ANCO/MOASC Presents

Precision Oncology Symposium

November 5, 2022

InterContinental Hotel San Francisco

ANCO

Educating and Empowering the
Northern California Cancer Community

MOASC

MEDICAL ONCOLOGY ASSOCIATION OF
SOUTHERN CALIFORNIA, INC.

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ANCO/MOASC
presents

Precision Oncology Symposium

Saturday, November 5, 2022; 8:00AM-5:00PM
InterContinental Hotel San Francisco

Agenda & Schedule

8:00 am	Registration, Continental Breakfast, and Engage with Exhibiting Supporters	
8:30 am	Welcome and Introduction	David R. Gandara, MD Ashkan Lashkari, MD Thach-Giao Truong, MD
8:35 am	Challenges & Opportunities to Clinical Application of Precision Oncology Across the Cancer Care Continuum	David R. Gandara, MD
8:45 am	Panel Discussion: Greatest Challenge & Greatest Opportunity in Various Tumor Types	**Moderator:** David R. Gandara, MD **Panelists:** Jennifer Caswell-Jin, MD Heinz-Josef Lenz, MD, FACP Mamta Parikh, MD, MS Jonathan Riess, MD, MS Sachdev Thomas, MD
9:15 am	Q and A	
9:25 am	Tissue versus Liquid Biopsy Diagnostics	Heinz-Josef Lenz, MD, FACP (Liquid) Carlos Suarez, MD (Tissue)
9:45 am	Q and A	
9:50am	Molecular Testing at Time of Initial Diagnosis of Advanced Stage Cancer	Eric Collisson, MD
10:05 am	Immunophenotyping at Time of Initial Diagnosis of Advanced Stage Cancer	Arta Monjazab, MD, PhD
10:20 am	Panel: Targeted Therapy Vs IO and the Challenges of Getting Therapy to the Right Patients with Initial Testing at Diagnosis	**Moderator:** Thach-Giao Truong, MD **Panelists:** Kim Margolin, MD Mamta Parikh, MD, MS Jonathan Riess, MD, MS
10:35 am	Coffee Break with Exhibiting Supporters	

10:50 am	Molecular Testing at Time of Acquired Resistance in Oncogene-Driven Cancers—Lung Cancer, Newest Treatment Approaches for a Prototype	Jonathan Riess, MD, MS
11:00 am	Molecular Testing at Time of Acquired Resistance in Other Histologies—The Experience in Breast Cancer	Jennifer Caswell-Jin, MD
11:10 am	Panel Discussion: Tumor Type-Specific Application of Molecular Testing at Initial Diagnosis & at PD in Oncogene-Driven Cancers	**Moderator:** David R. Gandara, MD **Panelists:** Chloe Atreya, MD, PhD Jennifer Caswell-Jin, MD Eric Collisson, MD Heinz-Josef Lenz, MD, FACP Mamta Parikh, MD, MS Jonathan Riess, MD, MS
11:40 am	Case-Based Molecular Tumor Board (Selected Cases from Various Tumor Types)	**Moderator:** Thach-Giao Truong, MD **Panelists:** Jennifer Caswell-Jin, MD Carlos Suarez, MD Sachdev Thomas, MD
12:05 pm	Germline Molecular Testing	James Ford, MD
12:20 pm	Q and A	
12:25 pm	Lunch and Engage with Exhibiting Supporters	
1:20 pm	Detection Of Post-Surgical Minimal Residual Disease (MRD) and Actionability in GI	Chloe Atreya, MD, Phd
1:30 pm	Detection Of Post-Surgical Minimal Residual Disease (MRD) And Actionability In GU	Mamta Parikh, MD, MS
1:40 pm	Panel Discussion: Tumor Type-Specific Application of MRD Detection	**Moderator:** Heinz-Josef Lenz, MD, FACP **Panelists:** Chloe Atreya, MD, PhD Ashkan Lashkari, MD Mamta Parikh, MD, MS Sachdev Thomas, MD

2:00 pm	Molecular Tumor Board: Tumor Type Agnostic Oncogene Targets	**Moderator:** Ashkan Lashkari, MD **Panelists:** James Ford, MD David R. Gandara, MD Mamta Parikh, MD, MS Sachdev Thomas, MD
2:20 pm	Panel Discussion: Patient Advocacy Meets Precision Oncology	**Moderator:** Danielle Hicks **Panelists:** Darcie Green Samantha Guild, JD Phuong Ly-Gallagher
2:50 pm	Q and A	
2:55 pm	Cellular Therapy in Solid Tumors	Mohamed Abou-el-Enein, MD, PhD, MSPH
3:15 pm	Application of Precision Medicine to Early Diagnosis & Screening	Mohammed Kashani-Sabet, MD
3:35 pm	Q and A	
3:50 pm	Closing Comments	David R. Gandara, MD Ashkan Lashkari, MD Thach-Giao Truong, MD
4:00 pm - 5:00 pm	Conference Reception with Exhibiting Supporters - Pacific Terrace	

Program Faculty

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Disclosure of Relevant Financial Relationships

The *Faculty* members have disclosed the following actual or potential conflicts of interest in regard to this program:

Mohamed Abou-el-Enein, MD, PhD, MSPH, disclosed that he does not have any relevant financial relationships with any commercial interests.

Chloe Atreya, MD, PhD, disclosed that she has received grant and or research support from Merck, Bristol-Meyers Squibb, Erasca, and Guardant Health. She also disclosed she is on the Advisory Board of Array Biopharma, Pfizer, Foundation Medicine, and Pionyr Immunotherapeutics.

Jennifer Caswell-Jin, MD, disclosed that she has received grant/research support from QED Therapeutics, and Effector Therapeutics.

Eric Collisson, MD, disclosed that he is a Board Member of Tatara and an advisor/reviewer for Valar. He also disclosed that he is a stock shareholder (excluding mutual funds) of Tatara, Valar, and Guardant Health.

James Ford, MD, disclosed that he has received grant and or research support from Genentech, Merus, and PUMA.

David R. Gandara, MD, disclosed that he is a has received institutional grant and or research support from Amgen, AstraZeneca, Genentech, and Merck. He also disclosed that he is an advisor/reviewer, panel member, and part of the Speakers Bureau for Adagene, Inc., AstraZeneca, Roche-Genentech, Guardant Health, IO Biotech, Oncocyte, and OncoHost. Additionally, he disclosed he is a consultant, honorarium recipient, and independent contractor of Lily, Merck, and Novartis.

Darcie Green disclosed that she does not have any relevant financial relationships with any commercial interests.

Samantha Guild, JD, disclosed that she does not have any relevant financial relationships with any commercial interests.

Danielle Hicks disclosed that she does not have any relevant financial relationships with any commercial interests.

Mohammed Kashani-Sabet, MD, disclosed that he is a consultant for Bristol-Meyers Squibb and panel member for DNARx, LLC. He also disclosed that he is a stock shareholder (excluding mutual funds) of Melanoma Diagnostics, Inc. and DNARx, LLC.

Ashkan Lashkari, MD, disclosed that he does not have any relevant financial relationships with any commercial interests.

Heinz-Josef Lenz, MD, FACP, disclosed that he does not have any relevant financial relationships with any commercial interests.

Phuong Ly-Gallagher, disclosed that

Kim Margolin, MD, disclosed that she does not have any relevant financial relationships with any commercial interests.

Arta Monjazab, MD, PhD disclosed that he has received grant/research support from Genentech, Merck, Incyte, Transgene, BMS, and EMD Serono. He also disclosed he is an Advisor/Reviewer and royalties/holder of intellectual property with MultiplexThera.

Mamta Parikh, MD, MS, disclosed that she has received grant/research support from Karyopharm. She also disclosed she is a consultant for Signatera and AstraSeneca.

Jonathan Riess, MD, MS, disclosed that

Carlos Suarez, MD, disclosed that he does not have any relevant financial relationships with any commercial interests.

Sachdev Thomas, MD, disclosed that he does not have any relevant financial relationships with any commercial interests.

Thach-Giao Truong, MD, disclosed that she does not have any relevant financial relationships with any commercial interests.

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Puma Biotechnology

Regeneron

Servier Pharmaceuticals

Stemline Therapeutics

Takeda Oncology

Challenges & Opportunities to Clinical Application of Precision Oncology Across the Cancer Care Continuum

David R. Gandara, MD

NOTES

Clinical Application of Precision Oncology across the Cancer Continuum of Care: Challenges & Opportunities

David R. Gandara, MD
University of California Davis
Comprehensive Cancer Center

1

Disclosures

Commercial Interest	Relationship(s)
Amgen	Research Grant (Institutional)
Astex	Research Grant (Institutional)
Genentech	Research Grant (Institutional)
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Astra Zeneca	Consultant (Institutional)
IO Biotech	Consultant (Institutional)
Guardant Health	Consultant (Institutional)
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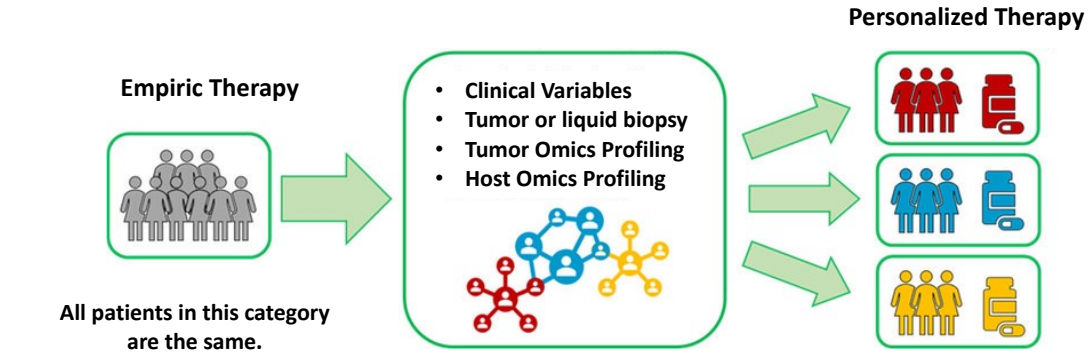
Merck	Advisory Board
Novartis	Advisory Board
Boehringer Ingelheim	Advisory Board
Regeneron	Advisory Board
Sanofi	Advisory Board
Amgen	Advisory Board

2

From Empiric Treatment Decision-Making → Precision Oncology (Personalized Therapy): Challenges and Opportunities



3

Challenge: "Precision medicine failing to deliver?"

"Nearly two decades after the first predictions of dramatic success, **we find no impact of the human genome project on the population's life expectancy** or any other public health measure."

it is time for the biomedical research community to **"reconsider its ongoing obsession" with genomic medicine"** and "reassess its research priorities."

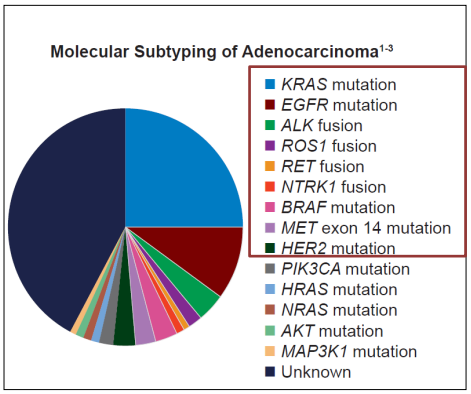
Oversimplification:
Cancer vs Non-cancer diseases
NSCLC vs Other Cancer Types

Joyner MJ and Paneth N. Promises, Promises, and Precision Medicine. J Clin Invest. 2019

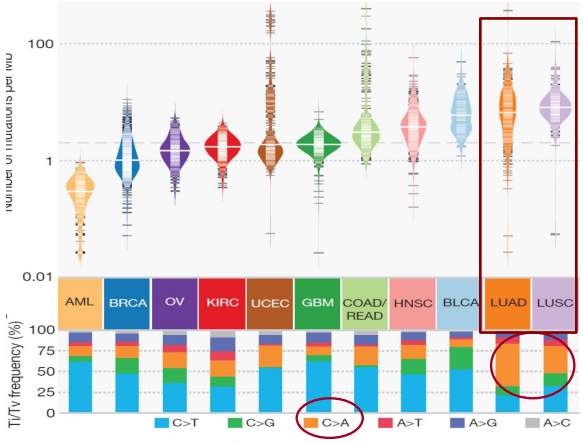
4

NSCLC is particularly well suited for Precision Oncology Strategies for both Targeted Therapies & Immunotherapy

- **Genomically complex cancers** with a multitude of potential oncogenes known to drive tumor growth
- **Quantitatively & Qualitatively well suited** for biomarker-driven **checkpoint immunotherapy**
- Improving the biomarker selection process in individual patients and **individualizing therapy** is now possible
- Newer technologies **(Next Gen Sequencing/NGS)** now in the clinic for both tissue & blood-based assays



Adapted from Kalemkerian et al. J Clin Oncol. 2018



Adapted from Kandoth et al *Nature* 2013

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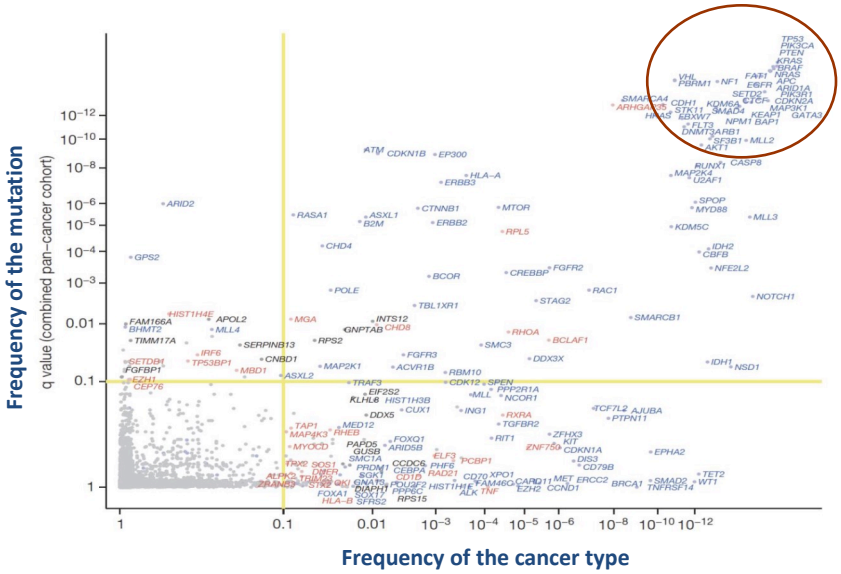
Challenge: Across all tumor types, only a few Cancer-related genes are currently "druggable"



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Opportunity: Tumor genomic alterations approved for Targeted Therapy in the advanced stage setting across multiple cancer types

Bladder

FGFR2/3 fusions

Breast

PIK3CA mutations

ERBB2(HER2) amplification

BRCA1/2 germline & somatic mutations

ESR1 mutations

Cholangiocarcinoma

FGFR2 fusions

IDH1 mutations

Colorectal

MSI-High

RAS mutations

BRAF V600E

ERBB2(HER2) amplification

EGFR mutations

Endometrial

MSI-high

ERBB2(HER2) amplification

Gastric/Gastroesophageal

ERBB2(HER2) amplification

GIST

KIT mutations

PDGFRA mutations

BRAF mutations

NSCLC

EGFR driver mutations

ALK fusions

ROS1 fusions

BRAF V600E mutations

RET fusions

KRAS G12C

MET exon 14 skipping

EGFR/ERBB2 exon 20 ins

NTRK

Melanoma

BRAF V600E/K

Ovarian

BRCA1/2 germline & somatic mutations

Pancreatic

BRCA1/2 germline & somatic mutations

Prostate

BRCA1/2 germline & somatic mutations

Thyroid

RET fusions

BRAF V600E

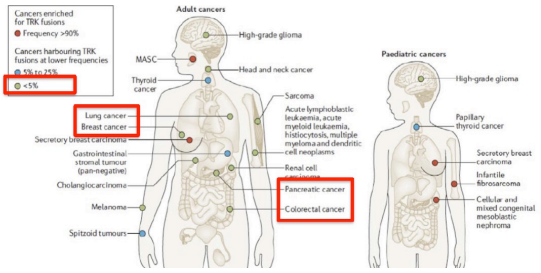
Courtesy of Caroline Weipert

7

Challenge: Tumor Type Agnostic vs Tumor Type-Specific Drug Activity

Hypothesis for Precision Medicine: In the future, Tumor Type will not matter. Genomics will drive therapeutic decision-making independent of tumor type.

Tumor Type Agnostic Indication:
NTRK (Entrectinib, Larotrectinib)



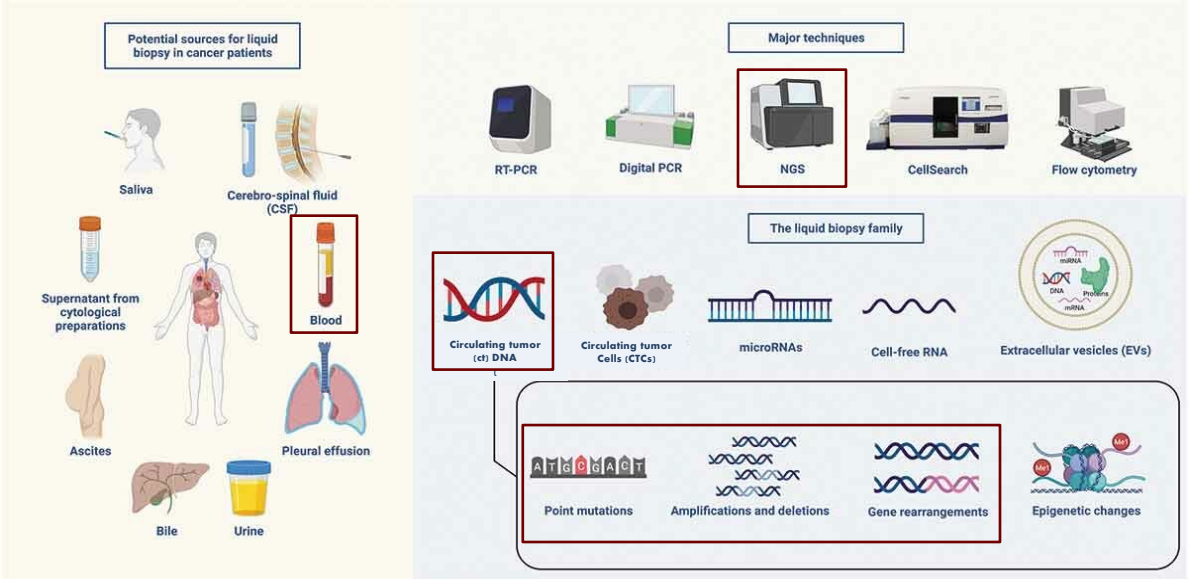
Tumor Type-Specific Activity:
examples of lack of activity of drugs/targets in NSCLC that are active elsewhere:

FGFR inhibitors
PIK3CA inhibitors
CDK 4/6 inhibitors
PARP inhibitors in BRCA-mutated

8

Challenge: "Speaking the Same Language" Terminology is Important

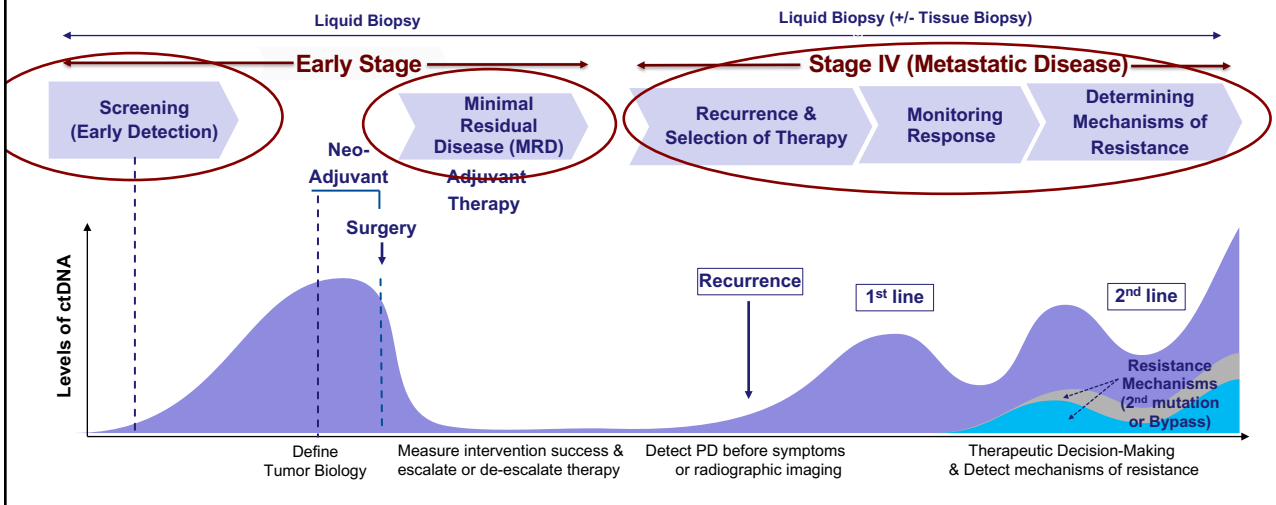
What do we mean by "Molecular Testing & "Liquid Biopsy"?



Malapelle, Gandara, Rolfo et al. Exp Rev Mol Diagnostics, 2021

9

Opportunity: Precision Oncology across the Cancer Care Continuum in Individual Patients



Gandara: ISLB Congress 2021 (Adapted from Wan, J.C.M., et al. *Nat Rev Cancer 2017)*

10

Challenge & Opportunity: Despite initial response development of Acquired Resistance to Targeted TKIs in Oncogene-driven NSCLC is almost universal

Target	Prevalence	Drug	Response Rate
EGFR	15%-60%	Osimertinib	70%
ALK	5%-10%	Alectinib, Brigatinib	70%
ROS1	1%-2%	Crizotinib, Entrectinib	72%
BRAF V600E	1%-2%	Vemurafenib Dabrafenib	42% 33%
MET exon 14 mutations	3%	Capmatinib, Crizotinib[1]	44-67%
High *MET* amplification	3%-4%	Crizotinib[2]	66%
HER2	1.7%	Afatinib[3] TDM1[4] TDX-d	100% 44% 62%
RET	1%-2%	Selpercatinib (LOXO-292)[5] Pralsetinib (BLU-667)[6]	80% 58%
NTRK1/2/3	3%	Entrectinib, Larotrectinib	80%

- Despite these high response rates, essentially no patients are cured
- All patients develop acquired resistance, either secondary resistance mutations or Bypass mechanisms

1. Drilon AE et al. *J Clin Oncol.* 2016;34(suppl 15):108. 2. Camidge et al. *J Clin Oncol.* 2014;32(suppl 15):8001. 3. Mazières J et al. *J Clin Oncol.* 2013;31:1997-2003. 4. Li et al. *J Clin Oncol.* 2018;36:2532. 5. Drilon AE et al. *J Clin Oncol.* 2015;33(suppl 15):8007. 6. Gainor J et al. ASCO 2019. Abstract 9008.

11

Opportunity: Progressive Disease (PD) after 1st line TKI Therapy in Oncogene-driven Advanced NSCLC (e.g., EGFR)

Progressive Disease after 1st line TKI

Empiric Approach: Choice of next line of therapy empirically:
-Next TKI
-Chemotherapy
-Immunotherapy

Precision Medicine Approach: Choice of next line of therapy based on repeat biopsy or plasma ctDNA

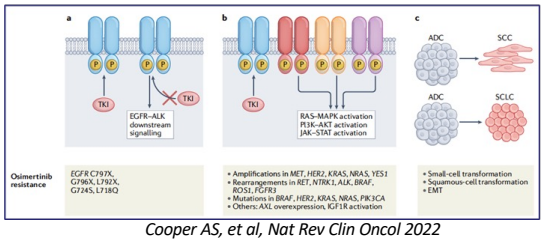
On-Target MOR (Resistance Mutations)

Off-Target MOR (Bypass Mechanisms Or Histologic Transformation)

On-Target: EGFR resistance mt

Off-Target: Diverse Bypass MOR

Histologic transformation

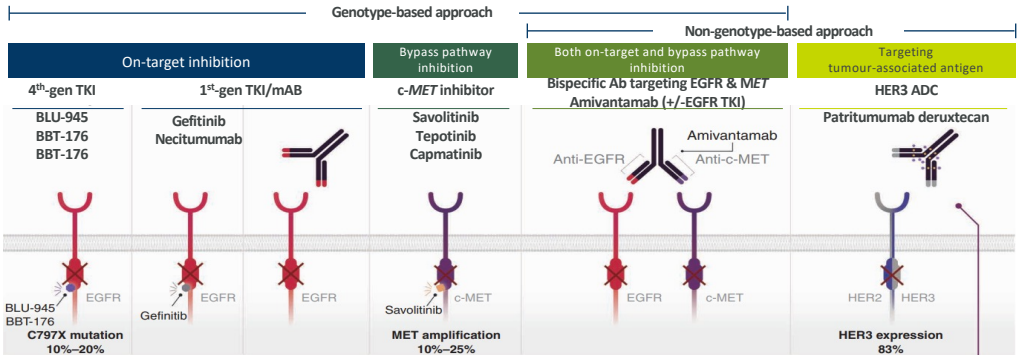


Cooper AS, et al, Nat Rev Clin Oncol 2022

Adapted from Melosky, Popat, Gandara. Clin Lung Cancer. 2017

12

Opportunity: Investigational Treatment Strategies for EGFR-mutated NSCLC with progressive disease after 1st-line Osimertinib

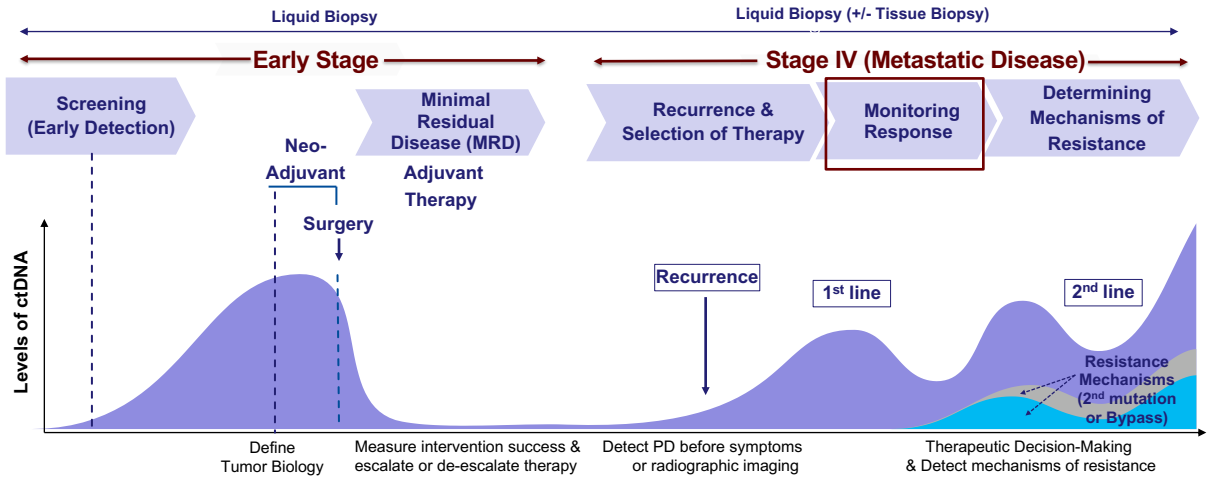


Lim SM, et al. Cancer Discov 2022;12:16–9

Presented by M Y Ahn WCLC 2022

13

Opportunity: Precision Oncology Across the Cancer Care Continuum



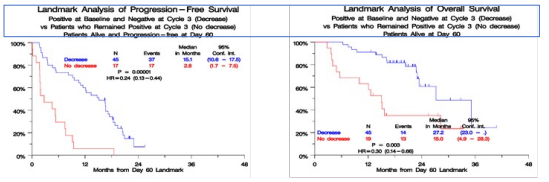
Gandara: ISLB Congress 2021 (Adapted from Wan, J.C.M., et al. *Nat Rev Cancer 2017)*

14

Opportunity: Response Monitoring by ctDNA in Advanced Stage NSCLC: Oncogene driver, Checkpoint Immunotherapy & Chemotherapy

Oncogene Driver

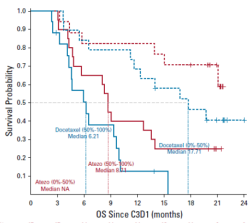
Clearance of ctDNA after Afatinib-Cetuximab (S1403)



