Personalized *versus* precision medicine

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Personalized medicine ;a less ‘precise’ term

- Can be misinterpreted that the treatment is uniquely developed for that particular individual
- Sipuleucel

Montague or Capulet

- Juliet :
  - “What’s in a name? That which we call a rose
  - By any other name would smell as sweet.”
    - *Romeo and Juliet , William Shakespeare*

Rationale

- Avoiding “one-size-fits-all”
- Encompasses new diagnostics
- Individually targets patient’s own genetic,biomarker,phenotypic and psychosocial characteristics
- Paving the way to a new ‘taxonomy’ of all human diseases

Technology

- As an example,one company product offers a targeted approach for the entire coding sequence of 315 cancer genes
- Luxury of using FFPE specimens

FOUNDATIONONE

Patient Name	Report Date	Tumor Type
		Lung adenocarcinoma

Date of Birth		Medical Facility			
Sex	Male	Ordering Physician		Specimen Received	
FMI Case #		Additional Recipient		Specimen Site	Lymph Node
Medical Record #		Medical Facility ID #		Date of Collection	
Specimen ID		Pathologist		Specimen Type	

ABOUT THE TEST:

FoundationOne™ is a next-generation sequencing (NGS) based assay that identifies genomic alterations within hundreds of cancer-related genes.

PATIENT RESULTS

11 genomic findings

10 therapies associated with potential clinical benefit

0 therapies associated with lack of response

19 clinical trials

TUMOR TYPE: LUNG ADENOCARCINOMA

Genomic Alterations Identified†

ERBB2 amplification – equivocal*
NF2 E427*
STK11 splice site 921-1G>C
CDKN1B E105fs*14
FOXP1 E490*
KDM5C W983*
LRP1B loss exons 6-14
SPTA1 Q1346fs*3, splice site 3570-2A>T
TP53 I255S

Additional Findings†

Tumor Mutation Burden TMB-High; 37.53 Muts/Mb

Additional Disease-relevant Genes with No Reportable Alterations Identified†

EGFR
KRAS
ALK
BRAF
MET
RET
ROS1

† For a complete list of the genes assayed and performance specifications, please refer to the Appendix
* See Appendix for details

THERAPEUTIC IMPLICATIONS

FOUNDATIONONE BioSequence

Patient Name	Report Date	Diagnosis
Jones, Jane	May 2012	Breast carcinoma

Date of Birth	1950-01-01	**Client**	City Hospital	**Specimen Received**	May 2012
Gender	Female	**Physician**	Smith, Susan	**Specimen Site**	Breast
FMI Case #	Sample	**Additional Recipient**	Lee, Laura	**Specimen Date**	August 2011
Medical Record #	Sample	**FMI Client #**	Sample	**Specimen Type**	Block
Block ID	Sample	**Pathologist**	Allen, Alison		

ABOUT THE TEST:

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PATIENT RESULTS

TUMOR TYPE: BREAST CARCINOMA

Genomic Alterations Identified

PIK3CA H1047R
CCND1 amplification
CDH1 E167*

THERAPEUTIC IMPLICATIONS

Genomic Alterations Detected	FDA Approved Therapies (in patient's tumor type)	FDA Approved Therapies (in another tumor type)	Potential Clinical Trials
PIK3CA H1047R	None	Everolimus Temsirolimus	Yes, see clinical trials section
CCND1 amplification	None	None	Yes, see clinical trials section
CDH1 E167*	None	None	None

Note: Genomic alterations detected may be associated with activity of certain FDA approved drugs; however, the agents listed in this report may have varied clinical evidence in the patient's tumor type. Neither the therapeutic agents nor the trials identified are ranked in order of potential or predicted efficacy for this patient, nor are they ranked in order of level of evidence for this patient's tumor type.

