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Albuquerque, New Mexico | November 16 - 19, 2023

Strategies to Target Minimal Residual Disease in Lung Cancer

Session Title: Lung Cancer Screening & The Next Frontier
Date: Friday November 17, 2023

Christine M. Lovly, MD, PhD @Christine_Lovly
Associate Professor of Medicine, Division of Hematology and Oncology
Ingram Associate Professor of Cancer Research
Vanderbilt University Ingram Cancer Center
Nashville, TN USA

What are the “Next Frontiers” in Lung Cancer?

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Estimated New Cases

	Males			Females	
Prostate	268,490	27%	Breast	287,850	31%
Lung & bronchus	117,910	12%	Lung & bronchus	118,830	13%
Colon & rectum	80,690	8%	Colon & rectum	70,340	8%
Urinary bladder	61,700	6%	Uterine corpus	65,950	7%
Melanoma of the skin	57,180	6%	Melanoma of the skin	42,600	5%
Kidney & renal pelvis	50,290	5%	Non-Hodgkin lymphoma	36,350	4%
Non-Hodgkin lymphoma	44,120	4%	Thyroid	31,940	3%
Oral cavity & pharynx	38,700	4%	Pancreas	29,240	3%
Leukemia	35,810	4%	Kidney & renal pelvis	28,710	3%
Pancreas	32,970	3%	Leukemia	24,840	3%
All Sites	**983,160**	**100%**	**All Sites**	**934,870**	**100%**

Estimated Deaths

	Males			Females	
Lung & bronchus	68,820	21%	Lung & bronchus	61,360	21%
Prostate	34,500	11%	Breast	43,250	15%
Colon & rectum	28,400	9%	Colon & rectum	24,180	8%
Pancreas	25,970	8%	Pancreas	23,860	8%
Liver & intrahepatic bile duct	20,420	6%	Ovary	12,810	4%
Leukemia	14,020	4%	Uterine corpus	12,550	4%
Esophagus	13,250	4%	Liver & intrahepatic bile duct	10,100	4%
Urinary bladder	12,120	4%	Leukemia	9,980	3%
Non-Hodgkin lymphoma	11,700	4%	Non-Hodgkin lymphoma	8,550	3%
Brain & other nervous system	10,710	3%	Brain & other nervous system	7,570	3%
All Sites	**322,090**	**100%**	**All Sites**	**287,270**	**100%**

CA A Cancer J Clinicians, Volume: 72, Issue: 1, Pages: 7-33, First published: 12 January 2022, DOI: (10.3322/caac.21708)

How do we continue to optimize outcomes for patients with lung cancer?

Develop strategies to PREVENT new cases

- Risk reduction
- Screening strategies

Develop strategies to IMPROVE OUTCOMES from established cases

- Develop new therapies
- Maximize our use of available therapies
- Develop strategies to treat Minimal Residual Disease

Defining and Treating Minimal Residual Disease (MRD) is a “next frontier” in Lung Cancer

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- **Minimal Residual Disease (MRD)** is defined as the detection of the remaining tumor cells after therapy.

- Why is it critical to detect, quantity, and eradicate MRD?
  - MRD = the tumor cells which persist after initial therapy (local therapy or systemic therapy).
  - These persister tumor cells may ultimately lead to local, regional, or metastatic relapse.
  - Goal → eradicate tumor cells which persist after therapy → improve patient outcomes

- MRD monitoring and detection are established and widely used in patients with hematological malignancies, but MRD assessments have been more difficult for solid tumors, such as lung cancer.
  - Why? Because MRD analyses necessitate serial evaluation of the tumor, which is relatively straightforward for heme malignancies but more difficult for solid tumors, until the advent of “liquid biopsies” evaluating cell free DNA (cfDNA) and circulating tumor cells (CTCs).
  - We will hear in great depth about cfDNA from Dr. Leighl.

- Two clinical contexts to consider when discussing MRD:
  - Early stage disease
  - Advanced / metastatic

Clinical contexts in which to consider the MRD state

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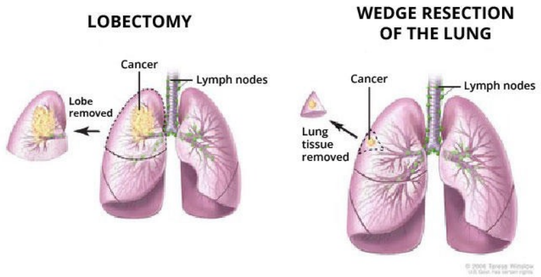
Early Stage / Surgically Resected Disease

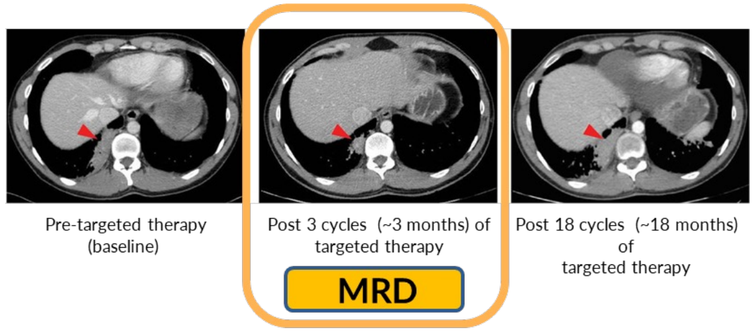


- NED after surgery
- Monitor for recurrence

Questions:

- What is the best way to monitor for recurrence? With what frequency?
- What strategies are available to prevent / delay disease recurrence?
- How do we treat recurrence once detected?

