ASTRO ANNUAL refresher COURSE 2021

BEST PRACTICES AND EMERGING TRENDS

March 19-21 *Live* Interactive Virtual Conference

Welcome

Molecular Radiogenomics

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Northwestern University

Disclosure

- Employee of Northwestern Medicine and Northwestern University.
- Patent holder on Deep Profiler and iGray: Image-based deep learning frameworks for individualizing radiation dose delivery to the lung.
- Travel and grant support from Siemens Healthcare, USA.
- Speaker's fees from American Society for Clinical Pathology

Learning Objectives

- Define molecular radiogenomics.
- Describe the genetic and phenotypic (radiation sensitivity) heterogeneity of cancer.
- Identify salient genetic radiotherapy biomarkers in cancer.
- Identify how NGS can augment tumor staging.
- Identify the role of liquid biopsy in understanding disease evolution and assessment of systemic disease burden.

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What is Radiogenomics?

- Radiogenomics is the cataloguing of genetic determinants of the tumor response to radiation.
- It is also used in the context of associating cancer imaging features (radiomics) with genetic determinants (genomics); hence, radiogenomics.
- Today, we will focus our discussion on the former.

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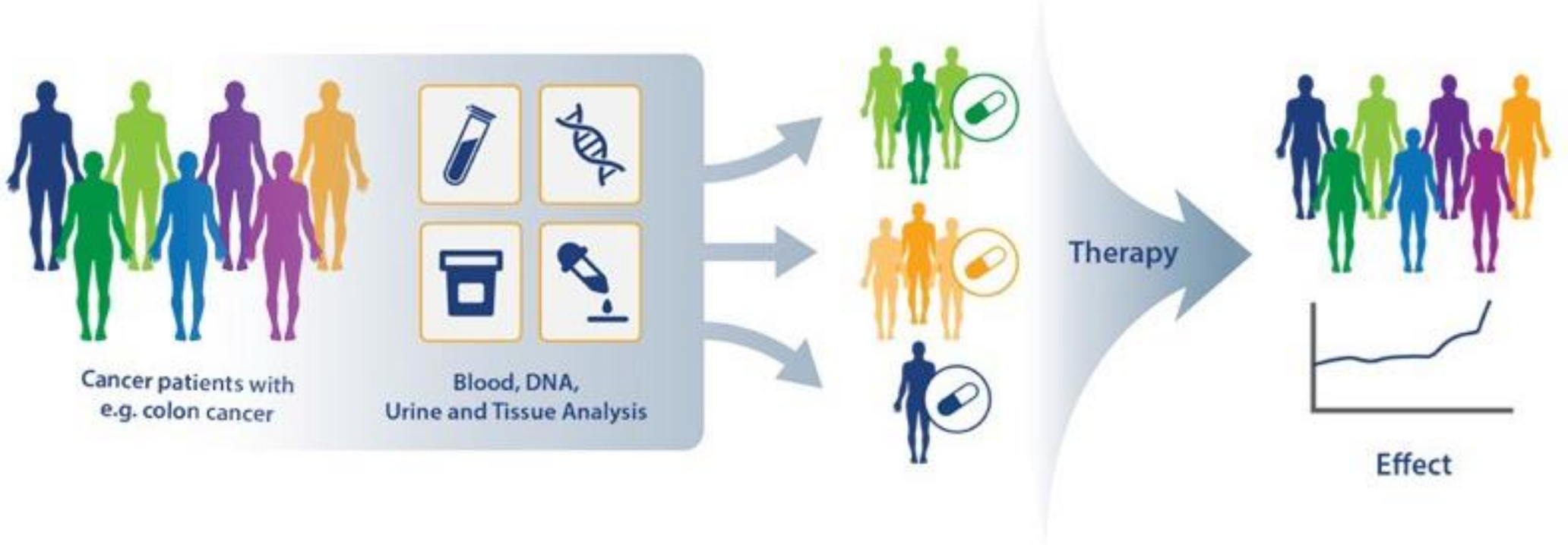
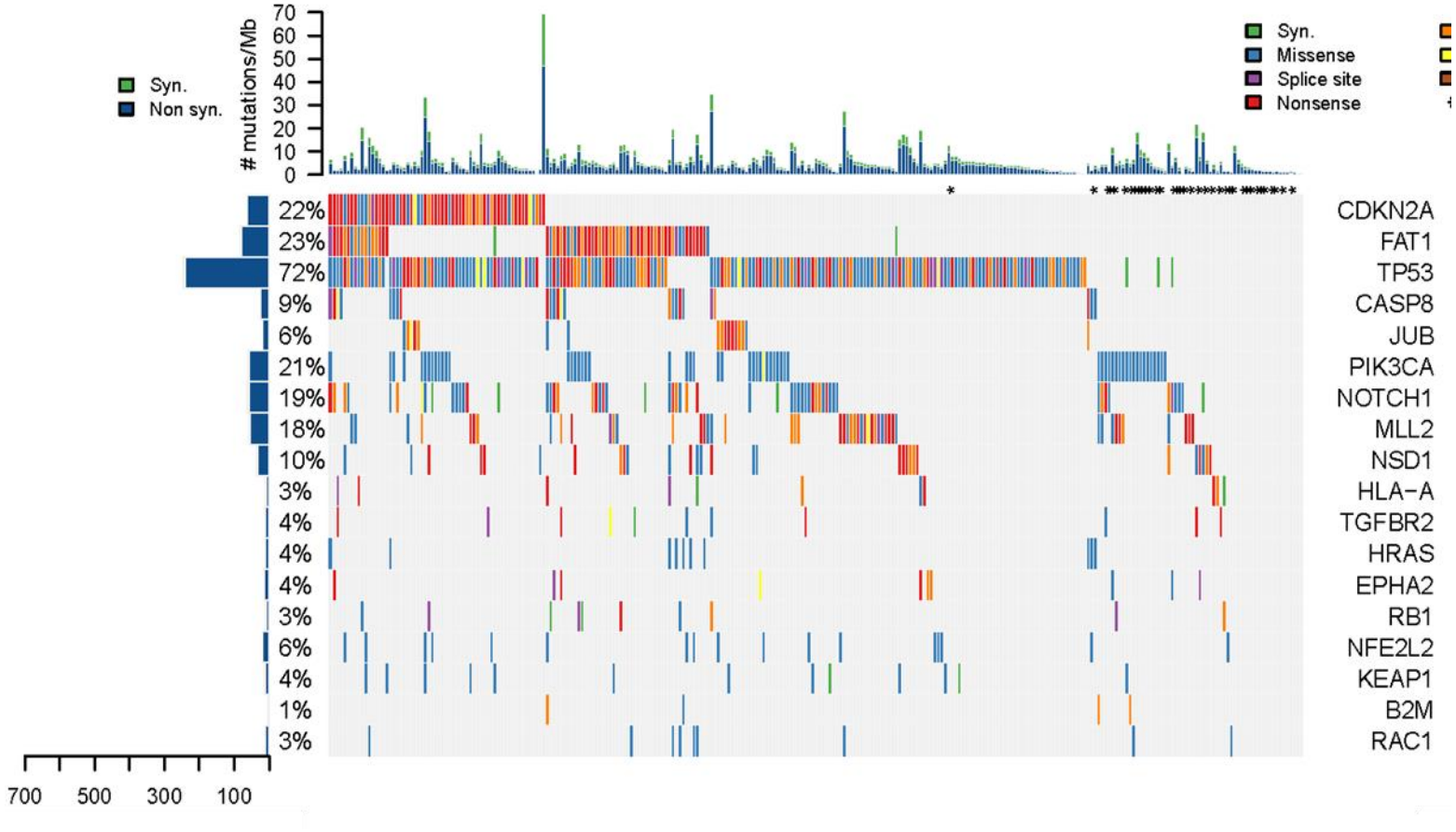
Personalized Medicine



