Precision Oncology(PO): “The new kid on the block”

Froedtert & Medical College of Wisconsin
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Disclosure of Conflicts of Interest

Aditya Shreenivas, MD, MS, has the following financial relationships to disclose:

- Research funding: Natera
- Advisory board member: Taiho Oncology
- I have no conflict of interest related to this presentation

Agenda

- Introduction
- Targetable mutations and who should be seen in our clinic?
- Workflow of the precision clinic
- Case discussions
- Why target multiple pathways at the same time?
- Examples of some studies in this space

Our Precision Oncology & Rare Cancer Team

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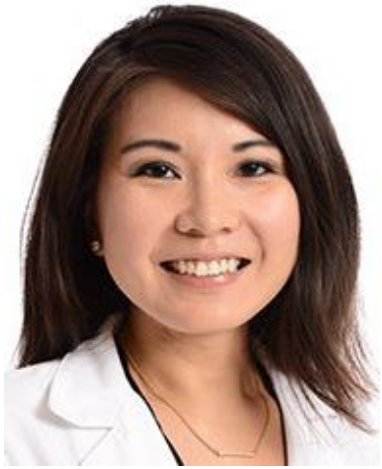

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not share.

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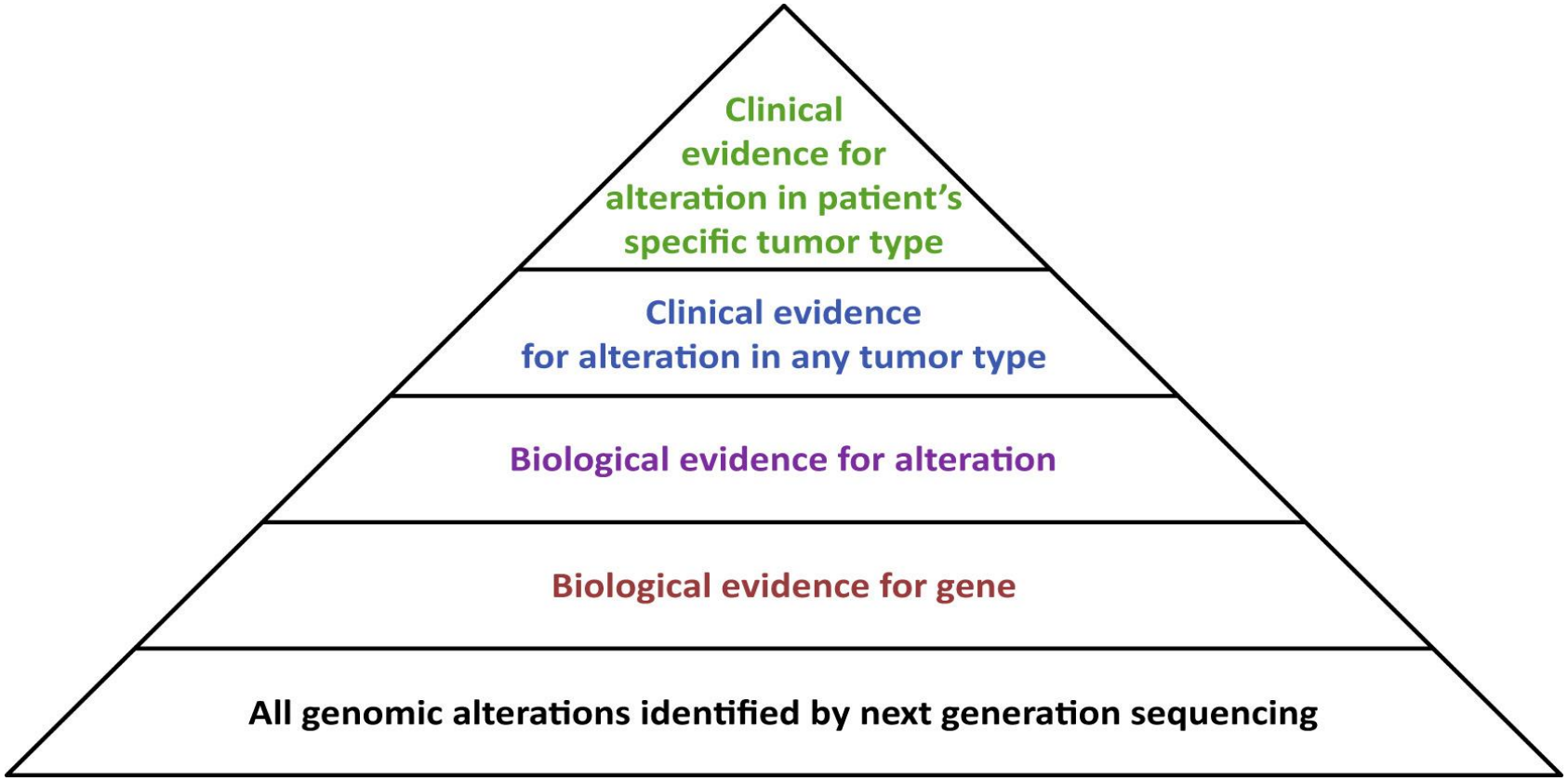
Not Enough Targetable Mutations

- Comprehensive genomic panel (CGP) can analyze a broad panel of genes to detect the four main classes of genomic alterations known to drive cancer growth:

1. Base substitutions,
2. Insertions and deletions,
3. Copy number alterations (CNAs)
4. Rearrangements or fusions

- The field of precision oncology has come a long way since the Human Genome project, but we still don't have enough targeted therapies.

Actionable Alterations Associated with Clinical Response



Ref : Hannah Wise et al Cancer Cell 2019 35825-826DOI: (10.1016/j.ccell.2019.05.009)

Who should be seen in our clinic?

- Advanced cancer patients that have progressed through at least 1 or 2 lines of therapy
- Rare and Ultra-Rare Cancers ~200 types of cancer
  - Rare <6 per 100,000 (~22% of cancers)
  - Ultra rare = prevalence 2000 per year in Europe and <2 per 100,000 in the USA (~5% of cancers)

- Rationale for including rare cancers:

1. Rare tumors occur in younger individuals and are associated with poorer outcomes
2. Dearth of standard of care options and clinical trials

Ref : Casali Paolo G., Trama Annalisa. Rationale of the rare cancer list: a consensus paper from the Joint Action on Rare Cancers (JARC) of the European Union (EU) ESMO Open 2020.
Ref: Gatta et al, Eur J Cancer 2011 Greenlee et al, Public Health Rep 2010

Workflow of Precision Clinic and Molecular Tumor Board

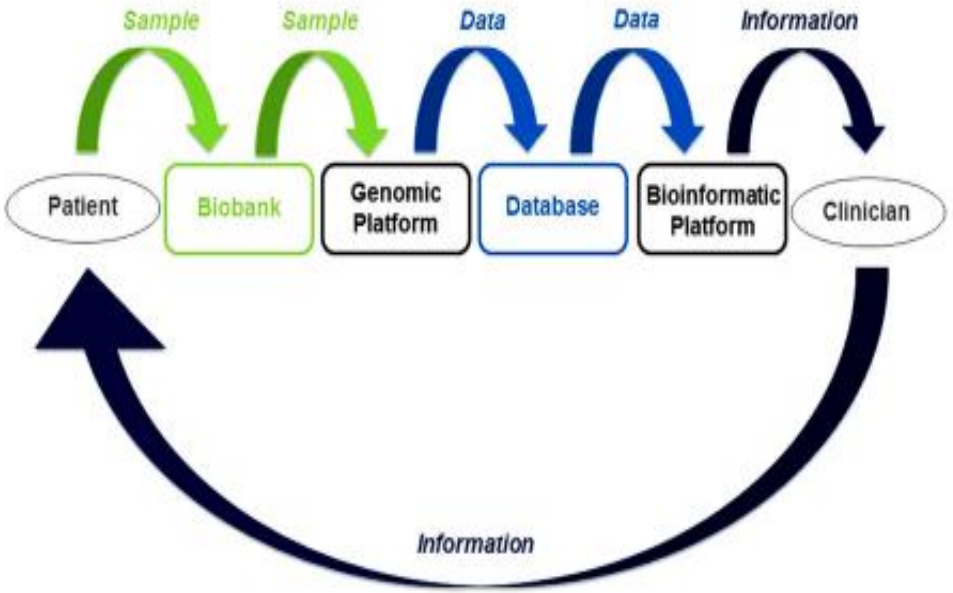
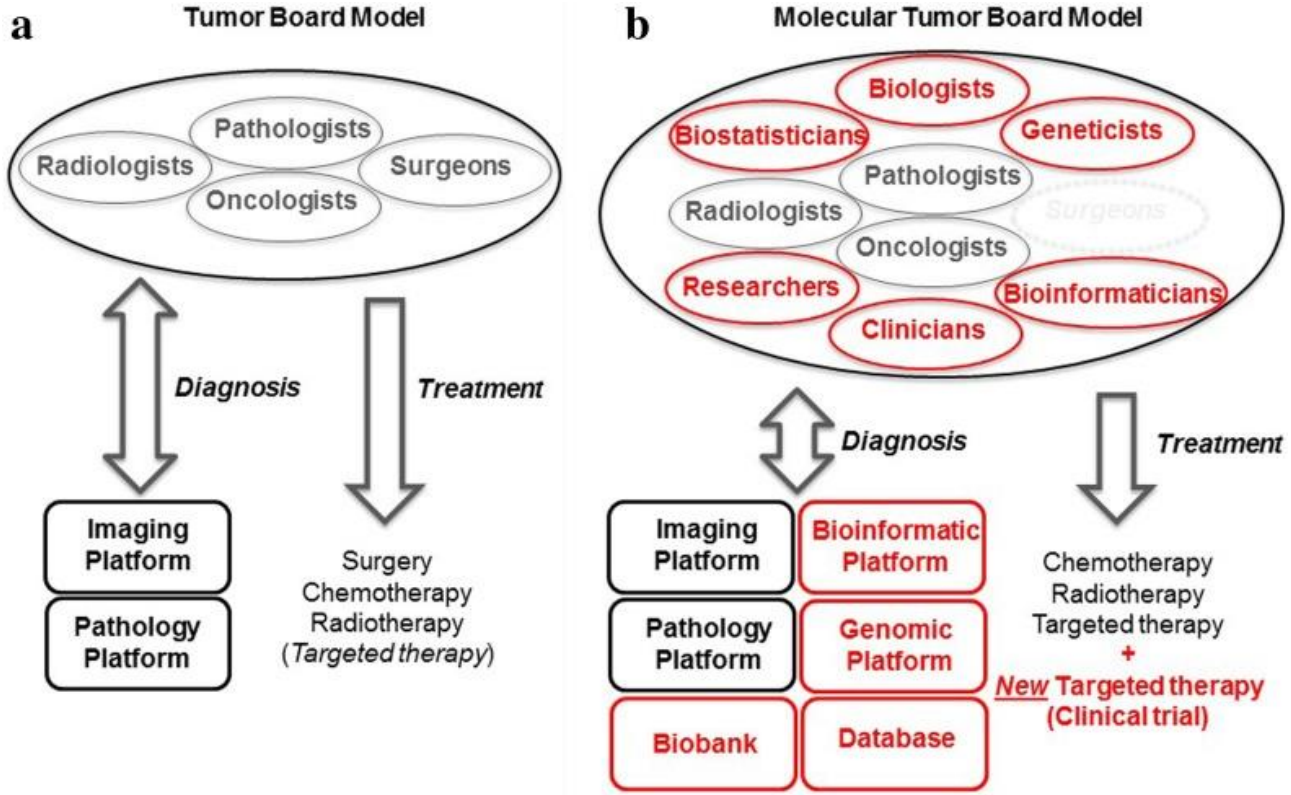
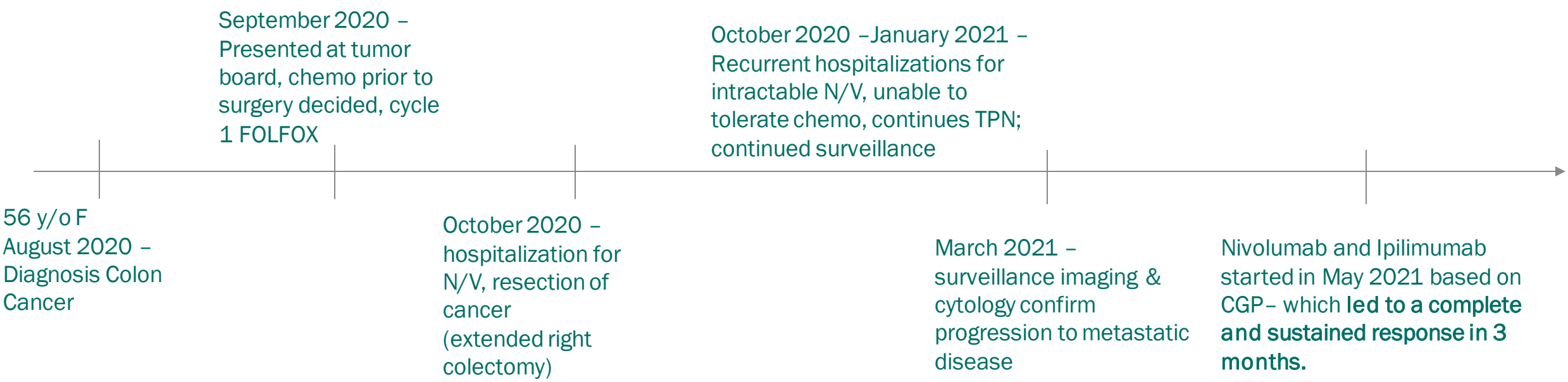