Advanced / Metastatic Disease



- MRD state in advanced disease = point of maximal tumor shrinkage on scans
- Monitor for disease progression / acquired resistance.

Questions:

- What is happening in the tumor at the time of maximal drug response, when residual disease is still present on scans?
- What strategies are available to prevent / delay disease recurrence?
- How do we treat acquired resistance to therapy once detected?

MRD FOR RESECTABLE NSCLC – use of ctDNA as a surrogate marker

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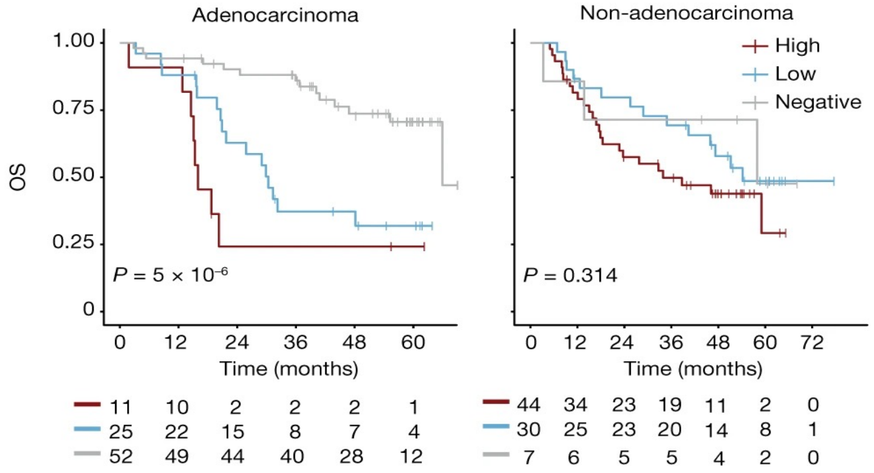
- Before the advent of sensitive "liquid biopsy" assays to evaluate circulating tumor DNA, recurrence in early stage disease was determined solely by imaging analyses.
- Multiple proof-of-concept data sets are now available to so support that ctDNA MRD is a prognostic and possibly a predictive biomarker for resectable NSCLC → making the possibility of detecting "molecular" recurrence a reality in lung cancer.
- Consider one of the first and largest studies of ctDNA to evaluate for residual tumor after curative intent therapy → TRACERx.

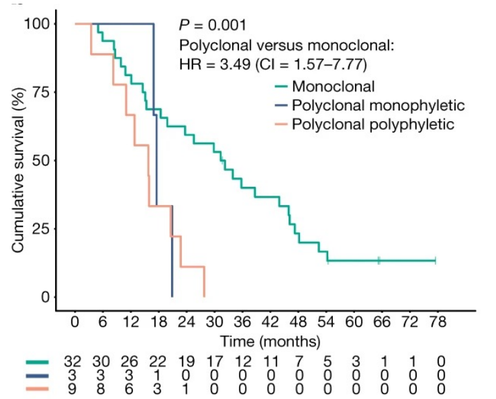
TRACERx study (Abbosh .... Swanton Nature 2023 PMID: 37055640)



Kaplan–Meier curves demonstrating the overall survival outcomes in ctDNA-high (dark red), ctDNA-low (blue) and ctDNA-negative (grey) patients with non-synchronous adenocarcinoma (left) and non-synchronous non-adenocarcinoma (right).

Adenocarcinoma:
2 year OS rates
- Pre-op ctDNA negative: 90%
- ctDNA low: 63%
- ctDNA high: 24%

Non-adenocarcinoma:
2 year OS rates were similar across groups



A Kaplan–Meier plot depicting differences in the overall survival between metastatic dissemination classes (n = 44 tumors, which had at least 1 high subclone sensitivity postoperative sample). A log-rank test was used to compare survival in the two groups.

- For patients who experienced disease relapse, OS was shorter in patients whose ctDNA profile exhibited polyclonal dissemination versus monoclonal dissemination.

ctDNA MRD FOR RESECTABLE NSCLC – open questions and trials for the future

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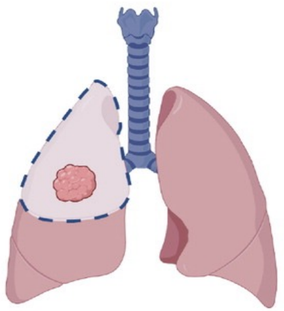

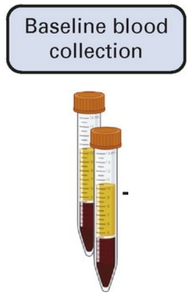

Neoadjuvant Therapy

1
MRD (+)
by ctDNA analysis

Surgery

2
MRD (–)
by ctDNA analysis

Surgery

Adjuvant Therapy
Vs.
Surveillance

3
MRD (+)

Adjuvant Therapy

4
MRD (–)

Adjuvant Therapy
Vs.
Surveillance

Surveillance

4 possible clinical scenarios to consider

1. Baseline ctDNA positive
2. Baseline ctDNA negative
3. Post surgery ctDNA positive
4. Post surgery ctDNA negative

<u>IMPORTANT QUESTIONS FOR THE FUTURE</u>

1. What assay is better for ctDNA analysis for MRD detection: tumor informed vs. tumor naïve?
2. What limit of detection is necessary for ctDNA detection?
3. How often does ctDNA need to be evaluated to guide treatment escalation or de-escalation?
4. Will treatment escalation based on ctDNA MRD state improve DFS and OS in the adjuvant setting?

