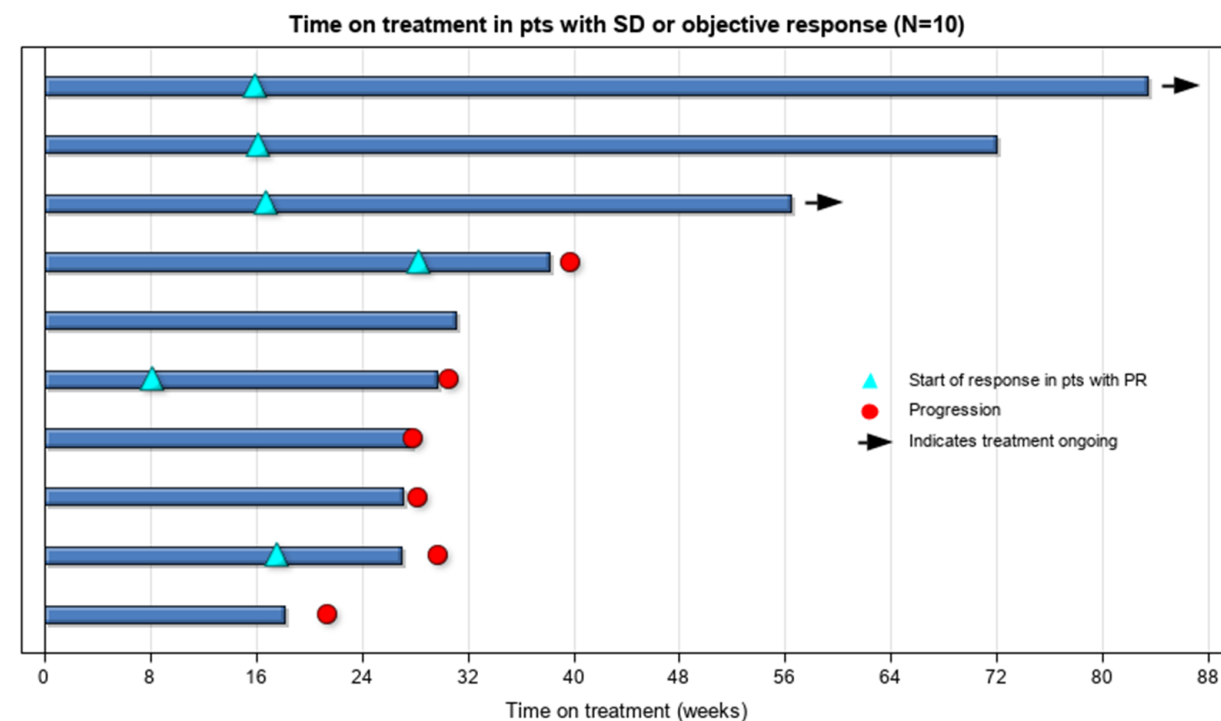
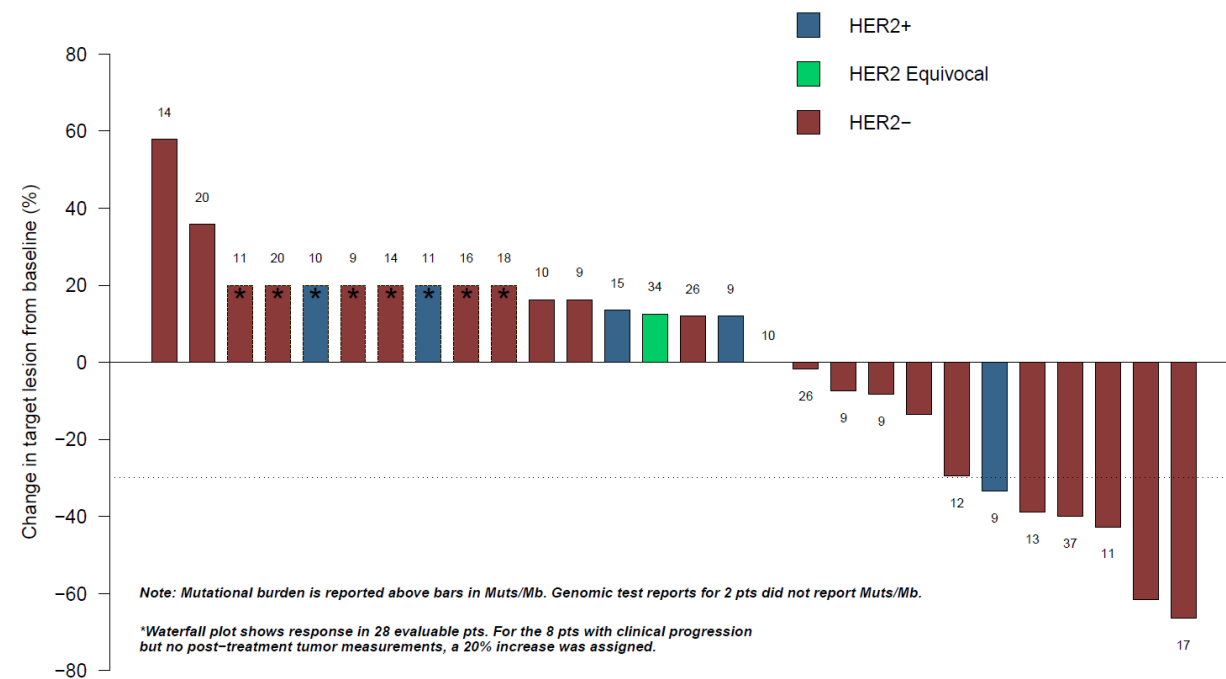