Mack, Gandara et al. Clin Cancer Res 2022

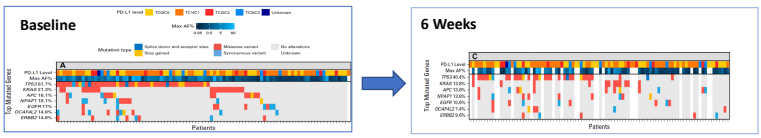
Immunotherapy & Chemotherapy

Metrics of ctDNA after Atezolizumab or Docetaxel



Zou, Gandara, Patel et al. JCO Precis Onc 2021

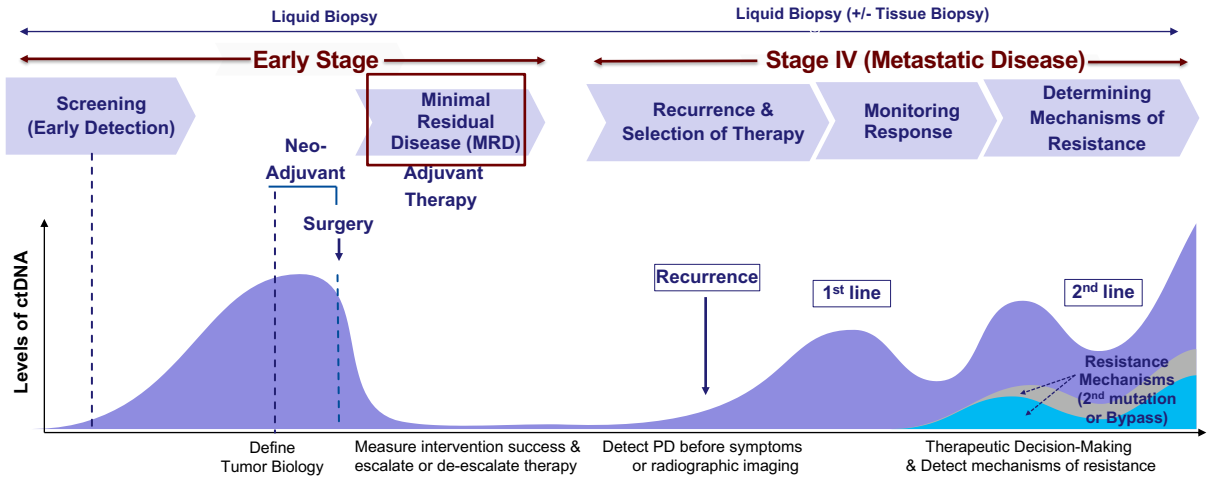
Reduction in mutation VAFs over time



Zou, Gandara, Patel et al. JCO Precis Onc 2021

15

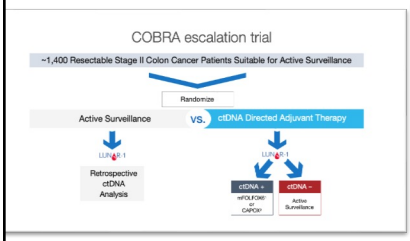
Opportunity: Precision Oncology Across the Cancer Care Continuum

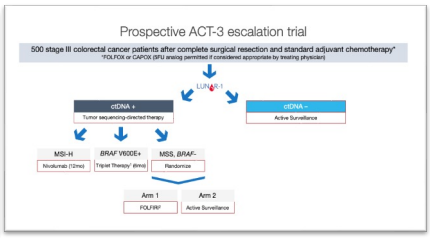


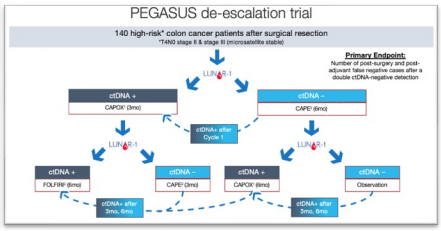
Gandara: ISLB Congress 2021 (Adapted from Wan, J.C.M., et al. *Nat Rev Cancer 2017)*

16

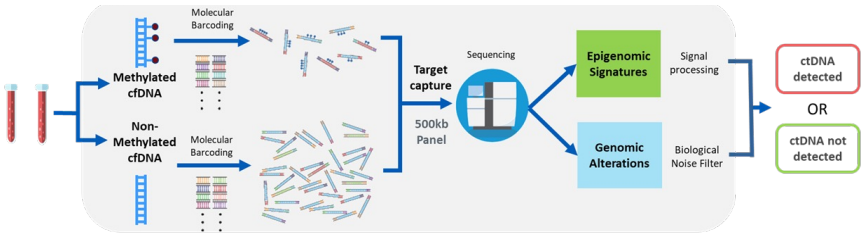
MRD detection by plasma ctDNA to escalate or de-escalate post-operative adjuvant therapy in stage II and stage III Colorectal Cancer







MRD assay integrating genomic & epigenomic assessment



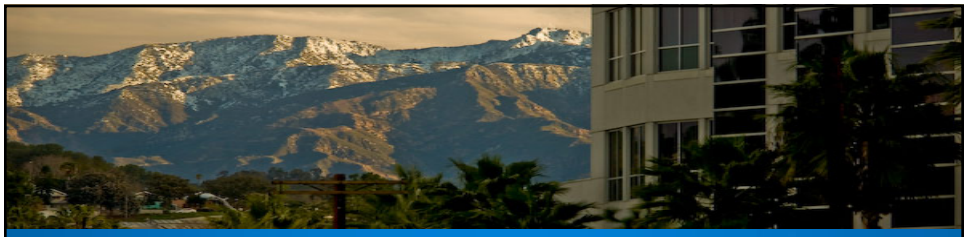
NCT04068103, NCT03803553, NCT04259944

17

Tissue versus Liquid Biopsy Diagnostics

Heinz-Josef Lenz, MD, FACP (Liquid)
and Carlos Suarez, MD (Tissue)

NOTES



Tissue vs Liquid Biopsy Diagnostics. Pro Liquid Biopsies

Heinz-Josef Lenz

Professor of Medicine and Preventive Medicine
Associate Director, Clinical Research

J Terrence Lanni Chair in Cancer Research

Co-Director, USC Center for Molecular Pathways and Drug Discovery

USC/Norris Comprehensive Cancer Center

Los Angeles, California

1

USC NORRIS

Disclosures

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- Clinical Trial Support: NCI, NIH, SWOG, Isofol, Pfizer, BMS, G1 Therapeutics, Cardiff, Amal-KISIMA, Mirati, Merck, Bayer, Idera, UCB, PsOxius, NGM, OBI Pharma

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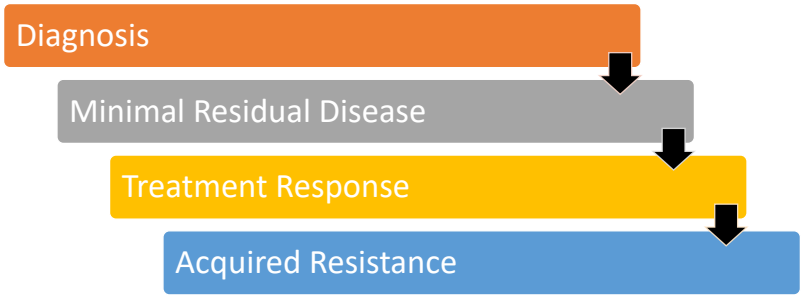
ctDNA is transforming and revolutionizing oncology

3

Clinical Applications for ctDNA



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ctDNA as Marker for MRD (molecular residual disease)

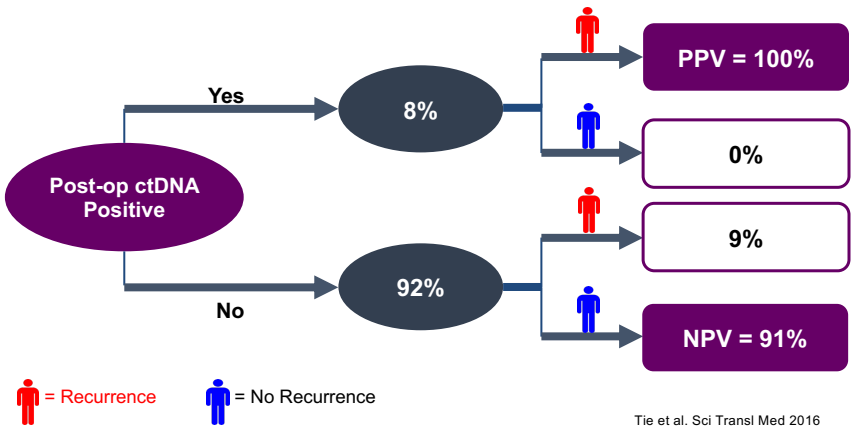
- **Two main types of tests:**
  - **Tumor-agnostic**
    - NGS or PCR panel of common mutations in CRC
      - E.g. REVEAL (Guardant – mutations + methylation)
    - Methylation markers
      - E.g. Colvera (Quest)

    Pro: easy logistics; Con: lower sensitivity
  - **Tumor-informed**
    - NGS or PCR panel of mutations detected in patient's primary tumor
      - E.g. Signatera (Natera)

    Pro: high sensitivity; Con: logistics more complicated

5

ctDNA and 3-year Recurrence Prediction Accuracy

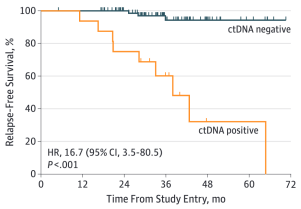


Tie et al. Sci Transl Med 2016

6

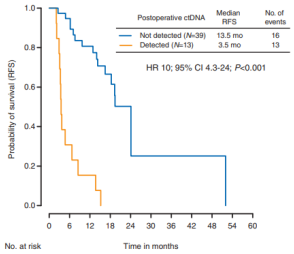
ctDNA Detection after Definitive Treatment Predicts Recurrence in Multiple Tumor Types

Early-Stage Breast Cancer



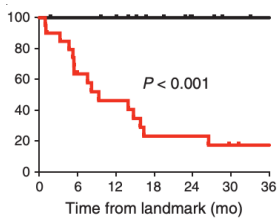
Garcia-Murillas et al, JAMA Oncol, 2019

Stage III Melanoma



Tan, …, Dawson. Ann Oncol, 2019

Localized Lung Cancer

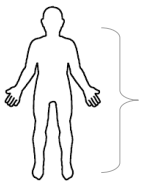


Chaudhuri et al. Cancer Discovery, 2017

7

Minimal Residual Disease: The Clinical Problem

Stage III CRC:
All patients get adjuvant chemo
>50% cured by surgery alone

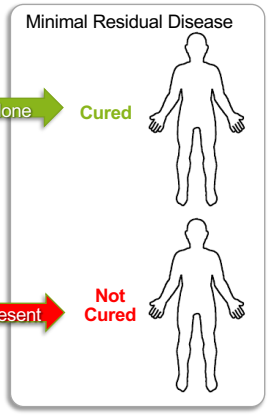


Curative Intent Surgery

Stage II CRC:
SOC is NO adjuvant chemo
10-15% of patients recur

Negative → None → Cured

Positive → Present → Not Cured

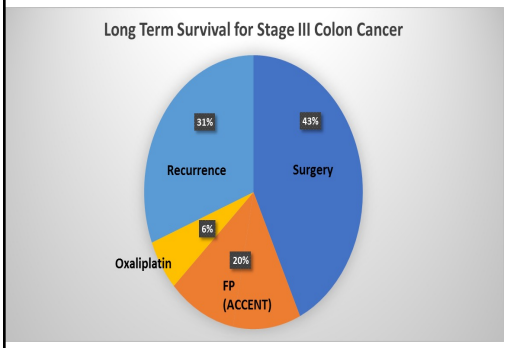


We have no way to determine who is cured and who will recur

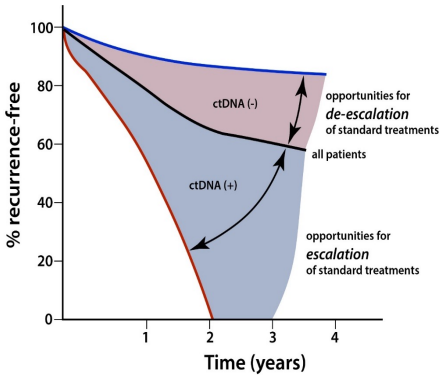
8

Adjuvant Therapy in Stage III CC : Room for Improvement

CURRENT (TNM):



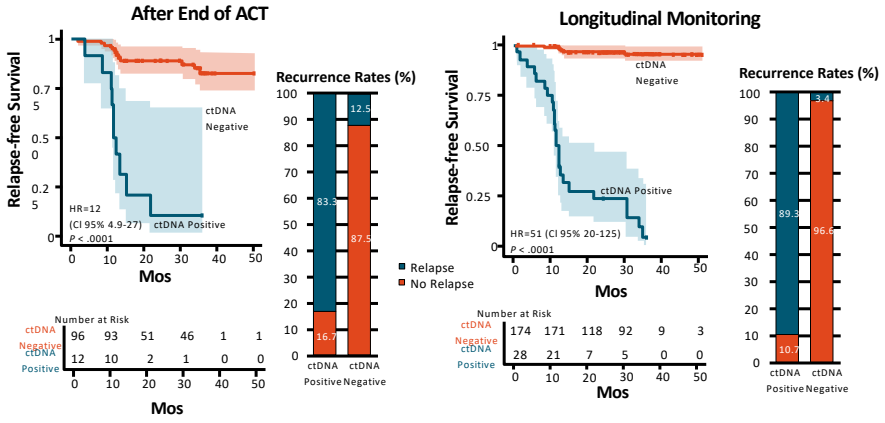
FUTURE (ctDNA):



Adapted from
Sargent et al, JCO 2009
Andre et al, JCO 2015

9

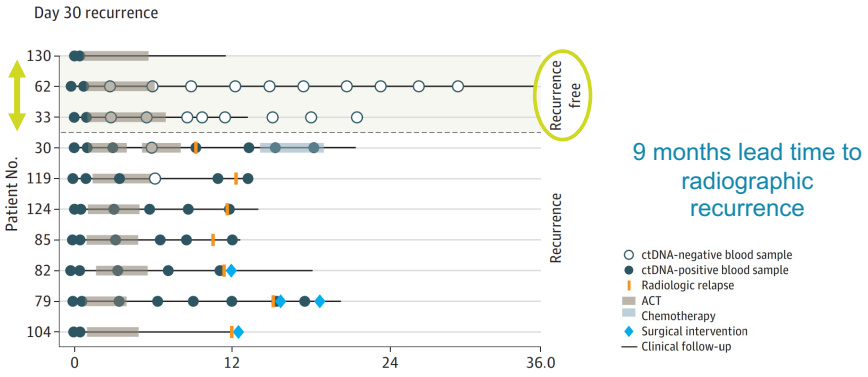
Post-treatment ctDNA Detection and CRC Recurrence



Henriksen et al., ASCO GI 2021

10

Prognostic and possible predictive of therapeutic response?

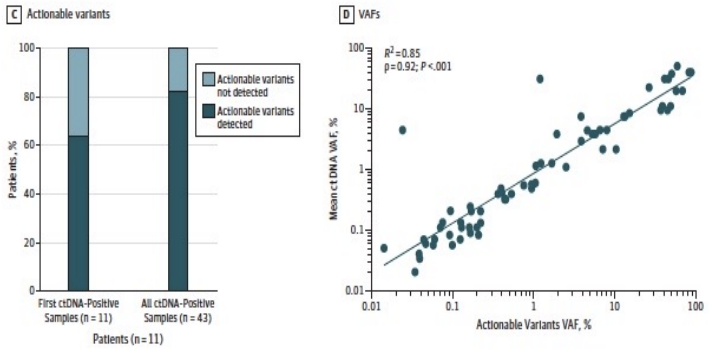


Reinert T, Henriksen TV, Christensen E, et al. JAMA Oncol. 2019 May 9;5(8):1124–31.

11

11

"Actionable" Variants Found in 82% of patients in ctDNA



Reinert T, Henriksen TV, Christensen E, et al. JAMA Oncol. 2019 May 9;5(8):1124–31

12

12

Minimal Residual Disease in 2022: Conclusions

ctDNA is prognostic and may be predictive of response to therapy

- Clearance is possible

Minimal residual disease applications have tremendous opportunity

- Requires larger, prospective cohorts
- Trials underway
- Great opportunities for novel drug development following ***biology*** of MRD

Attention to false positives and improving sensitivities will be critical to ensure success of this effort

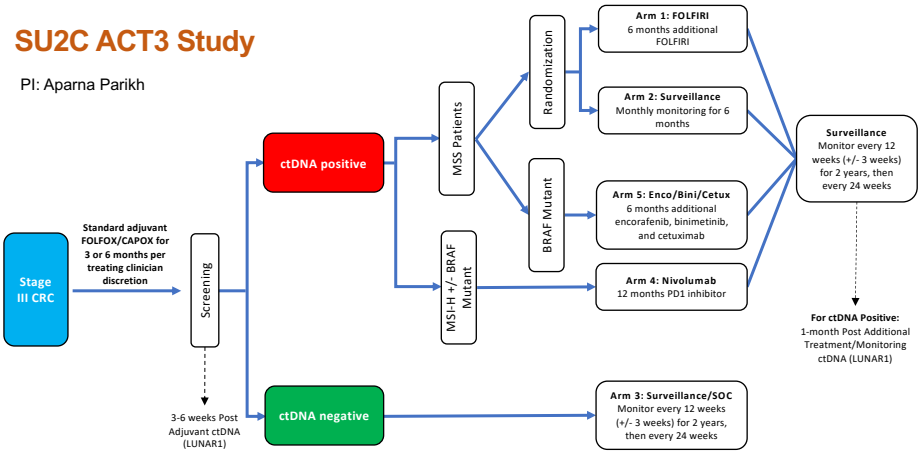
- Bioinformatically informed pipelines can address sources of false positives
- More data on Tumor Informed vs Uninformed approach to minimize false positives and ensure clinical relevance of the findings

13

Post-Chemo ctDNA Enrichment → Expedite Drug Development

SU2C ACT3 Study

PI: Aparna Parikh

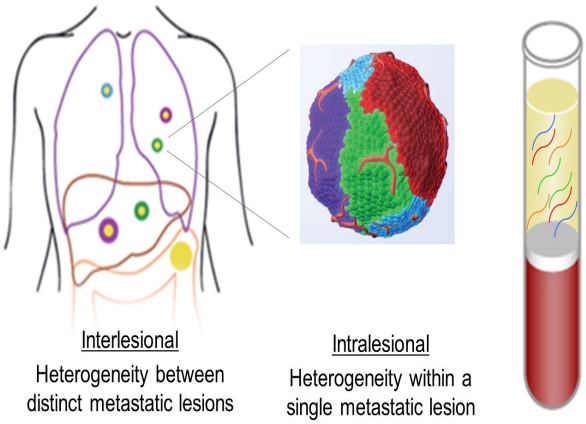


14

What are the potential applications of ctDNA?
Metastatic Disease

15

Tumor heterogeneity and acquired resistance



Interlesional
Heterogeneity between distinct metastatic lesions

Intralesional
Heterogeneity within a single metastatic lesion

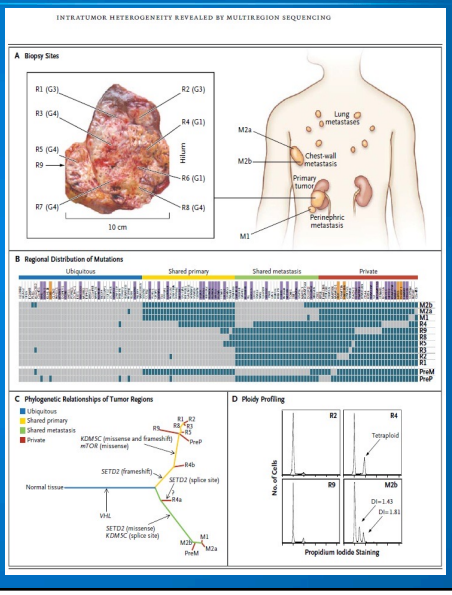
- A single needle biopsy may vastly underrepresent molecular heterogeneity
- Liquid biopsy may detect alterations in ctDNA shed by tumor cells throughout the body

Adapted from Bardelli, ASCO 2013; Misale, Cancer Discovery 2014

16

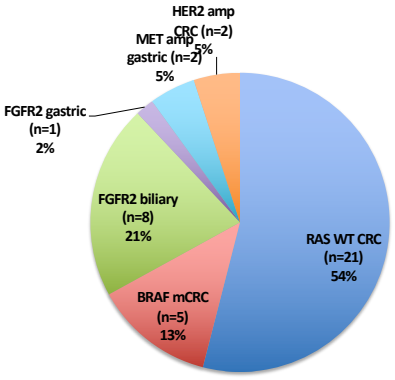
Heterogeneity also exists within individual tumors

- Ding et al., Nature 2010
  - Mutations present in 5–90% of sequencing reads from one tumor
- Navin et al., Nature 2011
  - Independent subclones coexisting in a single anatomic site in breast
- Gerlinger et al., NEJM 2012
  - Two-thirds of mutations in single biopsies were not uniformly detectable throughout all sampled regions
  - Both sensitive and resistant RNA expression patterns



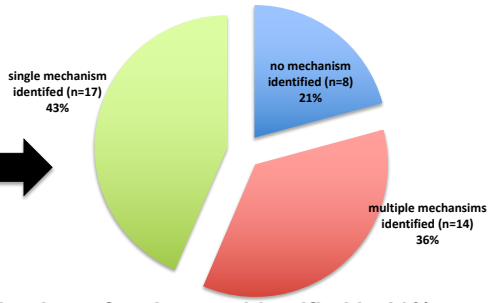
17

MGH GI Cancer Center Liquid Biopsy Program



N=39

Routine liquid biopsy assessment can effectively identify mechanisms of resistance across different tumor types and treatments



Mechanism of resistance identified in 80%

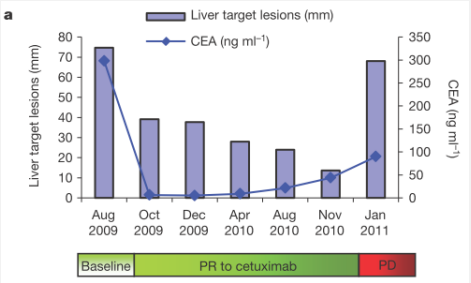
36% with multiple resistance mechanisms (range 2-12; median 3)

In patients with matched tumor biopsies, ctDNA identified additional resistance mechanisms in 64%

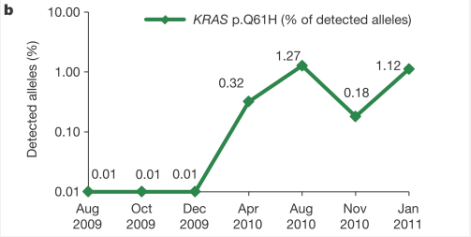
18

KRAS mut/ampl under pressure

Initial response to cetuximab followed by PD



Quantitative analysis of KRAS(Q61H) mutant DNA in plasma, as assessed by BEAMing

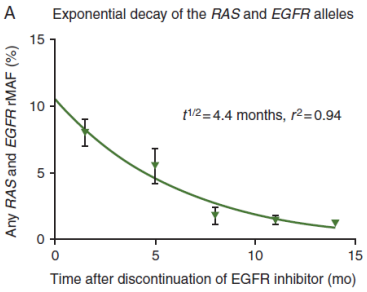


Misale S, et al. Nature 2012
Diaz E, et al. Nature 2012

19

Monitoring of Resistance during anti-EGFR treatment


ESMO
ORIGINAL ARTICLE
Anti-EGFR-resistant clones decay exponentially after progression: implications for anti-EGFR re-challenge

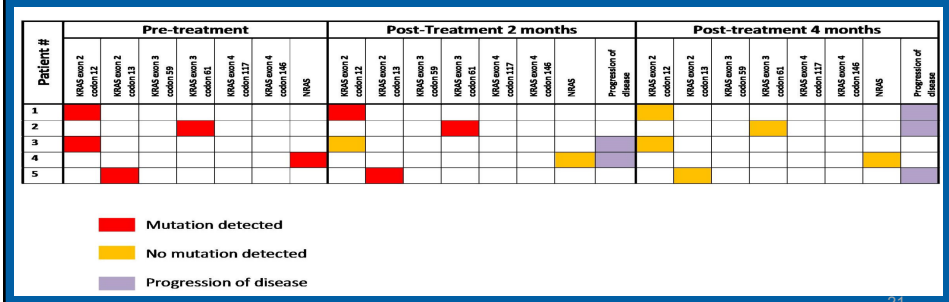


Parseghian et Ann Oncol. 2019 Feb 1;30(2):243-249.

20

Interesting Findings

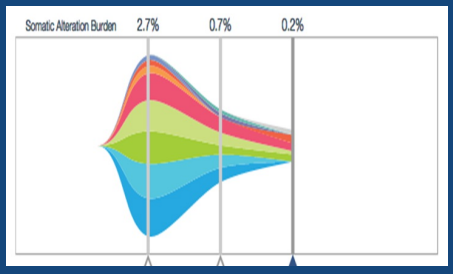
1. In a small series of 10 patients who all had mt ras in tissue and liquid biopsy treated with bev based chemotherapy. 5/10 changed to wt Ras under chemotherapy) Gazzaniga et al Annals of Oncology (2017) 28 (suppl_5): v573-v594)
2. Case report in JCO Precision Oncology from same group reported PR in one of this patient treated with cetuximab

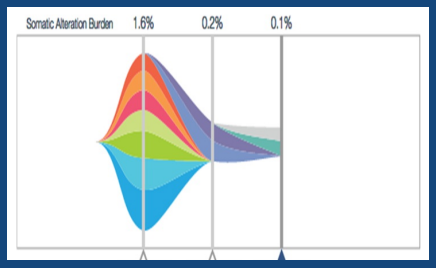


21

21

Example for Monitoring for Response and Resistance
Change of ctDNA levels and Loss and Grain of new ctDNA





In 84 patients with metastatic CRC receiving serial monitoring, 87% had either gain (61%) or loss (63%) of clones over time

Strickler et al., *J Clin Oncol*. 35, 2017 (suppl 4S; abstract 584). Presented at GI ASCO 2017.

Heinz-Josef Lenz

PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18 Slides are the property of the author, permission required for reuse. PRESENTED BY:

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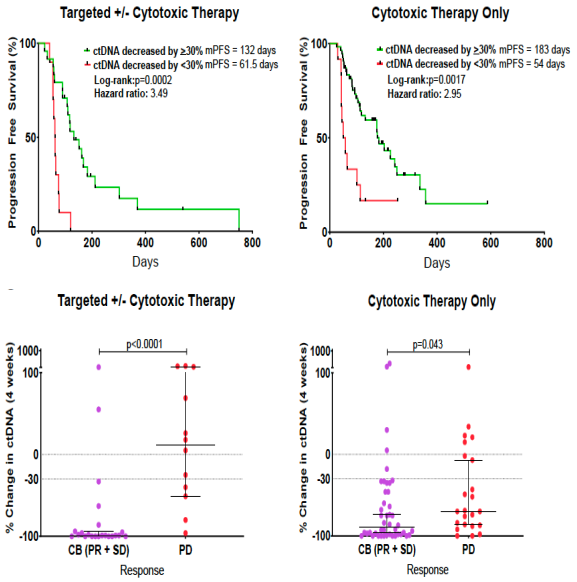
ctDNA Change at 4 Weeks Predict PFS in Patients Receiving Targeted Therapy with/without Chemotherapy



Parikh AR, et al. Clin Cancer Res. 2020 Apr 15;26(8):1877-1885.

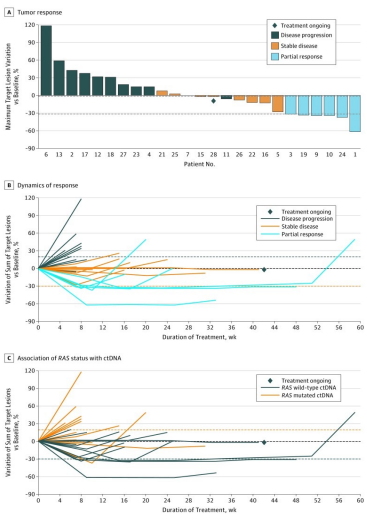
MASSACHUSETTS GENERAL HOSPITAL CANCER CENTER

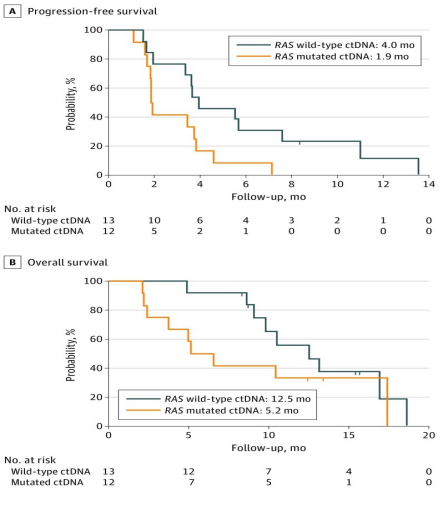
23

23

Rechallenge EGFR Strategy – 25 patients

Response rate, 21%; 95% CI, 10%-40%;
Disease control rate, 54%; 95% CI, 36%-70%





Cremolini C et al. *JAMA Oncol.* 2018;4(4):529-536.