Fig. 1 Model of the data medicine process. Biological sample flows and biobanks are shown in *green*. Data flows and databases are shown in *light blue*. Information flows are shown in *dark blue*



Ref: Molecular Tumor Boards: Ethical Issues in the New Era of Data Medicine Henri-Corto Stoekle et al Sci Eng Ethics (2018) 24:307–32

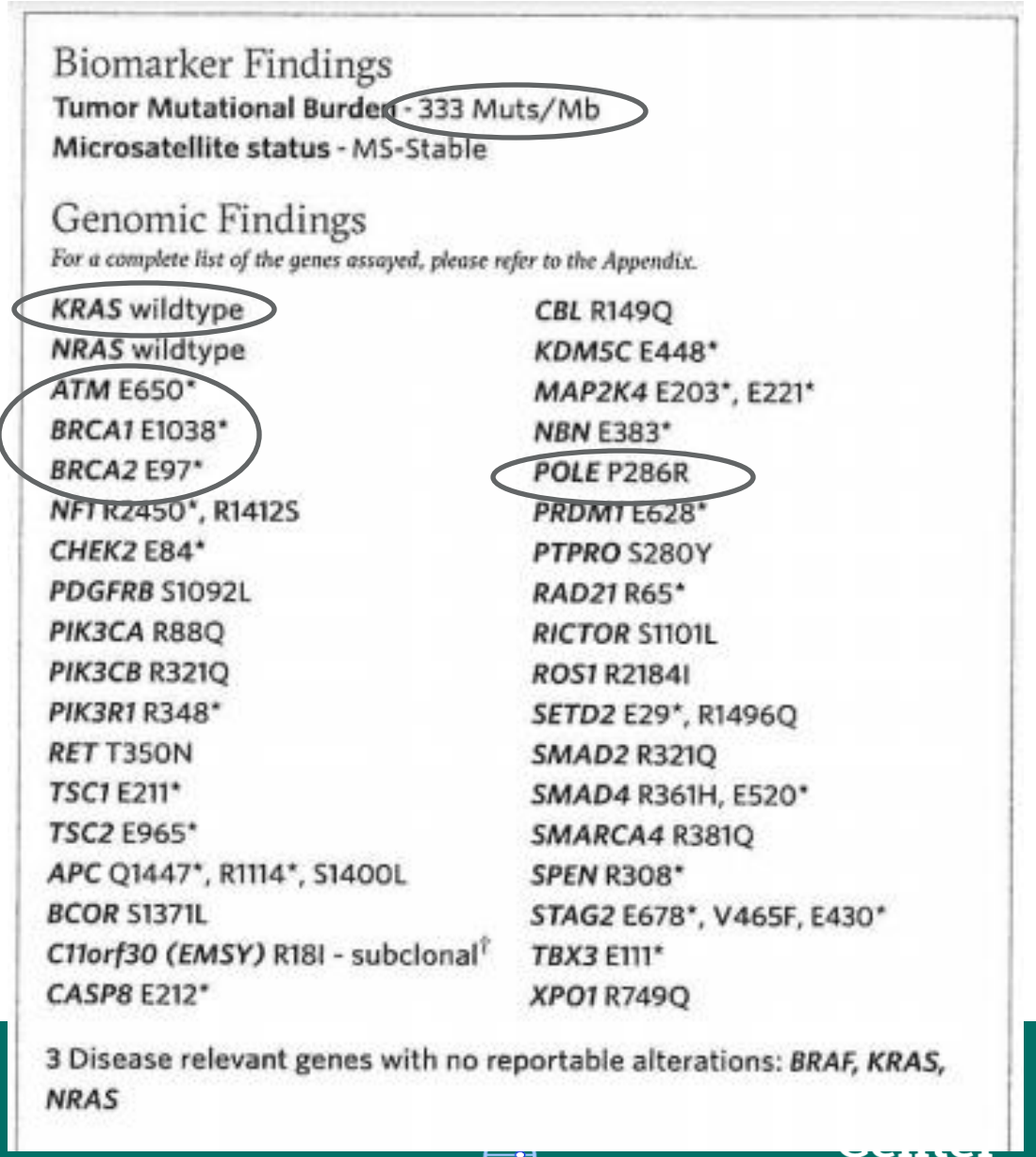
Case discussion:Metastatic Colon Cancer with a rare POLE mutation



Easy to miss minute details

- Tumor Mutation Burden – the number of somatic mutations present in a cancer cell
- Reported as number of mutations seen in a section of DNA, reported as mutations/Megabase
- The higher the number, the more likely you are to see a response with immune checkpoint inhibitors
  - Cancers with a TMB of 10mut/Mb or greater have a higher response rate
  - Our patient had 333 muts/Mb –that is a *LOT* of mutations!

Our patient's genomic profile



Biomarker Findings

Tumor Mutational Burden - 333 Muts/Mb
Microsatellite status - MS-Stable

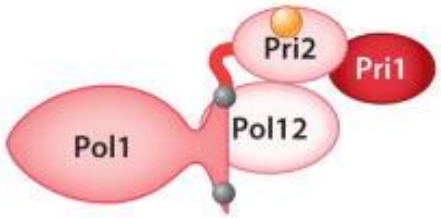
Genomic Findings

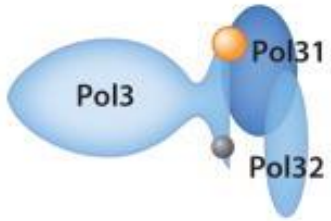
For a complete list of the genes assayed, please refer to the Appendix.

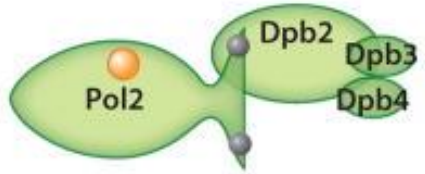
KRAS wildtype
NRAS wildtype
ATM E650*
BRCA1 E1038*
BRCA2 E97*
NF1 R2450*, R1412S
CHEK2 E84*
PDGFRB S1092L
PIK3CA R88Q
PIK3CB R321Q
PIK3R1 R348*
RET T350N
TSC1 E211*
TSC2 E965*
APC Q1447*, R1114*, S1400L
BCOR S1371L
C11orf30 (EMSY) R181 - subclonal†
CASP8 E212*
CBL R149Q
KDM5C E448*
MAP2K4 E203*, E221*
NBN E383*
POLE P286R
PRDM1 E628*
PTPRO S280Y
RAD21 R65*
RICTOR S1101L
ROS1 R2184I
SETD2 E29*, R1496Q
SMAD2 R321Q
SMAD4 R361H, E520*
SMARCA4 R381Q
SPEN R308*
STAG2 E678*, V465F, E430*
TBX3 E111*
XPO1 R749Q

3 Disease relevant genes with no reportable alterations: ***BRAF, KRAS, NRAS***

Genes that encode DNA polymerase epsilon (POLE)

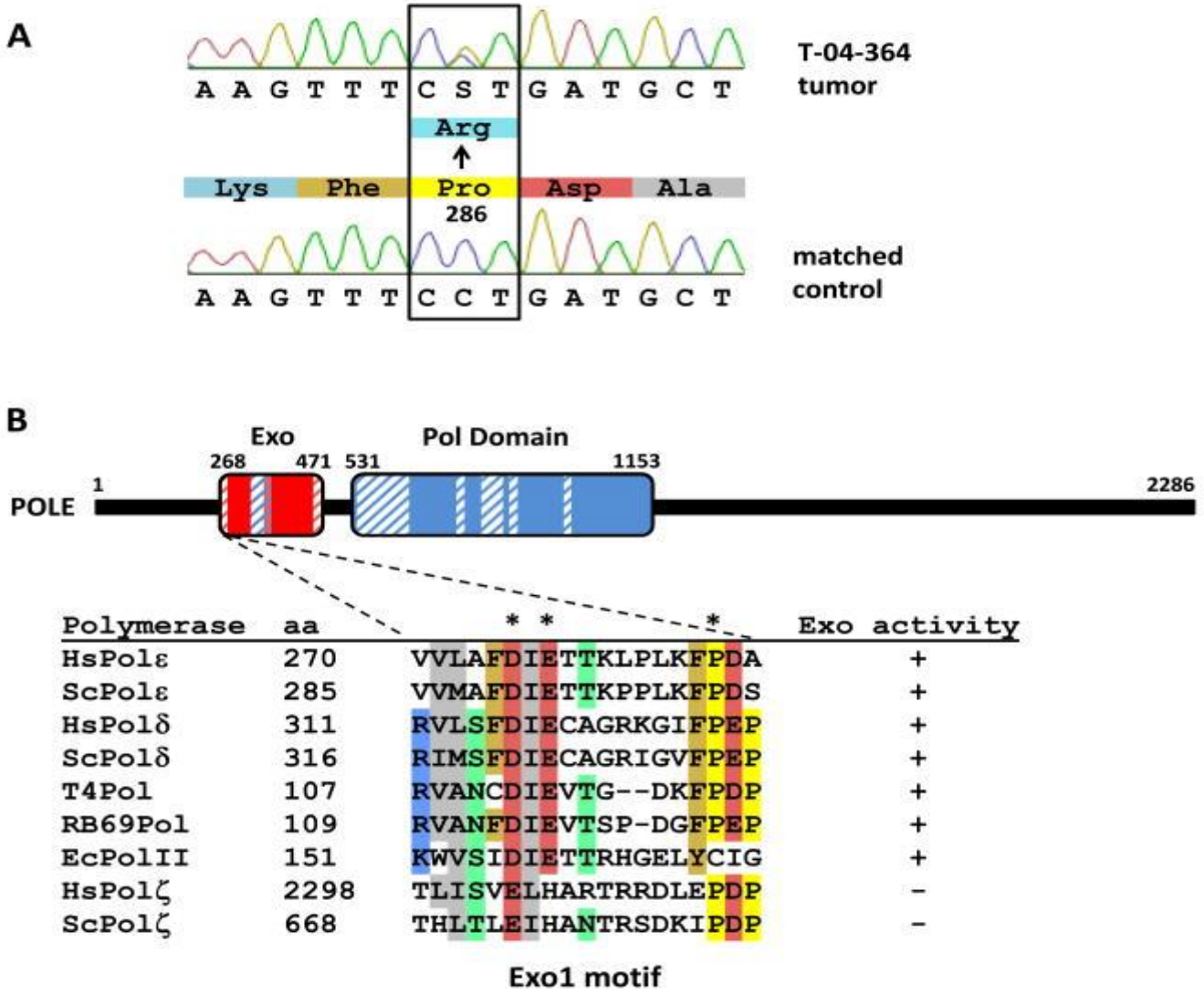






	Pol α	Pol δ	Pol ε
Activities	Polymerase	Polymerase 3'-exonuclease	Polymerase 3'-exonuclease
Fidelity	$10^{-3} - 10^{-4}$	$10^{-4} - 10^{-6}$	$10^{-5} - 10^{-6}$
Strand displacement activity	n.d.	yes	no
Processivity	low	low	high
PCNA stimulation of processivity	–	+++	+
Interactions	Mcm10, Pol δ, Ctf4	PCNA, Pol α	Cdc45, GINS, PCNA, Ctf4