Study Treatment	Tumor Type	Variant	Signal
Palbociclib	Gallbladder and Bile Ducts	CDKN2A mutation or loss	
Palbociclib	Pancreatic Cancer	CDKN2A mutation or loss	
Cetuximab	Breast Cancer	KRAS, NRAS and BRAF wildtype	
Cetuximab	NSCLC	KRAS, NRAS and BRAF wildtype	
Cetuximab	Ovarian	KRAS, NRAS and BRAF wildtype	
Sunitinib	Colorectal Cancer	FLT-3 mutation or amplification	
Olaparib	Pancreatic Cancer	BRCA1/BRCA1 mutation	
Olaparib	Prostate Cancer	BRCA1/BRCA1 mutation	
Palbociclib	NSCLC	CDKN2A loss or mutation	
Pembrolizumab	Breast Cancer	HTMB	
Pembrolizumab	Colorectal Cancer	HTMB	
Pertuzumab + Trastuzumab	Colorectal Cancer	ERBB2 amplification	
Vemurafenib + Cobimetinib	Colorectal Cancer	BRAF_V600E/D/K/R mutation	



Pembrolizumab in Breast Cancer with HTMB

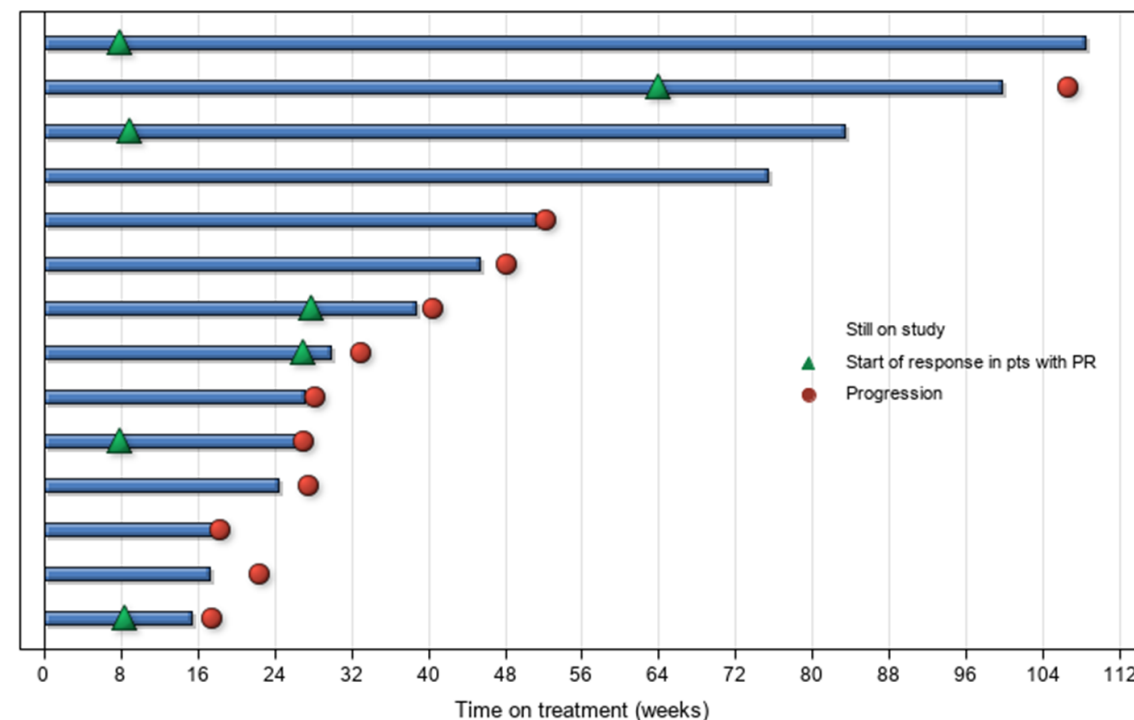
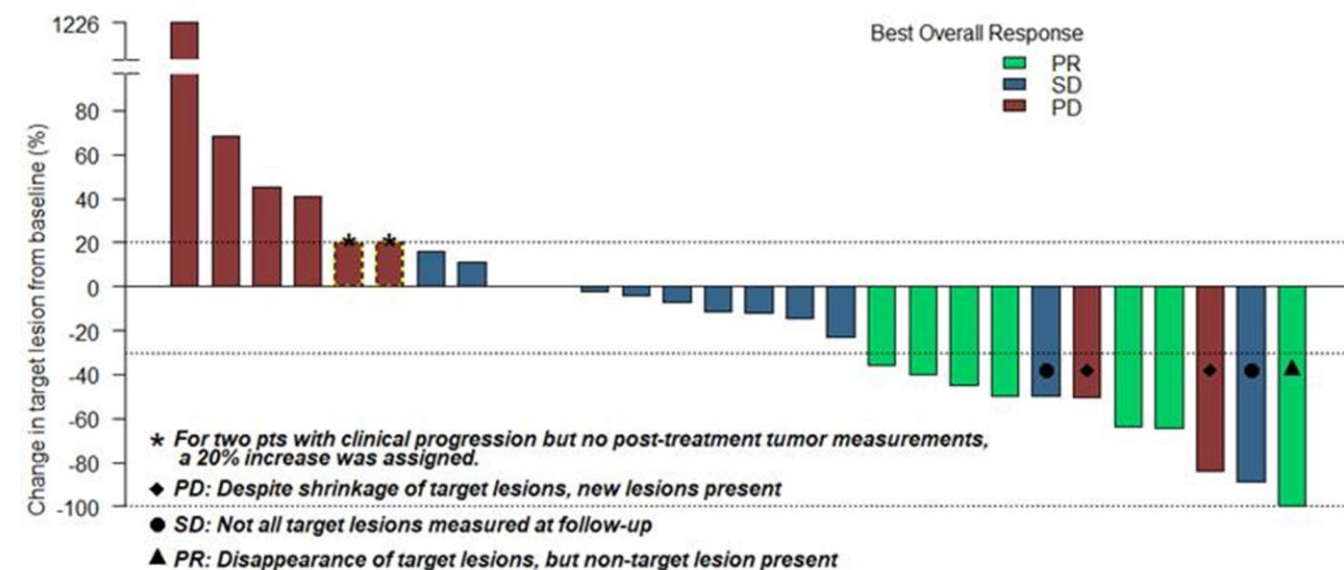
Disease Control Rate 37% [90% CI 24, 46]