24

Conclusions

1. Liquid biopsies are already being tested in prospective studies in stage II and III colorectal cancer but shown to impact treatment changes beyond standard of care therapies (de escalation or escalation) as targeted therapies or irinotecan have not shown to have benefit? Need to select patients?
2. Liquid biopsies are playing an increasing role in monitoring patients with metastatic disease with focus of mechanisms of resistance (rechallenge)
3. Questions remain what technologies (genetics, epigenetics, CTC) gives best specificity and sensitivity. Genetics may be not enough and require tissue in many cases that is time limiting?
4. No doubt Liquid biopsies will become routine in the future when technologies are refined

Precision Oncology Symposium

Tissue Biopsy: Pro and Cons for Molecular Studies

Carlos Jose Suarez, MD, MSc
Molecular Pathologist
Department of Pathology
Stanford University School of Medicine

November 5, 2022
InterContinental Hotel San Francisco
San Francisco, CA

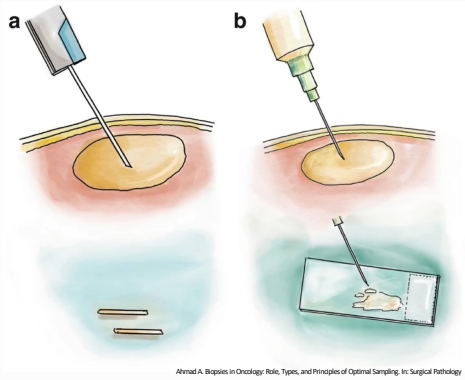
PRESENTED BY: ANCO Educating and Empowering the Northern California Cancer Community | Medical Oncology Association Of Southern California, Inc.

1

Precision Oncology Symposium

Definitions: Tissue Biopsy

- Direct tissue sample from a tumor
- Common methods:
  - (a) Core needle biopsy
  - (b) Fine needle biopsy/aspirate



Ahmad A. Biopsies in Oncology: Role, Types, and Principles of Optimal Sampling. In: Surgical Pathology

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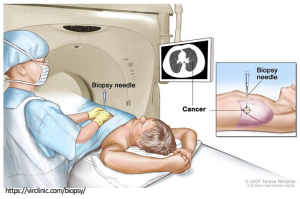
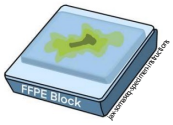
Process and Traditional Analysis

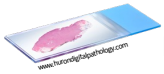
Procedure to obtain tissue



Tissue Processing



Preparation of glass slides



Microscopic Evaluation by a pathologist

Purpose: What is it? (Diagnosis)

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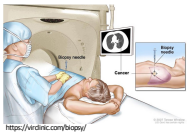
Precision Oncology Symposium

Process and Analysis in the Era of Precision Oncology

Purpose: What is it? (diagnosis)

How to treat it? (targeted therapy)

Procedure to obtain tissue



Tissue Processing

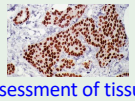
Preparation of glass slides

Microscopic evaluation

Tumor content assessment

FFPE tissue processing, sequencing, data processing

Genetic evaluation



Assessment of tissue-based biomarkers (e.g. PD-L1, ER)

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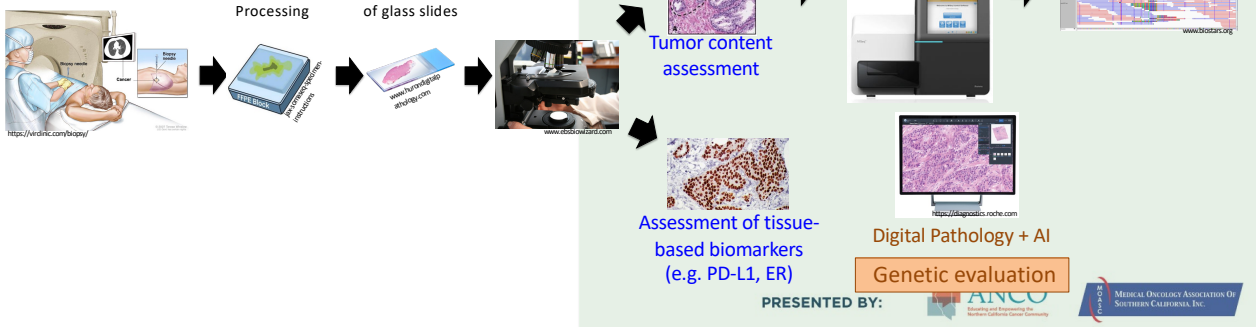
Precision Oncology Symposium

Process and Analysis in the Era of Precision Oncology

Purpose: What is it? (diagnosis)

How to treat it? (targeted therapy)



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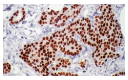
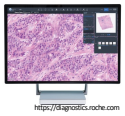
Precision Oncology Symposium

Tissue Biopsy: Advantages

Histopathologic evaluation by a pathologist



Assessment of tissue-based biomarkers (e.g. PD-L1, ER)



Genetic Evaluation: Digital Pathology + AI

- ✓ Allows histopathologic evaluation
  - Histopathologic diagnosis is needed **when** a **tumor** is **first detected** (What is it?)
  - Assessment of tissue-based biomarkers

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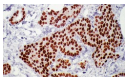
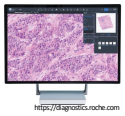
Precision Oncology Symposium

Tissue Biopsy: Advantages

Histopathologic evaluation by a pathologist



Assessment of tissue-based biomarkers (e.g. PD-L1, ER)



Genetic Evaluation: Digital Pathology + AI

- ✓ Allows histopathologic evaluation
  - Histopathologic diagnosis is needed **when a tumor is first detected** (What is it?)
  - Assessment of tissue-based biomarkers

PMID: 34246791

- ✓ Well-established **clinical validity** and clinical utility for all tumor types
  - Clinical trials for targeted therapies have used it for many years

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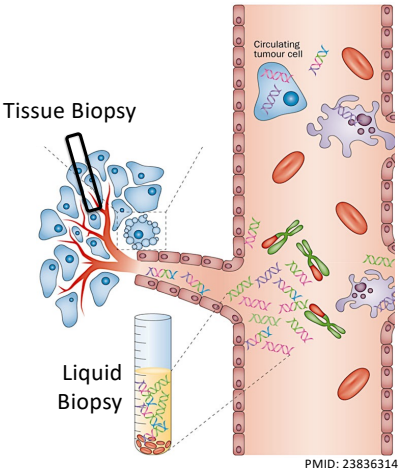
Tissue Biopsy: Advantages



PMID: 23836314

- ✓ The tumor is directly sampled
  - Sensitivity for genomic testing not affected by factors such as stage and tumor type
    - Factors that can affect the amount of ctDNA, circulating tumor cells (CTCs), or exosomes in the blood stream

https://www.cap.org/member-resources/articles/the-liquid-biopsy

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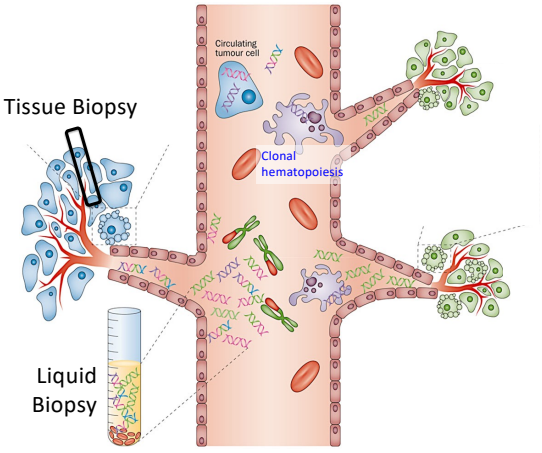
Tissue Biopsy: Advantages



PMID: 23836314

- ✓ The tumor is directly sampled
  - Less interference by genetic alterations from neoplastic/clonal processes in other tissues/organs (e.g. CHIP)

https://www.cap.org/member-resources/articles/the-liquid-biopsy

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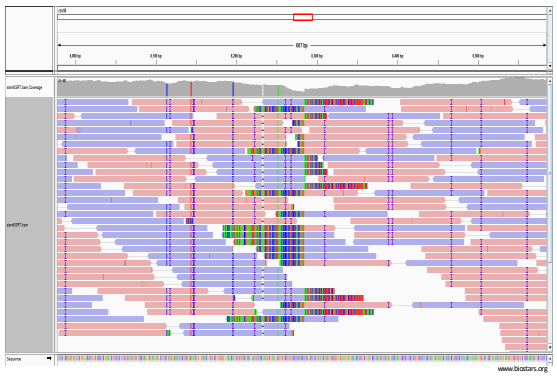
Precision Oncology Symposium

Tissue Biopsy: Technical Advantages



- ✓ The tumor is directly analyzed
  - The sequencing depth required to detect tumor variants is lower
    - Larger gene panels

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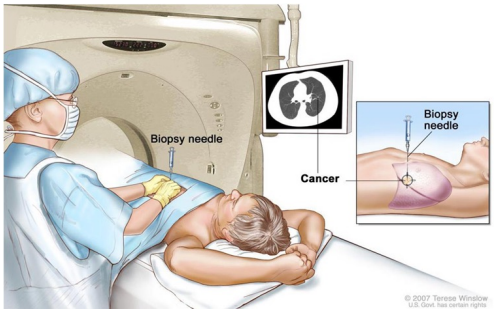
Tissue Biopsy: Disadvantages



- x Invasive
  - Lesion may not be accessible for a biopsy procedure
  - It may not be feasible in patients with poor performance status
  - Tissue obtained sometimes insufficient for genetic evaluation

PMID: 34246791

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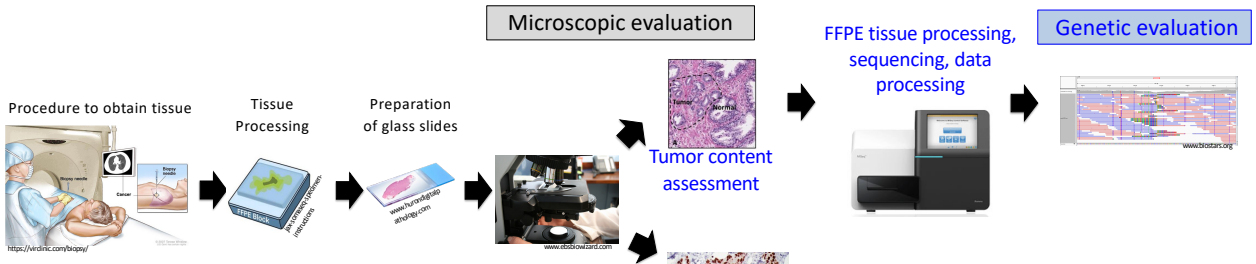
Tissue Biopsy: Disadvantages

- x Longer turnaround time and overall increased cost



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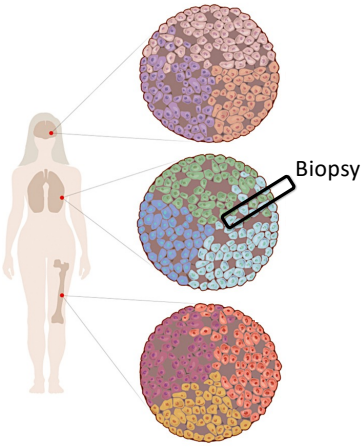
Tissue Biopsy: Disadvantages



PMID: 24048069

- x Small sample of the neoplastic disease
  - Tumor heterogeneity
    - Poor assessment of genetic landscape of the cancer in patients with advance disease

https://www.cap.org/member-resources/articles/the-liquid-biopsy
https://www.aacr.org/blog/2021/03/19/how-liquid-biopsies-can-complement-tissue-biopsies/

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Tissue Biopsy: Disadvantages

- x Limited repeatability over time
  - Serial biopsies may be unsafe and cost-prohibited
  - Monitoring molecular evolution (e.g. emergence of resistant mutations or new targetable mutations) may not be feasible

PMID: 34246791

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Molecular Testing at Time of Initial Diagnosis of Advanced Stage Cancer

Eric Collisson, MD

NOTES

Biomarker Testing at Initial Diagnosis

Eric Collisson MD Medical Oncology, UC San Francisco

1

Disclosures

- EC Stock: Tatara, BloodQ, Clara, Guardant
- EC Research Support: Merck KgA, Astra Zeneca, Loxo/Bayer.

2

Diseases We will Discuss

- Lung cancer
- Colon Cancer
- Cholangio
- Prostate Cancer
- Bladder Cancer
- Pancreas Cancer

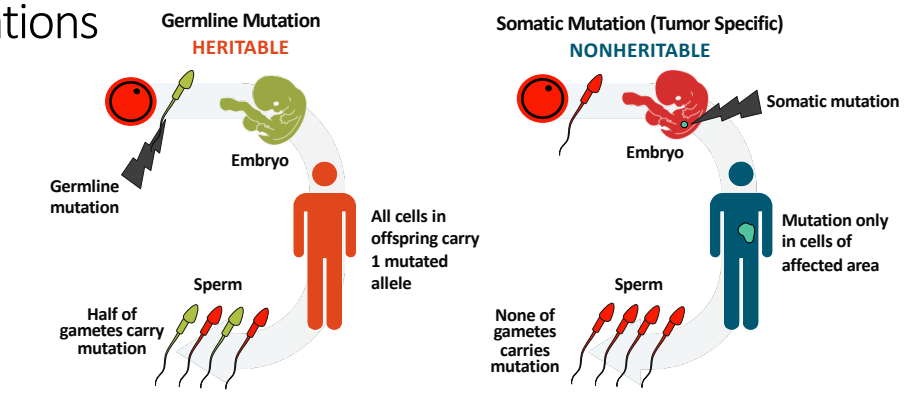
3

What Test to Order?

- Mutations on Tissue?
- Mutations in Germline?
- Mutations in Blood?
- RNA in Tissue?
- Primary Site or Metastatic Specimen?
- In House or Send Out?

4

Germline vs Somatic Mutations



Griffiths AJ, et al. An Introduction to Genetic Analysis. 7th edition. 2000.

5

DNA tests: Germline vs. Somatic

- **Germline**: You're Born with it.
  - Blood or Buccal swabs

color

Myriad

INVITAE

- **Somatic** : (Mutation acquired in cancer cell, wt in the germline)

CARIS LIFE SCIENCES

STRATA oncology

FOUNDATION MEDICINE

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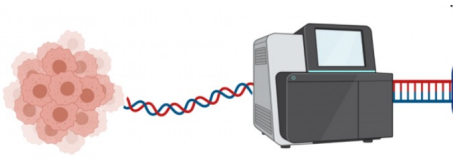
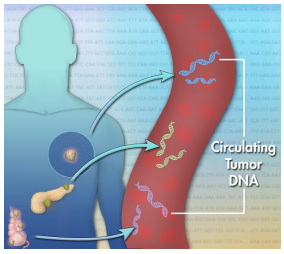
DNA Somatic Tests: Blood vs. cfDNA



Tissue Seq: Picks up somatic and Germline Mutations (sequence normal to disambiguate)



Cell Free DNA sequencing: picks up somatic and germline AND clonal hematopoiesis (CHIP)

7

ctDNA vs. Tissue

- cfDNA pros
  - "summary" of the dominant clone
  - Faster than finding
- cfDNA cons
  - TND in 10-20% of cases
  - CHIP / heterogeneity of mutation source
  - Allows TMB but not PDL1
- Tissue Pros
  - Linked to histology / IHC / PDL1
  - Lower (but non zero) nondetected rate
- Tissue Cons
  - Slow (finding slides and release and shipping)
  - Misses heterogenity

8

Lung

Adeno*:
Mutations: KRAS, EGFR, MET exon 14, BRAF, ERBB2
Fusions: NTRK, RET, ALK, ROS1, NRG1
Squamous : evolving
Small Cell: NTD

*NB: ctDNA often used for first line decision making due to TnT advantage

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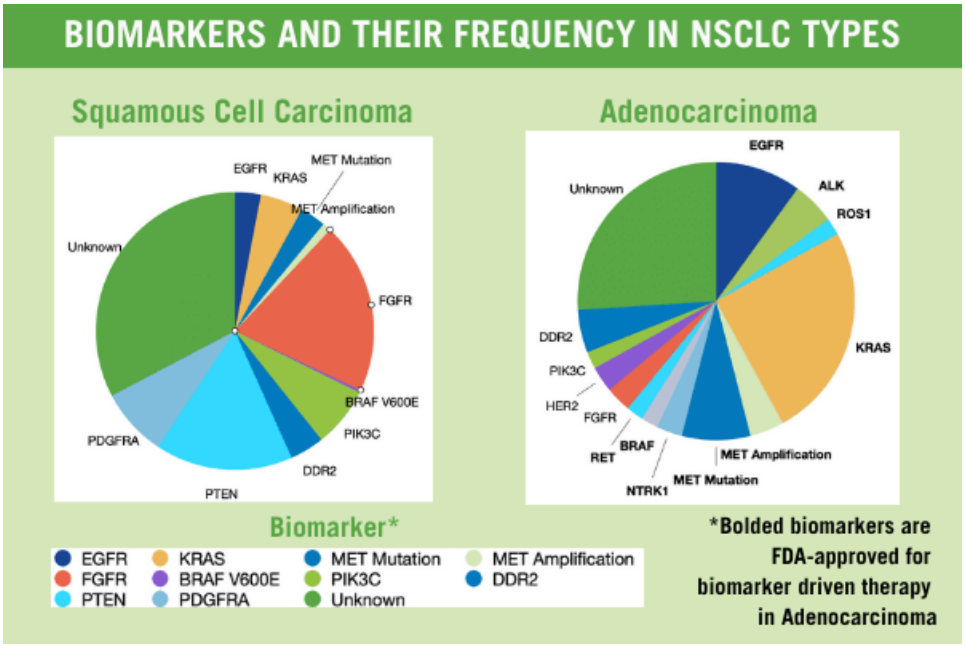

Lung Cancer Foundation

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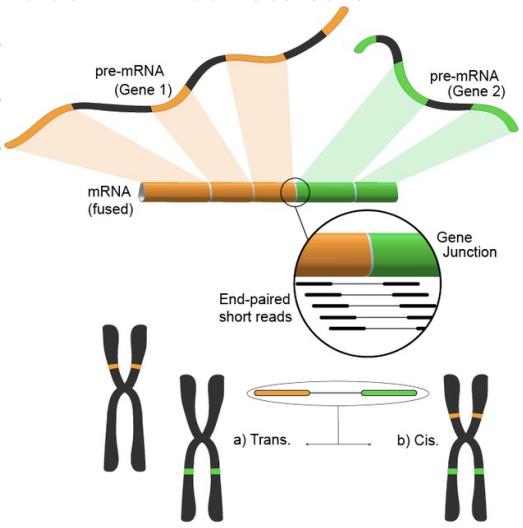


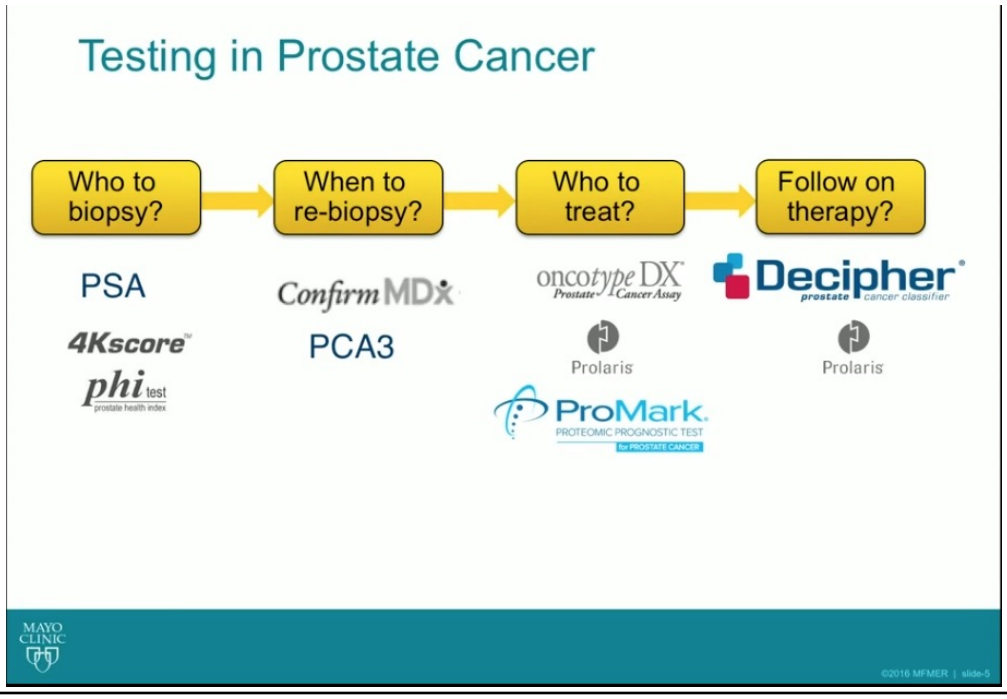
AdenoCA:

If No Driver Mutations: KRAS, EGFR, MET exon 14, BRAF, ERBB2 found on DNA seq…..

Think Fusions: NTRK, RET, ALK, ROS1, NRG1

Consider mRNA testing

11



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Prostate

All Patients: Germline Testing
Hormone Sensitive (nothing to do)

Castrate Resistant→Somatic Profiling: MSI TMB
BRCA1/2
*** *consider metastatic site rebiopsy*

13

Urothelial

Upper Track: Germline Testing to r/o Lynch

Emerging: *FGFR2/3* Fusions and Pt Mutations

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Colorectal

Germline:
APC or MSI-H

Somatic Panel:
KRAS, NRAS, BRAF, ERBB2, MSI

15

Cholangio

Somatic Panel:
- IDH1/2
- FGFR fusions

16

Pancreas

Germline Panel:
BRCA1/2

Somatic Panel:
KRAS often have BRAF or fusions which may be actionable

17

Conclusions

- DNA testing is here to stay
- What test you order matters
- What genes you test matters
- Interpretation matters

- Watch for:
  - RNA assays in Tissue and blood
  - Predict response
  - Fusions are best found with RNA

18

Immunophenotyping at Time of Initial Diagnosis of Advanced Stage Cancer

Arta Monjazab, MD, PhD

NOTES

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Immunophenotyping at Time of Initial Diagnosis of Advanced Stage Cancer

Arta Monir Monjazeb, MD, PhD
UC Davis Comprehensive Cancer Center
Professor of Radiation Oncology
Immuno-Oncology Initiative Co-Director
Laboratory of Cancer Immunology

November 5, 2022
InterContinental Hotel San Francisco
San Francisco, CA

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Disclosures

Arta M. Monjazeb has a financial interest, arrangement or affiliation with:

Name of Organization	Relationship
Genentech	Clinical Trial Support
Incyte	Clinical Trial Support, Advisory Board
EMD Serono	Clinical Trial Support
Merck	Clinical Trial Support, Research Support
BMS	Clinical Trial Support, Advisory Board
Transgene	Clinical Trial Support
Multiplex Thera	Consultant, Stock Options

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Baseline Immunophenotyping (state of the science)

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  - TMB / **MSI**
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  - TCR repertoire
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Patient

- PBMC phenotype
- Microbiome
- SNPs

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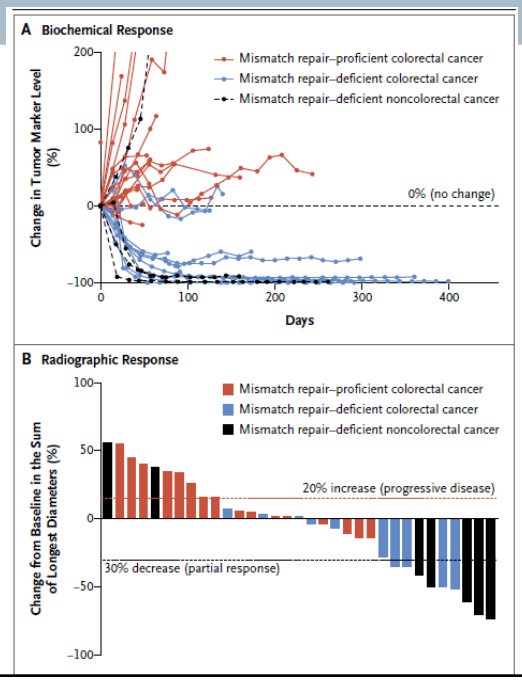
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

D.T. Le, J.N. Uram, H. Wang, B.R. Bartlett, H. Kemberling, A.D. Eyring, A.D. Skora, B.S. Luber, N.S. Azad, D. Laheru, B. Biedrzycki, R.C. Donehower, A. Zaheer, G.A. Fisher, T.S. Crocenzi, J.J. Lee, S.M. Duffy, R.M. Goldberg, A. de la Chapelle, M. Koshiji, F. Bhaijee, T. Huebner, R.H. Hruban, L.D. Wood, N. Cuka, D.M. Pardoll, N. Papadopoulos, K.W. Kinzler, S. Zhou, T.C. Cornish, J.M. Taube, R.A. Anders, J.R. Eshleman, B. Vogelstein, and L.A. Diaz, Jr.