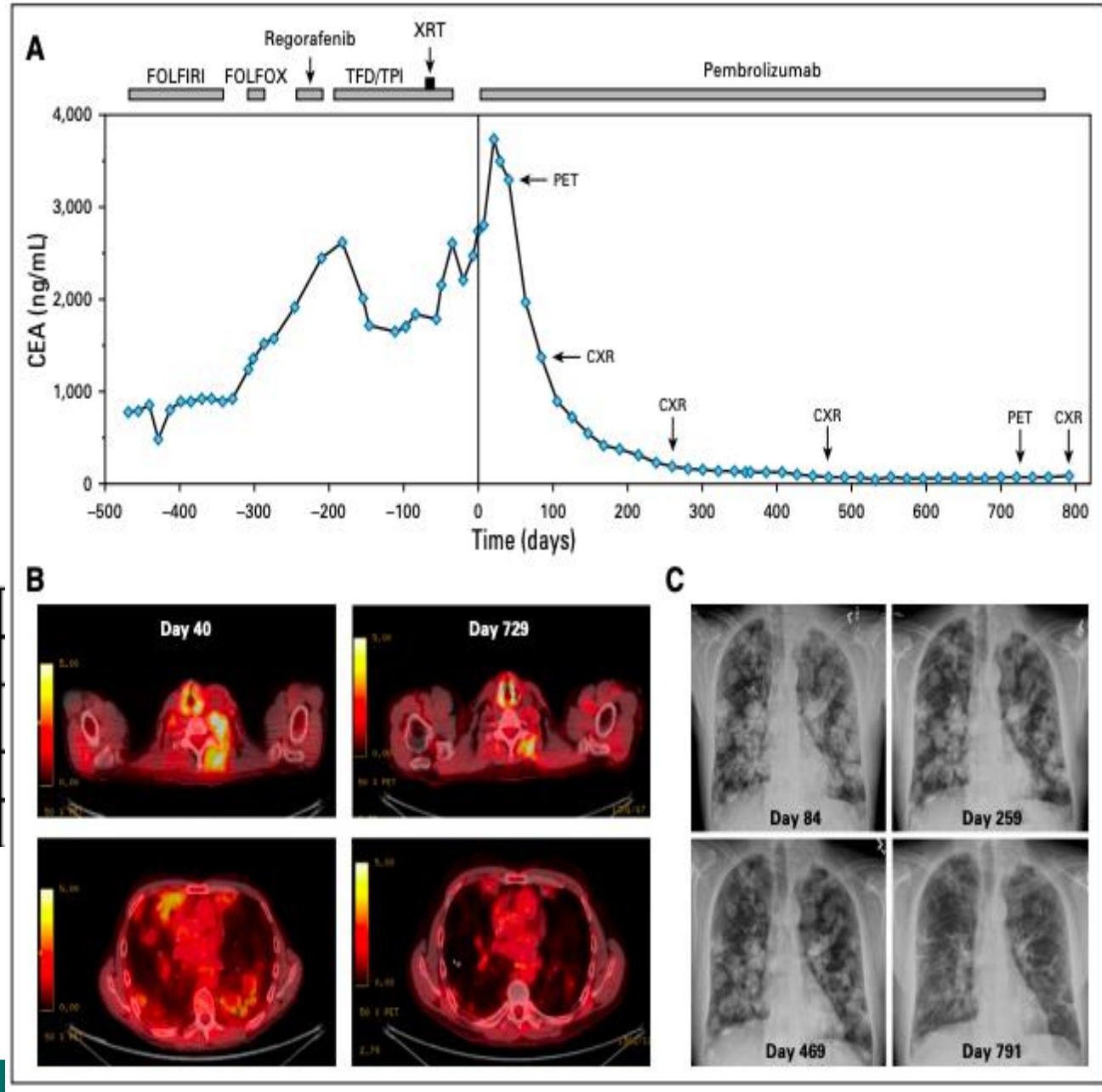
DNA polymerase ∈ mutations are associated with elevated TMB



- Exonucleolytic proofreading and DNA mismatch repair (MMR) act in series to maintain high-fidelity DNA replication and to avoid mutagenesis
- Hypermutable colorectal tumors with functional MMR can carry amino acid substitutions in the exonuclease domain of DNA polymerase ε (Polε).
- Loss of the proofreading activity of Polε is a driver of some sporadic colon cancers
- Study identified a somatic P286R substitution in the conserved ExoI motif of Polε in a collection of 52 sporadic colorectal tumor specimens.

Complete and Prolonged Response to Immune Checkpoint Blockade in *POLE*-Mutated Colorectal Cancer

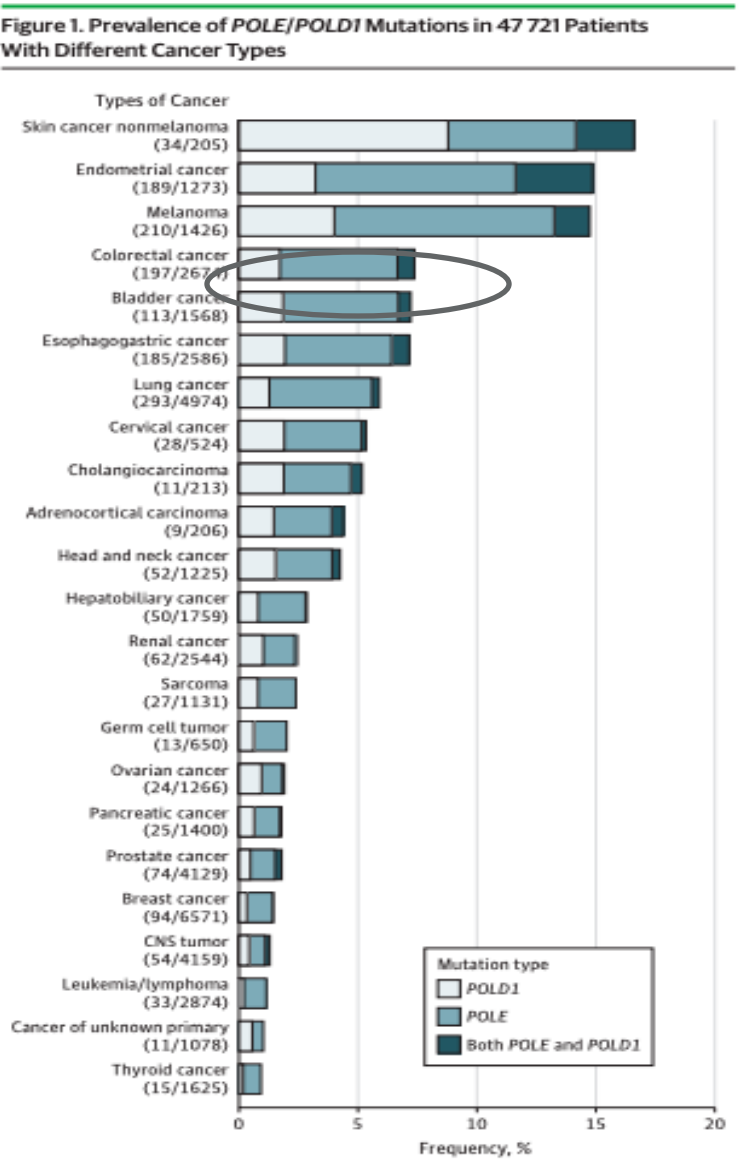
Robyn Silberman, MS[1]; David F. Steiner, MD, PhD[1]; Amy A. Lo, MD[1]; Adam Gomez, MD[2]; James L. Zehnder, MD[1]; Gilbert Chu, MD, PhD[1]; and Carlos J. Suarez, MD[1]

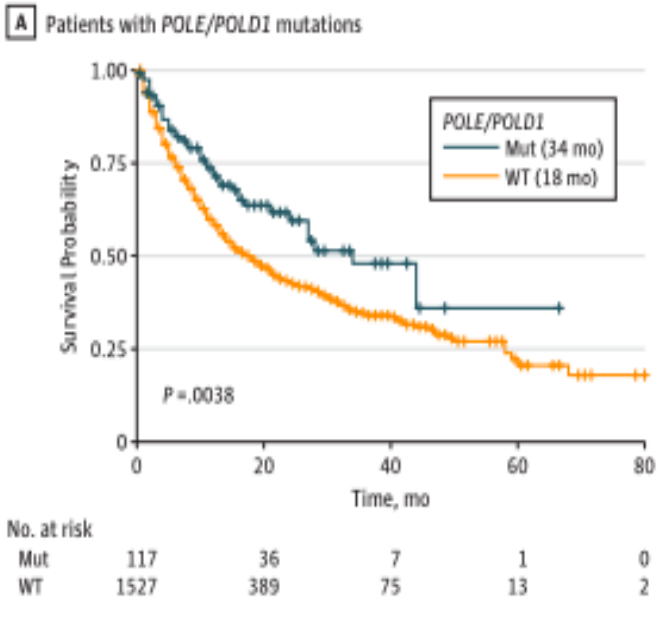


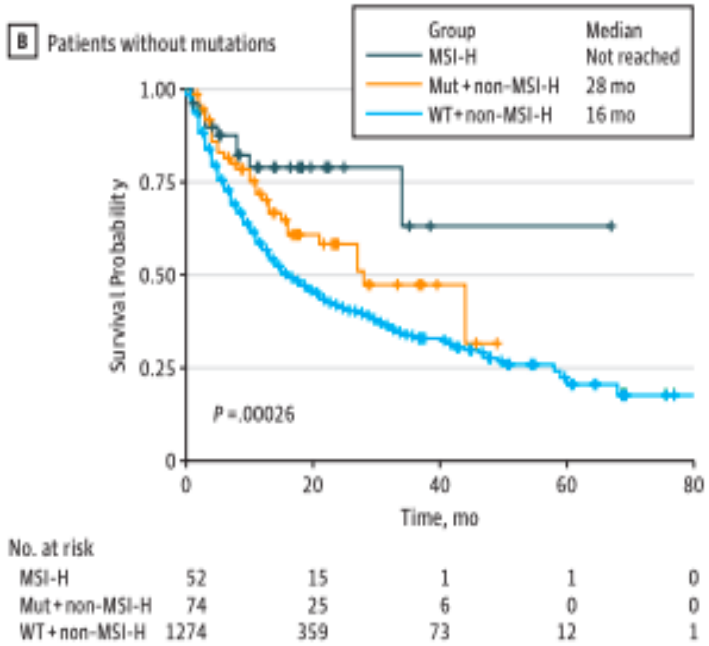
***POLE*-mutant tumor characteristics and responses**

POLE mutn	Patient	Tumor	TMB/Mb	PD-L1	Treatment (mo)	Response (mo)
V411L	44 yM	CRC	200	Negative	Pembro (25)	CR (> 28)
V411L	81 yM	CRC	122	Negative	Pembro (> 12)	CR (> 12)
V411L	53 yF	EC	150	Positive	Pembro (> 14)	PR (> 14)
P286R	57 yF	EC	117	Weakly positive	Nivo (> 7)	PR (> 7)

DNA polymerase ∈ mutations are associated with elevated TMB respond to ICI







- Study investigated the association between POLE/ POLD1 mutations and overall survival (OS) in the ICI treatment cohort.
- As shown in Figure, patients with either POLE or POLD1 mutations showed a significantly longer OS of 34 months vs 18 months in the wild-type population.
- 74/100 patients with POLE/POLD1 mutations were microsatellite stable (MSS).