Limitations

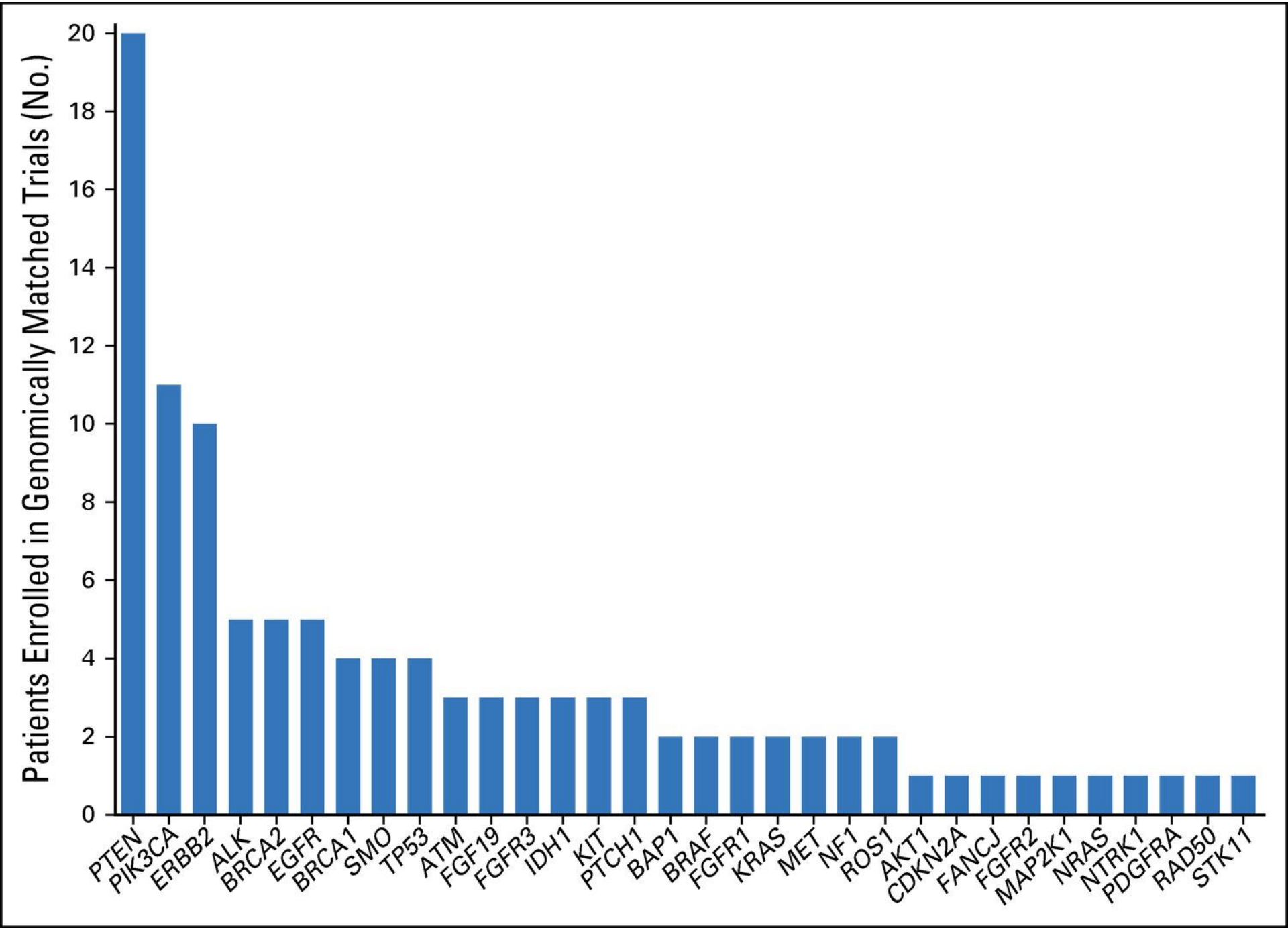
- Specimen Quality
- Distinguishing driver and passenger mutations
- Tumor heterogeneity
- Incidental germ-line mutations
- Pretreatment of tumors with cytotoxic therapies leading to genomic instability