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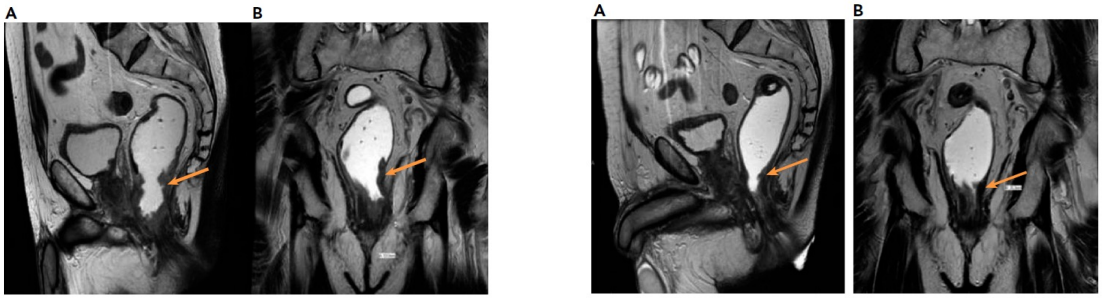
Neoadjuvant Immunotherapy–Based Systemic Treatment in MMR-Deficient or MSI-High Rectal Cancer: Case Series

Rahel Demisse, MD[1,2]; Neha Damle, MD[1]; Edward Kim, MD, PhD[1]; Jun Gong, MD[3]; Marwan Fakih, MD[4]; Cathy Eng, MD[5]; Leslie Oesterich, MD[1]; Madison McKenny, MD[6]; Jingran Ji, MD[1]; James Liu, MD[1]; Ryan Louie, BS[7]; Kit Tam, MD[1]; Sepideh Gholami, MD[8]; Wissam Halabi, MD[9]; Arta Monjazeb, MD, PhD[10]; Farshid Dayyani, MD[11,*]; and May Cho, MD[1,*]



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Baseline Immunophenotyping (state of the science)

Tumor

- TME (Transcriptomics / Proteomics)
  - **TMB** / MSI
  - **TILs**
  - **PD-L1**
  - TCR repertoire
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  - TCR repertoire

Patient

- PBMC phenotype
- Microbiome
- SNPs

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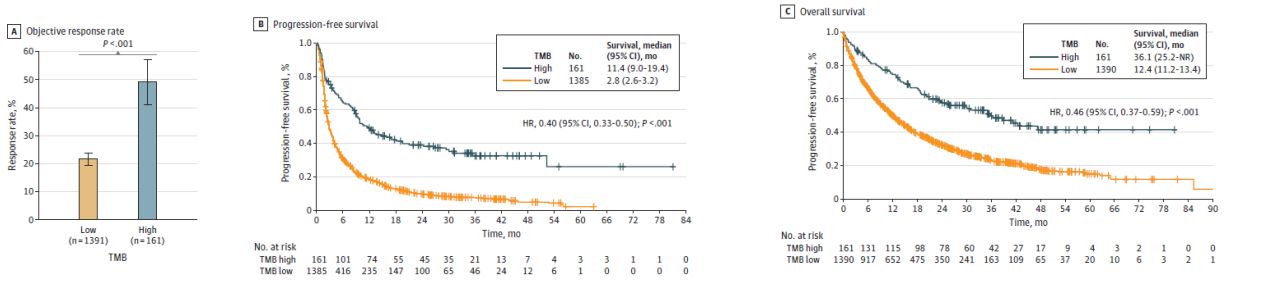
JAMA Oncology | Original Investigation

Association of High Tumor Mutation Burden in Non-Small Cell Lung Cancers With Increased Immune Infiltration and Improved Clinical Outcomes of PD-L1 Blockade Across PD-L1 Expression Levels

Biagio Ricciuti, MD; Xinan Wang, PhD; Joao V. Alessi, MD; Hira Rizvi, BA; Navin R. Mahadevan, MD; Yvonne Y. Li, PhD; Andrew Polio, MD; James Lindsay, MD; Renato Umeton, PhD; Rileen Sinha, PhD; Natalie I. Vokes, MD; Gonzalo Recondo, MD, PhD; Giuseppe Lamberti, MD; Marissa Lawrence, BS; Victor R. Vaz, MD; Giulia C. Leonardi, MD; Andrew J. Plodkowski, MD; Hersh Gupta, BA; Andrew D. Cherniack, PhD; Michael Y. Tolstorukov, PhD; Bijaya Sharma, BS; Kristen D. Felt, MS; Justin F. Gainor, MD; Arvind Ravi, MD, PhD; Gad Getz, PhD; Kurt A. Schalper, MD, PhD; Brian Henick, MD; Patrick Forde, MD; Valsamo Anagnostou, MD, PhD; Pasi A. Jänne, MD; Eliezer M. Van Allen, MD; Mizuki Nishino, MD; Lynette M. Sholl, MD; David C. Christiani, MD, PhD; Xihong Lin, PhD; Scott J. Rodig, MD, PhD; Matthew D. Hellmann, MD; Mark M. Awad, MD, PhD



TMB high > 19 per MB

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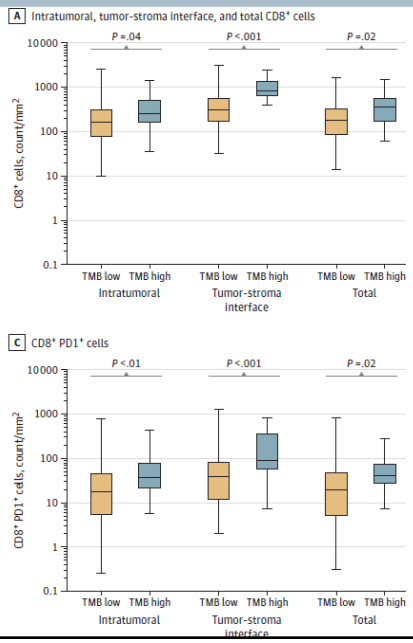

Outcome and PD-L1 tumor proportion score	Low TMB	High TMB	*P* value
Objective response rate, % (95% CI)			
<1%	8.7 (5.5-12.9)	46.7 (28.3-65.7)	<.001
1%-49%	18.7 (14.1-23.9)	50.0 (31.3-68.7)	<.001
≥50%	38.1 (33.3-43.0)	56.5 (41.1-71.1)	.02
Progression-free survival, median (95% CI), mo			
<1%	2.1 (2.0-2.4)	10.7 (8.2-24.4)	<.001
1%-49%	2.9 (2.5-3.6)	13.6 (8.6-NR)	<.001
≥50%	5.2 (4.6-6.2)	18.1 (8.6-NR)	<.001
Overall survival, median (95% CI), mo			
<1%	10.4 (7.9-13.6)	23.9 (16.7-NR)	.07
1%-49%	11.3 (9.6-14.7)	NR (21.2-NR)	<.001
≥50%	21.4 (17.5-25.9)	47.7 (35.4-NR)	.02

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Baseline Immunophenotyping (near future directions)

Tumor

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  - TILs
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  - TCR repertoire
  - Lipidomics
  - Multiplex & Spatial Analysis
  - Single Cell Analysis
- Blood based
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Patient

- Clinical Factors
  - Age, Sex, BMI, "Exposome"
- PBMC phenotype
- HLA phenotype
- Microbiome
- SNPs

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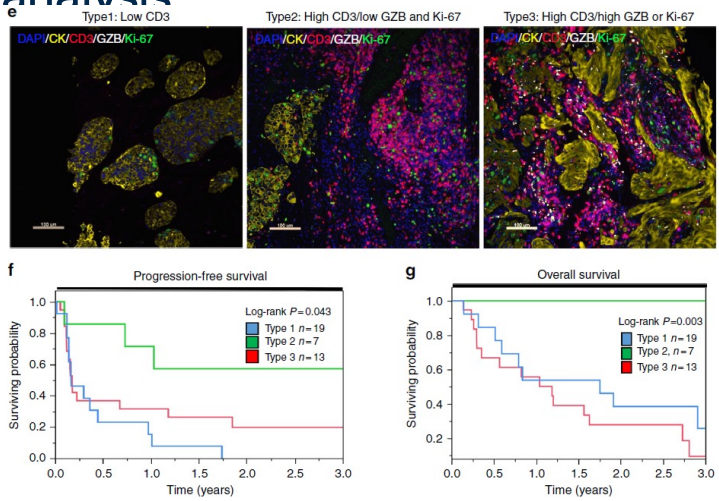
Multiplex & Spatial TME analysis

nature COMMUNICATIONS

A dormant TIL phenotype defines non-small cell lung carcinomas sensitive to immune checkpoint blockers

S.N. Gettinger[1], J. Choi[2], N. Mani[3,4], M.F. Sanmamed[5], I. Datar[3,4], Ryan Sowell[5], Victor Y. Du[5], E. K S. Goldberg[1], W. Dong[2], D. Zelterman[6], K. Politi[1,3], P. Kavathas[5,7], S. Kaech[5], X. Yu[6], H. Zhao[2,6], J. Schlessinger[8], R. Lifton[2], D.L. Rimm[1,3], L. Chen[5], R.S. Herbst[1] & K.A. Schalper[1,3,4]



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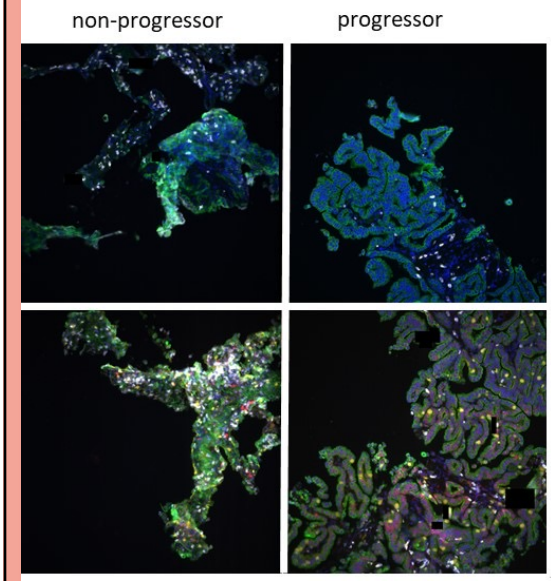

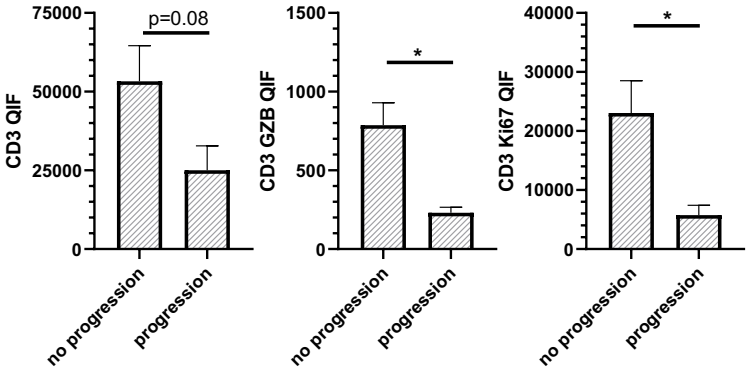

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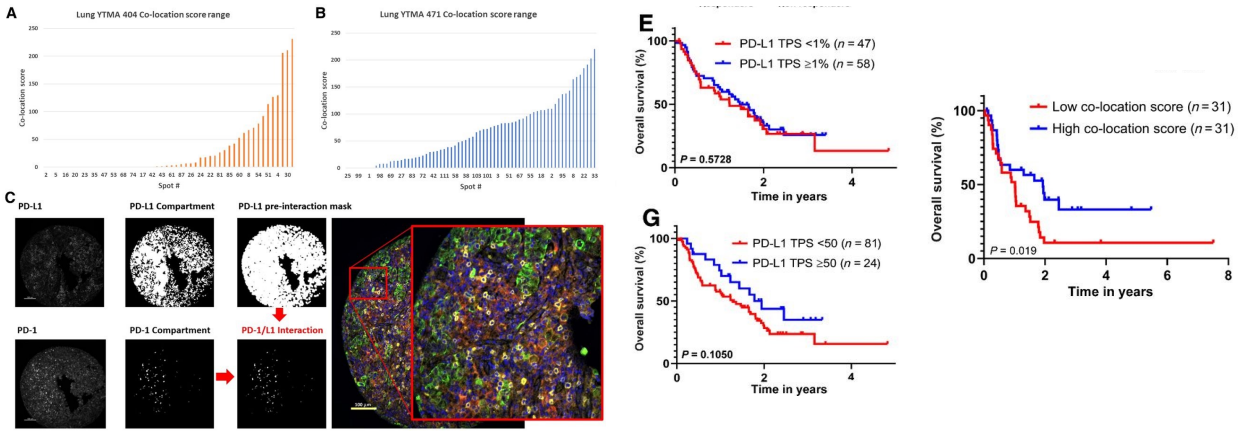
Multiplex & Spatial TME analysis



Gavrielatou N et al. CCR 2021

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- Microbiome
- SNPs

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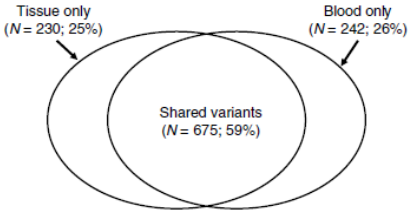
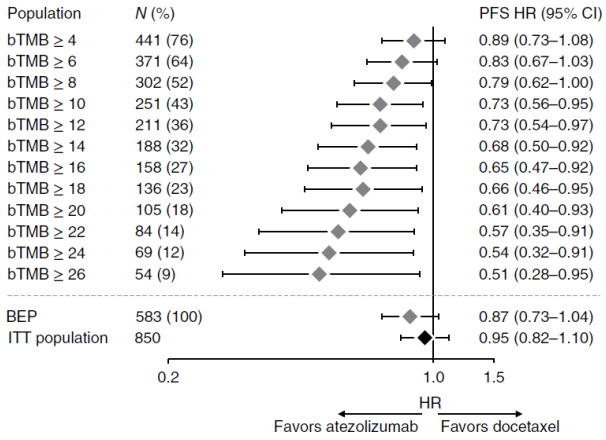
Liquid Biopsy (ctDNA)

nature medicine ARTICLES https://doi.org/10.1038/s41591-018-0134-3

Blood-based tumor mutational burden as a predictor of clinical benefit in non-small-cell lung cancer patients treated with atezolizumab

David R. Gandara[1,7*], Sarah M. Paul[2,7], Marcin Kowanetz[2,7], Erica Schleifman[2,7], Wei Zou[2,7], Yan Li[2], Achim Rittmeyer[3], Louis Fehrenbacher[4], Geoff Otto[5], Christine Malboeuf[5], Daniel S. Lieber[5], Doron Lipson[5], Jacob Silterra[5], Lukas Amler[2], Todd Riehl[2], Craig A. Cummings[2], Priti S. Hegde[2], Alan Sandler[2], Marcus Ballinger[2], David Fabrizio[5], Tony Mok[6*] and David S. Shames[2*]





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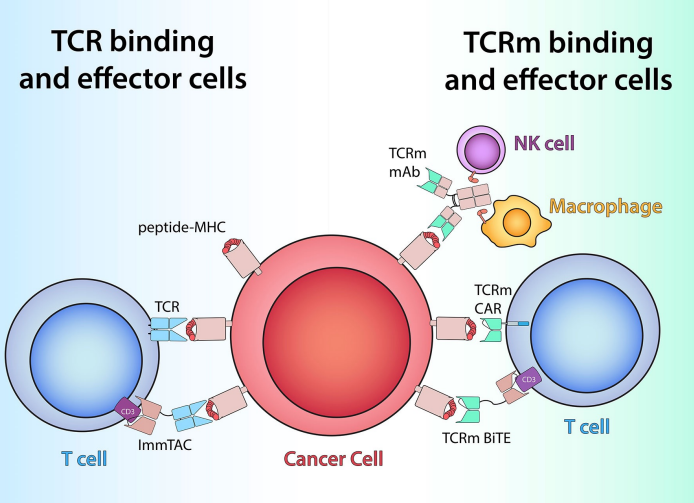
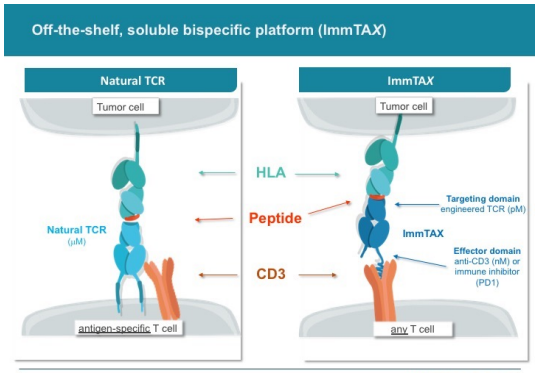
HLA Phenotyping





Tebantafusp-tebn
Gp100 in uveal melanoma

Jones HF et al. Front. Immunol. 2021

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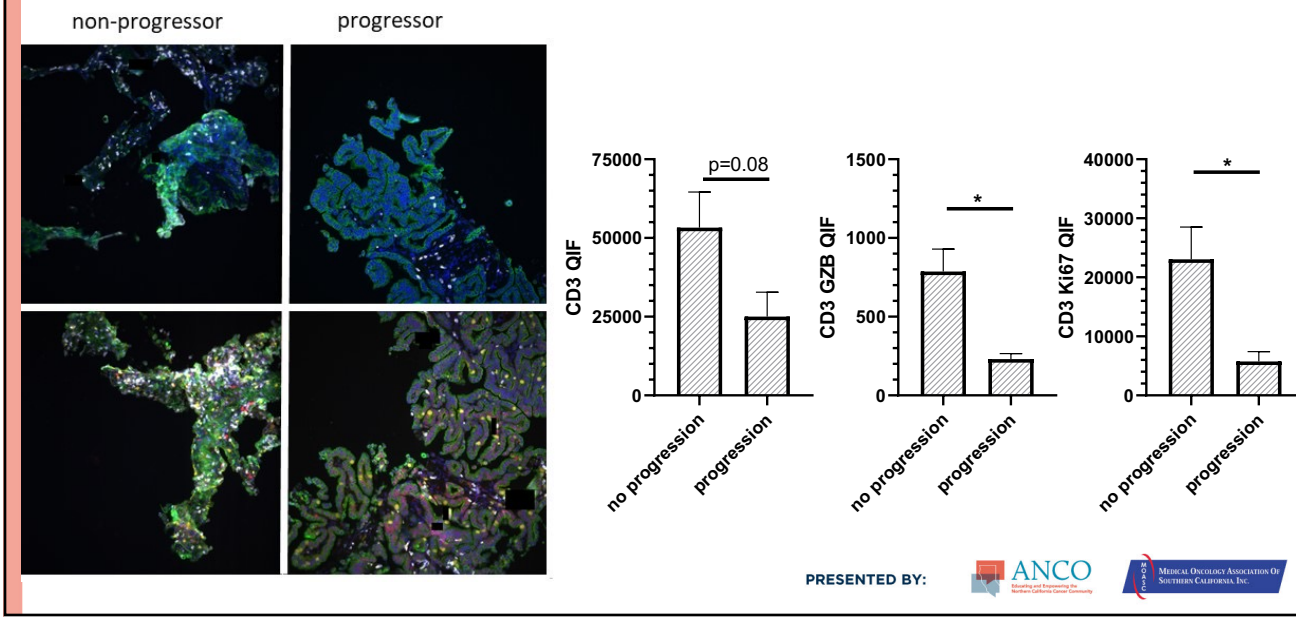

19

Precision Oncology Symposium

nature medicine

ARTICLES

https://doi.org/10.1038/s41591-018-0221-5

Paradoxical effects of obesity on T cell function during tumor progression and PD-1 checkpoint blockade

Ziming Wang[1,20], Ethan G. Aguilar[1,20], Jesus I. Luna[1], Cordelia Dunai[1], Lam T. Khuat[1], Catherine T. Le[1], Annie Mirsoian[1], Christine M. Minnar[1], Kevin M. Stoffel[1], Ian R. Sturgill[1], Steven K. Grossenbacher[1], Sita S. Withers[2], Robert B. Rebhun[2], Dennis J. Hartigan-O'Connor[3,4,5], Gema Méndez-Lagares[4,5], Alice F. Tarantal[5,6,7], R. Rivkah Isseroff[1,8], Thomas S. Griffith[9], Kurt A. Schalper[10], Alexander Merleev[1,11], Asim Saha[12], Emanual Maverakis[1,11], Karen Kelly[13], Raid Aljumaily[14], Sami Ibrahimi[14], Sarbajit Mukherjee[14], Michael Machiorlatti[15], Sara K. Vesely[15], Dan L. Longo[16], Bruce R. Blazar[17], Robert J. Canter[18], William J. Murphy[1,13,21]* and Arta M. Monjazeb[19,21]

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21

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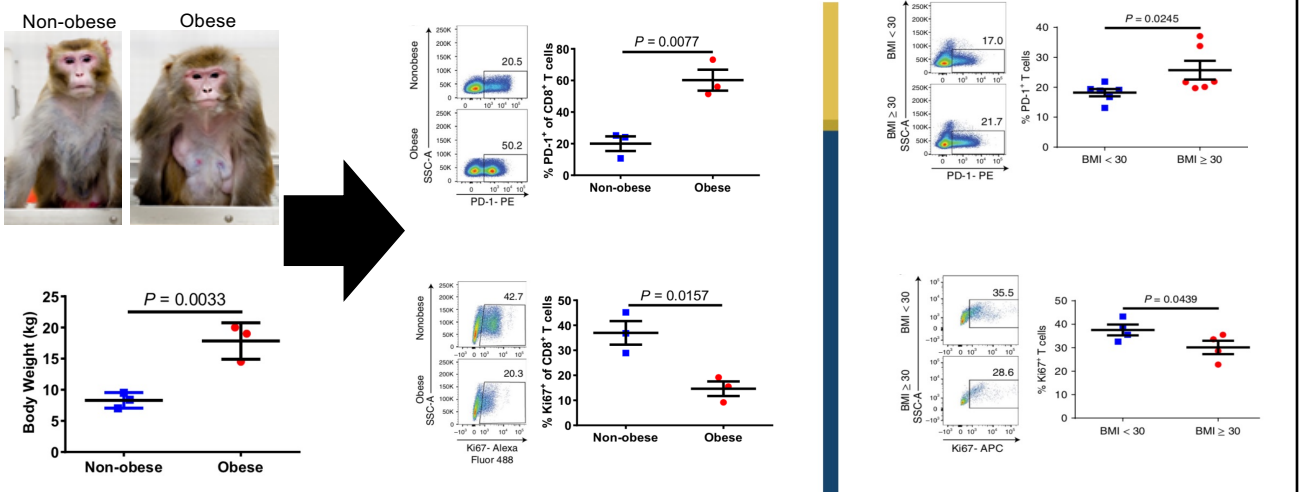

Wang Z. et al. Nature Med. 2019.

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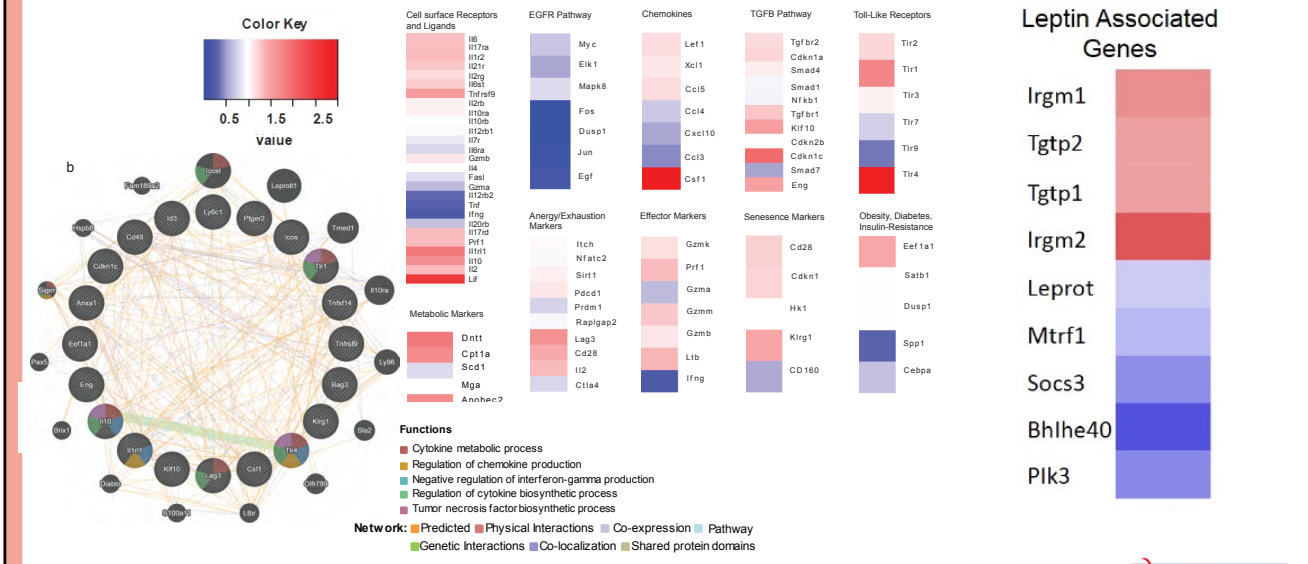

Wang Z. et al. Nature Med. 2019.

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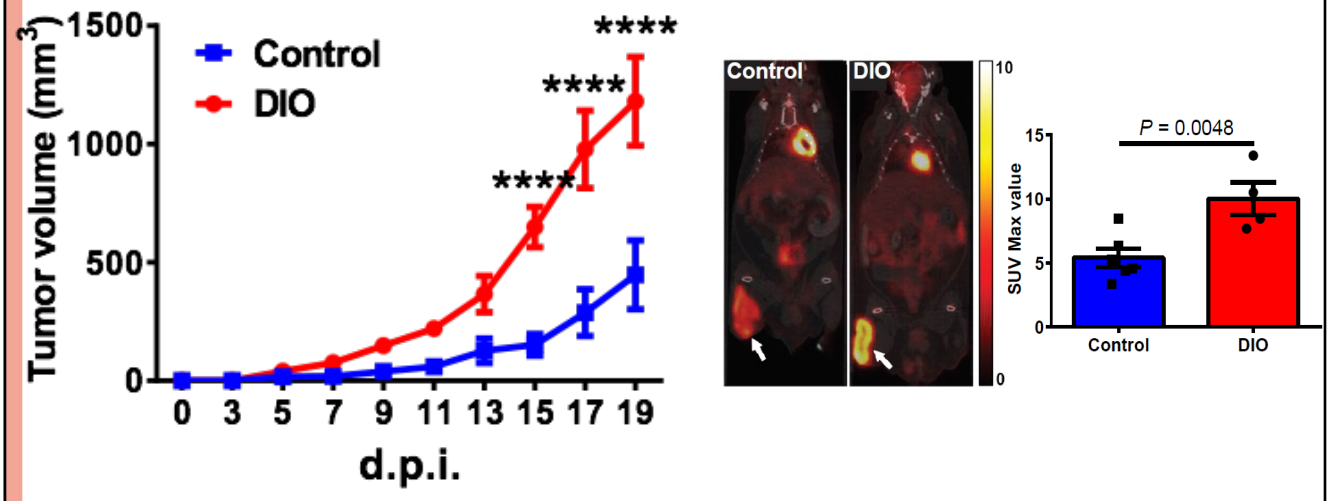
Obesity Accelerates Tumor Growth and Metabolism



Wang Z. et al. Nature Med. 2019.

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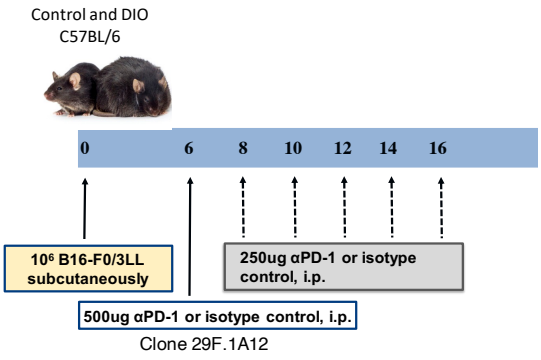

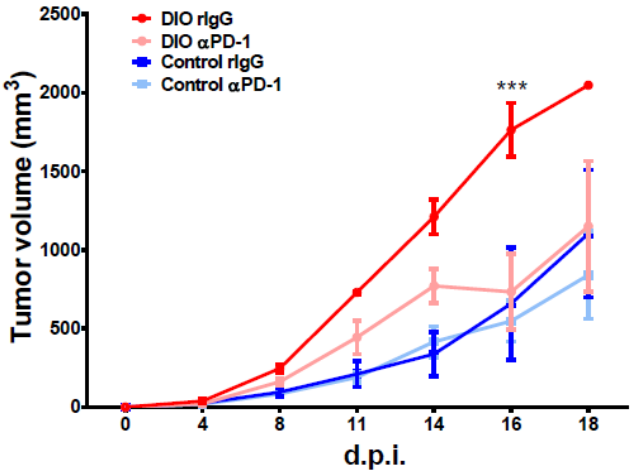

Wang Z. et al. Nature Med. 2019.

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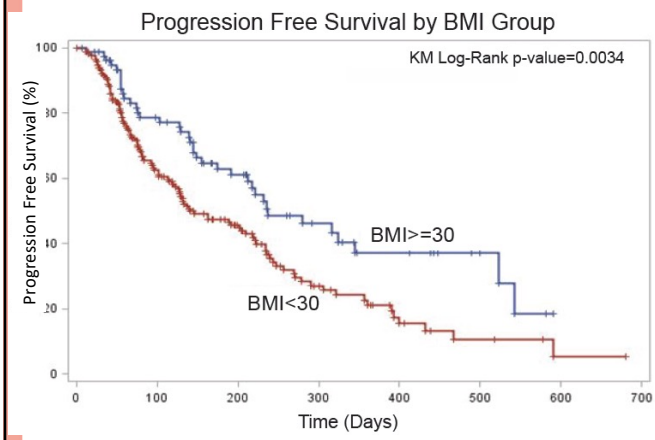
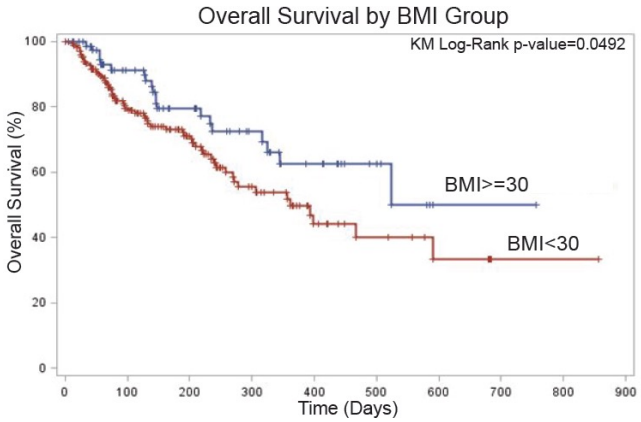
Obesity Impacts the Efficacy of PD-1/PD-L1 Checkpoint Blockade in Cancer Patients





Wang Z. et al. Nature Med. 2019.