Ref: Wang et al. POLE mutations JAMA oncology 2019

Genomic & Precision Sciences Medicine Center

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Excellent Response With Alpelisib and Bicalutamide for Advanced Salivary Duct Carcinoma With PIK3CA Mutation and High Androgen Receptor Expression—A Case Report

Hardik Sheth, MBBS[1]; Prashant Kumar, PhD[2,3,4]; Aditya Shreenivas, MD, MS[5]; Janani Sambath, MTech[2,3];

Reply to S. Cavalieri et al

Sewanti Limaye, MBBS, MD, MS, Prashant Kumar, PhD, Rajan Datar, BE, and Aditya Shreenivas, MBBS, MD, MS

- Majority of SDC cases express AR (66.7%-96.4%) and/or HER2 (15%-44%), thus making HER2-directed therapy a viable treatment option
- Phase II study, 57 patients with HER2-positive SDC received trastuzumab and docetaxel: ORR of 70.2%
- AR-positive aSDC, androgen deprivation therapy has shown to have a better ORR and lower adverse events.
- First PIK3CA-mutated, AR-overexpressed aSDC case to have an excellent response to combination therapy with alpelisib and bicalutamide in the setting of HER2-directed therapy resistance

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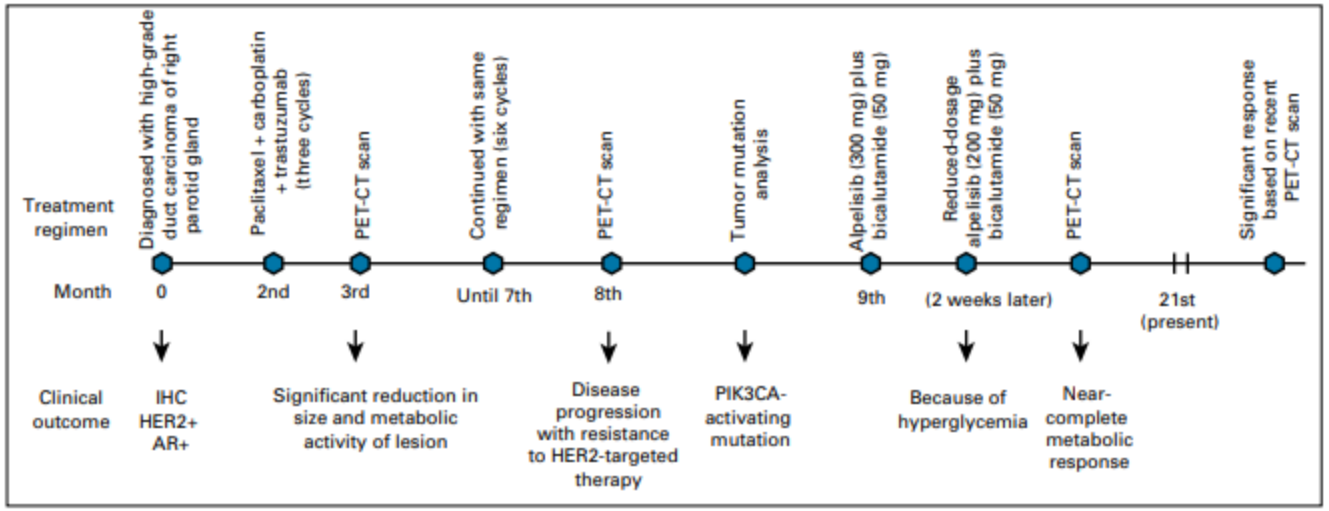


FIG 3. Depiction of treatment regimen and timeline of the patient with salivary duct carcinoma. AR, androgen receptor; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; PET-CT, positron emission tomography-computed tomography.

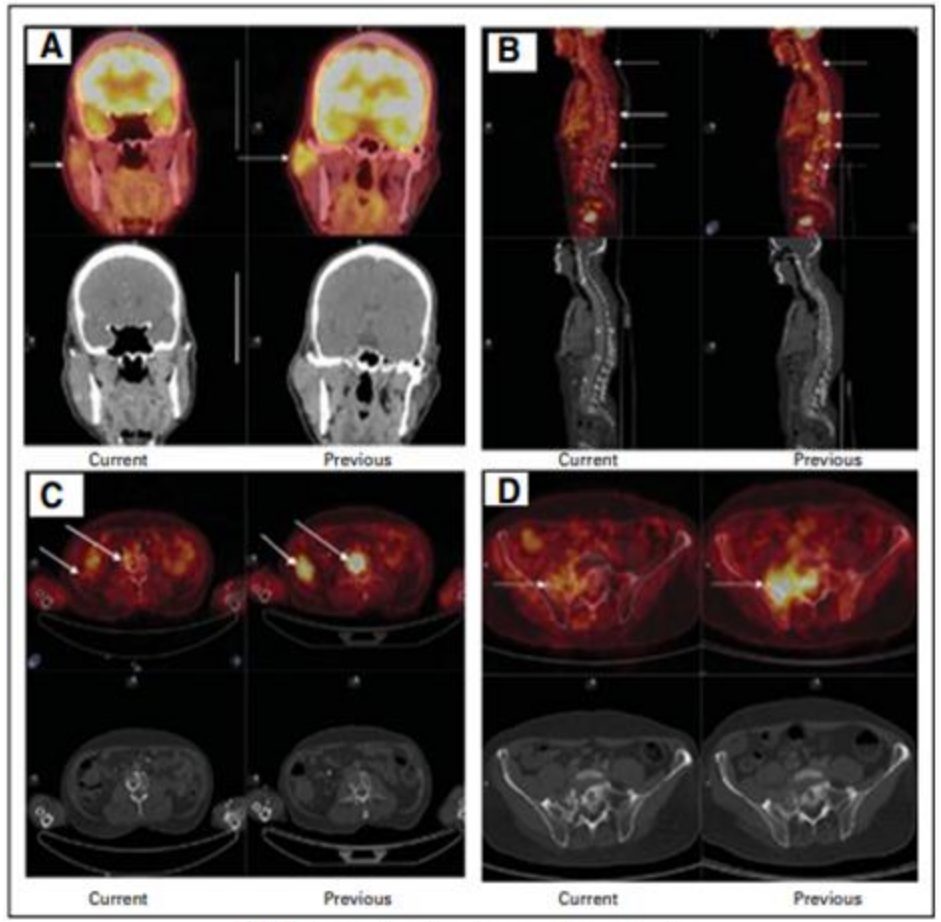
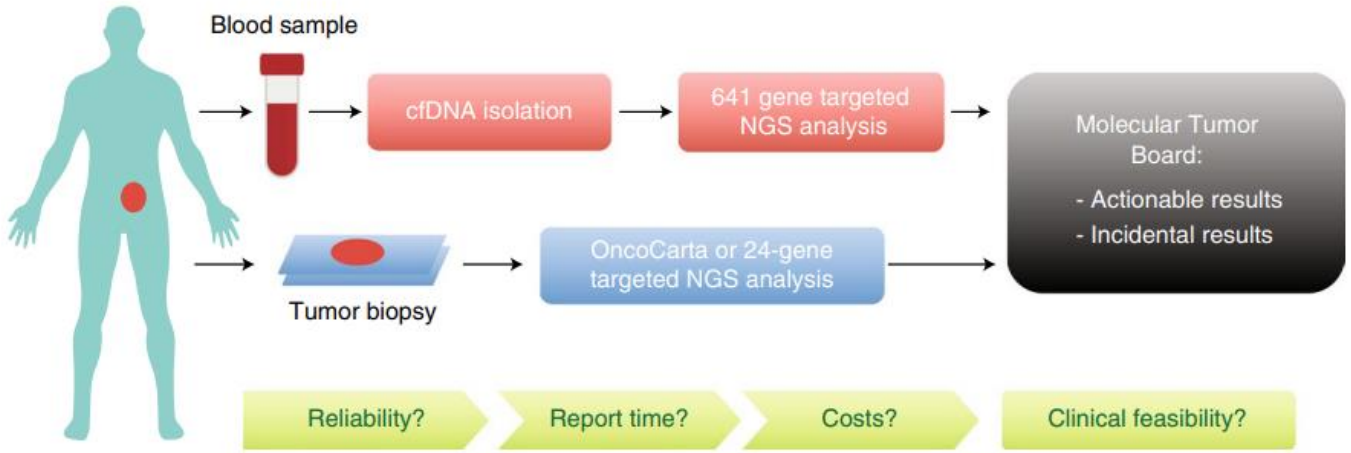
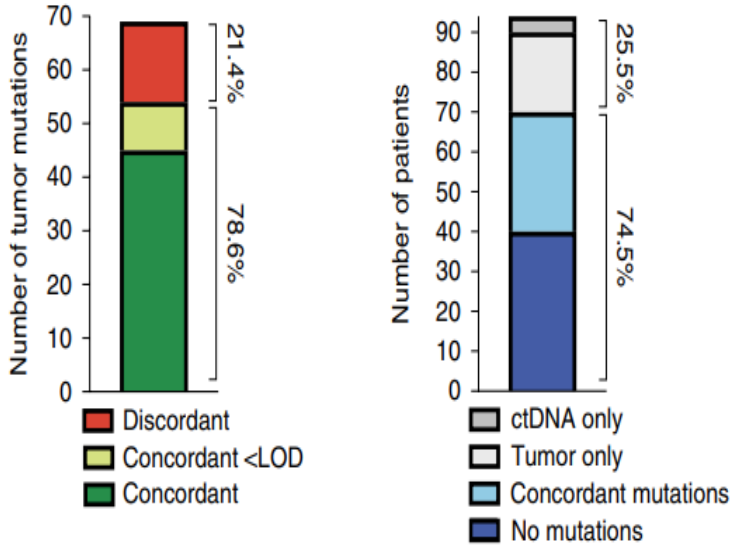


FIG 2. Current and previous positron emission tomography-computed tomography scans demonstrating response to treatment from *PIK3CA* and androgen receptor inhibitors. (A) Arrows show near-complete metabolic resolution of the primary lesion when compared with prior scans. (B) Arrows show complete metabolic resolution of the vertebral metastasis when compared with prior scans. (C) Arrows show complete metabolic resolution of the lung and vertebral metastasis when compared with prior scans. (D) Arrows show near-complete metabolic resolution of the primary lesion when compared with prior scans.

Analysis of circulating tumor DNA (ctDNA)when tissue insufficient





- 641 cancer-associated-gene panel in a single ctDNA assay.
- 100 TARGET study patients, ctDNA data showed good concordance with matched tumor
- Actionable mutations were identified in 41 of 100 patients

Ref: Rothwell et al Nat Med . 2019 May;25(5):738-743. doi: 10.1038/s41591-019-0380-z. Epub 2019 Apr 22.

CA:
A Cancer Journal for Clinicians

Carcinoma of unknown primary: Molecular tumor board-based therapy

The first two authors contributed equally to this article.