Interpretation

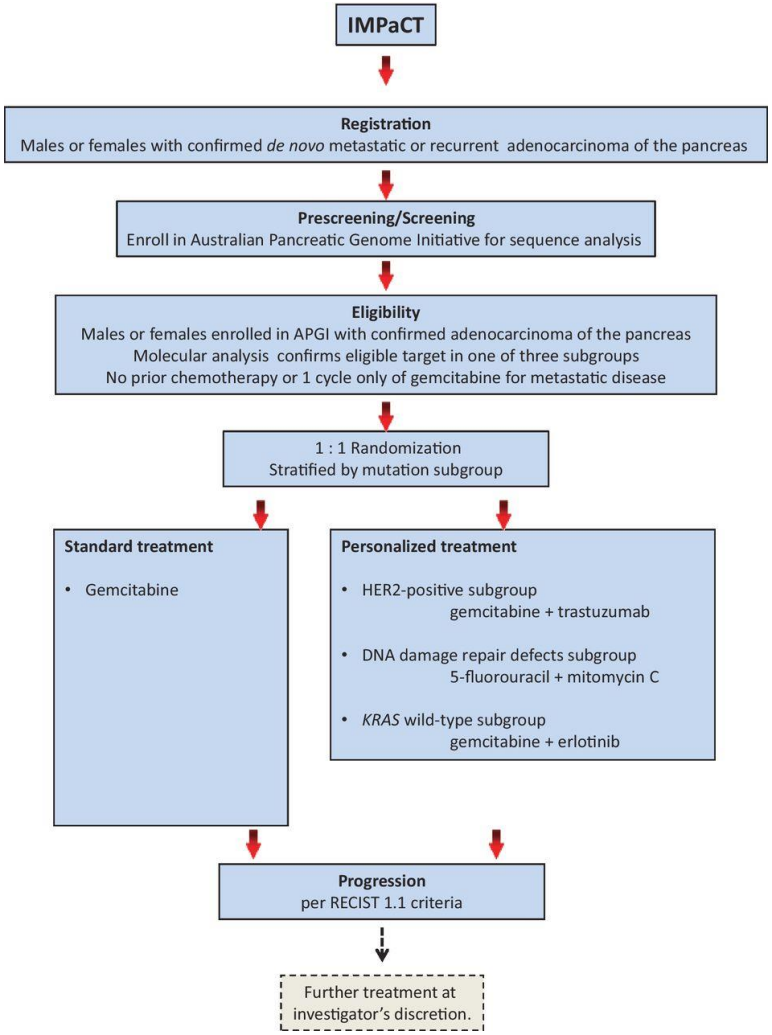
- Clinical sequencing typically turn up far more passenger mutations with unclear biologic and clinical significance
- Many of the clinically and biologically significant mutations are not ‘actionable”

Low clinical utility

- Only one-half of patients enrolled in a trial at MDACC received genotype-relevant drug!
  - Meric-Bernstamm et al
    - *J Clin Oncol 2016*
- Clinically validated mutations are present in < 10% of patients


Patients Enrolled in Genomically Matched Trials (No.)
0
2
4
6
8
10
12
14
16
18
20
PTEN
PIK3CA
ERBB2
ALK
BRCA2
EGFR
BRCA1
SMO
TP53
ATM
FGF19
FGFR3
IDH1
KIT
PTCH1
BAP1
BRAF
FGFR1
KRAS
MET
NF1
ROS1
AKT1
CDKN2A
FANCJ
FGFR2
MAP2K1
NRAS
NTRK1
PDGFRA
RAD50
STK11