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26

Molecular Testing at Time of Acquired Resistance in Oncogene-Driven Cancers—Lung Cancer, Newest Treatment Approaches for a Prototype

Jonathan Riess, MD, MS

NOTES

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Molecular Testing at Time of Acquired Resistance In Oncogene-Driven Cancers—Lung Cancer, Newest Treatment Approaches for A Prototype

Jonathan W. Riess, MD MS
Associate Professor
Medical Director Thoracic Oncology
UC Davis Comprehensive Cancer Center

November 5, 2022
InterContinental Hotel San Francisco
San Francisco, CA

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1

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DISCLOSURES

Commercial Interest	Relationship(s)
Blueprint, Beigene, Daiichi Sankyo, EMD Serano, Janssen, Regeneron, Sanofi, Biodesix, Bayer, Turning Point, Bristol Myers Squibb, Jazz Pharmaceuticals, Novartis, Roche/Genentech, Boehringer Ingelheim	Consulting/Advisory Board
Merck, Boehringer Ingelheim, Novartis, AstraZeneca, Spectrum, Revolution Medicines	Research Funding (To Institution)

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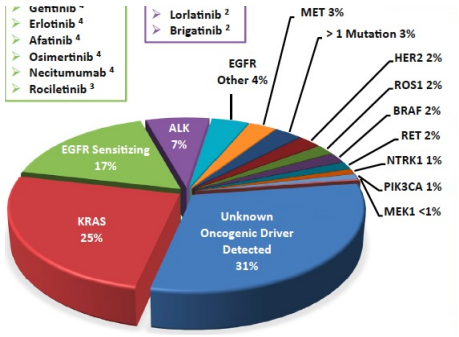
Progress in Targeted Therapy in Lung Adenocarcinoma



KRAS G12C
adagrasib, sotorasib

EGFR exon 20 insertions
mobocertinib, poziotinib, amivantamab

EGFR:
gefitinib, afatinib, erlotinib, osimertinib, dacomitinib

ALK:
Crizotinib, ceritinib, alectinib, brigatinib, lorlatinib, ensartinib, entrectinib

ROS1:
Crizotinib, cabozatinib, ceritinib, brigatinib, lorlatinib, entrectinib, ropotrectinib

BRAF:
Dabrafenib/trametinib, vemurafenib, dabrafenib

MET:
Crizotinib, cabozatinib, capmatinib, tepotinib, savolitinib, merestinib, glesatinib

HER2:
Trastuzumab emtansine, afatinib, dacomitinib, poziotinib, neratinib-temsirolimus, XMT-1522, TAK-788, Trastuzumab deruxtecan

RET:
Cabozatinib, alectinib, vandetanib, sunitinib, ponatinib, lenvatinib, apatinib, selpercatinib,pralsetinib, RXDX-105

NTRK:
Larotrectinib, entrectinib, LOXO-195, DS-6051b, ropotrectinib

FDA

Adapted by L Bazhenova from Tsao AS, et al. J Thorac Oncol. 2016;11:613-638.

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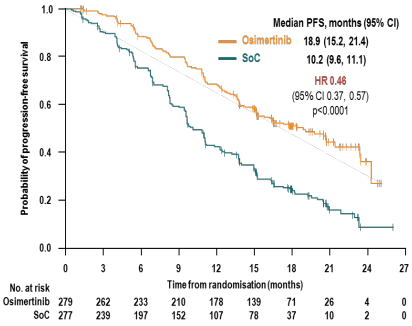
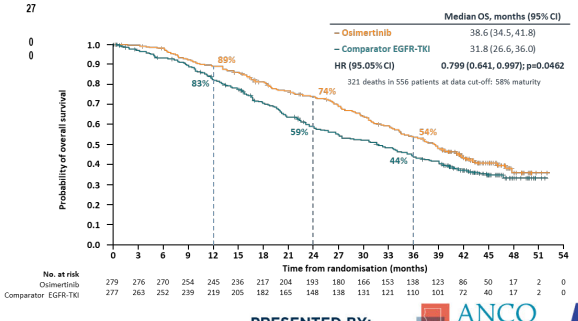


FLAURA: Osimertinib vs comparator EGFR-TKI as first-line treatment for EGFRm advanced NSCLC Improves OS and PFS



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Ramalingam SS, et al. ESMO 2019. Abstract LBA5_PR

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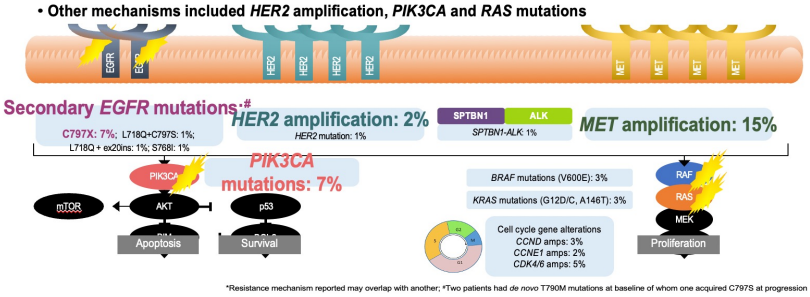
RESULTS of CURRENT STUDY: CANDIDATE ACQUIRED RESISTANCE MECHANISMS WITH OSIMERTINIB (n=91)*

- No evidence of acquired EGFR T790M
- The most common resistance mechanisms were *MET* amplification and *EGFR* C797S mutation
  - Other mechanisms included *HER2* amplification, *PIK3CA* and *RAS* mutations



*Resistance mechanism reported may overlap with another; #Two patients had *de novo* T790M mutations at baseline of whom one acquired C797S at progression

SCLC (Histologic Transformation)

Ramalingam SS, et al. ESMO 2019. Abstract LBA5_PR.

5

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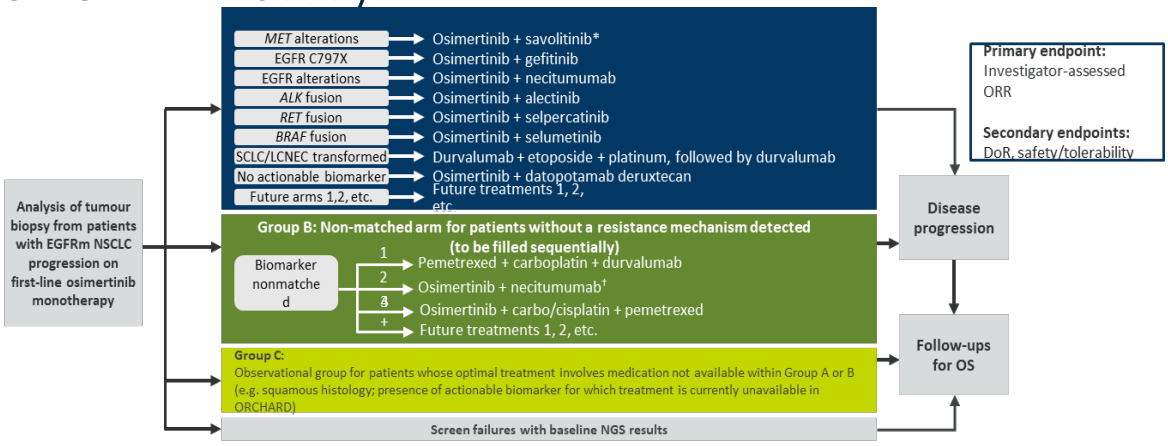
ORCHARD Study



P53/RB1 – High rate of SCLC transformation. - ~20%

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Ramalingam SS, et al. ESMO 2019. Abstract LBA5_PR.

6

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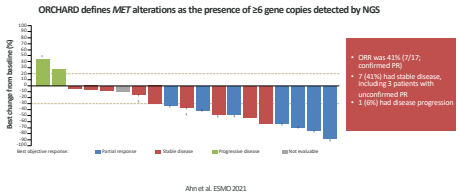
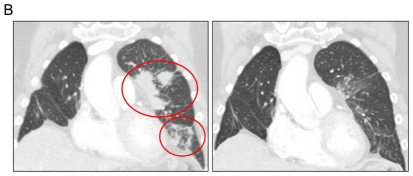
Bypass Tract

ORCHARD: Osimertinib + Savolitinib in MET-amplified EGFR-mutated NSCLC after PD on 1st line Osimertinib



Ahn et al. ESMO 2021

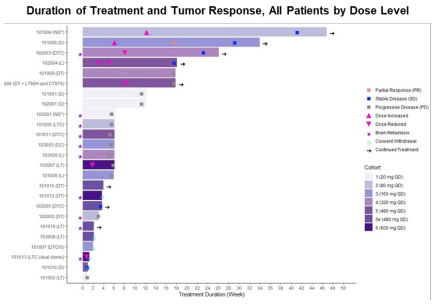
Pralsetinib + Osimertinib in Acquired Resistance Mediated by RET Fusion



Z. Piotrowska et al. Cancer Discovery 2022

On Target

BBT 176 – 4th Generation EGFR-TKI – C797X



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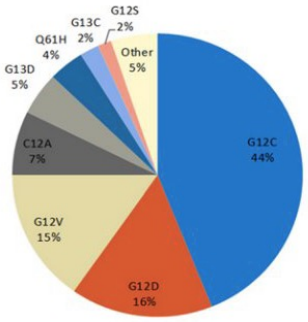
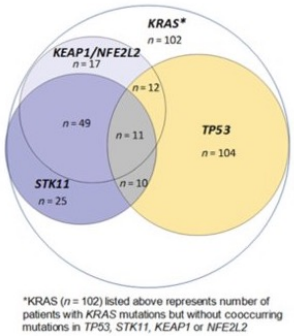
Spectrum of KRAS mutations and Co-Mutations in NSCLC





*KRAS (n = 102) listed above represents number of patients with *KRAS* mutations but without cooccurring mutations in *TP53*, *STK11*, *KEAP1* or *NFE2L2*

Arbour et al CCR 2018

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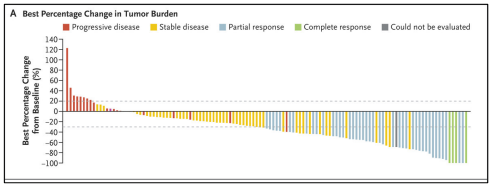
KRAS G12C inhibitors have activity in *KRAS* G12C NSCLC

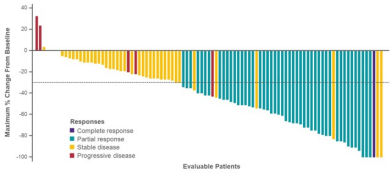
Sotorasib
CodeBreaK100 (Ph 2)



N=124 pts at 960 mg po qd
Median 2 prior lines of therapy
81% received both platinum and anti-PD-(L)1
ORR 37.1% (95% CI 28.6-46.2) // **DCR 80.6%** (95% CI 72.6-87.2)
mDOR 11.1 mo (95% CI 6.9-NE); **mPFS 6.8 mo** (95% CI 5.1-8.2)
mOS 12.5 mo (95% CI 10.0-NE)*

*median f/u 15.3 months F Skoulidis et al. N Engl J Med 2021;384:2371-2381.

Adagrasib
KRYSTAL-1 study (Ph 1/1b & 2)



N=112 pts at 600 mg po bid
98% received both chemo and anti-PD-(L)1
ORR 43% // **DCR 80%** // **mPFS 6.5 months** (95% CI 4.7-8.4)
mOS 12.6 months (95% CI 9.2-19.2)
Spira A. ASCO 2022

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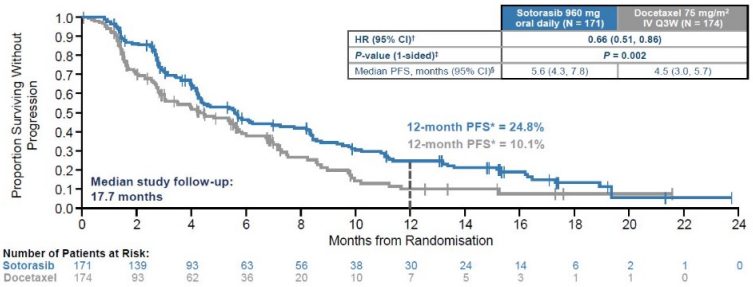
Primary Endpoint: PFS by BICR



CodeBreaK 200 met its primary endpoint with sotorasib demonstrating superior PFS over docetaxel (HR 0.66, *P* = 0.002); 12-month PFS rate was 24.8% for sotorasib and 10.1% for docetaxe

ORR 28.1% vs. 13.2%
mOS 10.6 (soto) vs. 11.3 months (doce). No difference in OS.
34% crossover in docetaxel arm

M. Johnson et al ESMO 2022

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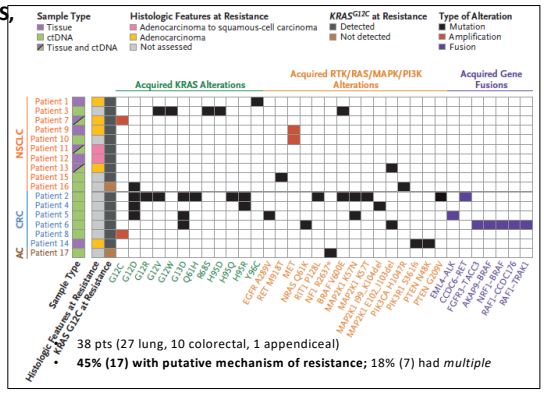
Acquired resistance to KRAS G12C inhibitors

- **On-target resistance (*in green*)**
  - *KRAS* G12D/R/V/W, G13D, Q61H, **R68S, H95D/Q/R, Y96C***
  - High level *KRAS* G12C amplification
- **Bypass resistance (*in orange*)**
  - *MET* amplification
  - Activating mutations in *NRAS, BRAF, MAP2K1, RET*
  - Oncogenic fusions *ALK, RET, BRAF, RAF1, FGFR3*
  - LOF *NF1, PTEN*
- **Histologic transformation**
  - 2/9 NSCLC adenoca→ squamous

*in switch II pocket

ADAGRASIB



38 pts (27 lung, 10 colorectal, 1 appendiceal)

- **45% (17) with putative mechanism of resistance;** 18% (7) had *multiple*

Awad M et al. N Engl J Med. 2021 Jun 24;384(25):2382-2393. Zhao et al Nature. 2021 Nov;599(7886):679-683.

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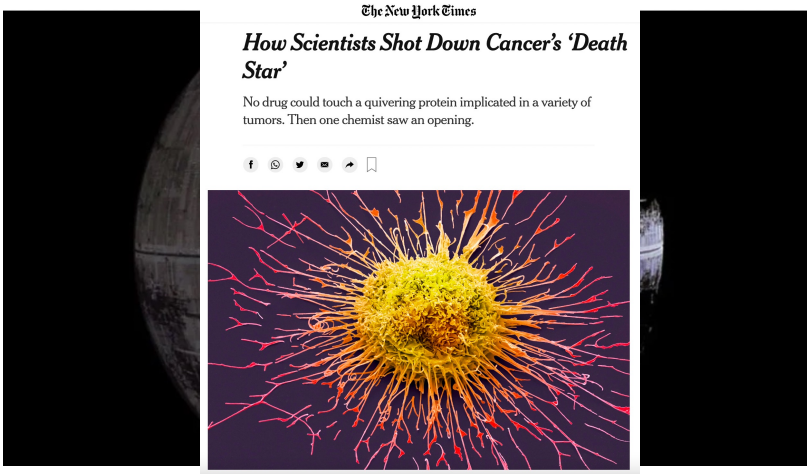

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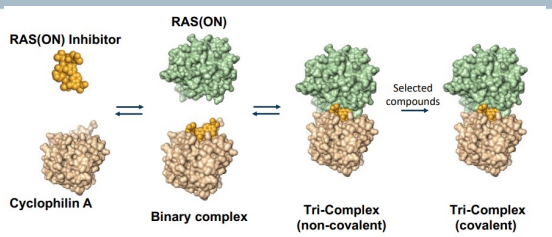
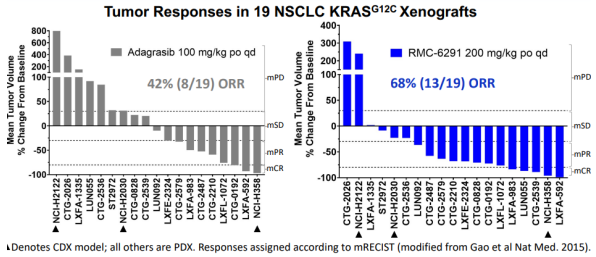
RAS(ON) Inhibitors

- Less susceptible to adaptive resistance compared to GDP bound RAS



- RMC-6291 KRAS G12C (ON) inhibitor
- RMC-9805 KRAS G12D (ON) inhibitor
- RMC-6236-Pan RAS(ON)



Denotes CDX model; all others are PDX. Responses assigned according to mRECIST (modified from Gao et al Nat Med. 2015).

Kelsey S. AACR-NCI-EORTC 2021. Hofmann MH, et al. Cancer Discov. 2022 Apr 1;12(4):924-937.

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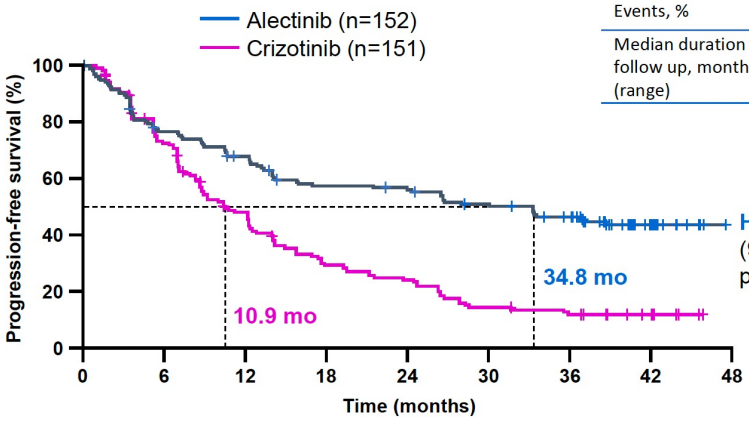
Updated Results: ALEX Trial in Advanced ALK NSCLC



	Alectinib	Crizotinib
Events, %	53	81
Median duration of follow up, months (range)	37.8 (0.5–50.7)	23.0 (0.3–49.8)

T. Mok et al. ESMO 2019

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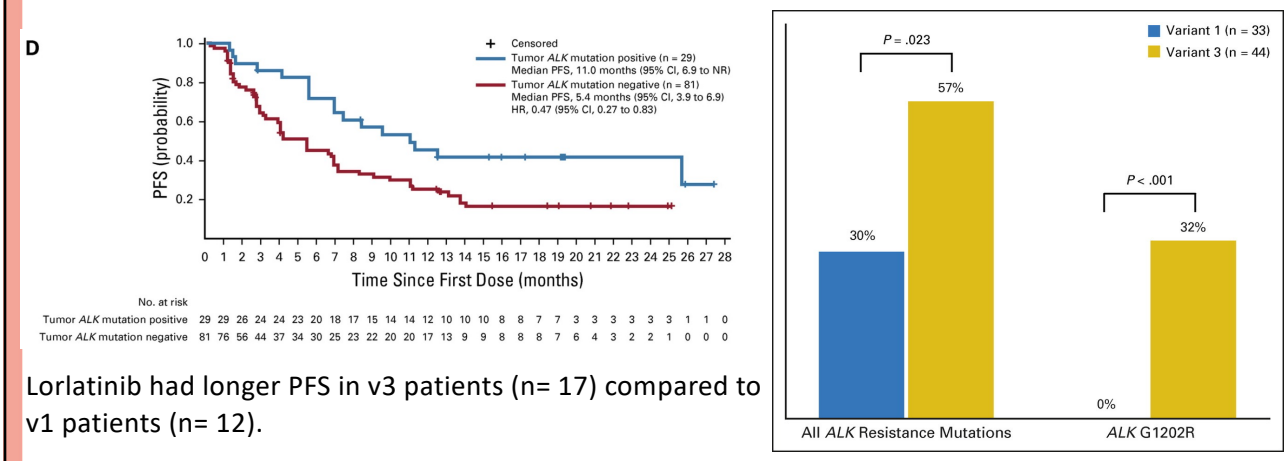
ALK mutation status / variants and efficacy of Lorlatinib



Lorlatinib had longer PFS in v3 patients (n= 17) compared to v1 patients (n= 12).

All patients were previously treated with crizotinib and another ALK inhibitor

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Lin et al JCO 2018, Shaw JCO 2019

15

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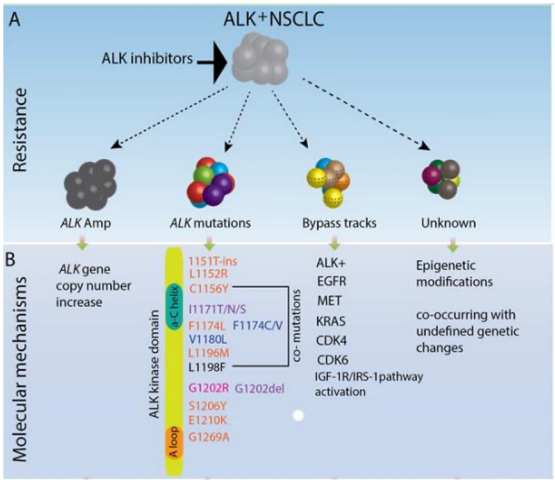
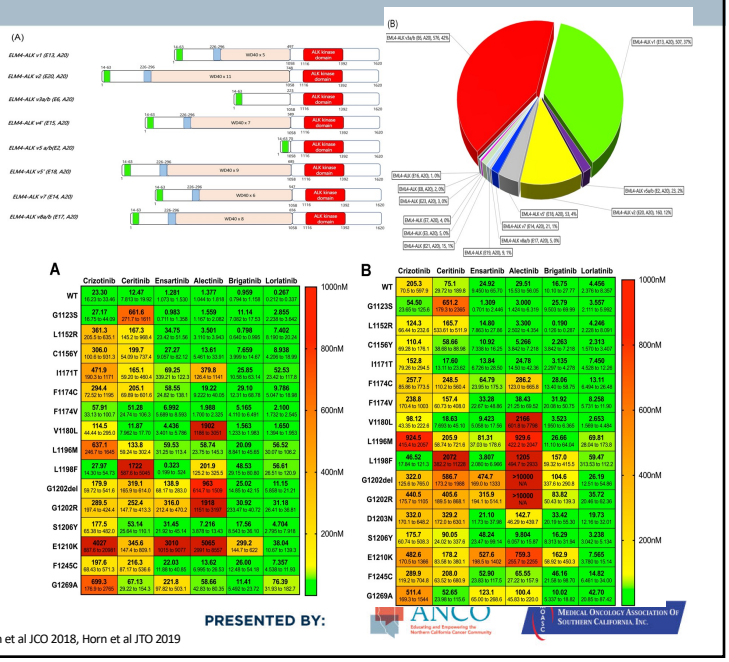
b



Wu, W et al. (2017). Cancers. 9. 164. 10.3390/cancers9120164.



PRESENTED BY:

Zhang et al. Lung Cancer 2019. Lin et al JCO 2018, Horn et al JTO 2019

16

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4th Generation ALK Inhibitors in Development

TPX-0131: cellular potency against WT, single and compound mutant ALK

- Potent against the *ALK* solvent front (e.g., G1202R) and hinge region (e.g., L1198F) resistance mutations
- Reduced potency against I1171X and G1269S mutations
- Potent against a range of *EML4-ALK* compound mutations refractory to approved ALK TKIs, including G1202R-based compound mutations

Cui JJ et al., AACR 2020; Brion WM et al., Mol Cancer Ther 2021

Cell proliferation IC_{50} values (nM)

EML4-ALK	TPX-0131	Crizotinib	Alectinib	Brigatinib	Ceritinib	Lorlatinib
WT	**0.4**	**50**	**7.4**	**12**	**3.9**	**0.8**
I1171N	516	254	4310	49	72	48
I1171S	189	188	306	31	27	31
I1171T	316	232	210	33	29	25
L1196M	**0.5**	**274**	**50**	**21**	**5.4**	**38**
L1198F	<0.2	18	397	74	618	30
G1202R	**0.2**	**434**	**2690**	**188**	**329**	**52**
G1269A	13	451	197	20	15	49
G1269S	701	1390	671	46	97	191
L1196M/L1198F	<0.2	252	2250	253	1410	1310
L1198F/C1156Y	<0.2	19.3	776	102	1310	140
L1198F/I1171N	1.6	626	236	55.1	64.1	78.7
G1202R/C1156Y	0.2	745	2420	810	1300	521
G1202R/L1196M	0.7	808	>10000	1100	1260	4780
G1202R/L1198F	<0.2	188	3000	2040	2010	1710
G1202R/G1269A	9.9	705	7200	164	303	636
G1202R/G1269A/L1204V	14.9	634	6740	176	345	673
G1202R/G1269A/L1198F	0.2	596	>10000	907	1670	6330

NVL-655: a selective, potent 4G ALK TKI

Kinase selectivity screen

↓ ALK IC_{50}	Kinase
1x	ALK, ROS1
1 - 10x	LTK, PYK2, TRKB, FAK
10 - 50x	SLK, TRKA, FER, MUSK, EPHA6, TRKC
>50x	323 other kinases

IC_{50} of NVL-655 and other ALK TKIs in Ba/F3 cell proliferation assays

	Cell expressing ALK fusion	NVL-655	Crizotinib	Ceritinib	Alectinib	Brigatinib	Lorlatinib
No kinase domain mutations	NCI-H3122 (EML4-ALK v1)	2.3	180	36	23	21	3.5
	NCI-H2228 (EML4-ALK v3)	0.70	90	55	13	13	< 1.1
	Karpas299 (NPM1-ALK)	2.0	59	25	18	7.8	3.5
	Ba/F3 EML4-ALK v1	1.6	270	90	25	42	< 3.6
G1202R+ mutations	Ba/F3, G1202R	< 0.73	950	570	1600	400	87
	Ba/F3, G1202R/L1196M	7.0	1500	1400	2200	820	3600
	Ba/F3, G1202R/G1269A	3.0	1100	350	1300	240	970
Non-G1202R+ mutations	Ba/F3, L1196M	29	1100	79	120	100	86
	Ba/F3, I1171N	27	320	140	570	30	59
	Ba/F3, I1171S	29	350	140	390	18	59
	Ba/F3, I1171T	35	400	140	260	16	51

Potency color legend: IC_{50} < 10 nM; 10 nM ≤ IC_{50} < 100 nM; IC_{50} ≥ 100 nM

- Potent WT ALK and ALK G1202R
- Potent against G1202R-based compound mutations

Preclinical Activity against many compound mutations/G1202R

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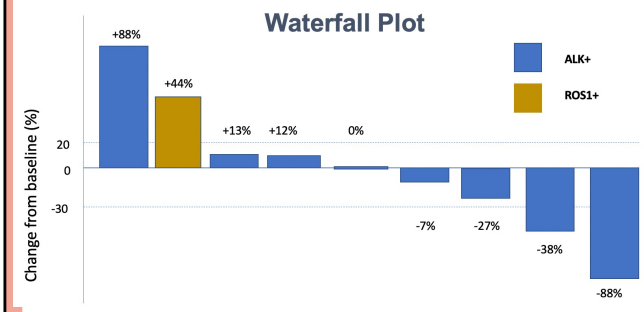
Precision Oncology Symposium

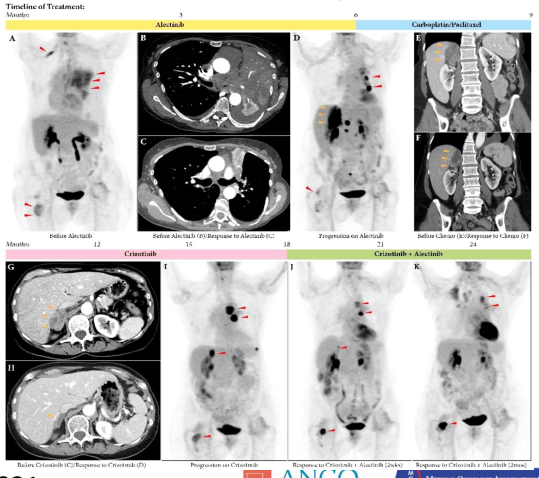
Bypass Tracts Also Matter in ALK TKI Resistance and are Actionable

A Phase 1 Study of Ceritinib and Trametinib



M. Lara, JW Riess, C. Blakely. WCLC 2021

Early Progression on Alectinib with MET amplification and Response to Crizotinib and Alectinib/Crizotinib



J. Jiang, R. Camidge, JW Riess. CLC 2021

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Summary of ROS1 TKIs in TKI-Naïve ROS1+ NSCLC

	Crizotinib* (PROFILE 1001)	Entrectinib* (ALKA-372-001, STARTRK-1, STARTRK-2)	Ceritinib (Korean Phase 2)	Taletrectinib (Chinese Phase 2)	Lorlatinib (Phase 1/2)	Repotrectinib# (TRIDENT-1 Phase 1/2)
N	53	161	20	15	21	22
ORR	72%	67% (n=108)	67%	93%	62%	91%
Median PFS	19.3 months	15.7 months	19.3 months	N/A	21.0 months	Not available
CNS activity	N/A	19/24 (79%) patients with measurable intracranial disease	2/5 (40%) patients with measurable or nonmeasurable intracranial disease	N/A	7/11 (64%) patients with measurable or nonmeasurable intracranial disease	3/3 (100%) patients with measurable intracranial disease
Reference	Shaw et al. Ann Oncol 2019	Dziadziuszko et al. JCO 2021	Lim et al. JCO 2017	Zhou C et al., ASCO 2021	Shaw et al. Lancet Oncol 2019	Cho et al. WCLC 2020; ASCO 2019

*FDA-approved

#granted FDA breakthrough therapy designation in 2020 for ROS1 TKI-naive NSCLC

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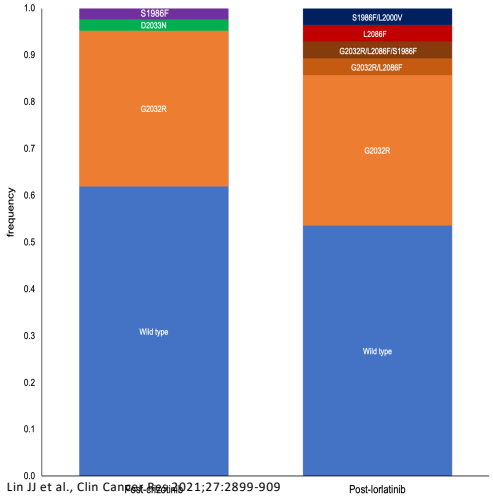
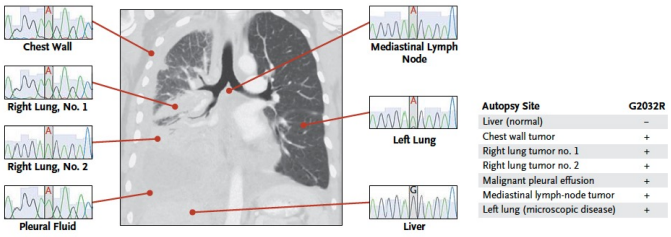
ROS1-Dependent Resistance to ROS1 TKIs



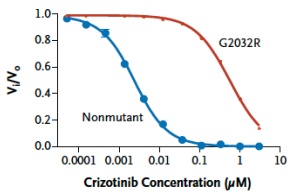
Lin JJ et al., Clin Cancer Res 2021;27:2899-909

Detection of ROS1 G2032R

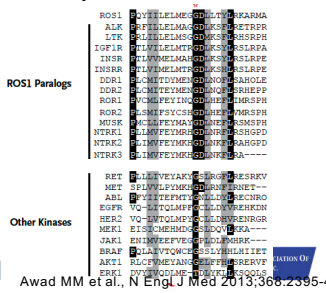


Autopsy Site	G2032R
Liver (normal)	–
Chest wall tumor	+
Right lung tumor no. 1	+
Right lung tumor no. 2	+
Malignant pleural effusion	+
Mediastinal lymph-node tumor	+
Left lung (microscopic disease)	+

ROS1 in vitro *kinase assay*



ROS1 G2032: highly conserved solvent front residue



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Awad MM et al., N Engl J Med 2013;368:2395-401

20

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Take Home Messages

- Can sometimes match targeted treatments to rational combination strategies with clinical efficacy (ideally on a clinical trial).
- Plasma First Approach. Tissue biopsy (especially p53/rb1).
- Caveat Emptor – Can start chemo while waiting for results. Often unclear if targeted combinations better than SOC (off trial) though some molecular alterations maybe better (MET amp in EGFR, RET fusion etc).
- Next gen targeted therapies promising across the board.