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& Clinical Cancer Genetics Program

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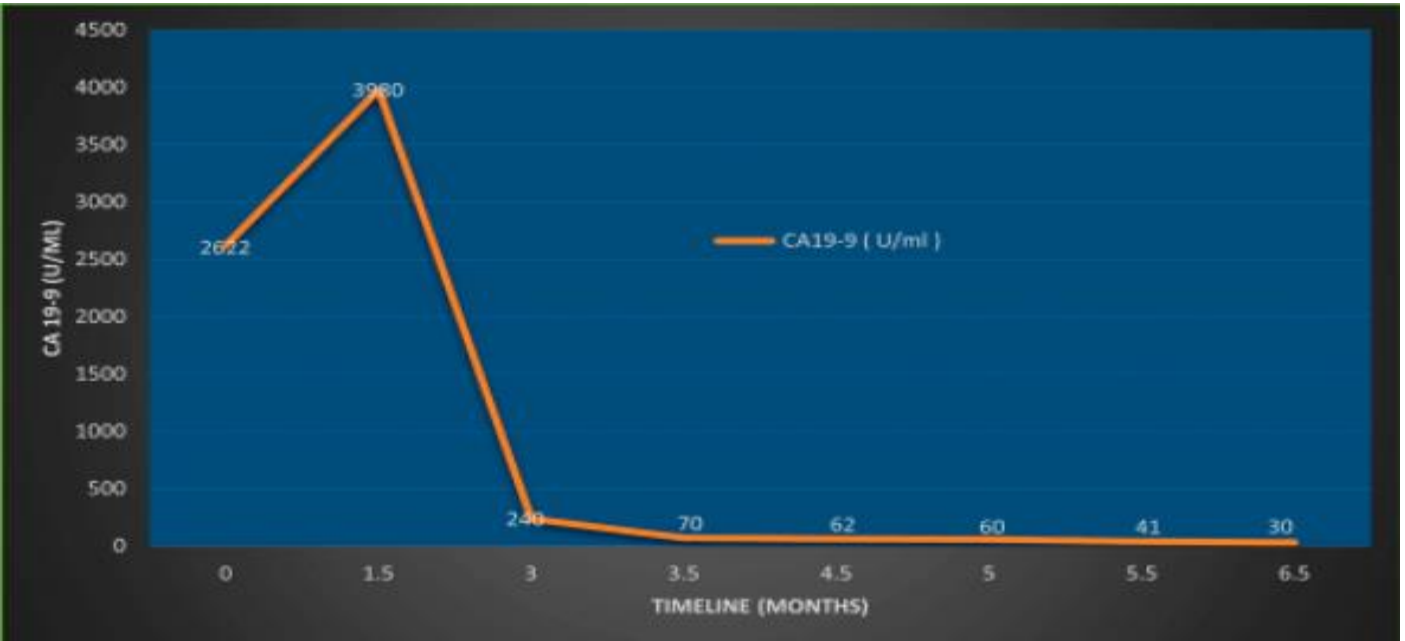
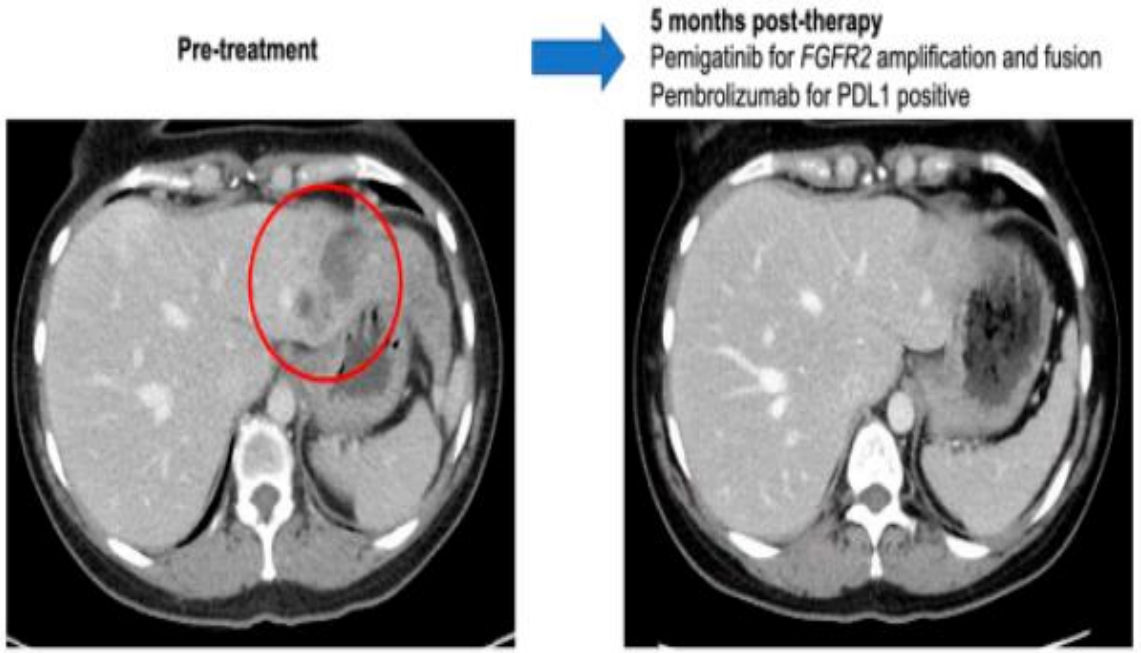
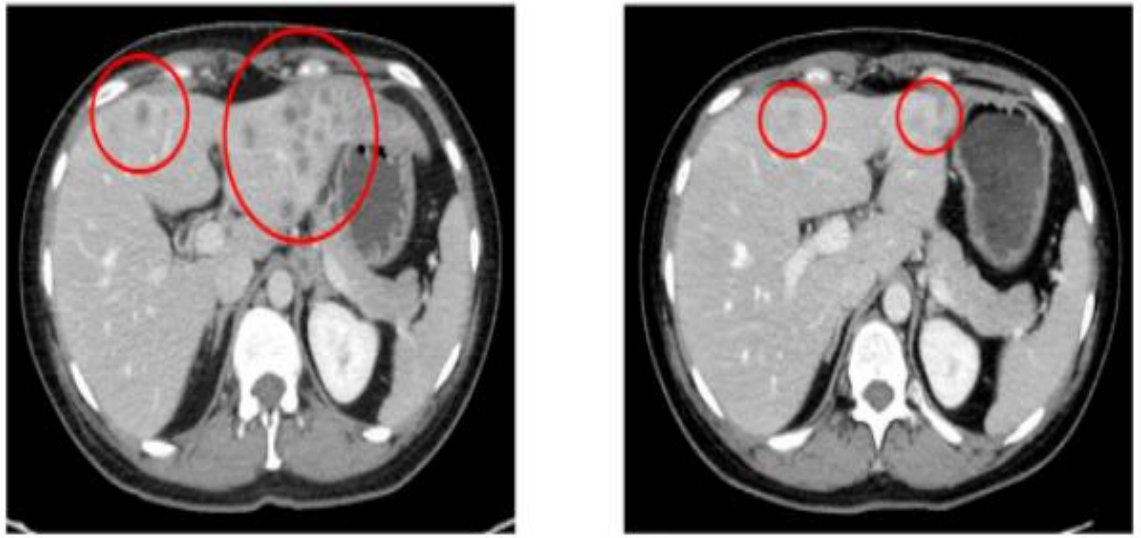
Preprint version





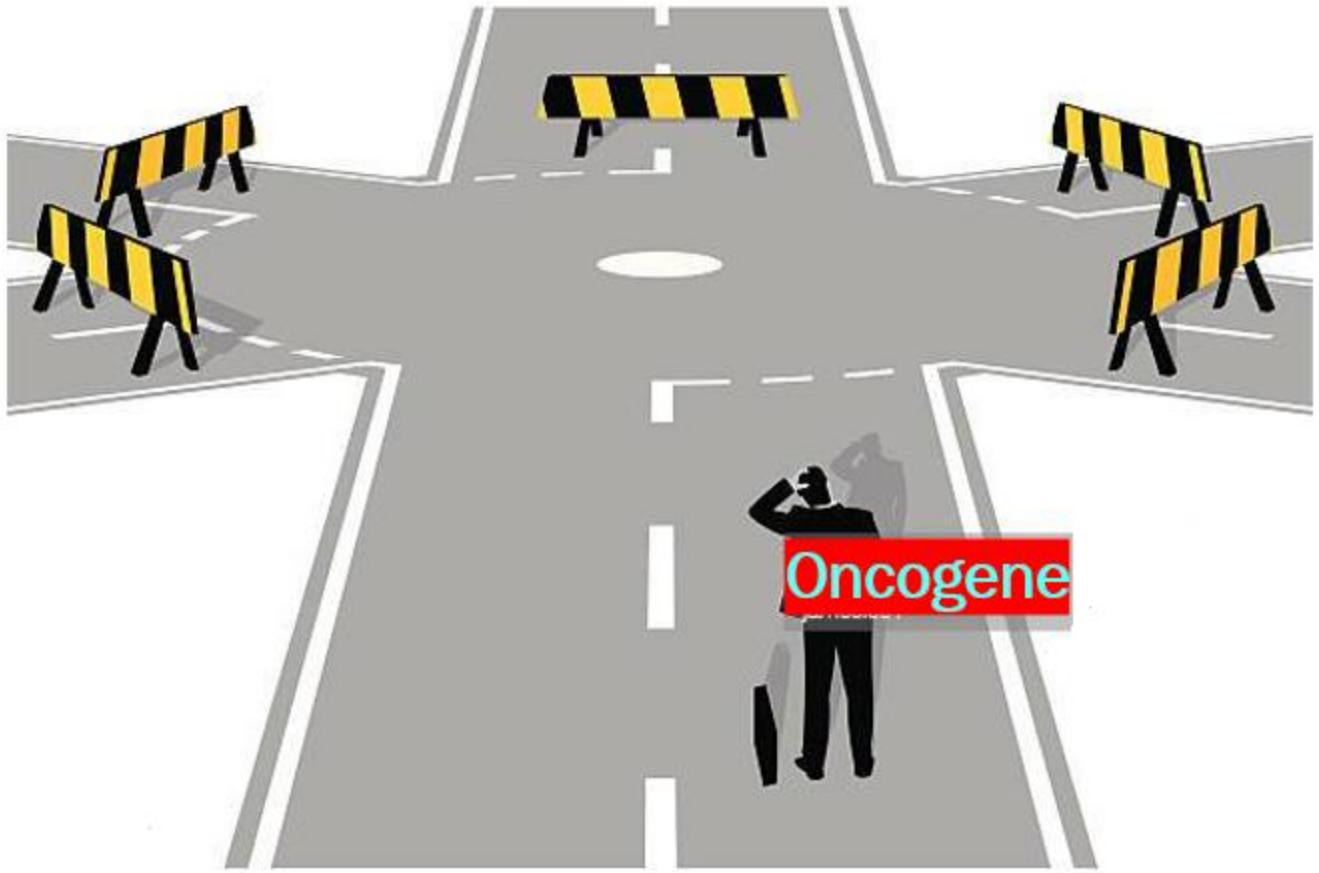


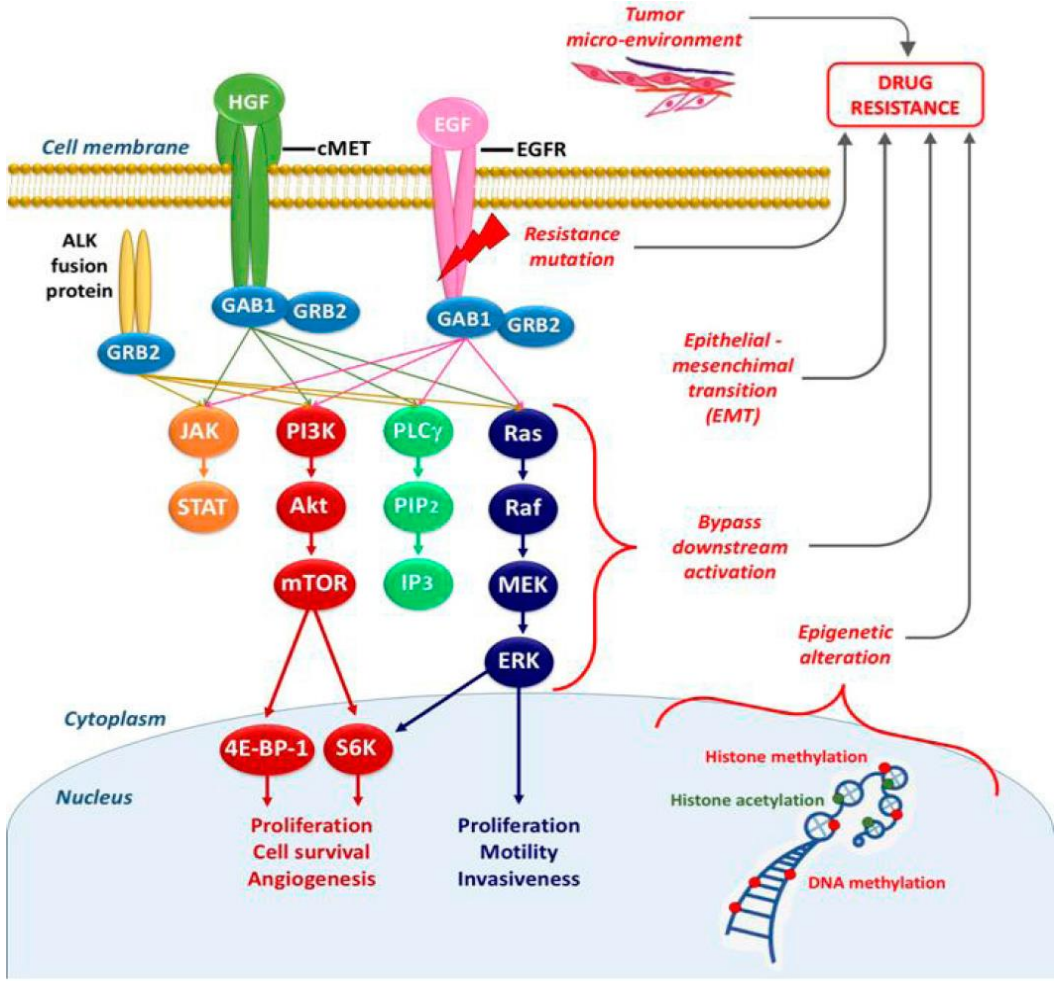
Tissue agnostic approval of targeted therapies

- First tissue-agnostic treatment approval was granted by the FDA to **pembrolizumab** in patients with high microsatellite instability (MSI-H) tumors in 2017.
- Followed by larotrectinib and entrectinib for the treatment of cancers harboring NTRK fusions in 2018 and 2019

FDA grants accelerated approval to dabrafenib in combination with trametinib for unresectable or metastatic solid tumors with BRAF V600E mutation

WHY TARGET MULTIPLE PATHWAYS AT THE SAME TIME?