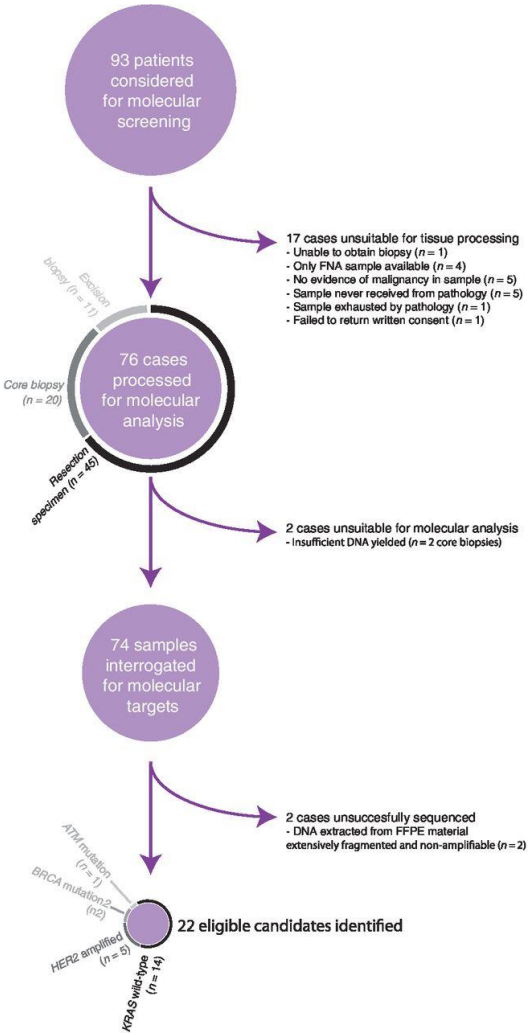
The original IMPaCT trial schema.



Lorraine A. Chantrill et al. Clin Cancer Res 2015;21:2029-2037

Clinical Cancer Research
AACR American Association for Cancer Research

An overview of the number of cases successfully screened for eligibility for the IMPaCT trial.



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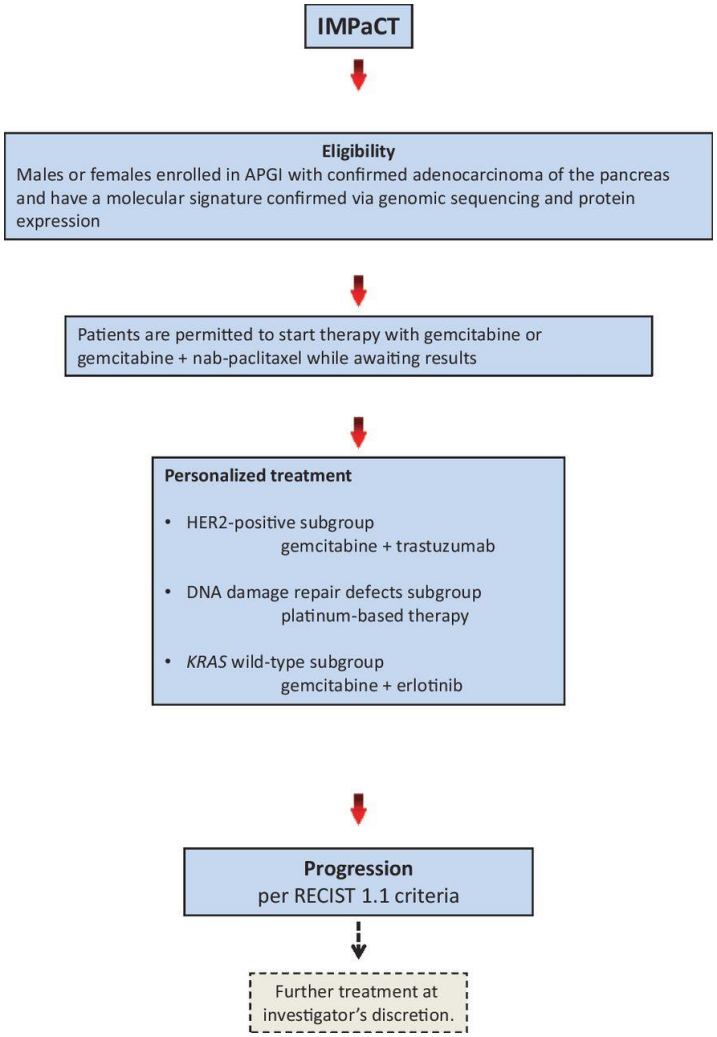
The amended trial is a single-arm pilot study.