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21

Molecular Testing at Time of Acquired Resistance in Other Histologies—The Experience in Breast Cancer

Jennifer Caswell-Jin, MD

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Precision Oncology Symposium

Molecular Testing at Time of Acquired Resistance in Other Histologies – The Experience in Breast Cancer

Jennifer Caswell-Jin, MD
Assistant Professor of Medicine (Oncology)
Stanford University School of Medicine

November 5, 2022
InterContinental Hotel San Francisco
San Francisco, CA

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1

Precision Oncology Symposium

Disclosures

- Funding to my institution from:
  - QED Therapeutics (trying FGFR inhibition for FGFR-amplified breast cancer; program shut down)
  - Effector Therapeutics (trying a translation inhibitor for FGFR-amplified breast cancer)

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Precision Oncology Symposium

Outline

- Subtype switching across metastasis and treatment
- Endocrine therapy resistance
  - *ESR1* mutations
- Other targeted therapy resistance
  - A couple of case studies
- A few words on interpreting results from a single patient

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Precision Oncology Symposium

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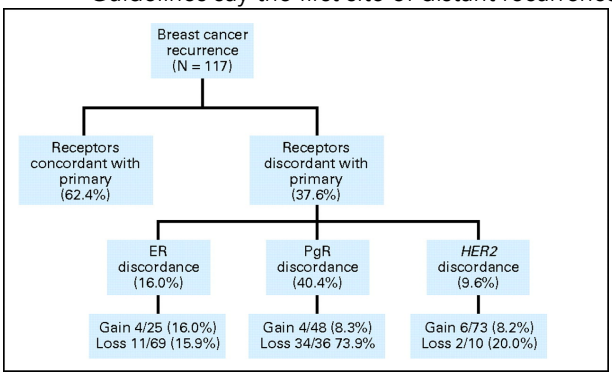
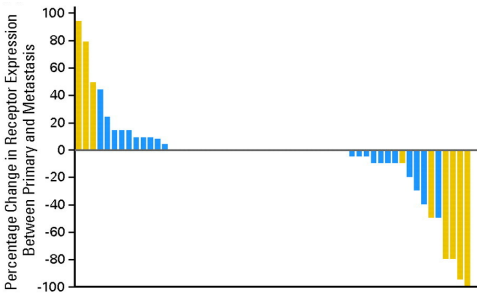
Subtype switching in breast cancer

- How often should we re-biopsy a patient to see if ER expression or HER2 expression has changed?
  - Guidelines say the first site of distant recurrence





Amir 2011 JCO
Schrijver 2018 JNCI

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Subtype switching in breast cancer

- How often should we re-biopsy a patient to see if ER expression or HER2 expression has changed?
  - What about after lines of treatment of metastasis?
  - First-biopsied to second-biopsied metastasis (50-70 patients)
    - ER 19%, PR 24%, HER2 10%
    - With these small numbers, only PR had a confidence interval not crossing 0

Zhao 2021 Therapeutic Advances in Medical Oncology

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Precision Oncology Symposium

Outline

- Subtype switching across metastasis and treatment
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  - ***ESR1* mutations**
- Other targeted therapy resistance
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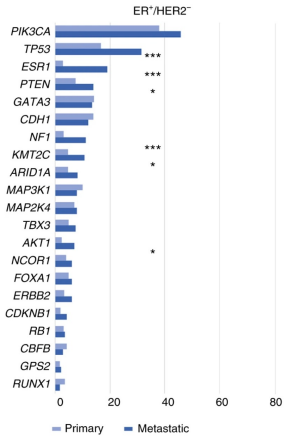
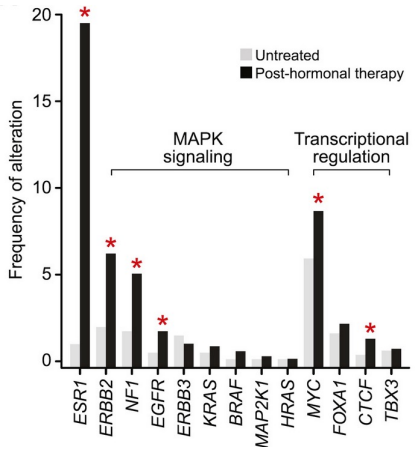
Endocrine therapy resistance: *ESR1* status





<1% in endocrine therapy naïve breast cancer

~5% in metastatic breast cancer after adjuvant aromatase inhibitor

~20-40% after aromatase inhibitor for metastatic breast cancer

Angus 2019 Nature Genetics
Razavi 2018 Cancer Cell

O. Brett 2021 Breast Cancer Research

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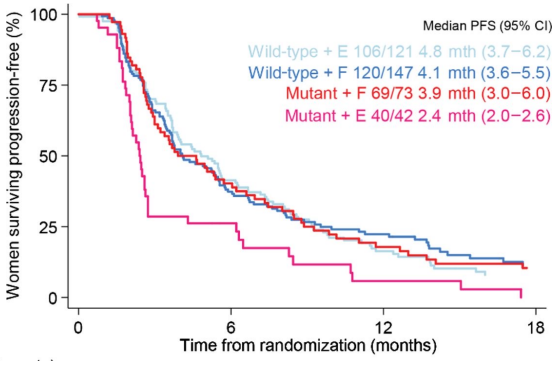
Endocrine therapy resistance: *ESR1* status

- SoFEA and EFECT: phase 3 trials randomizing postmenopausal women with metastatic HR+/HER2- breast cancer to fulvestrant or exemestane after nonsteroidal aromatase inhibitor



Turner 2020 Clin Cancer Res

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Endocrine therapy resistance: *ESR1* status

- PADA-1 trial: women with ER+/HER2- metastatic breast cancer on first-line therapy with aromatase inhibitor and palbociclib
- *ESR1* mutation status assessed in ctDNA at baseline, after 1 month, and then every 2 months
- When *ESR1* mutation rose: randomized to continue to receive aromatase inhibitor or to switch to fulvestrant (palbociclib unchanged)
- 1017 patients enrolled
- After ~3 years: 279 had an increase in *ESR1* mutation in ctDNA (27%), 69 (24%) of which had a synchronous progression
- 172 randomized

Bidard 2022 Lancet Oncology

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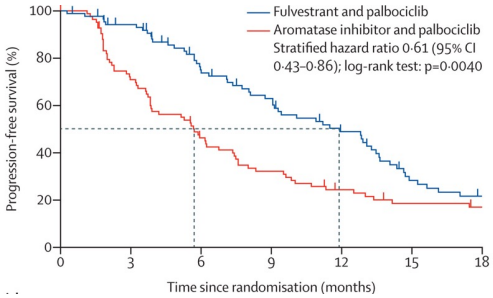
Endocrine therapy resistance: *ESR1* status

- Median PFS: 11.9 months after switch to fulvestrant versus 5.7 months after no switch



- Median time to strategy failure was 11.9 months after switch to fulvestrant versus 10.6 months after no switch

Bidard 2022 Lancet Oncology

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11

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Outline

- Subtype switching across metastasis and treatment
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12

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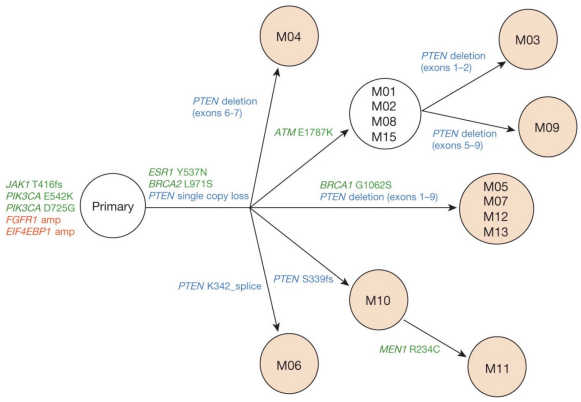
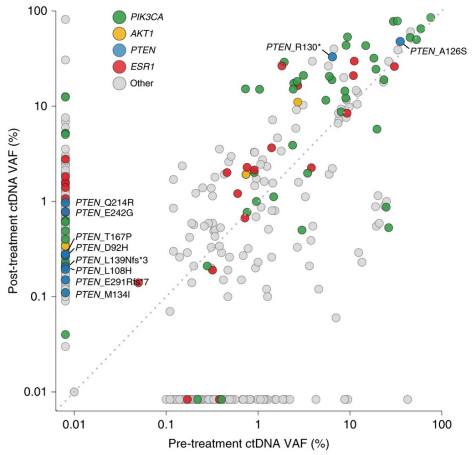
PI3K inhibitor resistance





Juric 2014 Nature
Razavi 2020 Nature Cancer

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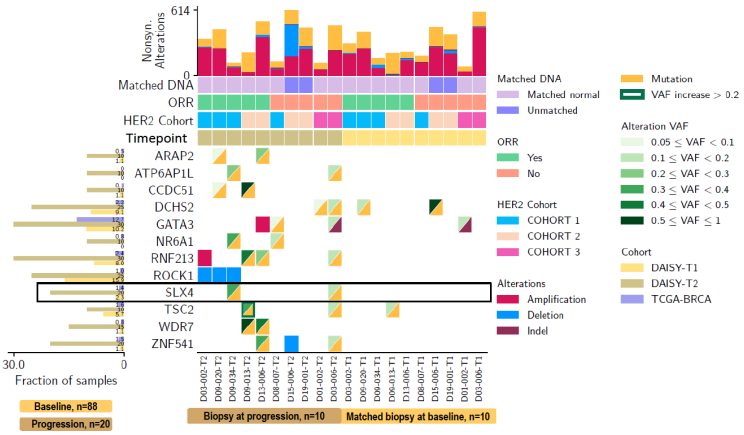
HER2-targeted therapy resistance



Mosele ESMO 2022
Shared with permission

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14

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Outline

- Subtype switching across metastasis and treatment
- Endocrine therapy resistance
  - *ESR1* mutations
- Other targeted therapy resistance
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- **A few words on interpreting results from a single patient**

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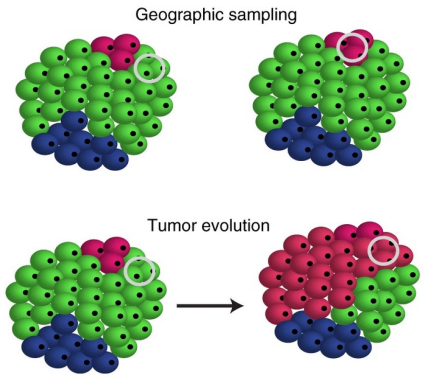
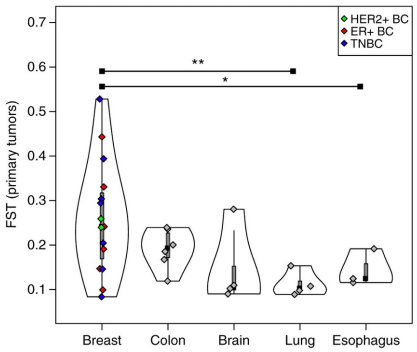
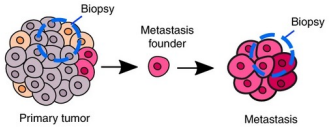
Single patient sampling can be misleading







Caswell-Jin 2019 Nat Commun
Hu 2020 Nat Genet

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Summary

- ER and HER2 status are how choose most of our therapies, and these can change across metastasis (~20%)
- In breast cancer, *ESR1* mutations are the best example of an alteration that can appear after targeted therapy that has therapeutic implications
  - But what therapeutic implications?
- There are several other examples (*KMT2C*, *NF1*, *MYC* for endocrine therapy; *PTEN* for PI3K inhibitor therapy; perhaps *SLX4* for trastuzumab deruxtecan) with no therapeutic implication yet
- Breast cancers are highly heterogeneous, so we must be careful in how we interpret "changes" across treatment

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Germline Molecular Testing

James Ford, MD

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STANFORD
CANCER INSTITUTE

Germline Genetic Testing for Cancer Risk and Cancer Therapeutics

James M. Ford, MD, FASCO
Professor of Medicine/Oncology and Genetics
Director, Clinical Cancer Genomics
Stanford University School of Medicine

1

Precision Medicine in Cancer: Germline Genetic Risk Assessment

- Identification of germline and familial genetic alterations that increase **risk** of cancer
- Development of targeted **screening and early detection** techniques prevent development of advanced cancers
- Incorporation of moderate and low-penetrant, common genetic variants in risk prediction and modification
- **Germline** genetic testing and risk assessment based on tumor genomic profiles
- Development of **drugs** that can effectively inhibit the function of these genetic alterations

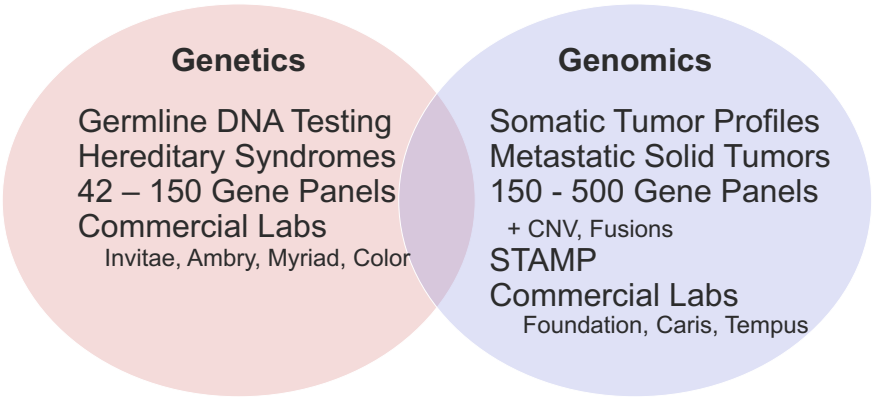
2

Precision Medicine in Cancer: Tumor Profiling and Therapeutics

- Identification of **genetic** alterations that drive carcinogenesis
- Disease **stratification** for better prognostic/predictive markers
- Molecularly **targeted** therapies that can effectively inhibit the function of oncogenic alterations or exhibit synthetic lethality with loss of tumor suppressor genes
- Assessment and prediction of drug **resistance** mechanisms

3

Testing Pathways



4

Familial Syndromes including Breast Cancer

Syndrome	Gene	Frequency	Breast Ca Risk
HBOC	*BRCA 1 & 2*	1/40 – 1/400	40 – 80%
Li-Fraumeni	*p53*	1/5000 – 1/50K	90%+
Cowden's	*PTEN*	1/100,000	25 – 50%
HDGC	*CDH1*	Very rare	~60% (lobular)
Peutz Jeghers	*STK11/LKB1*		44 – 50%
Lynch Syndrome	*MMR*	1/440	1 - 5

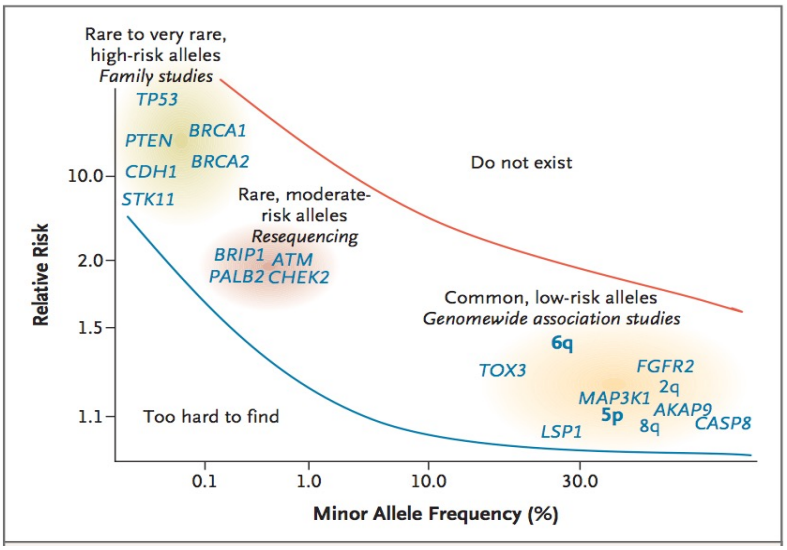
5

Familial Syndromes including Colorectal Cancer

Syndrome	Gene(s)
Lynch syndrome	*MLH1, MSH2, MSH6, PMS2, EPCAM*
Adenomatous polyposis	
Familial Adenomatous Polyposis(FAP)	*APC*
Attenuated FAP	*APC*
MYH-associated polyposis	*MYH (biallelic)*
Hamartomatous polyposis	
Peutz-Jeghers Syndrome	*STK11*
Juvenile Polyposis Syndrome	*SMAD4/BMPR1A*
Cowden Syndrome	*PTEN*

6

Breast Cancer Risk Genes



7

Multigene Panel Study

Hypothesis: A Next-Gen Sequencing multiple cancer-gene panel provides actionable results

APC	*FANCE*	*PMS2*
ATM	*FANCF*	*PRSS1*
BLM	*FANCG*	*PTCH1*
BMPR1A	*FANCI*	*PTEN*
BRCA1	*FANCL*	*RAD51C*
BRCA2	*LIG4*	*RET*
BRIP1	*MEN1*	*SLX4*
CDH1	*MET*	*SMAD4*
CDK4	*MLH1*	*SPINK1*
CDKN2A	*MLH2*	*STK11*
EPCAM	*MSH6*	*TP53*
FANCA	*MUTYH*	*VHL*
FANCB	*NBN*	
FANCC	*PALB2*	
FANCD2	*PALLD*	

8

Multiple-Gene Panel Testing: Basic Statistics

Study	N	Population	Race/Ethnicity	Gene Panel	Non-*BRCA* PVs	VUS
Kurian J Clin Oncol 2014	198	Met *BRCA1/2* guidelines	70% White, 20% Asian	42 genes (Invitae)	11%	88%
Tung Cancer 2014	2,158	Cancer genetics clinic sample	Mostly White	25 genes (Myriad)	4%	42%
Desmond JAMA Oncol 2015	1,046	Cancer genetics clinic sample	82% White	25 genes (Invitae)	4%	41%
LaDuca Genet Med 2014	2,079	Clinical testing lab database	72% White, 2-3% other	13-24 genes (Ambry)	10%	25%
Maxwell Genet Med 2014	278	Breast cancer, age <40	69% White, 24% Black	22 genes (Agilent)	11%	19%
Selkirk Fam Cancer 2014	63	Cancer genetics clinic sample	81% White	13-24 genes (Ambry)	7%	20%
Couch J Clin Oncol 2014	1,824	Triple-negative breast cancer	97% White	17 genes (Agilent)	4%	NR
Churpek BrCa Res Trt 2015	289	Cancer genetics clinic sample	100% Black	10 genes (BROCA)	5%	<1%
Thompson J Clin Oncol 2016	2,000	Cancer genetics clinic sample	Not reported (Australia)	18 genes	4%	NR
Tung J Clin Oncol 2016	488	Breast oncology clinic sample	89% White	25 genes (Myriad)	5%	33%
Norquist JAMA Oncol 2016	1,915	Ovarian cancer, unselected	89% White	20 genes (BROCA)	4%	NR
Slavin NPJ Breast Ca 2017	2,134	Cancer genetics clinic sample	81% White	26 genes	8%	NR
Shimelis JNCI 2018	10,901	Triple-negative breast cancer	Most White; >1K Black	17-21 genes (Ambry)	6%	NR
Idos/Kurian JCO Precis Oncol 2018	2,000	Prospective clinical sample	39% Hispanic, 12% Asian	25-28 genes (Myriad)	8%	34%

- Informative results (pathogenic variants) increased by ~ two-fold
- Uninformative results (VUS) increased by ten-fold

9

Multiple Gene Panels: Challenges

- New approach to Genetic Counseling
- Unexpected gene mutations in non-syndromic families (p53, CDH1)
- Variants of Uncertain Significance Common
- Genes with Low or Moderate CA Risk
- Clinical Utility and Impact on Care

10

Paired Tumor/Germline: New Challenges

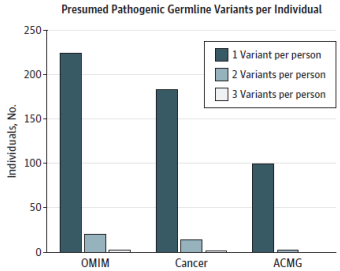
Research
JAMA Oncol. 2016;2(1):104-111. doi:10.1001/jamaoncol.2015.5208
Original Investigation

Germline Variants in Targeted Tumor Sequencing Using Matched Normal DNA

Kasmintan A. Schrader, MBBS, PhD, FRCPC, DABMG; Donavan T. Cheng, PhD; Vijai Joseph, PhD; Meera Prasad, MS; Michael Walsh, MD; Ahmet Zehir, PhD; Ai Ni, PhD; Tinu Thomas, MS; Ryma Benayed, PhD; Asad Ashraf, MS; Annie Lincoln, MS; Maria Arcila, MD; Zsofia Stadler, MD; David Solit, MD; David Hyman, MD; Liying Zhang, MD, PhD; David Klimstra, MD; Marc Ladanyi, MD; Kenneth Offit, MD; Michael Berger, PhD; Mark Robson, MD

- 16% had a presumed pathogenic germline variant
- 59% of these were not concordant with the patient's cancer type
- 100% had at least one VUS
- *How to address the clinical implications for patients and relatives?*

Figure 1. Individuals With at Least 1 Presumed Pathogenic Germline Variant in OMIM Genes, Including the Cancer and ACMG Subsets



	OMIM	Cancer	ACMG
1 Variant per person	224	183	99
2 Variants per person	20	14	2
3 Variants per person	2	1	

The number of genes in the entire Online Mendelian Inheritance in Man (OMIM) subset is 187 (http://omim.org), which includes the Cancer subset of 93 genes and the partially overlapping American College of Medical Genetics (ACMG) subset of 26 genes[8] (eTable 4 in the Supplement).

11

Mutation on tumor testing that has implications in the germline

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2022
Breast, Ovarian, and/or Pancreatic Cancer Genetic Assessment

NCCN Guidelines Index
Table of Contents
Discussion

GENERAL TESTING CRITERIA[a]

Testing is clinically indicated in the following scenarios:
• Individuals with any blood relative with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene
• Individuals meeting the criteria below but tested negative with previous limited testing (eg, single gene and/or absent deletion duplication analysis) interested in pursuing multi-gene testing
• A mutation identified on tumor genomic testing that has clinical implications if also identified in the germline
• To aid in systemic therapy and surgical decision-making[b]

Is this a gene in which a germline mutation is known to cause disease?
To investigate: *ATM, BRCA1, BRCA2, CHEK2, CDH1, PALB2, MLH1, MSH2*, etc.
Not to investigate: *KRAS, HRAS, ERBB2*, PIK3CA, etc.
Sometimes, but rarely: *TP53, RB1, PTEN*

12

Determining germline vs. somatic

- A germline variant should have ~50% VAF
  - Range of 30-70% commonly accepted as likely heterozygous variant
- VAF is affected by
  - Tissue heterogeneity (purity of sample – tumor vs normal cells)
    - A heterozygous germline variant VAF should not change significantly based on tumor purity
  - Tumor heterogeneity (the existence of different clones within tumor)
  - Copy number abnormalities (gains and losses of the genome within cancer cells)

ctDNA test

- Somatic will have much smaller VAF's

Bottom line: do NOT use VAF to make decisions about germline testing

13

Determining germline vs. somatic

Other tumor features

- Microsatellite instability
  - Tumors with MSI-H have a 16% chance of having germline mutation in MMR gene
  - →germline testing should be prompted
- Hypermutable phenotype
  - Characterized by high tumor mutational burden
  - Often MSI high
  - If high TMB and MSI stable, unlikely to be due to a germline mutation
  - Rare germline mutations like *POLE* and *POLD1*. Polymerase proofreading associated polyposis (PPAP)

14

Germline mutations not identified by guidelines

	# of patients with both tumor and germline	Germline mutation	Met germline testing criteria
Meric-Bernstam et al (2016)	1,000	4.3%	65%
Mandelker et al (2017)	1,040	17.5%	45%
Van Ziffle et al (2018)	1,468	14.2%	42%

Testing patients who meet criteria only, we will miss A LOT of people with hereditary cancer

Important to refer all individuals with possibly germline mutations on tumor testing

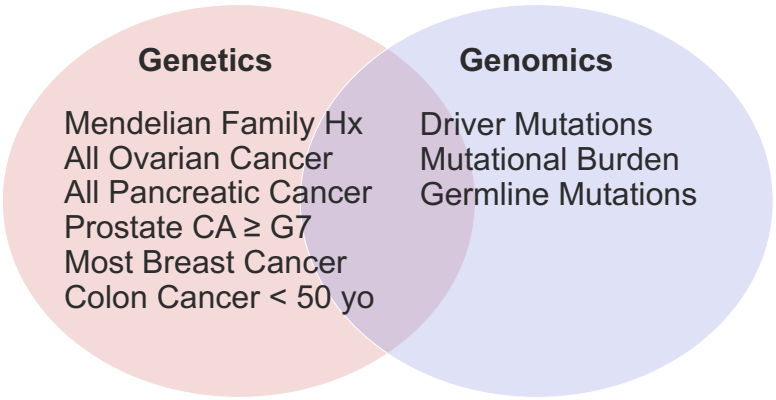
15

Indications for referral/testing: A moving target

Genes	Previously	Now	Future?	Yield
BRCA1, BRCA2, PALB2, TP53, ATM, CHEK2 Others	Breast cancer <45 Triple negative breast cancer <60 Breast cancer and AJ ancestry	Breast cancer <50 Breast cancer >50+ family history Metastatic breast cancer All HER2 neg, Stage II-III Mutation on tumor testing that has implications in the germline	All patients <60 All patients with breast cancer	2.5-20%
MLH1,MSH2, EPCAM, MSH6, PMS2	MSI-H colorectal cancer MSI-H uterine cancer	CRC <50 Endometrial cancer <50 Mutation on tumor testing that has implications in the germline	All patients with CRC	10-16%
BRCA2, HOXB13 Lynch syndrome Others	Prostate cancer not a solo indication	High grade prostate cancer	___	12-15%
BRCA2, PALB2, ATM, Others	Pancreatic cancer not a solo indication	All pancreatic adenocarcinomas	___	10-12%
BRCA1, BRCA2, RAD51C, RAD51D, BRIP1	All epithelial ovarian cancers	___	____	15-20%

16

Testing Indications

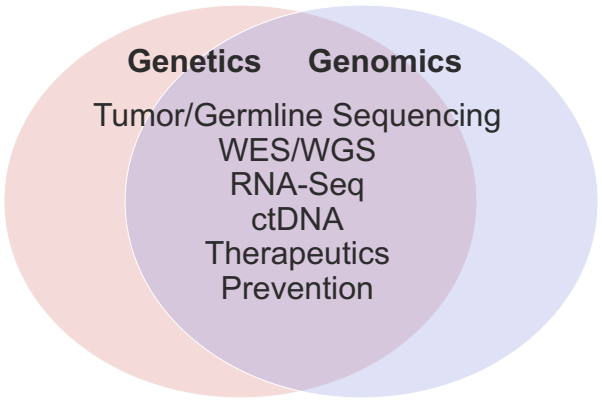


Therapeutic Indications
PARP inhibitors – BRCA1/2 . . .
IO - MSH2, MLH1 . . .