Adapted from Pellini and Chaudhuri
JCO 2022 PMID: 34985936 and
Frisone Curr Oncol Rep 2021
PMID: 34735646

MRD for Advanced/Metastatic NSCLC

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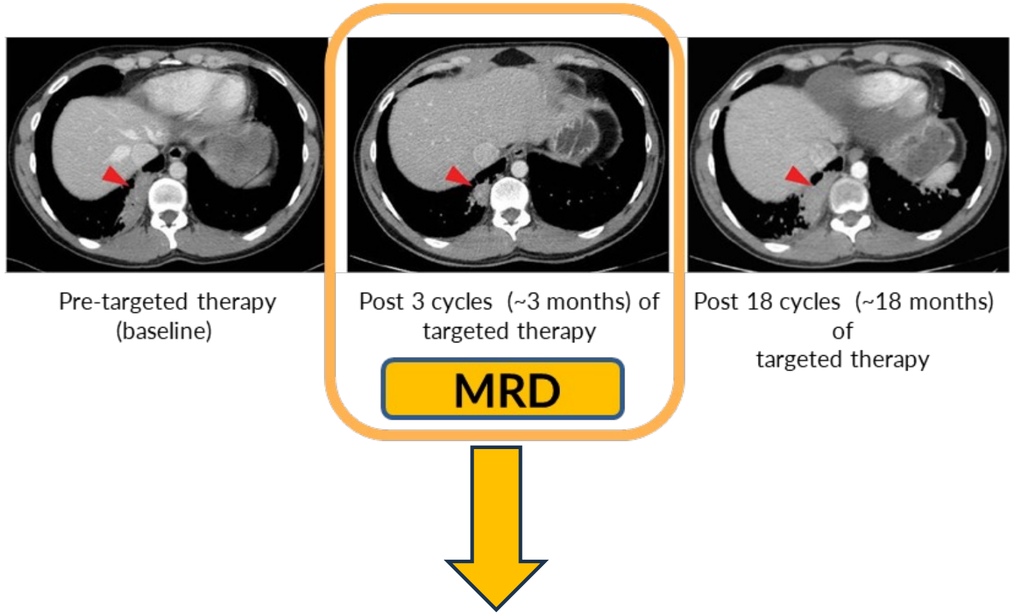

MRD in the advanced/metastatic setting = point of maximal tumor shrinkage prior to eventual tumor progression.

Challenges and Barriers to Understanding the MRD state in the advanced / metastatic setting

- We lack do not sample (biopsy) the tumor at the time of best response. Therefore, we lack a comprehensive understanding of the biological and immunological basis of the clinical MRD state.
- We have yet to define tumor cell autonomous and tumor cell non-autonomous mechanisms driving drug tolerant persister cells.
- We have no proven combination therapies aimed at eradicating the clinical MRD state.
- We do not have a clinical trial framework for testing new agents at the clinical MRD state.

GOAL: To target and eradicate MRD for patients with advanced / metastatic disease, in order to take a partial responses to a complete responses → and ultimately long term disease control.

Drug Tolerant Persister Cells (DTPCs)

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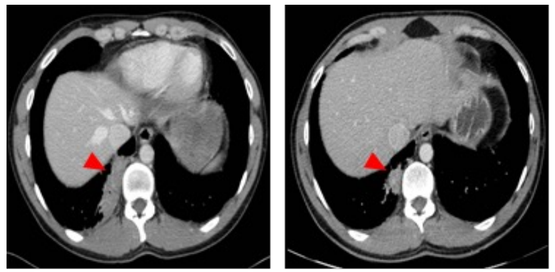
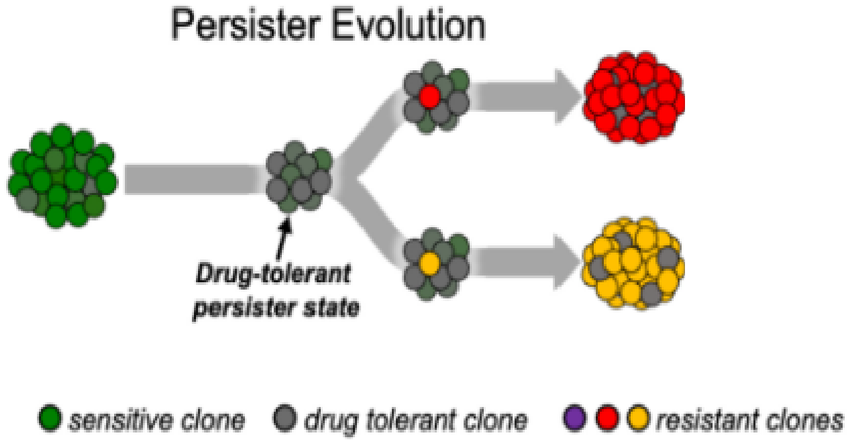
What are DTPCs?



pre-treatment after 3 cycles EGFR TKI

Clinically: evidence of response with residual measurable disease before frank progression.