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Basket trials

- Some mutations are predictive as ‘tissue agnostic’ e.g. anti-PD-1 for MMR phenotype and possibly TMB
- Some not,e.g. BRAF for colorectal cancer ; tumor microenvironment and epigenetics dictate the outcome
- ERBB2 amplification in colorectal,pancreatic and NSCLC (MyPathway trial)

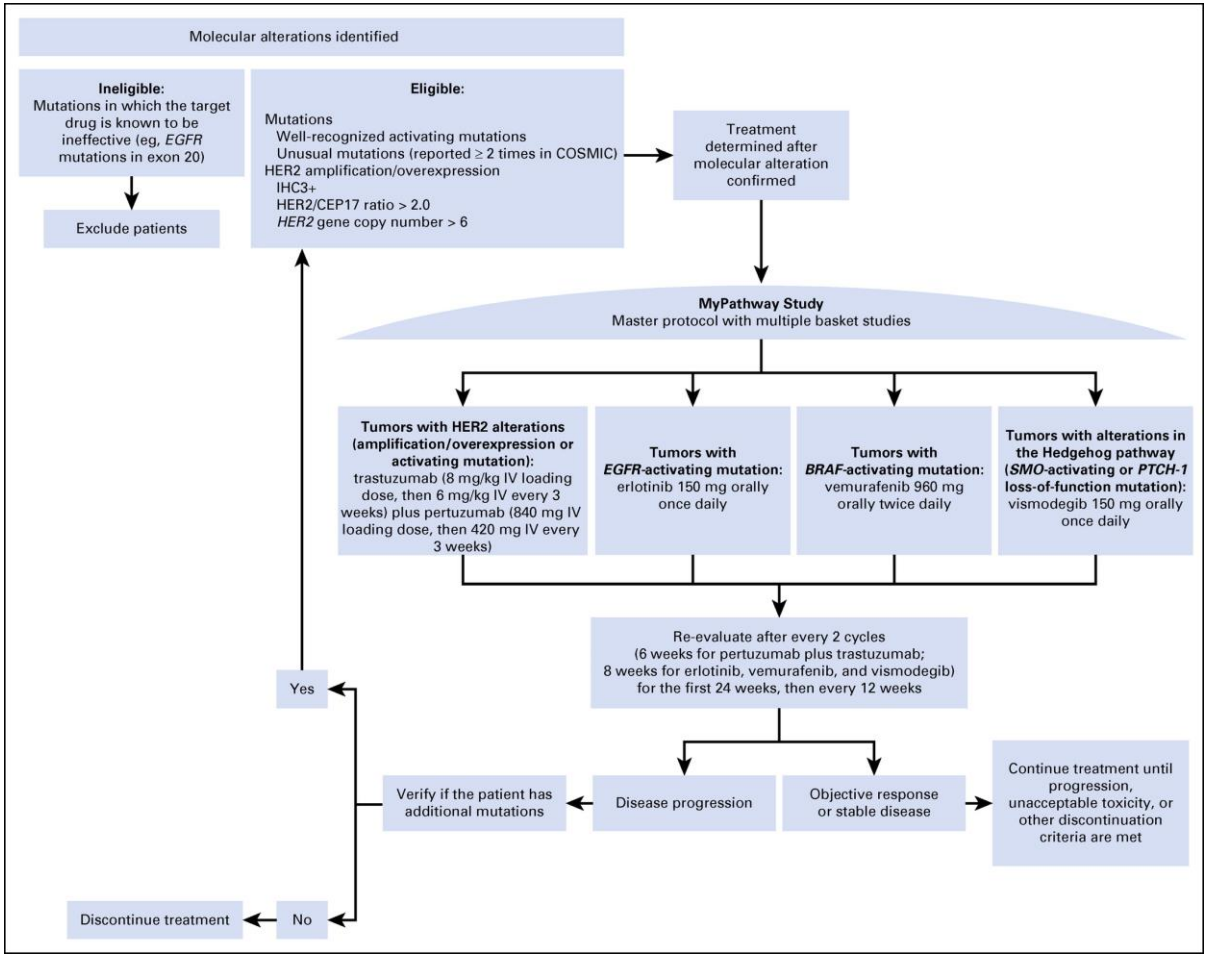

Molecular alterations identified
Ineligible:
Mutations in which the target drug is known to be ineffective (eg, EGFR mutations in exon 20)
Exclude patients
Eligible:
Mutations
Well-recognized activating mutations
Unusual mutations (reported ≥ 2 times in COSMIC)
HER2 amplification/overexpression
IHC3+
HER2/CEP17 ratio > 2.0
HER2 gene copy number > 6
Treatment determined after molecular alteration confirmed
MyPathway Study
Master protocol with multiple basket studies
Tumors with HER2 alterations (amplification/overexpression or activating mutation): trastuzumab (8 mg/kg IV loading dose, then 6 mg/kg IV every 3 weeks) plus pertuzumab (840 mg IV loading dose, then 420 mg IV every 3 weeks)
Tumors with EGFR-activating mutation: erlotinib 150 mg orally once daily
Tumors with BRAF-activating mutation: vemurafenib 960 mg orally twice daily