Unexpected Familial Risk
Therapeutic Implications
IO - MSI-H, TMB

17

Future Approach



18

Summary and Conclusions

- ~10% of most common cancers will have potentially targetable DNA repair defects associated with germline genetic mutations
- Germline > Somatic alone
- Poorly predicted by age, family history
- Consider screening high-risk individuals
- Prognostic and predictive value
- Role for checkpoint inhibitors, PARP inhibitors, others

19

Detection Of Post-Surgical Minimal Residual Disease (MRD) And Actionability In GI

Chloe Atreya, MD, PhD

NOTES

Precision Oncology Symposium

Detection of Post-Surgical Minimal Residual Disease (MRD) and Actionability in GI Cancers

Chloe E. Atreya, MD, PhD
Associate Professor in Residence
University of California, San Francisco
Helen Diller Family Comprehensive Cancer Center

November 5, 2022
InterContinental Hotel San Francisco
San Francisco, CA

PRESENTED BY: ANCO — Medical Oncology Association Of Southern California, Inc.

1

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Disclosures

Research support (institution): Merck, Bristol Meyer Squibb, Erasca, Guardant Health, Gossamer Bio

Scientific Advisory Board: Foundation Medicine, Inivata, Pionyr Immunotherapeutics, Sumitomo Pharma

Honoraria: More Health, Research to Practice, OncLive

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2

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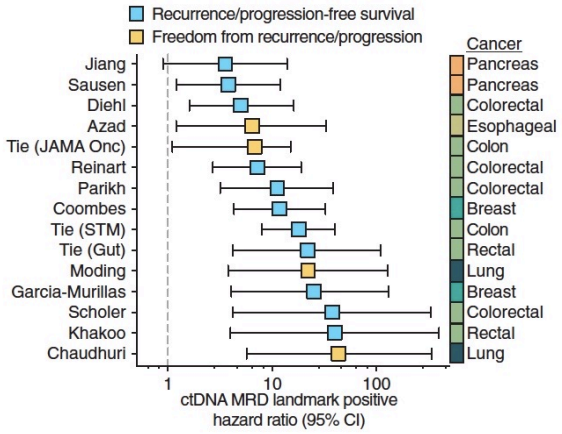
ctDNA After Treatment Predicts Recurrence Across Studies



Moding EJ, et al. *Cancer Discov*. 2021;11:2968

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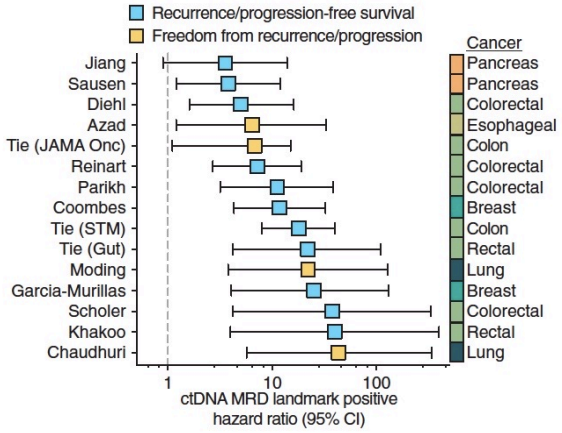
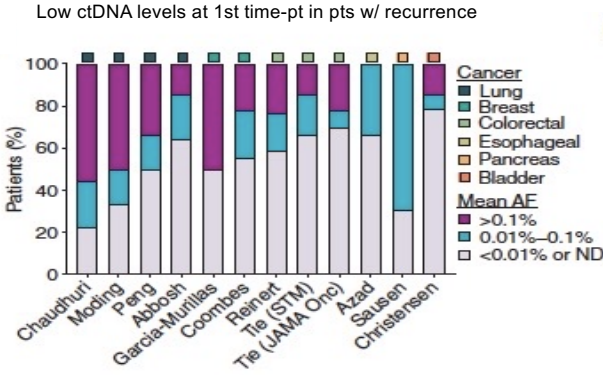
Precision Oncology Symposium

ctDNA After Treatment Predicts Recurrence Across Studies



Low ctDNA levels at 1st time-pt in pts w/ recurrence



Moding EJ, et al. *Cancer Discov*. 2021;11:2968

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Precision Oncology Symposium

Prognostic Utility of ctDNA in Resected Colorectal Cancer

Study	Stage	Recurrence Risk (Detectable Post-op ctDNA)
Henriksen et al, ASCO GI 2021	I-III	HR 11.0, 95% CI 5.9-21.0
Parikh et al, *Clin Cancer Res.* (2021)	I-III	HR 11.2, P<0.0001
Tie et al, *Science Transl Med.* (2016)	II	HR 18, 95% CI 7.9-40
Tie et al, *JAMA Oncol.* (2019)	III	HR 3.8, 95% CI 2.4-21.0
Henriksen et al, ASCO 2021	III	HR 7.2, 95% CI 3.8-13.8
Overman et al, ASCO 2017	IV – post liver metastectomy	HR 3.1, 95% CI 1.7-9.1
Tie et al, *PLoS One*. (2021)	IV – post liver metastectomy	HR 6.3, 95% CI 2.6-15.2
Chee et al, ASCO 2021	IV – post locoregional	HR 5.6, 95% CI 2.3-13.7
Yukami et al, ASCO 2021	*IV – post locoregional*	*OR 16.9, 95% CI 2.3-197.4*
Loupakis et al, *JCO PO.* (2021)^	IV – post locoregional	HR 5.8, 95% CI 3.5-9.7
Nimeiri et al, ASCO GI 2022^	IV	HR 5.0, 95% CI 2.7-9.2
Kotaka et al, ASCO GI 2022	I-IV	HR 13.3, 95% CI 8.0-22.2

^Same cohort but different assay and follow-up
Credit: Dr. Aparna Parikh, used with permission

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What Proportion of Recurrences Are Predicted With Post-Op ctDNA?

Study	Stage	Proportion of recurrences detected immediately post-op
Henriksen et al, ASCO GI 2021	I-III	7/17 (41.2%) recurrences ctDNA positive post-op
Parikh et al, *Clin Cancer Res.* (2021)	I-III	15/27 (55.6%) recurrences ctDNA positive post-op
Tie et al, *Sci Transl Med*. (2016)	II	11/30 (36.7%) recurrences ctDNA positive post-op
Tie et al, *JAMA Oncol.* (2019)	III	10/25 (40%) recurrences ctDNA positive post-op
Overman et al, ASCO 2017	IV	31/54 (57%) recurrences ctDNA positive post-op
Tie et al, *PLoS One*. (2021)	IV	10/21 (47.6%) recurrences ctDNA positive post-op
Chee et al, ASCO 2021	IV	23/29 (79.3%) recurrences ctDNA positive post-op
Yukami et al, ASCO 2021	IV	6/7 (85.7%) recurrences ctDNA positive post-op*
Loupakis et al, *JCO PO.* (2021)^	IV	59/82 (72.0%) recurrences ctDNA positive post-op**
Nimeiri et al, ASCO GI 2022^	IV	29/49 (60.4%) recurrences ctDNA positive post-op
Kotaka et al, ASCO GI 2022	I-IV	91/143 (63.6%) recurrences ctDNA positive post-op

^Same cohort but different assay and follow-up
Credit: Dr. Aparna Parikh, used with permission

·Median follow up only 4.2 months
**Median follow up of only 10.7 months
^Same cohort but different assay and follow up

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Does Adjuvant Chemotherapy Clear MRD?

Study	Stage	Ability of Adjuvant Therapy to Convert ctDNA+ to ctDNA-
Reinert et al, *JAMA Oncol.* (2020)	I-III	3/10 (30%) ctDNA positive post-op cleared
Parikh et al, *Clin Cancer Res.* (2021)	I-III	1/6 (16.7%) ctDNA positive post-op cleared
Tie et al, *Sci Transl Med.* (2016)	II	3/6 (50%) ctDNA positive post-op cleared
Tie et al, *JAMA Oncol.* (2019)	III	5/20 (25%) ctDNA positive post-op cleared
Henriksen et al, ASCO 2021	III	4/20 (20%) ctDNA positive post-op cleared
Tie et al, *PLoS One.* (2021)	IV	3/11 (27.3%) ctDNA positive post-op cleared
Kotaka et al, ASCO GI 2022	I-IV	65/96 (68%) ctDNA positive post-op cleared!

Likely around 20-30% with FOLFOX clear

*studies were adjuvant FOLFOX or presumed FOLFOX based on indication

^Same cohort but different assay and follow-up
Credit: Dr. Aparna Parikh, used with permission

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Precision Oncology Symposium

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Henriksen et al, ASCO 2021	III	4/20 (20%) ctDNA positive post-op cleared
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What To Do With ctDNA Results? (stage II/III CRC)

	Australia Stage II	Australia / Canada Stage III	US / Canada Stage II	US Stage III	Germany/ Austria/ Sweden Stage II	Netherlands Stage II low risk
Name	DYNAMIC	DYNAMIC III	COBRA	Circulate-US	CIRCULATE	MEDOCC-CrEATE
Assay	Safe-SeqS	Safe-SeqS	Guardant Reveal	Natera Signatera	Dresden NGS	PDGx elio
Methodology	Escalate	De-escalate or escalate	Escalate	De-escalate and escalate	Escalate	Escalate
De-escalation to:	n/a	Multiple options depending on pre-specified plans	n/a	5-FU single agent preferred	n/a	n/a
Escalate to:	Chemo	Multiple options	FOLFOX x6m	FOLFOXIRIx6 m	Chemo	Chemo
Sample size	450	1000	1400	~ 2000	3609 stage II (4812 screen)	1320
Phase	II	II	III	III	III	III

ESCALATE:
Need high specificity
PPV >90-95%

DE-ESCALATE:
Need high sensitivity

Credit: Dr Aparna Parikh, used with permission; slide adapted from Dr. Scottt Kopetz

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What To Do With ctDNA Results? (stage II/III CRC)

	France Stage II	Japan Stage III	UK Stage II/III	Denmark Low risk Stage I/ II	Denmark High risk stage II or Stage III	Italy Stage II HR /III
Name	CIRCULATE-Prodige	CIRCULATE-Japan / VEGA	TRACC	IMPROVE-IT	IMPROVE-IT2	Pegasus-0
Assay	Methylation probes x 2	Natera Signatera	In house NGS	Natera Signatera	Natera Signatera	Torino assay
Methodology	Escalate	Escalate and de-escalate	Escalate	Escalate	Escalate	Assigned based on ctDNA
De-escalation to:	n/a	No therapy	No therapy	Observation	n/A	5FU
Escalate to:	Chemo	n/a	n/a	CAPOX	More intensive imaging	CAPOX
Sample size	1980	1240	1621	64	254	140
Phase	III	III	III	II	III	II

In the US, Medicare & Medicaid endorse reimbursement for MRD determination in colorectal cancer

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10

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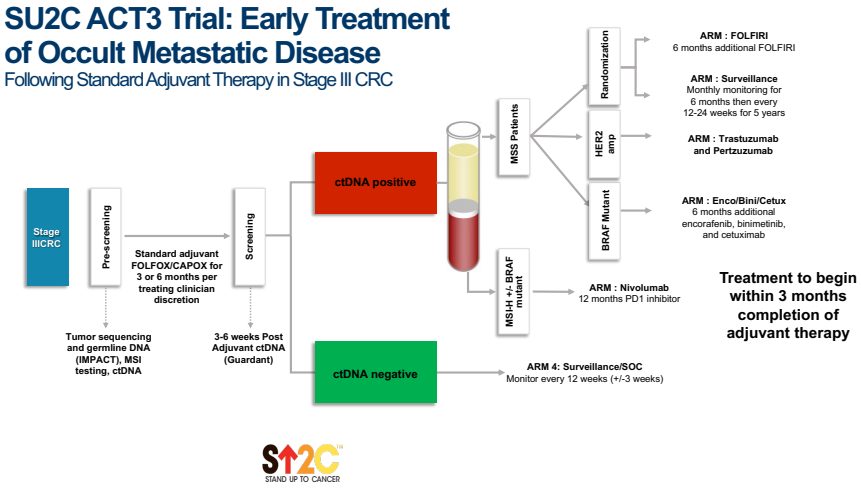
What To Do With ctDNA Results? (stage III CRC, following adjuvant tx)



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What To Do With ctDNA Results? (stage IV CRC, DETECTIVE Study)

If rate of ctDNA positivity 40-50% of the ~65% that recur, will need to screen 468 patients

mCRC, Resected liver metastases, ≤3 months of prior chemo

Immediate testing for presence of ctDNA to guide adjuvant therapy

Baseline + ctDNA

RANDOMIZE

- Adjuvant FOLFIRINOX X 6 cycles
- Adjuvant FOLFOX x 6 cycles

Primary End Point ctDNA + Pts:
ctDNA Clearance after Chemotherapy (ie. ctDNA+ → ctDNA-)
Goal: increasing clearance from 25->45% clearance 6 months after chemo completed
Patients receive CT at 3 months and if visible disease, 6 month time point not needed to say failure to clear
1-sided α=0.05 Power=80%
Requires 138 ctDNA + patients (+10% for drop out=152)
Secondary End Points: OS, DFS

Baseline - ctDNA

RANDOMIZE

- Enhanced ctDNA Surveillance
- Adjuvant FOLFOX x 6 cycles

CT + ctDNA q 3 months x 2 years

Convert to ctDNA+ but no radiographic disease

FOLFIRINOX X 6 cycles followed by investigator's choice

Primary End point ctDNA – Pts:
DFS – superiority of immediate adjuvant
Goal: DFS HR 0.72, assumes 5-year DFS of 45% in ctDNA -
1-sided α=0.05 Power=77%
N=316
Secondary End Points: OS, TTTF2 ctDNA clearance

Stratify for:
- Synchronous vs metachronous
- Prior chemo Y/N
- Concurrent RFA or microwave ablation

- All patients: CT CAP q3 month x 2 years then q6 months in year 3. The imaging schedule is fixed, regardless of ctDNA results or intervening treatment. Imaging surveillance beyond 3 years is at investigator discretion.
- Therapy is at investigator discretion at time of radiographic recurrence

Credit: Dr Aparna Parikh, used with permission

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Conclusions

- Detection of **post-surgical MRD with ctDNA(+) is prognostic** in esophageal, pancreas and colorectal cancer
- Many adjuvant tx escalation and de-escalation strategies are being evaluated in stage II/III CRC
  (fewer for stage IV CRC & other GI cancers)

- **Actionability strongest for stage II CRC** (DYNAMIC study: Tie J, et al. ASCO 2022. Abstract LBA100)
  - > ctDNA(-) and low clinical risk: no adjuvant chemo
  - **> ctDNA(+): adjuvant chemo improves RFS**

- Harmonization of ctDNA and imaging time-points is needed

- Further information:
  2022 ASCO Ed book

American Society of Clinical Oncology Educational Book > List of Issues > Volume 42 >

GASTROINTESTINAL CANCER—GASTROESOPHAGEAL, PANCREATIC, AND HEPATOBILIARY

Circulating Tumor DNA: An Emerging Tool in Gastrointestinal Cancers

PMID: 35471832

Olatunji B. Alese, MD, FWACS[1]; Natalie Cook, MD, PhD[2,3]; Ana Ortega-Franco, MD[2]; Mark B. Ulanja, MD, MPH[4]; Lavinia Tan, MBBS, FRACP[5,6]; and Jeanne Tie, MBChB, MD, FRACP[5,6,7]

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13

Detection Of Post-Surgical Minimal Residual Disease (MRD) And Actionability In GU

Mamta Parikh, MD

NOTES

Precision Oncology Symposium

Detection of Post-Surgical Minimal Residual Disease (MRD) in Genitourinary Malignancies

Mamta Parikh, MD,MS
UC Davis Comprehensive Cancer Center

November 5, 2022
InterContinental Hotel San Francisco
San Francisco, CA

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Purpose of Post-Surgical MRD evaluation

- Identify patients at high risk
  - If an adjuvant treatment is available
- Identify patients who can be spared from unnecessary treatment

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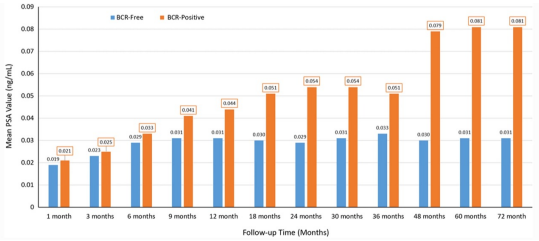
Prostate Specific Antigen- the original MRD investigation

- A PSA ≥ 0.2 is indicative of biochemical recurrence and is currently criteria for further intervention post-prostatectomy
- Ultrasensitive PSA: detects PSA at ≤ 0.2
  - Appears to catch MRD early
- Indolent Disease compared to other malignancies
- **Ideally, MRD evaluation should guide treatment decisions**



Zakaria *et al* World Journal of Urology 2021

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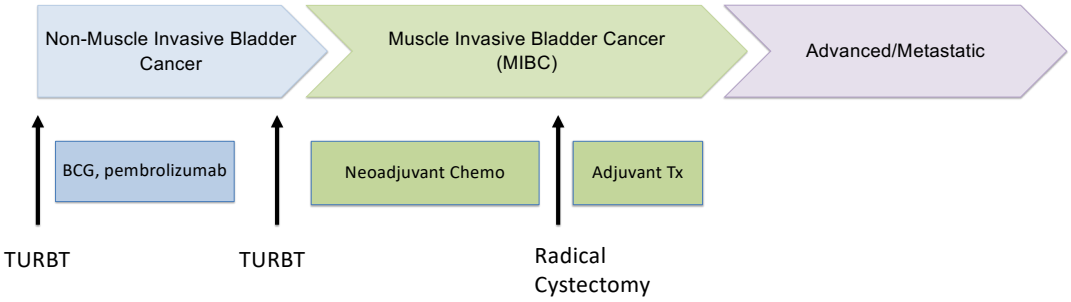
Bladder Cancer Management- Surgical Interventions



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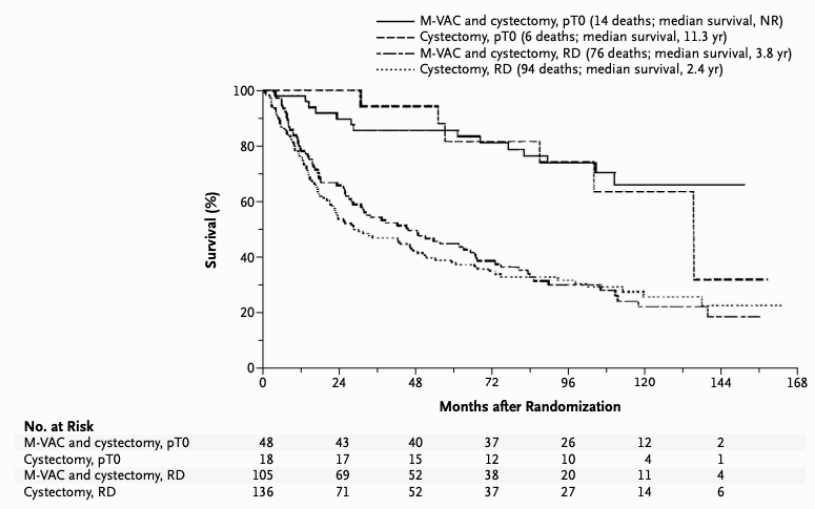
Muscle Invasive Bladder Cancer (MIBC)



SWOG 8710:

- Neoadjuvant chemotherapy followed by RC had improved OS compared to RC alone, but:
- regardless of intervention, patients with pT0 disease had improved OS and those with residual disease had poor OS

Grossman *et al* NEJM 2003

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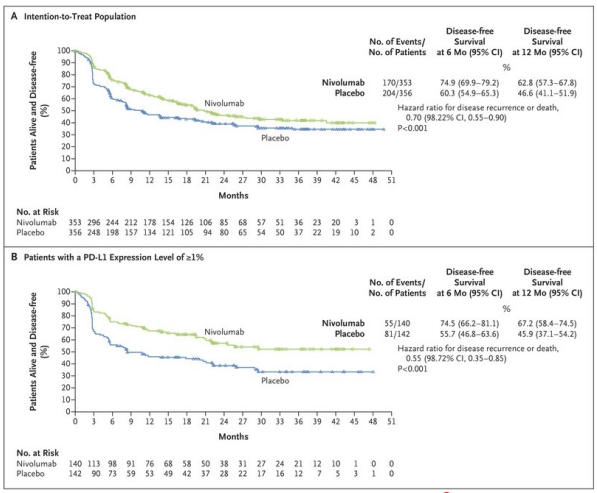
Muscle Invasive Bladder Cancer (MIBC)

CheckMate-274 Phase III Study

- Patients with pT3+ or any pN+ if no neoadjuvant chemotherapy received, or ypT2+ or any pN+ if cisplatin-based chemotherapy received
- Randomized 1:1 to receive nivolumab or placebo for 1 year (blinded)
- DFS benefit regardless of PD-L1 expression (but more pronounced with PD-L1 IHC ≥ 1%)
- Overall Survival benefit has not been demonstrated
- FDA approved for adjuvant therapy in August 2021



Bajorin *et al*. N Engl J Med 2021

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6

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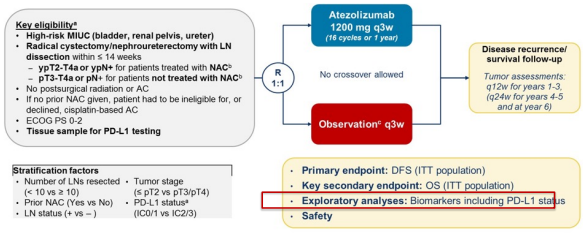
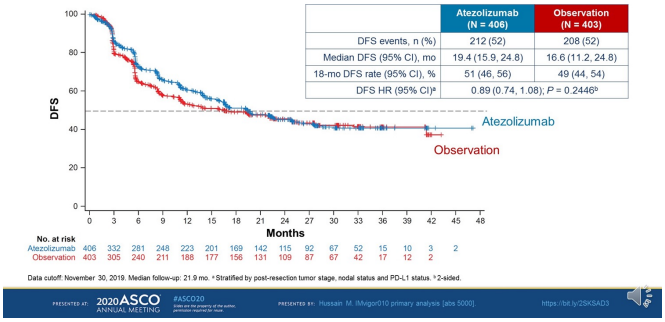
IMVigor-010 Phase III Trial



DFS in ITT Population



	Atezolizumab (N = 406)	Observation (N = 403)
DFS events, n (%)	212 (52)	208 (52)
Median DFS (95% CI), mo	19.4 (15.9, 24.8)	16.6 (11.2, 24.8)
18-mo DFS rate (95% CI), %	51 (46, 56)	49 (44, 54)
DFS HR (95% CI)[a]	0.89 (0.74, 1.08); *P* = 0.2446[b]	

Data cutoff: November 30, 2019. Median follow-up: 21.9 mo. [a]Stratified by post-resection tumor stage, nodal status and PD-L1 status. [b]2-sided.

PRESENTED AT: 2020 ASCO ANNUAL MEETING #ASCO20 Slides are the property of the author, permission required for reuse. PRESENTED BY: Hussain M. IMvigor010 primary analysis [abs 5000]. https://bit.ly/2SK5AD3

- No DFS benefit in ITT population or by PD-L1 expression
- ctDNA was collected as part of the exploratory analyses
  - WES on tumor and matched normal samples → 16 patient-specific clonal tumor mutations → bespoke multiplex PCR assay run on cell-free DNA from plasma samples

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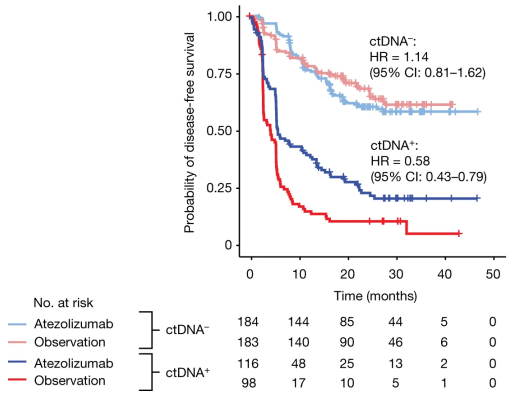
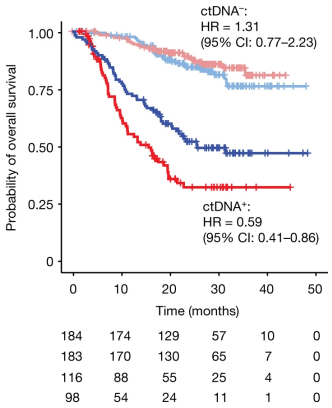
IMVigor 010 Biomarker Evaluable Population (BEP) Outcomes

- ctDNA positivity defined as 2+ patient-specific tumor mutations
- ctDNA negative patients had similar outcomes regardless of treatment or observation
- ctDNA positive patients appear to benefit from atezolizumab therapy





Powles *et al*. Nature 2021

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Issues with IMVigor 010 BEP

- Exploratory endpoint that was not statistically designed to be a validated finding
- About 30% of ctDNA negative patients went on to relapse
- Some urothelial carcinomas are low-shedding
- Atezolizumab is not currently approved for adjuvant treatment of bladder cancer

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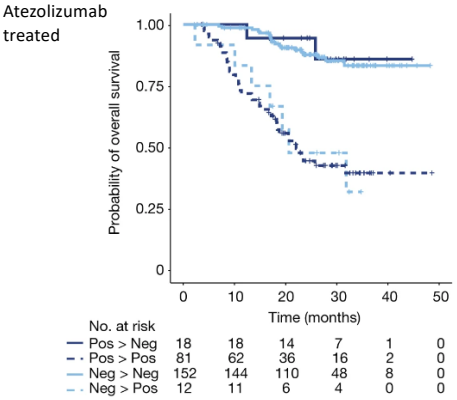
Should we really be focused on **post-surgical** MRD?

- Patients with MIBC treated in a neoadjuvant study of atezolizumab had ctDNA drawn at C1D1 and C3D1
- Patients with ctDNA conversion to negative did as well as those who were ctDNA negative at initiation of atezolizumab
  - Reminiscent of SWOG 8710
- ctDNA positive disease after treatment associated with poor outcomes



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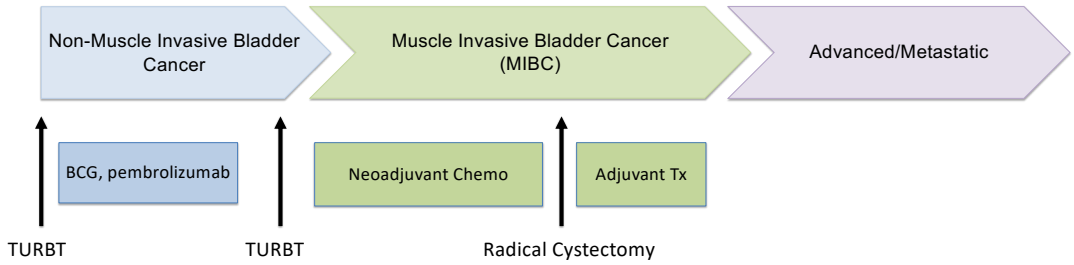
Shifting the definition of post-surgical MRD in Bladder Cancer



- **NMIBC post-TURBT specimens** → plasma unlikely to be adequate, urine ctDNA tests coming!
- **MIBC** → evaluate post-TURBT plasma
  - Proceed with neoadjuvant therapy
  - Assess for response to neoadjuvant therapy

Prospective Trials Needed!