DTPCs on a cellular level



- Small population of cells persists despite suppression of oncogenic signaling
- Reversible if drug removed
- Subsequent accumulation of resistance driver alterations drives expansion of fully resistant clones

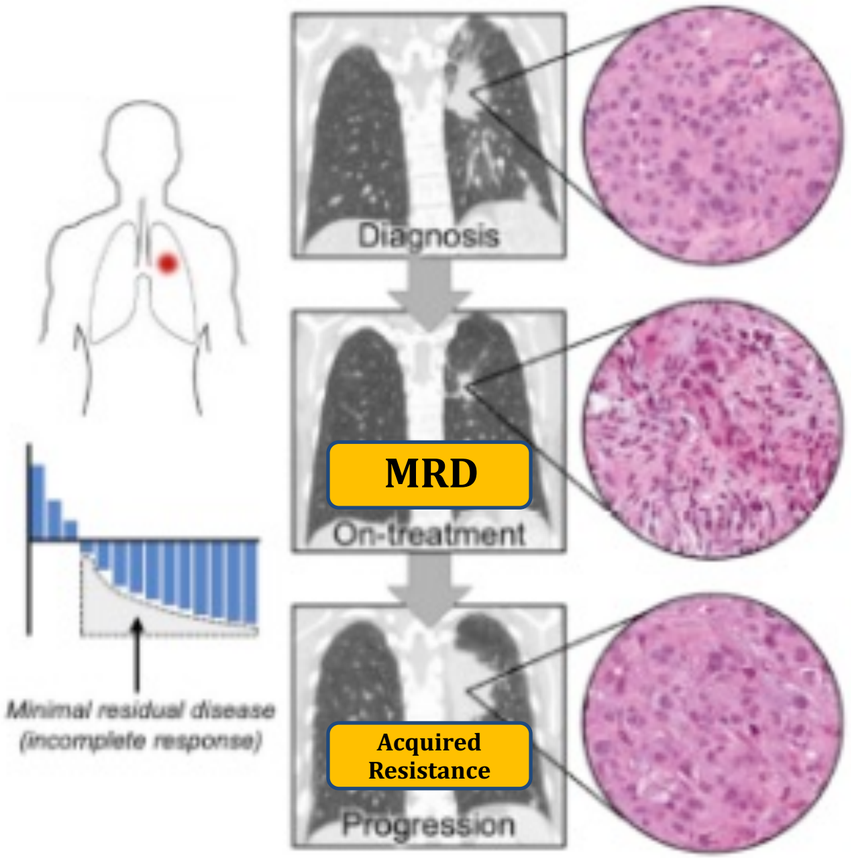
What study DTPCs?

- To identify new vulnerabilities in tumors which, when therapeutically targeted, can maximize the depth and duration of benefit to first-line therapy.
- The vulnerabilities could be tumor-cell autonomous or tumor cell non-autonomous (to account for the tumor microenvironment).
- **Goal: Target and Eradicate MRD.**

What is known about DTPCs in lung cancer?

- The existing datasets are limited and predominantly use cell lines and PDX models.
- Clinically, analysis of DTPCs requires on-treatment biopsy, which is not standard of care.
- What drives drug tolerance? Most of the data comes from analysis of EGFR-mutant and ALK-positive lung cancer.
- Targets / mechanisms implicated for driving drug tolerance include: AXL, YAP/TEAD, NFκB, AurkA.
- See: Cabanos and Hata Cancers 2021 and Maynard A Cell 2020.

Strategies to treat the MRD state in the advanced / metastatic setting



Cabanos and Hata Cancers 2021

- Current standard of care, we treat at diagnosis and at progression → current practice is to wait until acquired resistance to 1st line therapy in the advanced/metastatic setting occurs before initiating next line of therapy.
- What if additional therapies could be initiated "on-treatment" ("B") to maximize response? These therapies could include:
  - Local therapies: surgery, XRT
  - Systemic therapies
  - Vaccines
- Could these therapies given at the MRD state be informed by ctDNA analyses?