Tumors with alterations in the Hedgehog pathway (SMO-activating or PTCH-1 loss-of-function mutation): vismodegib 150 mg orally once daily
Re-evaluate after every 2 cycles (6 weeks for pertuzumab plus trastuzumab; 8 weeks for erlotinib, vemurafenib, and vismodegib) for the first 24 weeks, then every 12 weeks
Disease progression
Objective response or stable disease
Continue treatment until progression, unacceptable toxicity, or other discontinuation criteria are met
Verify if the patient has additional mutations
Yes
No
Discontinue treatment

Table 2. Tumor Types and Molecular Alterations

Primary Site	HER2	BRAF	Hedgehog Pathway	EGFR	Total
Lung, non–small-cell	30	21	3	0	54
Colorectal	40	2	0	0	42
Biliary	11*	3	0	1	15
Ovary	8	4	2	0	14
Bladder	13	0	0	0	13
Pancreas	9	4	0	0	13
Uterus	7	0	0	0	7
Breast	2†	0	2	2	6
Salivary gland	5	0	1	0	6
Small intestine	4	0	1	1	6
Prostate	1	3	1	0	5
Unknown primary	1	3	1	0	5
Other (21 tumor types)	20	9	10	5	44
Total	151 (66%)	49 (21%)	21 (9%)	9 (4%)	230

NOTE. N = 230.

Abbreviations: BRAF, murine sarcoma viral (v-raf) oncogene homolog B1; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor-2.

*One patient had a tumor with an RBMS-NRG1 fusion.

†Both had *HER2* mutations without amplification or overexpression.