Ref: Resistance to epidermal growth factor receptor inhibition in non-small cell lung cancer Steen et al Cancer Drug Resist 2018;1:230-4924:307–32

Real World Prospective Clinical Trial of Targeted Therapies

(I PREDICT)Investigation of Profile-Related Evidence Determining Individualized Cancer Therapy

Activation Date: February 13, 2015
Total Consented: N = 506
Total Treated: N = 267 (53%)
Treatment Decisions Guided by: CGP and MTB discussion

Study Novelty
- Customized combinations
- Newly diagnosed patients with lethal malignancies

PI: Razelle Kurzrock, MD
Director, Center for Personalized Cancer Therapy

Ref: I PREDICT Sicklick et al, Nature Medicine 2019

(I PREDICT)Investigation of Profile-Related Evidence Determining Individualized Cancer Therapy

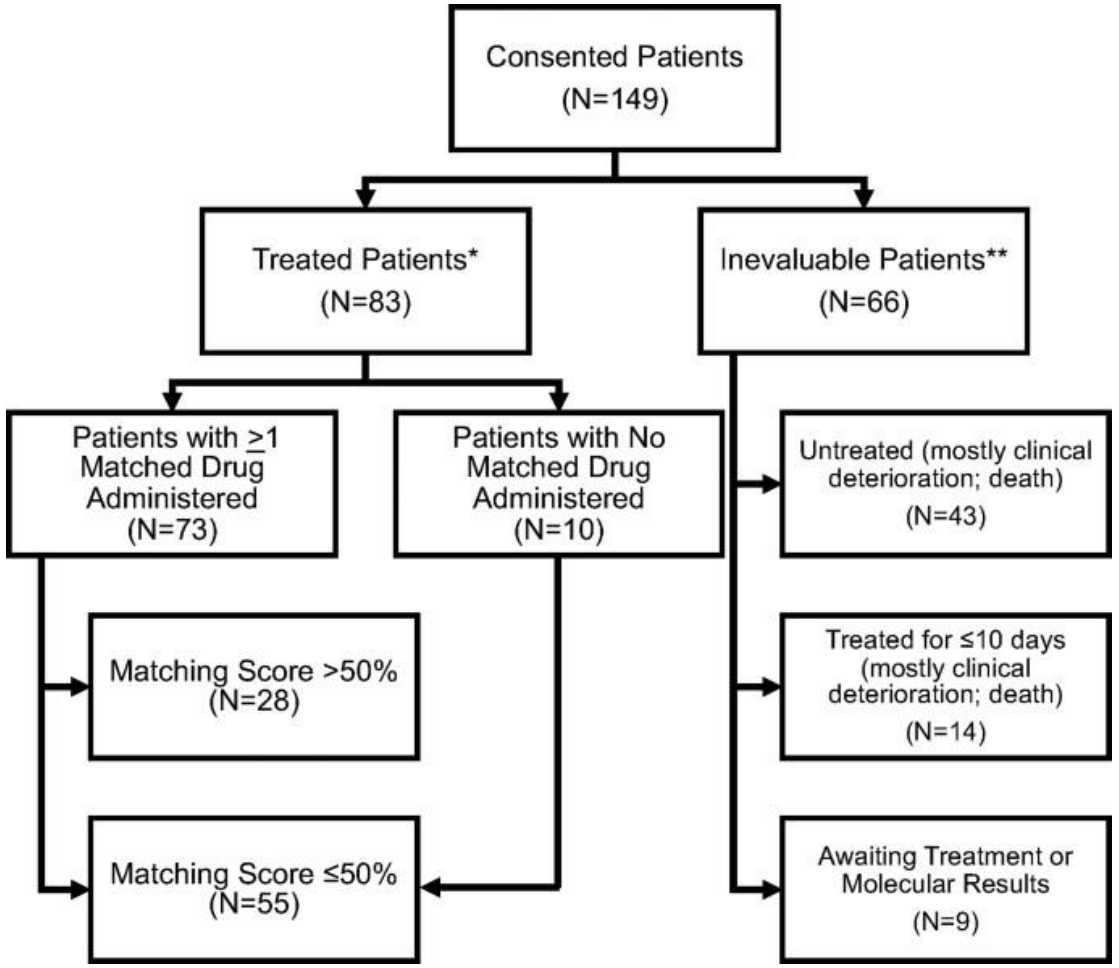


Table 1 | Patient demographics, molecular pathology, and treatment history

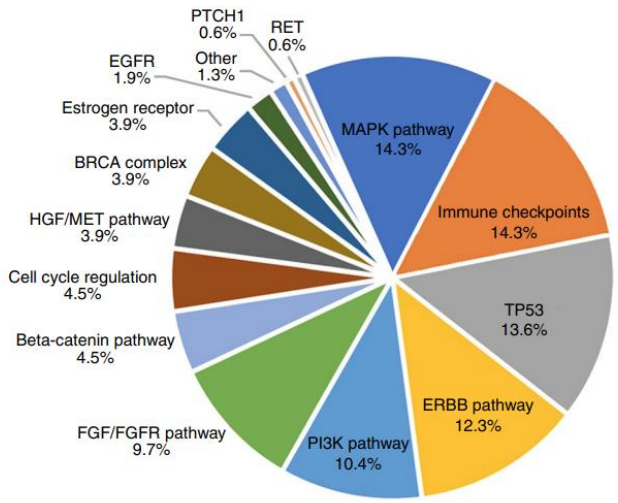
Consented patients (*N*)	149
Treated patients (*N* (% of consented patients))	83 (55.7)
Patients with ≥1 matched treatment (*N* (% of consented patients))	73 (49.0)
Patients with no matched treatments administered (*N* (% of consented patients))	10 (6.7)
Age[a] (median, 95% CI, range)	62 (59–65, 21–86)
Sex[a] (*N* (%))	
Women	55 (66.3)
Men	28 (33.7)
Ethnicity[a] (*N* (%))	
White	67 (80.7)
Asian	4 (4.8)
African-American	1 (1.2)
Other or unknown	11 (13.3)
Tumor type[a] (*N* (%))	
Gastrointestinal and hepatopancreatobiliary	35 (42.2)
Gynecologic	14 (16.9)
Breast	12 (14.5)
Central nervous system	6 (7.2)
Genitourinary	3 (3.6)
Head and neck	3 (3.6)
Lung	3 (3.6)
Other[b]	7 (8.4)
Number of total genomic alterations[1] (median, range; VUS-excluded)	5 (1–19)
Number of administered drugs[1] (median, range)	2 (1–5)
Median number of prior therapies in the metastatic setting[1] (median, IQR)	2 (1–3)

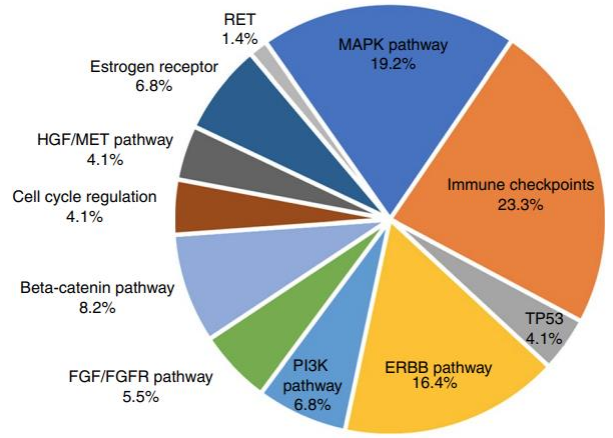
Matching score, defined as the number of alterations targeted with an administered drug divided by the total number of actionable alterations detected in the patient's tumor

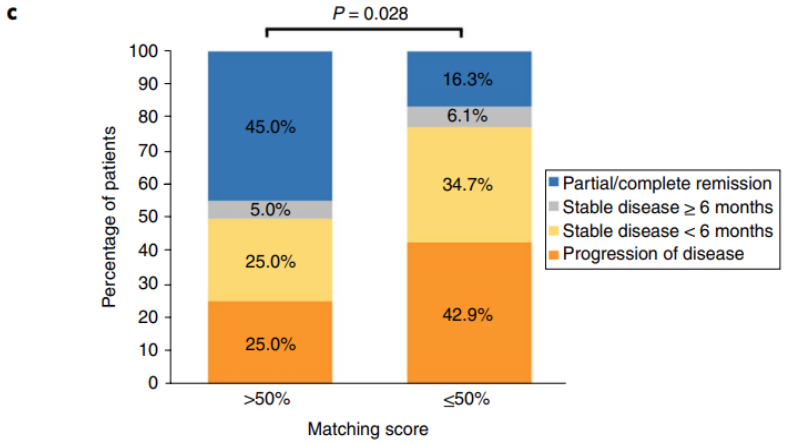
Ref: I PREDICT Sicklick et al, Nature Medicine 2019

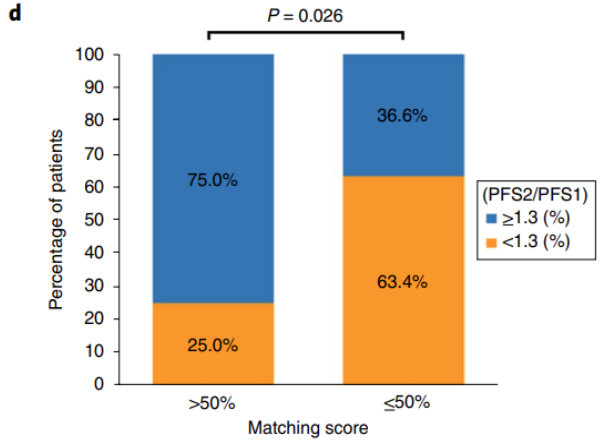
https://doi.org/10.1038/s41591-019-0407-5

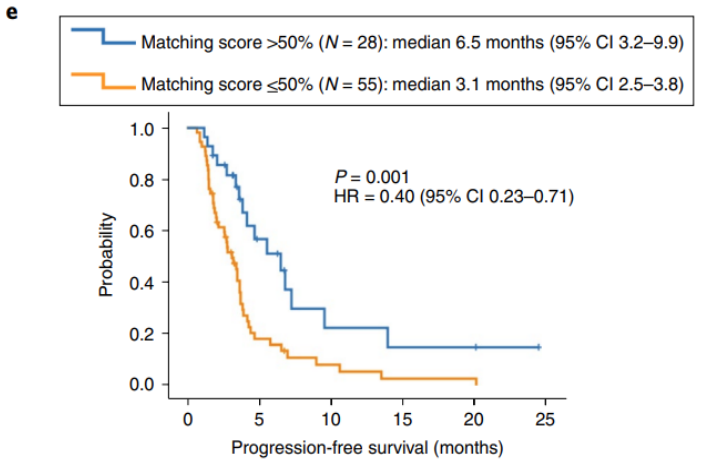
(I PREDICT)Investigation of Profile-Related Evidence Determining Individualized Cancer Therapy