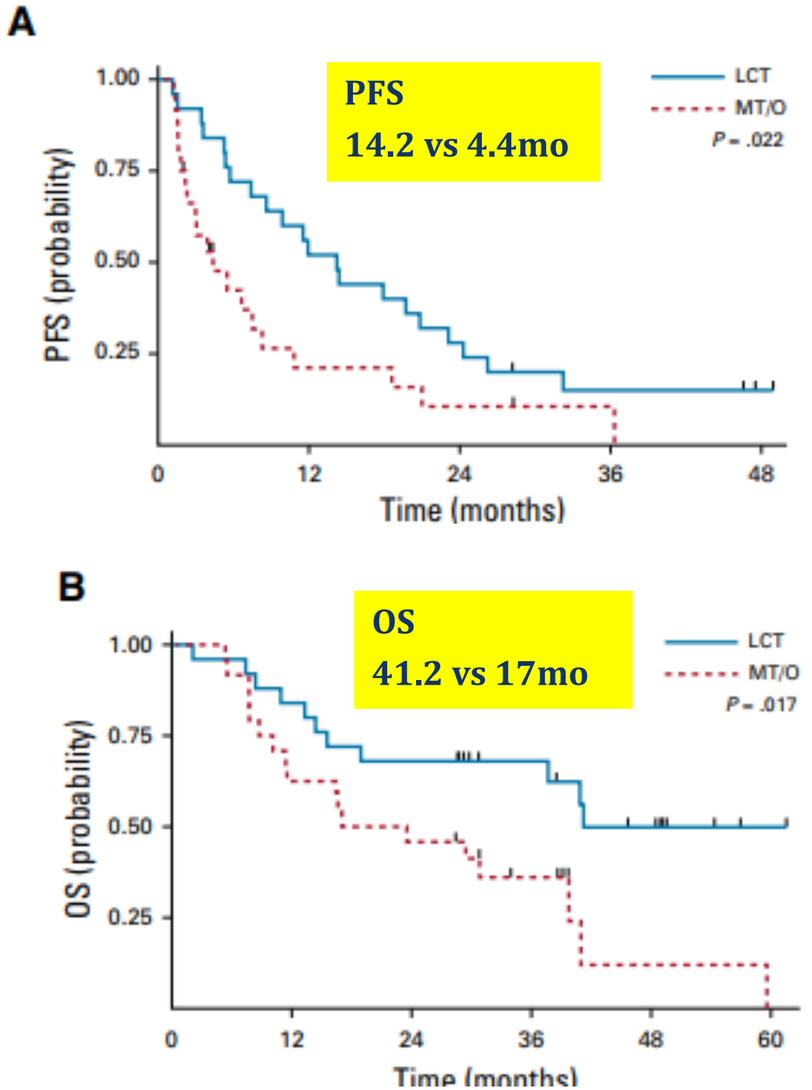
Local Consolidation Therapy of MRD

- Approach: Add local therapy after initial "run in" of systemic therapy, continue systemic therapy.

- Single institutional study (PMID 30343004): patients with *EGFR* mutant lung cancer to receive EGFR TKI alone or EGFR TKI plus local consolidation therapy:
  - PFS was 36 months in the local consolidation therapy group versus 14 months in the control arm.

- In a multi-center study led by Gomez and colleagues (PMID 31067138), patients =< 3 metastases and no progression >= 3 months after start of frontline systemic therapy were randomized one to one to receive systemic therapy alone or systemic therapy with local consolidation therapy.
  - The median follow-up time was 38.8 months.
  - The median PFS was 14.2 months with local consolidation therapy versus 4.4 months without local consolidation therapy.
  - The overall survival was 41.2 months with local consolidation therapy versus 17 months without local consolidation therapy.

- Several ongoing studies in this space.
  - Osimertinib, Surgery, and Radiation Therapy in Treating Patients With Stage IIIB or IV Non-small Cell Lung Cancer With EGFR Mutations, NORTHSTAR Study PI: Dr. Yasir Elamin, NCT03410043)



Reference: Gomez et al JCO 2019, PMID 30343004

Assessing ctDNA MRD for advanced/metastatic NSCLC

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- ctDNA can also be used to guide molecular response / molecular relapse in patients with metastatic lung cancer.

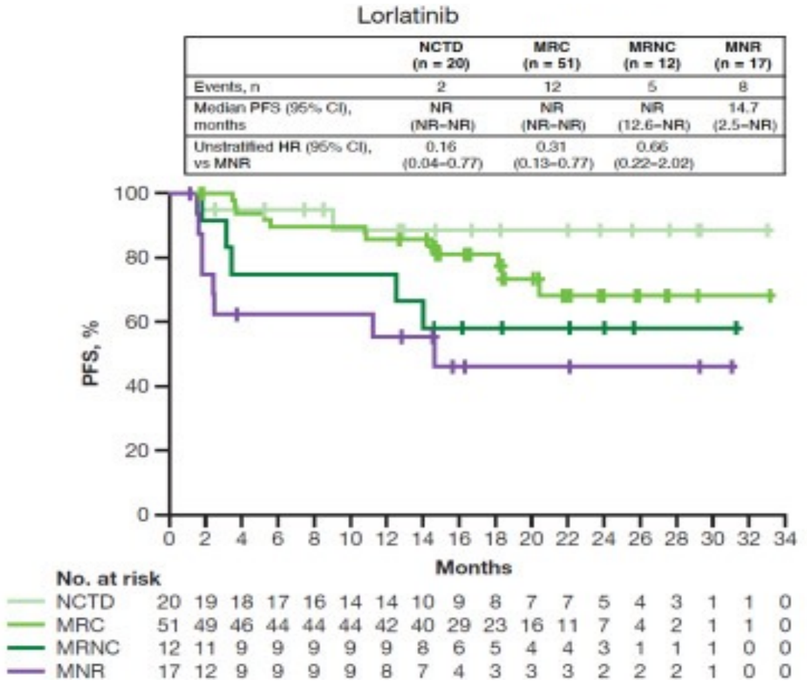
- Advantages to a ctDNA guided approach in the metastatic setting:
  - Detect molecular progression before frank progression on imaging.
  - Clarify ambiguous findings on imaging studies.
  - Clarify heterogeneity in imaging responses.

- Ultimately, ctDNA would be used in combination with imaging studies (CT scans, PET scans) to better risk stratify response.