Pertuzumab + Trastuzumab in *HER2*-Amplified mCRC

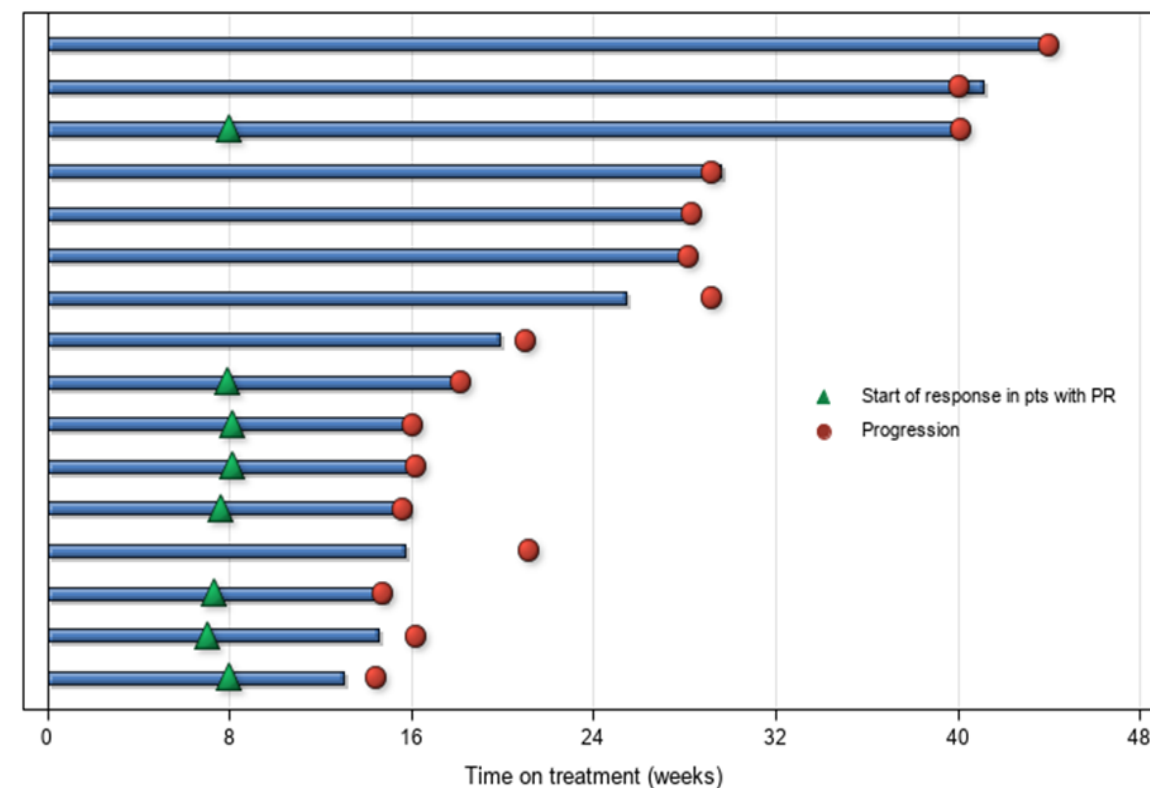
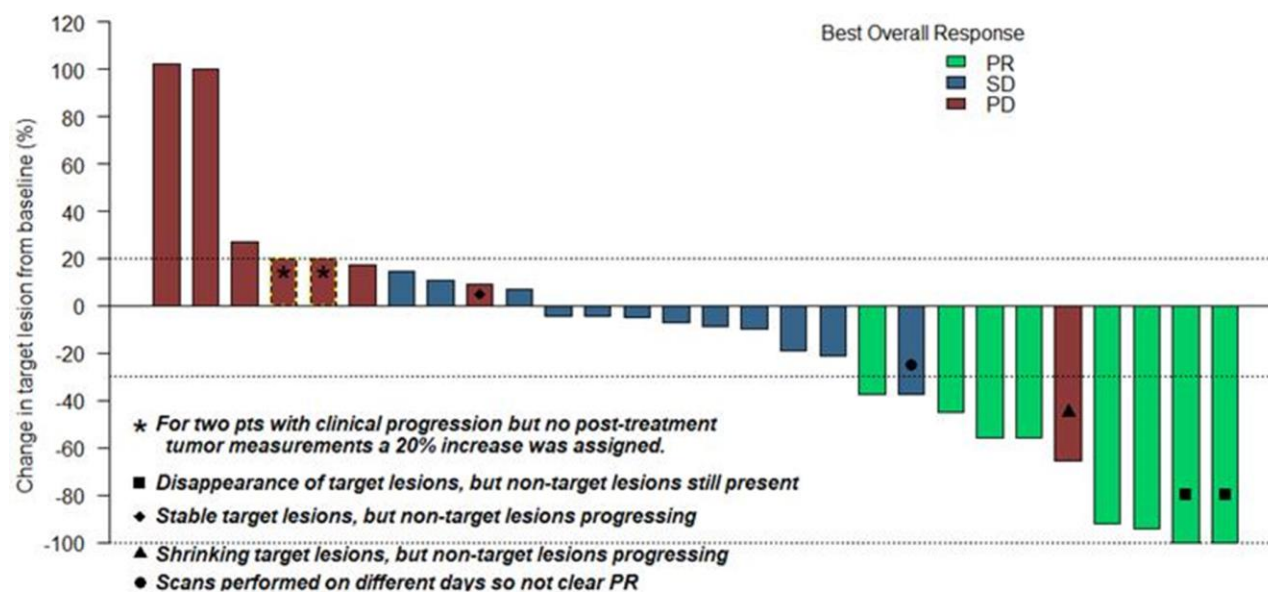
Disease Control Rate 50% [90% CI 36,60]