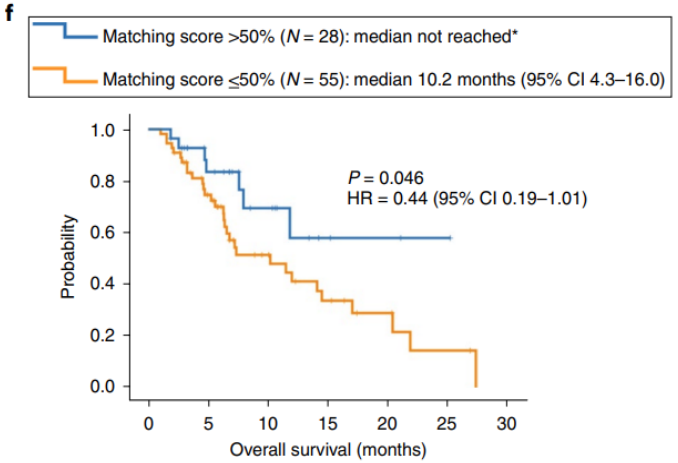










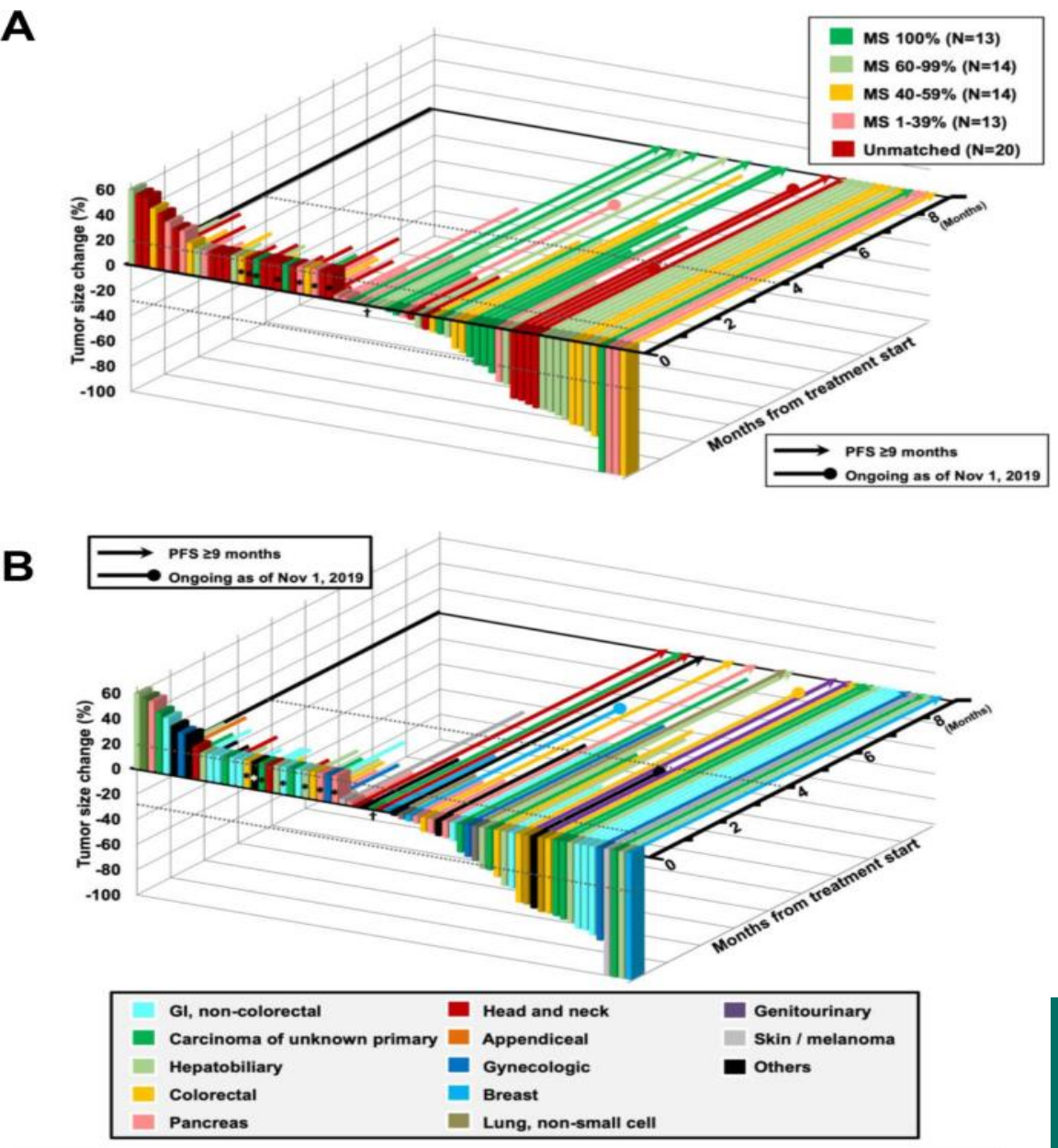


A higher matching score translated into significantly better response rate, progression-free survival and overall survival

Ref: I PREDICT Sicklick et al, Nature Medicine 2019

https://doi.org/10.1038/s41591-019-0407-5

(I PREDICT)Investigation of Profile-Related Evidence Determining Individualized Cancer Therapy (treatment naïve population)



- 76 of 145 patients (52%) were treated
- Most commonly for non-colorectal gastrointestinal cancers, carcinomas of unknown primary, and hepatobiliary malignancies
- 53% women; median age, 63 years.
- median number of deleterious genomic alterations per patient was 5.
- 44 treated patients received ≥ 1 molecularly matched therapy.

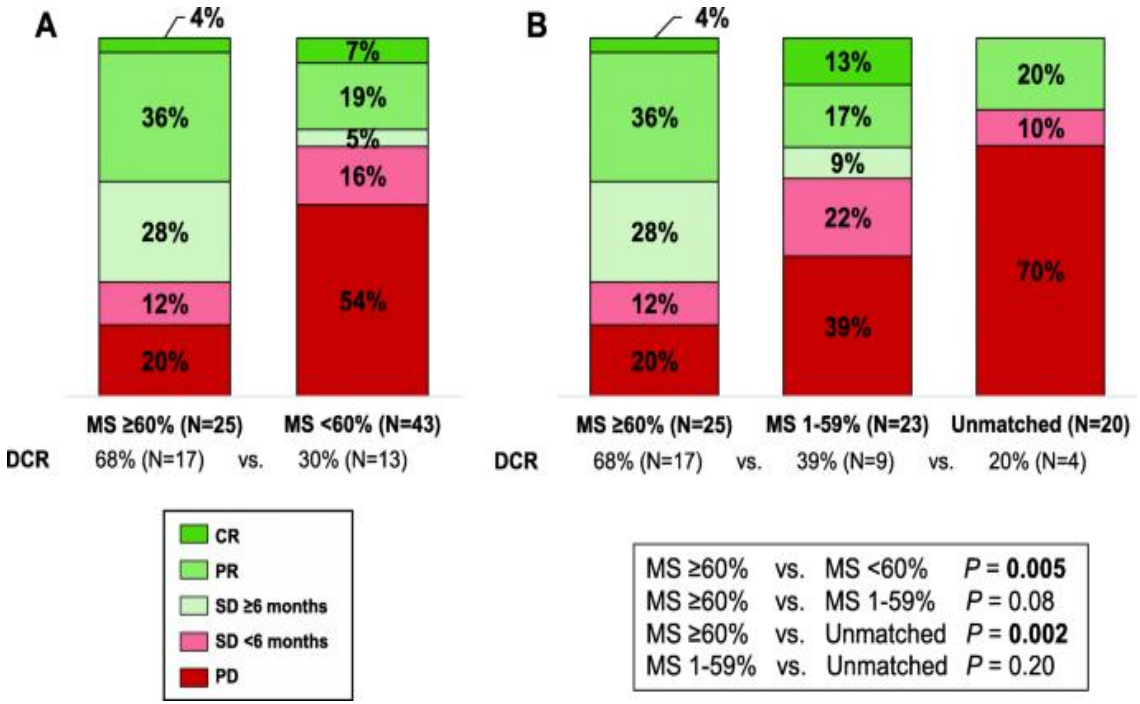
Matching score, defined as the number of alterations targeted with an administered drug divided by the total number of actionable alterations detected in the patient's tumor

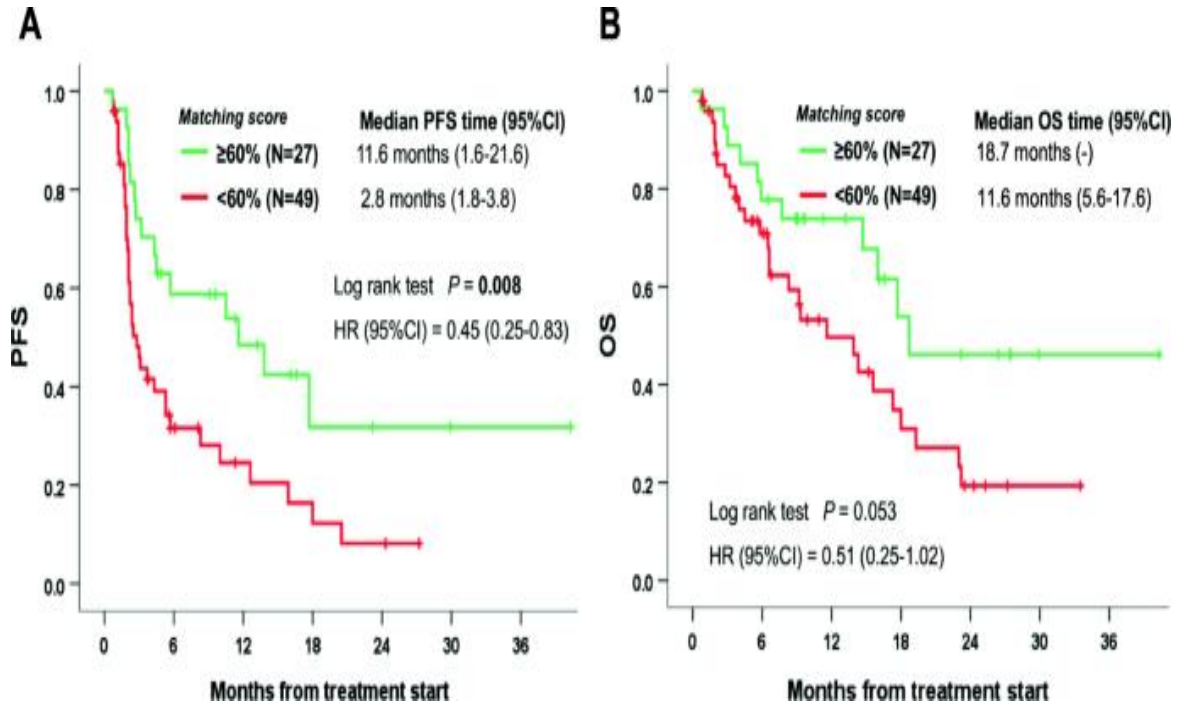
Ref: I PREDICT Sicklick et al, Genome Medicine 2019

https://doi.org/10.1186/s13073-021-00969-w

Genomic Sciences & Precision Medicine Center

(I PREDICT)Investigation of Profile-Related Evidence Determining Individualized Cancer Therapy





A higher matching score translated into significantly better response rate, progression-free survival and overall survival

Whole-genome and transcriptome analysis enhances precision cancer treatment options