- There are now many examples, predominantly retrospective to date, showing that ctDNA dynamics correlate with tumor response and resistance in the metastatic setting – across multiple types of systemic therapies – targeted therapy, chemotherapy, immunotherapy.

ctDNA data from the Phase 3 CROWN study (NCT03052608)

Lorlatinib vs. Crizotinib in patients with stage 4 ALK+ lung cancer



12 month PFS on Lorlatinib:

- NCTD (no ctDNA detected) group: 89%
- MRC (molecular responder cleared) group: 96%
- MRNC (molecular responder not cleared) group: 75%
- MNR (molecular nonresponder) group: 56%
- Ref: Soo et al Journal of Thoracic Oncology November 2023

Anagnostou Clin. Cancer Res. 23, 4959–4969 (2017).

ctDNA response after pembrolizumab in non-small cell lung cancer: phase 2 adaptive trial results

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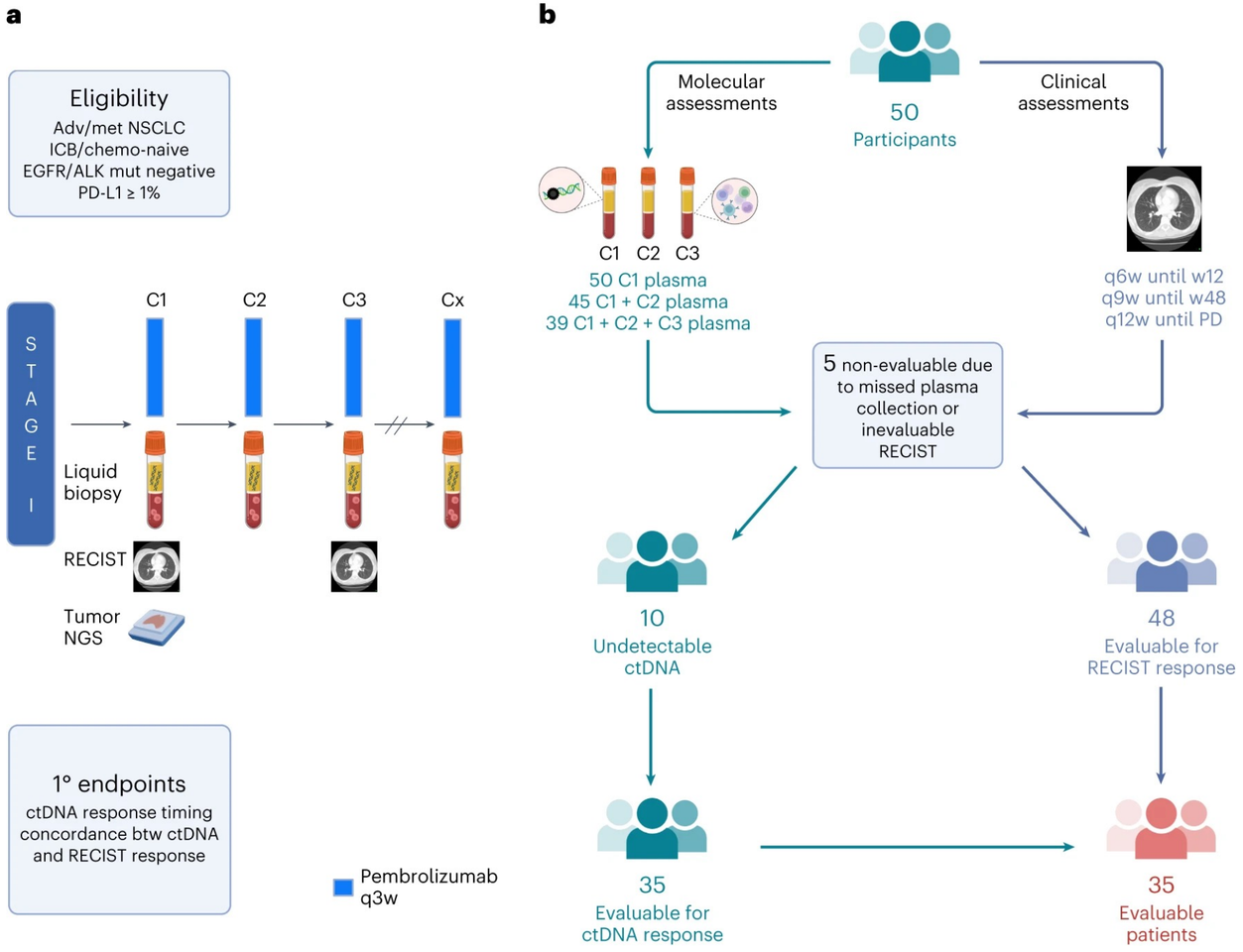
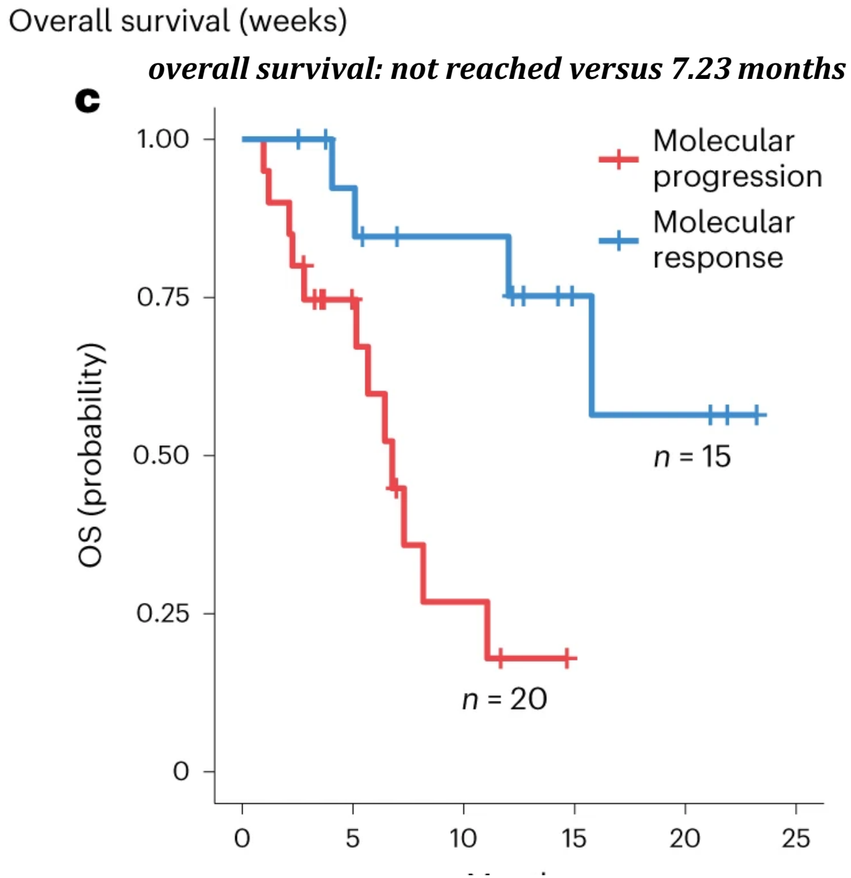
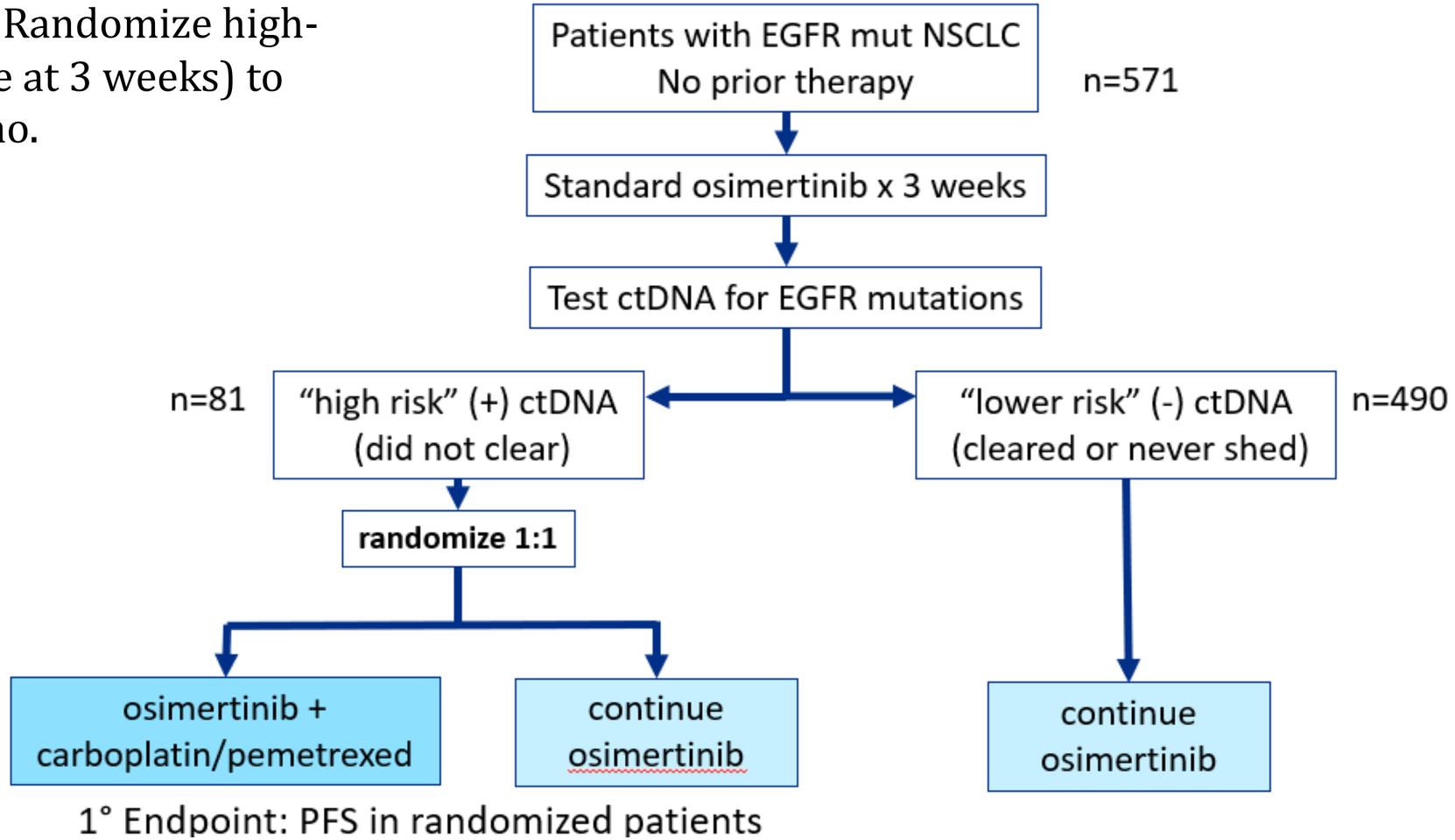