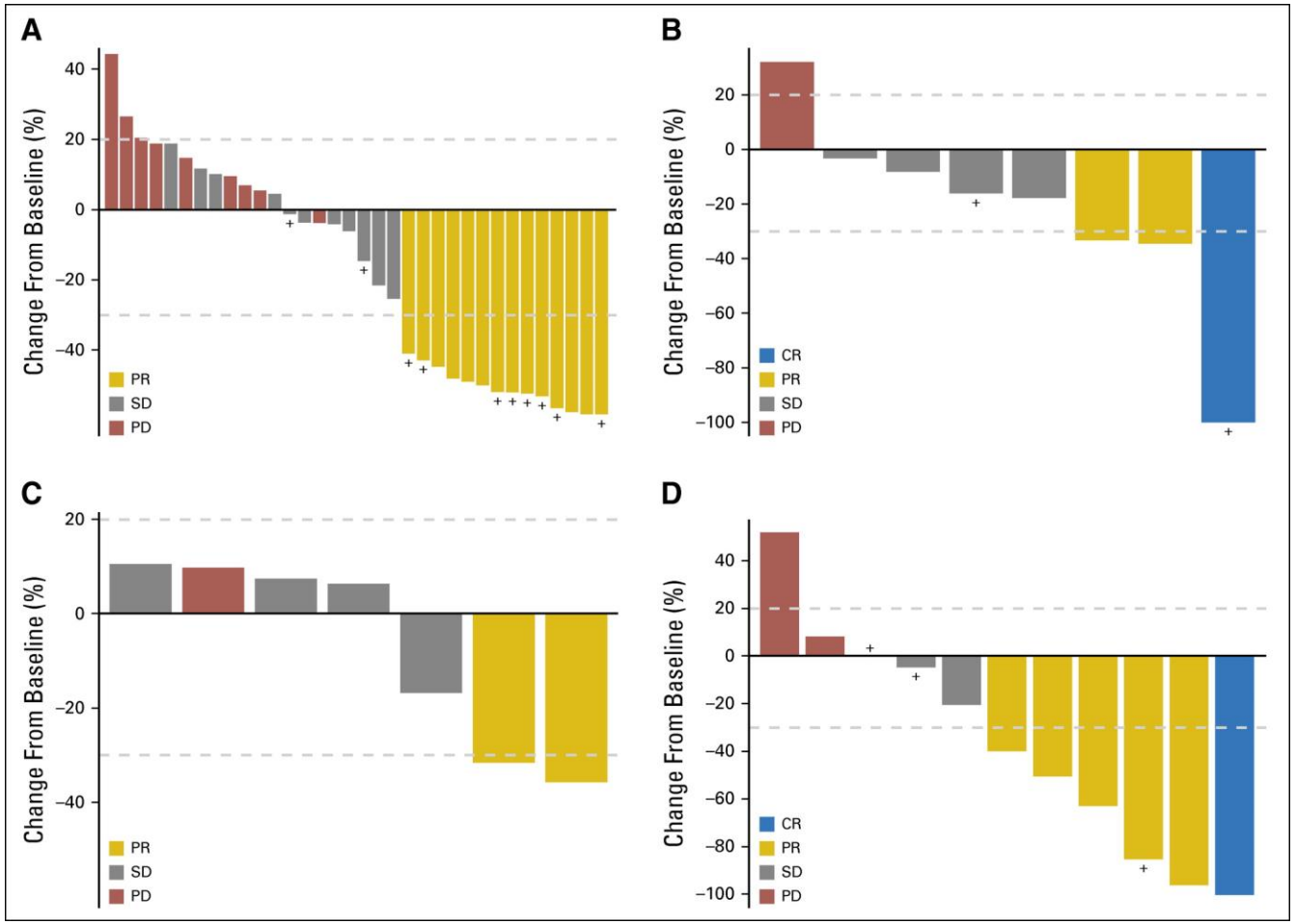
Table 3. Efficacy of Treatment With Trastuzumab Plus Pertuzumab in Patients With HER2 Amplification/Overexpression

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).


A
Change From Baseline (%)
40
20
0
−20
−40
PR
SD
PD
B
Change From Baseline (%)
20
0
−20
−40
−60
−80
−100
CR
PR
SD
PD
C
Change From Baseline (%)
20
0
−20
−40
PR
SD
PD
D
Change From Baseline (%)
40
20
0
−20
−40
−60
−80
−100
CR
PR
SD
PD

TAPUR Trial

- Collecting ‘real-world’ data about the off-label use of FDA-approved drugs in genetically-profiled patients
- Participating pharma
  - Astra Zeneca
  - Bayer
  - BMS
  - Eli Lilly
  - Genentech
  - Merck
  - Pfizer

TAPUR drugs

- Axitinib
- Bosutinib
- Crizotinib
- Palbociclib
- Sunitinib
- Temsirolimus
- Trastuzumab-Pertuzumab
- Vemurafenib-Cobimetinib
- Cetuximab
- Dasatinib
- Regorafenib
- Olaparib
- Pembrolizumab
- Nivolumab-Ipilimumab

Precision Medicine ; Is It ready for prime time?

- I guess ‘Not yet’..

Precision medicine ; is it ready for prime time?

- Probably not,but getting there pretty fast…