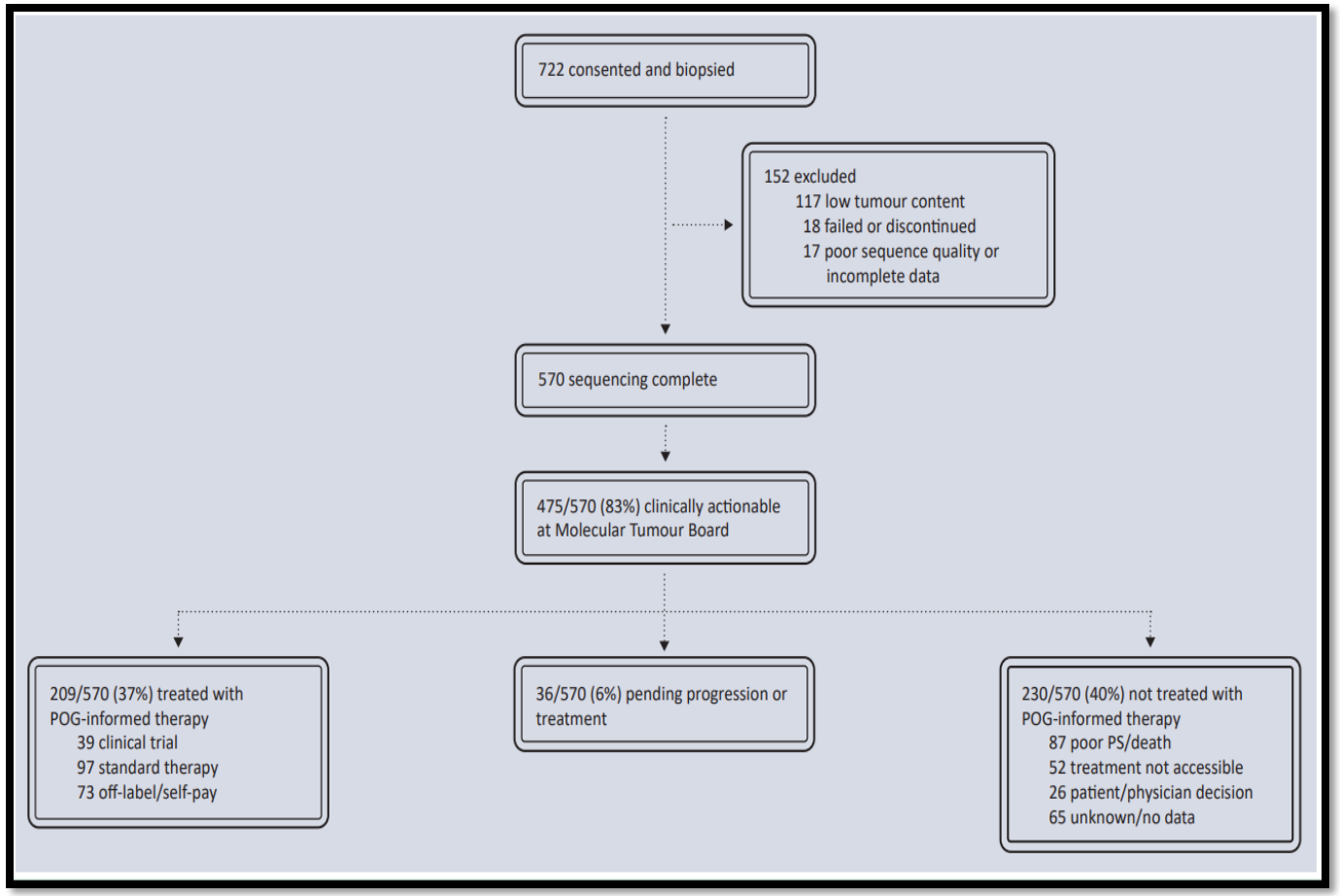


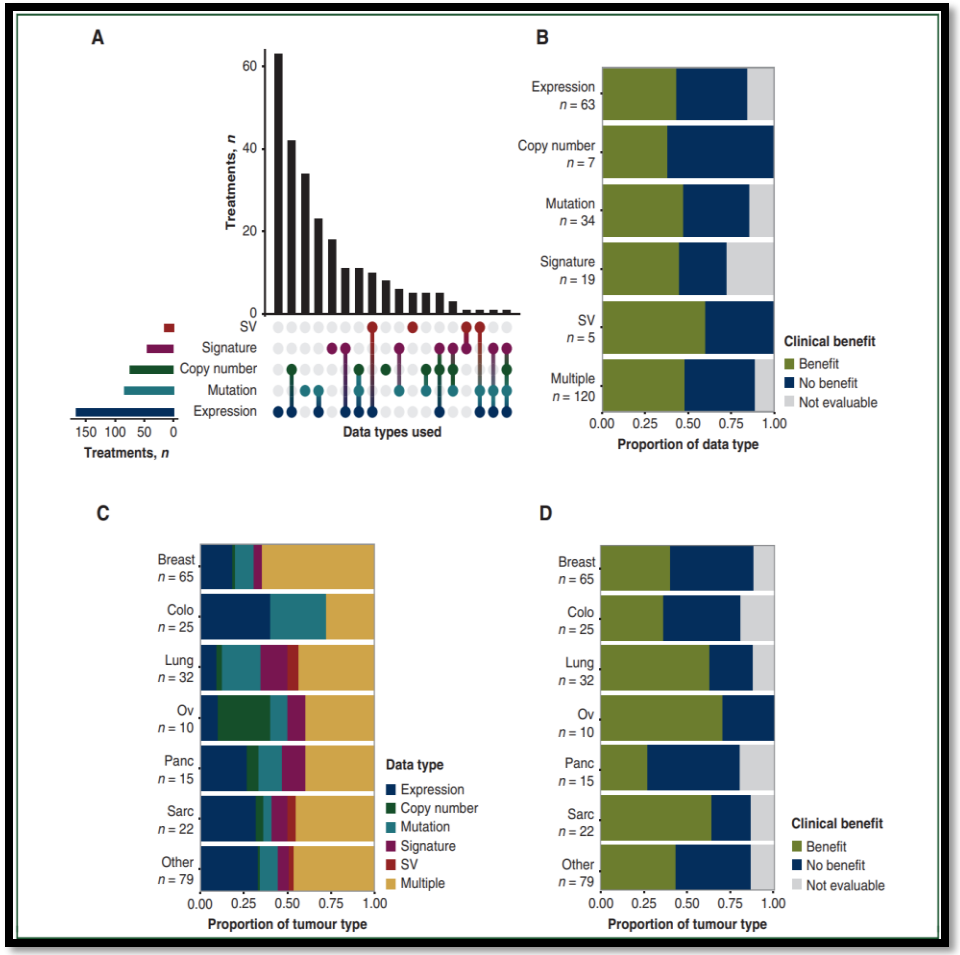
Table 1. Patient demographics

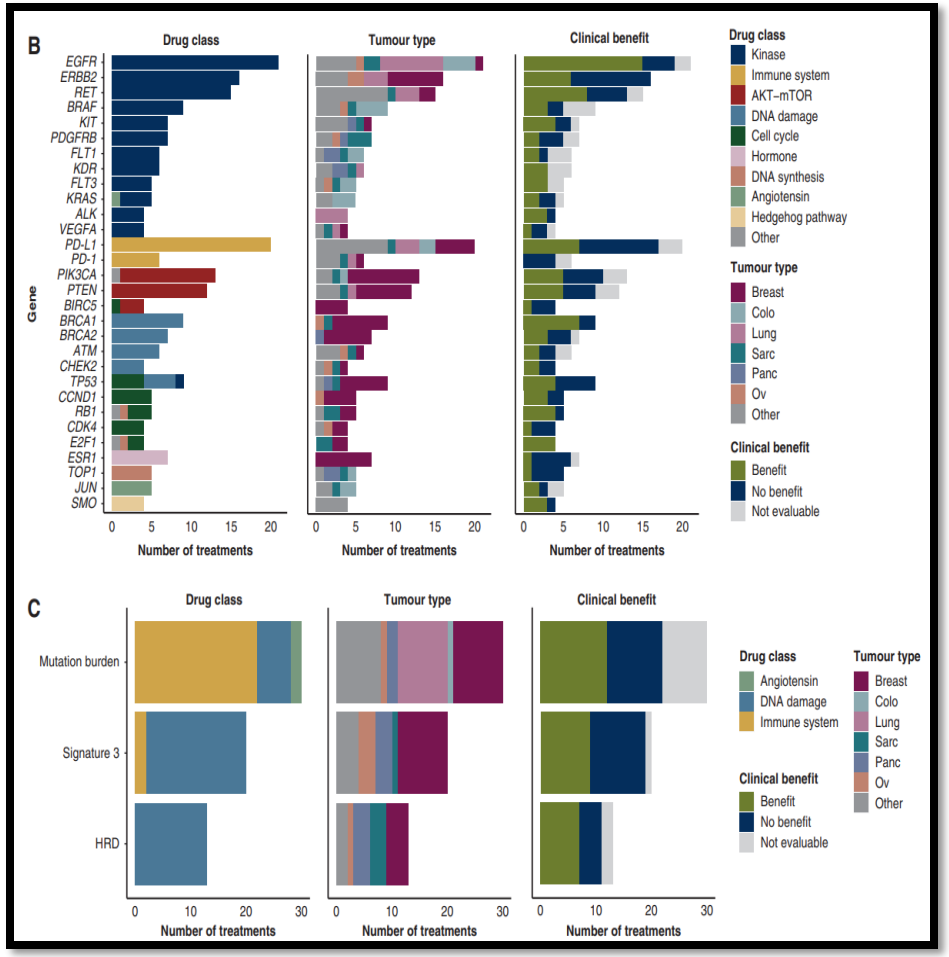
Characteristic	Cases (n = 570)
Median age at advanced disease diagnosis	57 (19-86)
Sex—no. (%)	
Female	359 (63)
Male	211 (37)
Tumour type- no. (%)	
Breast	144 (25)
Colorectal	87 (15)
Lung	67 (12)
Sarcoma	47 (8)
Pancreatic	42 (7)
Ovarian	28 (5)
Upper gastrointestinal (esophageal, stomach)	21 (4)
Melanoma (cutaneous, uveal)	19 (3)
Nervous system (central, peripheral)	17 (3)
Cholangiocarcinoma	14 (2)
Lymphoma	11 (2)
Uterine corpus endometrial carcinoma	11 (2)
Other (incl. adrenocortical, basal cell, bladder, cervical, hepatocellular, head and neck, prostate, secretory, thyroid, thymic, and other)	62 (11)
Lines of prior therapy—no. (%)	
0	104 (18)
1-3	368 (65)
≥4	98 (17)

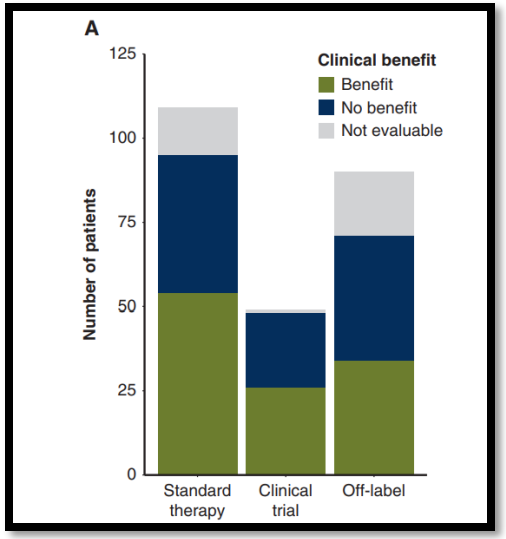
- Clinically actionable targets identified for 83% of patients, of which 37% of patients received WGTA-informed treatments.
- Of a total 248 WGTA-informed treatments, 46% resulted in clinical benefit.

Ref: E. Pleasance et.al Annals of Oncology 2022
https://doi.org/10.1016/j.annonc.2022.05.522

Whole-genome and transcriptome analysis enhances precision cancer treatment options







- Patients accessed WGTA-informed treatments through clinical trials (19%), off-label use (35%) and as standard therapies (46%) including those which would not otherwise have been the next choice of therapy.

Ref: E. Pleasance et.al Annals of Oncology 2022
https://doi.org/10.1016/j.annonc.2022.05.522

QUESTIONS FROM THE GROUP ?

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