Anagnostou Nature Medicine October 2023

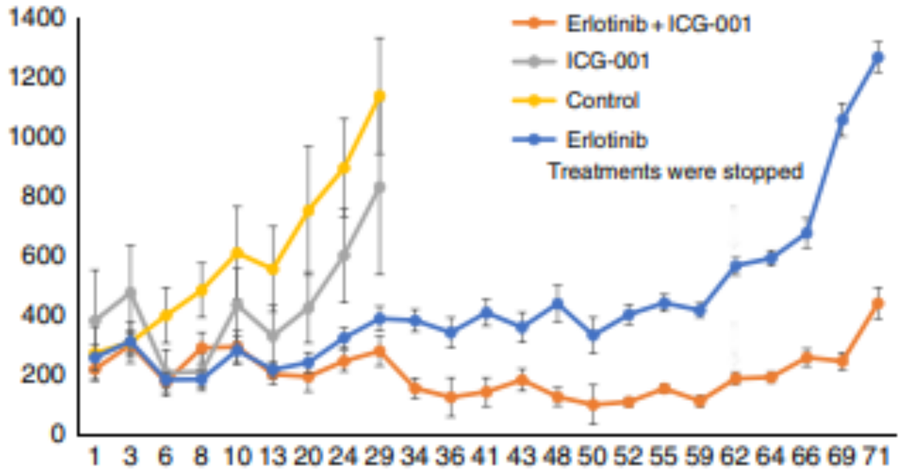
Can we use ctDNA or other liquid based analytes to non-invasively determine which patients need intensification of therapy?

- NCT04410796 PI: Dr. Helena Yu: Randomize high-risk patients (no ctDNA clearance at 3 weeks) to osimertinib vs osimertinib/chemo.



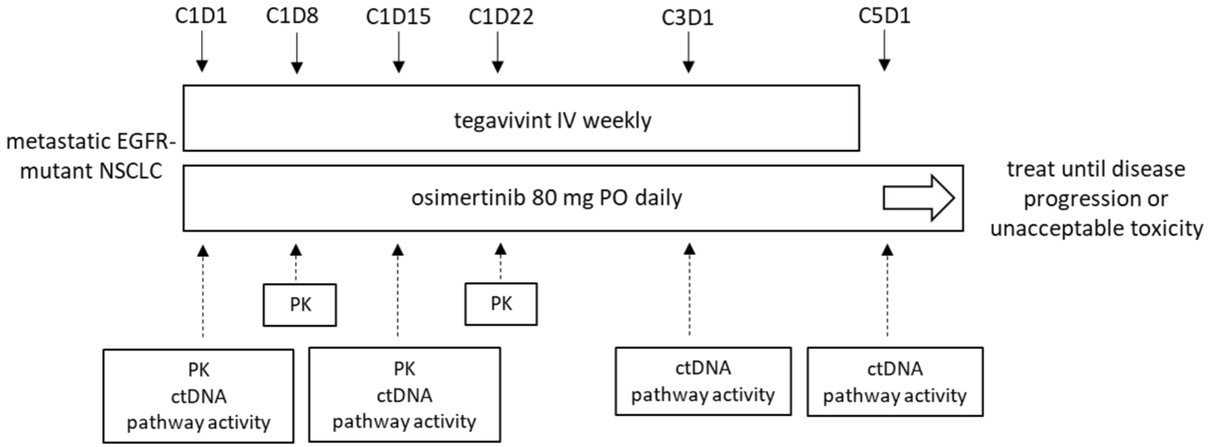
What systemic therapies can be utilized to combat DTPCs and eradicate MRD in patients with advanced/metastatic disease?

Pre-clinical studies: EGFR TKI + β-catenin inhibitor inhibited DTPCs and prolonged response to EGFR TKI therapy.



*ICG-001= β-catenin inhibitor

A phase 1 trial of tegavivint in combination with osimertinib for the treatment of previously untreated patients with metastatic EGFR mutant lung cancer.
NCT04780568, PI Regan Memmott, MD, PhD, Ohio State University



Arasada, R.R., et al., *Nat Commun*, 2018

Summary and Future Directions

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- **The MRD state - the "next frontier" in driving precision medicine for lung cancer.**
  - For early stage / resected disease: To improve cure rates, we need quantitative, highly sensitive metrics to define risk of relapse and viable strategies for treating high risk populations.
  - For advanced / metastatic disease: We need to move beyond a "watch and wait" approach to treating advanced tumors to a more dynamic, risk-stratified approach, adapting treatment before the onset of frank acquired resistance.

- **Multiple studies are underway in the adjuvant setting and in the metastatic setting using ctDNA to help prognosticate risk and predict molecular relapse.**
  - Such studies are made possible by an explosion of technology development, especially in the realm of ctDNA assays, which continue to push the bounds to increasingly more sensitive tests with increasingly lower LOD.
  - ctDNA molecular correlates will also be coupled with digital imaging (e.g., of path slides) and radiomics to further increase the precision with which response and risk of relapse are defined.

- **Local Therapy (surgery, XRT) when used at the clinical MRD time point has shown tremendous promise towards increasing overall survival in patients with advanced / metastatic lung cancer.**
  - The Gomez trial (consolidation therapy) is cited in the NCCN NSCLC guidelines.

- **In the future, we will need rigorous pre-clinical studies to inform which systemic therapies can be used to overcome DTPCs in the clinical MRD state and we will need an innovative clinical trial framework for evaluating the addition of systemic therapies at the MRD state.**
  - Overcoming MRD is the much needed next wave in precision medicine to transform the care for our patients, driving towards the ultimate goal of achieving durable control or cure for as many patients as possible.

THANK YOU!

Happy to discuss anytime!

@Christine_Lovly

Our inspirations!

Members of the ALK Positive Patient group visiting the Lovly Lab.