Cobimetinib + Vemurafenib in *BRAF* V600 Mutant mCRC

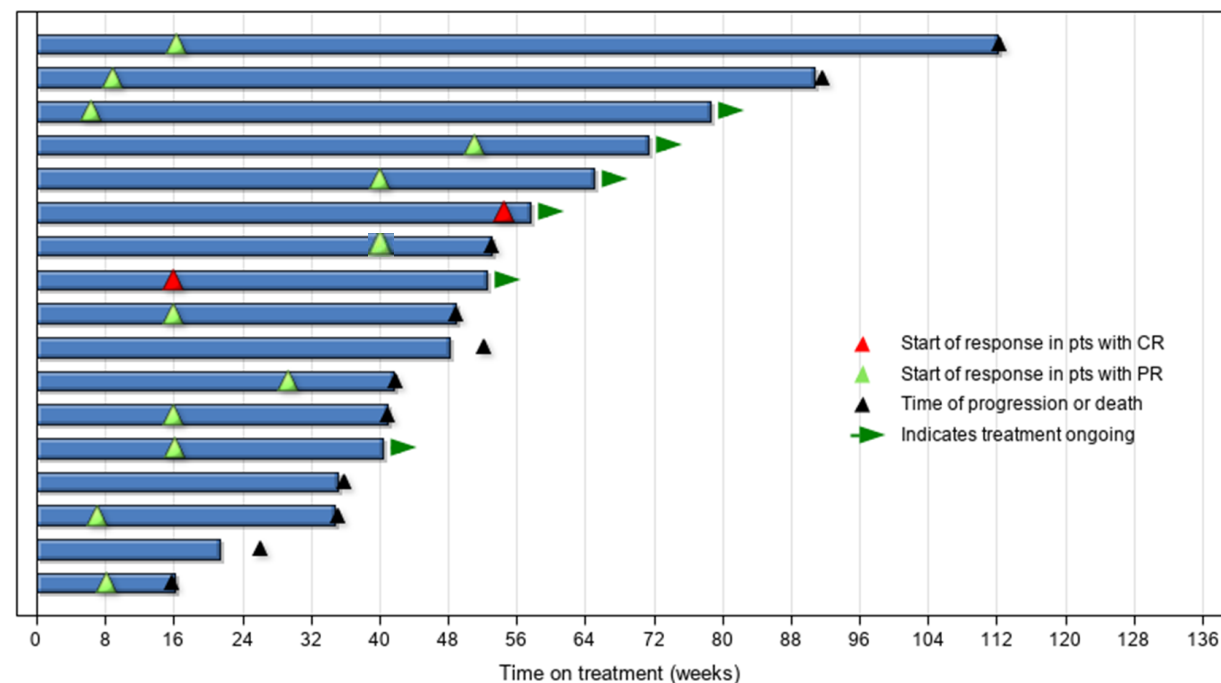
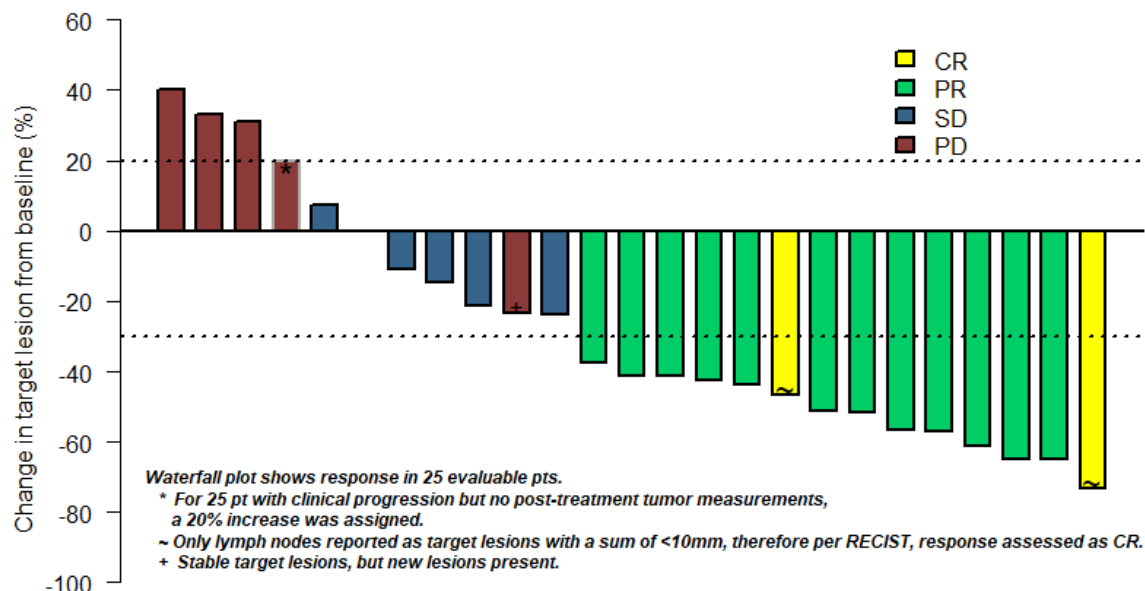
Disease Control Rate 57% [90% CI 43,67]