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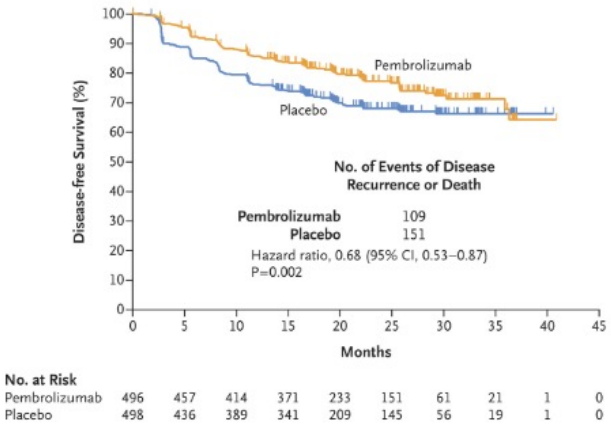
Renal Cell Carcinoma- KN-564

- For patients with pT2 (Grade 4 or sarcomatoid differentiation) or pT3+, any pN+, or M1 with NED
- DFS benefit, no OS benefit to date
- Both pembrolizumab and sunitinib (for 1 year duration) are approved for adjuvant RCC therapy
- MRD studies under way



Choueiri *et al* N Engl J Med 2021

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14

Cellular Therapy in Solid Tumors

Mohamed Abou-el-Enein, MD, PhD, MSPH

NOTES

CAR T Cells in Solid Tumors: Challenges and Opportunities

Mohamed Abou-el-Enein, MD, PhD, MSPH
Executive Director, USC/CHLA Cell Therapy Program
Associate Professor of Clinical Medicine (Oncology), Pediatrics, and Stem Cell Biology & Regenerative Medicine

Precision Oncology Symposium - Nov 5, 2022

0

Agenda

- The promise of CAR T cells
- Challenges of CAR T cells in solid tumors
- Engineering approaches to overcome challenges
- Summary

1

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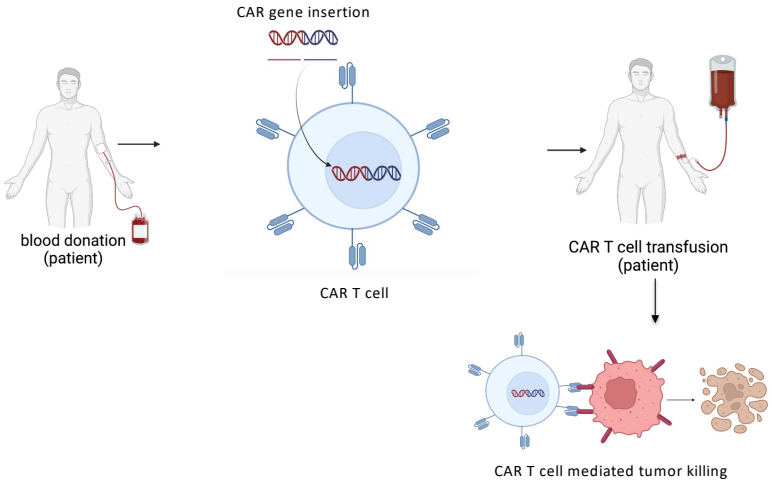
The promise of CAR T cells

***Ex vivo* engineering of CAR T cells**



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2

The promise of CAR T cells

2017
- KYMRIAH® (tisagenlecleucel) Suspension for IV infusion
  - -Pediatric and young adult patients (age 3-25 years) with relapsed or refractory B-cell precursor **ALL**
  - -Adult patients with relapsed or refractory **LBCL**
  - -Adult patients with relapsed or refractory **FL**
- YESCARTA® (axicabtagene ciloleucel) Suspension for IV infusion
  - -Adult patients with relapsed or refractory **LBCL**
  - -Adult patients with relapsed or refractory **FL**

2020
- TECARTUS™ (brexucabtagene autoleucel) Suspension for IV infusion
  - -Adult patients with relapsed/refractory **MCL**
  - -Adult patients with relapsed or refractory B-cell precursor **ALL**

2021
- Breyanzi® (lisocabtagene maraleucel) SUSPENSION FOR IV INFUSION
  - -Adult patients with relapsed or refractory **LBCL**
- Abecma® (idecabtagene vicleucel) SUSPENSION FOR IV INFUSION
  - -Adult patients with relapsed or refractory **MM**

ALL; acute lymphoblastic leukemia, LBCL; large B-cell lymphoma, FL; follicular lymphoma, MCL; mantle cell lymphoma, MM; multiple myeloma

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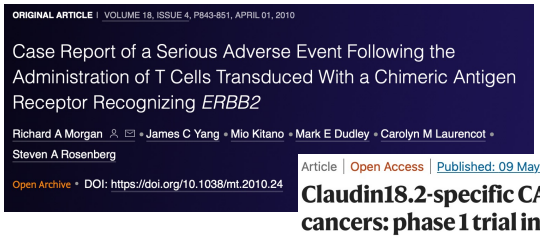
CAR T cells in solid tumors



ORIGINAL ARTICLE | VOLUME 18, ISSUE 4, P843-851, APRIL 01, 2010

Case Report of a Serious Adverse Event Following the Administration of T Cells Transduced With a Chimeric Antigen Receptor Recognizing *ERBB2*

Richard A Morgan • James C Yang • Mio Kitano • Mark E Dudley • Carolyn M Laurencot • Steven A Rosenberg

Open Archive • DOI: https://doi.org/10.1038/mt.2010.24

Article | Open Access | Published: 09 May 2022

Claudin18.2-specific CAR T cells in gastrointestinal cancers: phase 1 trial interim results

Changsong Qi, Jifang Gong, Jian Li, Dan Liu, Yanru Qin, Sai Ge, Miao Zhang, Zhi Peng, Jun Zhou, Yanshuo Cao, Xiaotian Zhang, Zhihao Lu, Ming Lu, Jiajia Yuan, Zhenghang Wang, Yakun Wang, Xiaohui Peng, Huiping Gao, Zhen Liu, Huamao Wang, Daijing Yuan, Jun Xiao, Hong Ma, Wei Wang, ... Lin Shen

Article | Open Access | Published: 07 February 2022

GD2-CAR T cell therapy for H3K27M-mutated diffuse midline gliomas

Robbie G. Majzner, Sneha Ramakrishna, Kristen W. Yeom, Shabnum Patel, Harshini Chinnasamy, Liora M. Schultz, Rebecca M. Richards, Li Jiang, Valentin Barsan, Rebecca Mancusi, Anna C. Geraghty, Zinaida Good, Aaron Y. Mochizuki, Shawn M. Gillespie, Angus Martin Shaw Toland, Jasia Mahdi, Agnes Reschke, Esther H. Nie, Isabelle J. Chau, Maria Caterina Rotiroti, Christopher W. Mount, Christina Baggott, Sharon Mavroukakis, Emily Egeler, ... Michelle Monje + Show authors

Nature **603**, 934–941 (2022) | Cite this article

33k Accesses | **52** Citations | **390** Altmetric | Metrics

4

4

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CAR T cells in solid tumors

Toxicity
- Cytokine Release Syndrome (CRS)
- Neurotoxicity
- On-target, off-tumor toxicity (OTOT)

Response

Efficacy:
- Immunosuppression by tumor microenvironment
- Tumor dissemination and adhesion molecule deficiency

Persistence:
- Antigen escape
- Immunogenicity

Manufacturing
- Individualized autologous treatment
- Cost and time
- Product availability/accessibility

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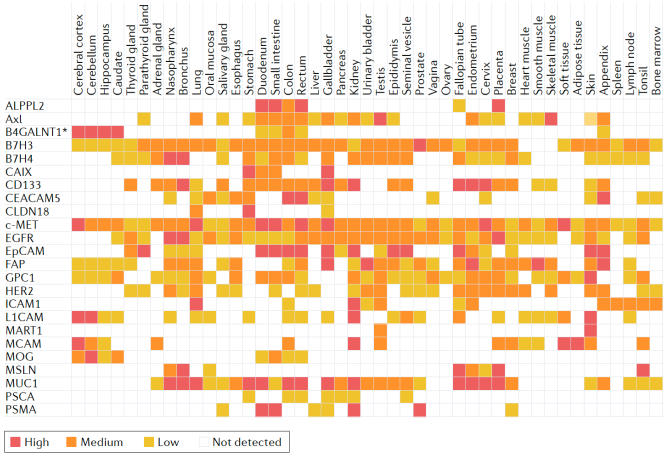
Overcoming OTOT: Target selection

- Lack of specific tumor antigen → Target expression in healthy tissue
- Risk of healthy tissue destruction **(OTOT)**



Flugel et al. Nat. Rev. Clin. Oncol. 2022, in press

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Overcoming OTOT: Approaches

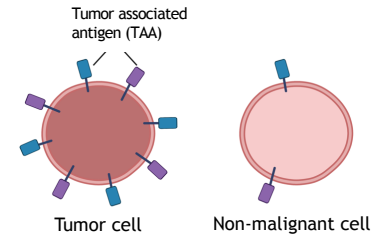
STEP 1:Determine Ag expression levels on tumor and healthy tissues & outline the therapeutic window

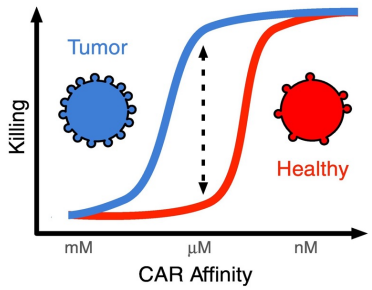
STEP 2: Construct design

Affinity tuning

Synthetic engineering circuits

Safety switches





Flugel et al. Nat. Rev. Clin. Oncol. 2022, in press
Mause et al. Trends Biotech. 2022

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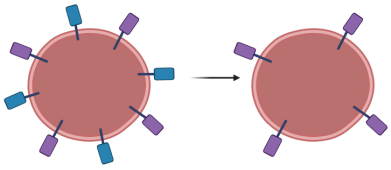
Overcoming antigen escape

Antigen Escape: Cancers evolve by modulating expression of their target antigens through

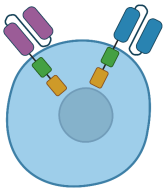
- loss of detectable antigen
- diminished expression of the antigen to a level below a threshold required for CAR T-cell activity



Tumor cell undergoing antigen escape

Mitigation:

- Dual targeting CAR T cells reduce risk of antigen escape
- Increase risk of OTOT



Dual-targeting CAR T cell

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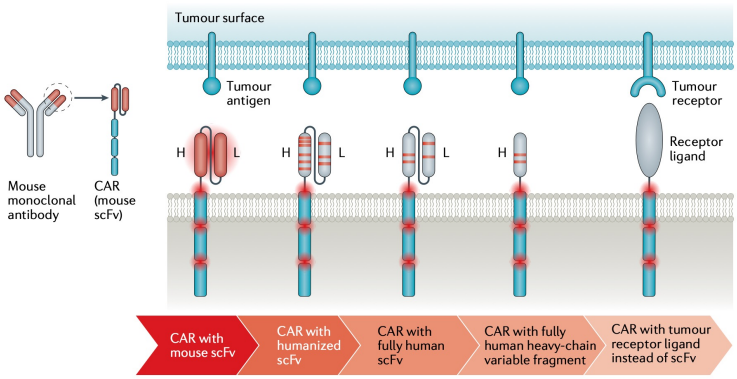
Overcoming immunogenicity

- Pre-existing and/or treatment-induced immunity to CAR constructs containing mouse-derived scFv
- Reduces CAR T cell persistence and anti-tumor efficacy
- Various approaches can be used to reduce the risk of anti-CAR immunity



Wagner et al. Nat. Rev. Clin. Oncol. 2021

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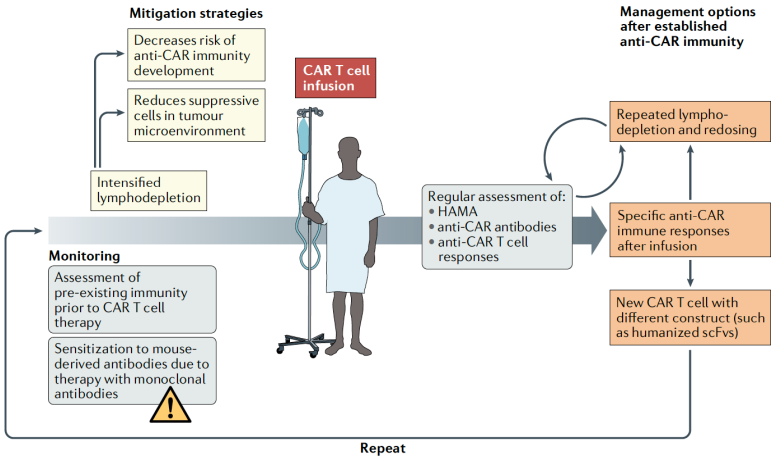
Overcoming immunogenicity



Wagner et al. Nat. Rev. Clin. Oncol. 2021

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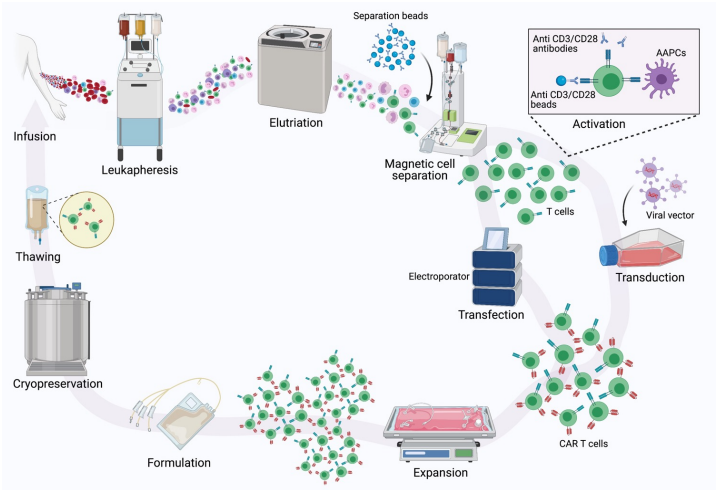
CAR T cell manufacture



Abou-el-Enein et. al. Blood Cancer Discov. 2021

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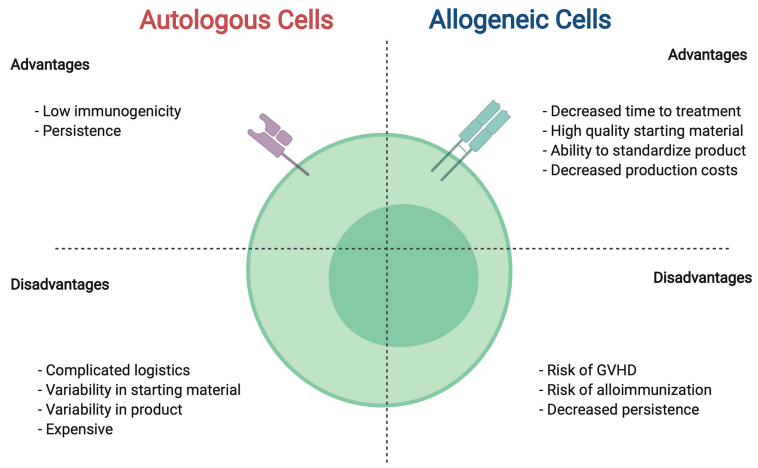
CAR T cell manufacture



Adopted from Caldwell et. al. Front. Immunol. 2021

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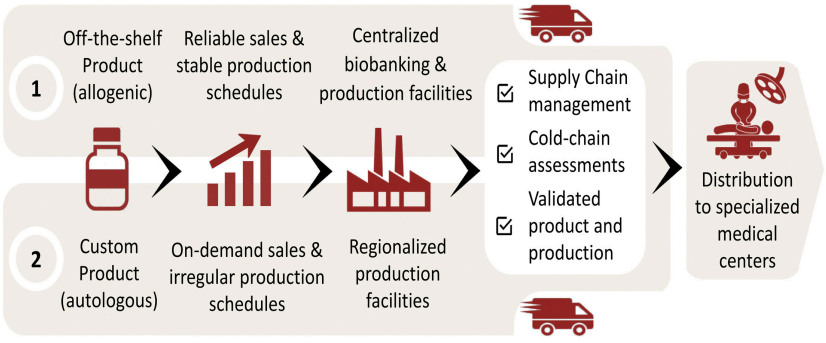
CAR T cell manufacture



Abou-el-Enein et al. cell stem cell. 2016

13

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Summary

- CAR T cells in **solid tumors** are faced by several efficacy and toxicity challenges
  - On-target, off-tumor toxicity
  - Antigen Escape
  - Anti-CAR T immune responses
  - Individualized manufacturing
- Several engineering approaches may overcome the current challenges facing solid tumor CAR T cell therapies
  - Affinity Tuning
  - Dual targeting of tumor antigens
  - Humanized CAR constructs
  - Allogeneic T cells

14

14

THANK YOU

QUESTIONS?

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15

15

Application of Precision Medicine to Early Diagnosis & Screening

Mohammed Kashani-Sabet, MD

NOTES

Precision Medicine in Management of Localized Melanoma

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Center for Melanoma Research and Treatment
California Pacific Medical Center Research Institute
San Francisco, California

1

Disclosures

- Stock/ownership interest- Melanoma Diagnostics; DNARx
- Consulting/ad board: Bristol-Myers Squibb

2

Talk Outline

- Improving precision in melanoma
  - Susceptibility
    - Role of NCOA3
  - Diagnosis
    - Role of artificial intelligence (AI) in melanoma diagnosis
  - Prognostic assessment
    - Role of gene expression profiling (GEP) assay
    - Role of mitotic rate

3

Melanoma Susceptibility

- Melanoma occurs as a combination of inherited susceptibility and exposure to ultraviolet (UV) light, characterized by uncontrolled proliferation and a high mutational load
- Molecular susceptibility to melanoma involves high-penetrance loci involving CDKN2A and CDK4, but only a minority of familial kindreds harbor mutations in known susceptibility genes
- To date, the precise molecular mechanisms by which melanoma develops following UV exposure are incompletely understood

4

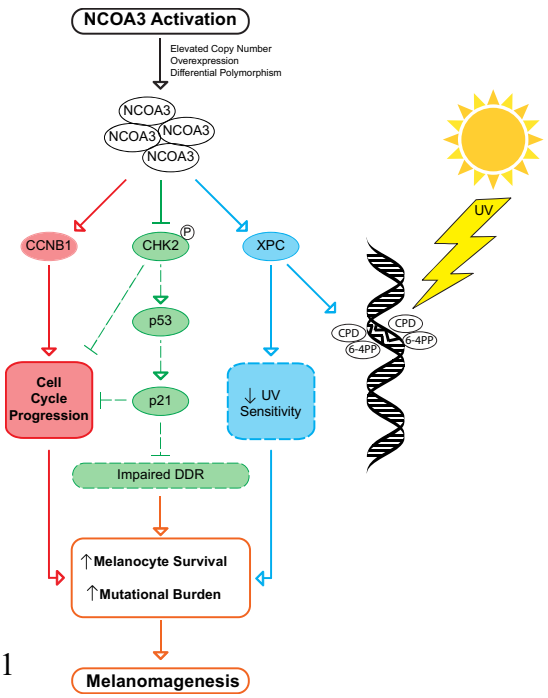
Nuclear Receptor Coactivator-3 (NCOA3)

- Member of nuclear hormone receptor coactivator family that interacts with nuclear receptors to promote gene expression
- Overexpressed in metastatic melanomas by gene expression profiling
- Demonstrated prognostic role in melanoma
  - First molecular marker to predict SLN status

Haqq, PNAS 2005; Rangel JCO 2006; Kashani-Sabet, CCR 2009, CCR 2017

5

NCOA3-Driven Model of Melanoma

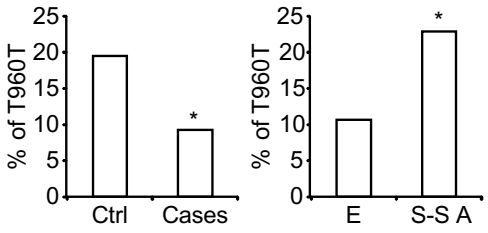


De Semir, Cancer Res. 2021

6

NCOA3 polymorphisms in familial melanoma susceptibility

- Role for NCOA3 T960T polymorphism in breast cancer susceptibility
- Prevalence of T960T polymorphism in U. of Utah cohort of familial melanoma lacking germline mutations in CDKN2A lower than control cohort without cancer
- Prevalence significantly lower in Sub-Saharan Africans vs. Caucasians
- T960T polymorphism present in 2/23 melanoma cell lines and 0/53 tumors



*P<0.05

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Model of Melanomagenesis by NCOA3 Polymorphism

- WT NCOA3 in melanocytes results in increased cell growth and resistance to UV cell killing, but with increased DNA mutations
- T960T polymorphism results in lower NCOA3 expression, with increased sensitivity to UV cell killing, and fewer DNA mutations
- Over the lifetime of the host, UV exposure results in the high TMB and uncontrolled cell growth that characterize melanoma
- Effects attenuated with T960T polymorphism, in which UV exposure results in cell death, protecting against carcinogenesis
- Model of melanoma tumorigenesis in which increased NCOA3 expression promotes cell survival following UV exposure, at the expense of accumulated DNA mutations

8

AI for Skin Cancer- Rationale

- Growing shortage of dermatologists per capita
- Potential access to large number of skin cancer images, with accompanying annotation (including dermoscopic images)
- In the case of melanoma, diagnostic accuracy of expert unaided visual inspection around 60%, which can be increased to 75-84% with dermoscopy

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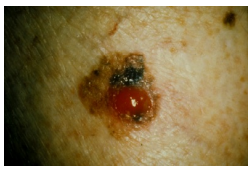
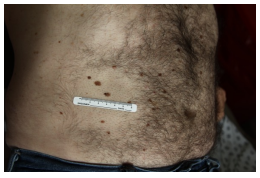
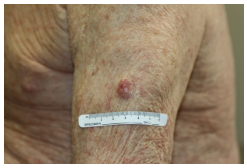
Melanoma Diagnosis







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Deep Learning in Skin Cancer

- Esteva et al., Nature, 542: 115, 2017
- Dataset of 127,463 training and validation images, and 1,942 biopsy-labeled test set; AI-based algorithm
- Two main questions
  - Lesion benign or malignant?
  - Biopsy/treat or reassure?
- AI- AUC over 91%, on par with derms' performance, and outperforms derm average

11

Siddhartha Mukherjee

ANNALS OF MEDICINE

46 The Algorithm Will See You Now

When it comes to diagnosis, will A.I. replace the M.D.?

SECTIONS LATEST POPULAR SEARCH THE NEW YORKER TNY STORE

ANNALS OF MEDICINE APRIL 3, 2017 ISSUE

A.I. VERSUS M.D.

What happens when diagnosis is automated?

By Siddhartha Mukherjee

12

Deep learning of suspicious pigmented lesions (SPL)

- Developed SPL analysis system for wide-field images using AI, applied to >38,000 dermatological dataset from 133 pts and publicly available images
- Obtained from consumer cameras and rated by dermatologists
- 90.3% sensitivity; 89.9% specificity in distinguishing SPLs from benign lesions
- Developed method to extract intrapatient differences (ugly ducking sign), with 82% agreement with dermatologists' ranking of atypical lesions

Soenksen, Sci. Transl. Med., 2021

13

Strengths and limitations

- Strengths- computer can assess data imperceptible to human eye; algorithms will continue to improve
- Weaknesses- Retrospective; don't consider clinical context
  - Lack of representation of different skin types
  - Specificity and access- can every patient with a suspicious lesion identified on a cell phone be seen?
  - Scaling up individual lesion assessment to exam of entire patient; mobile apps unregulated
  - Liability issues will need to be worked out
  - System is opaque- don't know why it calls a given lesion benign or malignant

14

Gene Expression Profiling (GEP) Assay in Melanoma Prognosis

- Prognostic impact of 31-gene expression signature in primary melanomas in retrospective cohort of 217 pts undergoing sentinel lymph node (SLN) biopsy
- Read out: molecularly defined low-risk (class 1) and high-risk (class 2) scores
- GEP score was significantly correlated with OS, and may be combined with SLN status to identify patients with differing risks of metastasis

Gerami, JAAD, 2015

15

Prospective Analysis of GEP

- Cohort of 523 patients, with 337 undergoing SLNB
- Class 1 associated with 5-yr DMFS of 93% vs. 60% for class 2
- GEP score independently predictive of DMFS on multivariate analysis (HR-2.7; P=0.002), but following SLN status (HR-3.0; P<.001)

Zager, BMC Cancer 2018

16

Use of GEP to Predict SLN Status

Two SLNB pt cohorts (N=584 and 837)
Look at T1 (< 1 mm thick) and T2 (1-2 mm thick) lesions combined

Age	SLN Positivity (class 1a)	SLN Positivity (class 2b)
< 55	9.9%	24%
55-64	7.1%	33.3%
≥ 65	2.2%	12.5%

Received Medicare coverage approval in 2018, based on positivity cut-off of 5%

Vetto, Future Oncology, 2019

17

GEP + Routine Factors for SLN Status

- Integrate GEP score with 4 factors (thickness, mitotic rate, age, ulceration) in SLNB prediction
- iGEP accuracy determined by analyzing 5% cut-off of SLNB positivity
- Sensitivity of model-95%; NPV-98%
- Suggests potential re-classification when compared with using T category alone
- No AUC analysis of iGEP, and how GEP alone performs alone, without the incorporation of additional factors

Whitman, JCO PO, 2021

18

Issues with GEP Studies

- Switching between different endpoints- RFS, DMFS, OS, MSS, SLN status
- Inclusion of heterogeneous patient subsets (node-positive vs. node-negative patients, and differing T categories)
- No adjuvant therapy or imaging implications identified of profiling results
- Contrast with development path in BRCA

19

Analysis of prognostic impact of mitotic rate- Case Presentation

- 75 y.o. male with melanoma on the left upper back, 1.5 mm, non-ulcerated
- S/P wide excision and negative SLN biopsy
- AJCC stage IB-97% 5-yr survival
- One year later- new onset cough and pulmonary mets on CT scan, bx-proven melanoma
- Review of primary melanoma pathology indicates mitotic rate of 7/mm^2

20

Improving the Prognostic Impact of Mitotic Rate in Melanoma

- Mitotic rate has known prognostic significance
- Incorporated as a T1b-defining feature in AJCC 7th edition, but removed in 8th edition
- Mitotic rate is a continuous variable (similar to thickness); hence, identifying its optimal cut-point is critical for a defined patient subset
- Neither the optimal cut-points for the entire scale of mitotic rate, nor for different tumor thickness subgroups, had been defined

21

Development of Cohort for Analysis of Mitotic Rate

- In collaboration with Melanoma Institute Australia (MIA), amassed dataset of 5,050 patients with primary cutaneous melanoma with following eligibility criteria:
- Died of metastatic melanoma at any time following initial diagnosis, or
- Had at least 8 years of follow-up without evidence of distant metastasis
- Median follow up-9.5 years

Kashani-Sabet, 2020 Cancer

22

Shape of relationship between various prognostic factors and survival

- Tumor thickness has a non-linear relationship with survival
  - AJCC-defined cut-points of 1, 2, and 4 mm
- Mitotic rate also has a non-linear relationship with survival
  - Optimal cut-points of 1, 2, 4, 7, and 11/mm^2
- Constructed index using these cut-points to analyze impact of mitotic rate on survival vs. impact when assessed as a continuous variable
- Then performed similar analyses in randomly generated training and validation cohorts (2025 patients each)

23

Multivariate Cox Regression Analysis of Survival- Validation Set

Covariate	Chi-square	Relative risk	P	Covariate	Chi-square	Relative risk	P
Thickness	218	1.69	< 0.0001	Thickness	138	1.58	<0.0001
Ulceration	46	1.60	< 0.0001	Mitotic rate (index of cut-points)	42	5.38	<0.0001
Mitotic rate (entire scale)	25	1.02	< 0.001	Ulceration	39	1.55	<0.0001

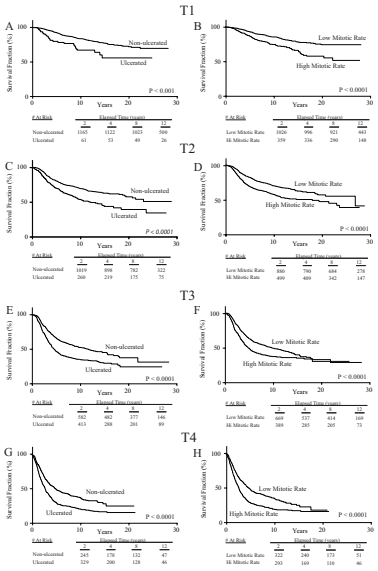
24

Impact of Mitotic Rate vs. Ulceration in each T category

- For mitotic rate to be useful in staging, it should refine survival information within a given T category
- Identified optimal cut-point for mitotic rate in each T category
  - T1- <2 vs. ≥ 2/mm2
  - T2- <4 vs. ≥ 4/mm2
  - T3- <6 vs. ≥ 6/mm2
  - T4- <7 vs. ≥ 7/mm2
- Evaluated impact of ulceration vs. elevated mitotic rate in each T category using Kaplan-Meier analysis

25

Survival According to Presence or Absence of Ulceration or Elevated Mitotic Rate by T category



26