Olaparib in Prostate Cancer with *BRCA1/2* Mutation

Disease Control Rate 68% [90% CI 53,77]



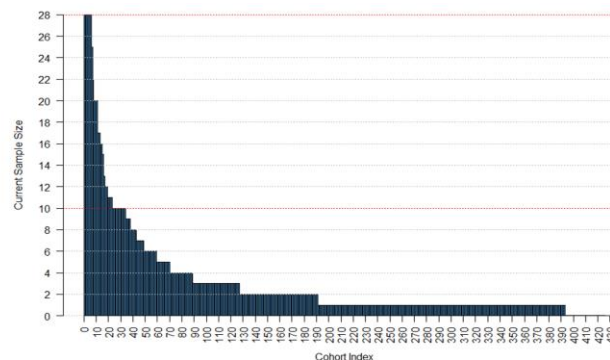


Cohort Collapsing Rule

Low enrolling histology-
specific cohorts:
Tumor type+Alteration+Drug

5 or fewer patients enrolled
in 18 months or <3 patients
enrolled in 12 months

Histology-
pooled cohort:
Alteration+Drug





Example of a Collapsed TAPUR Study Cohort

Study Drug	Variant	Total Enrolled in Collapsed Cohort	Tumor type	Number Enrolled in Cohort
Temsirrolimus (TORISEL)	PTEN mutation	34	Anal Cancer	1
			Breast Cancer	4
			Head and Neck Cancer	4
			Malignant carcinoid tumors of the appendix, large intestine, and rectum	1
			Malignant neoplasm of bronchus and lung	5
			Malignant neoplasm without specification of site	2
			Prostate Cancer	10
			Soft tissue sarcoma	5
			Stomach Cancer	1
			Uterine Cancer	1



Conclusions

- No single best approach to tumor agnostic drug trials
- Understand the target/pathway
- Use a validated biomarker test to select patients
- Plan prospectively
- Include as many tumor types as possible
- Collect post-market data to verify histology agnostic activity and understand heterogeneity of response