The Genetic Diversity of Cancer

Problem: Cancer is genetically heterogenous.

Solution(s): Identify omic predictors of radiotherapeutic response and stratify patients based on these alterations.



The Cancer Genome Atlas

Variation in the Vulnerability of Cancer to Ionizing Radiation

nature COMMUNICATIONS

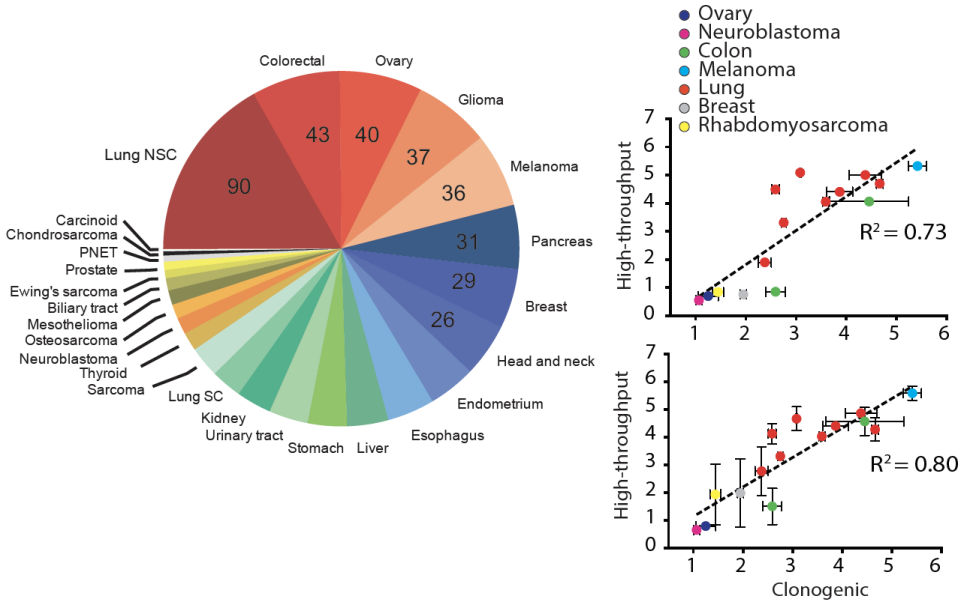
ARTICLE

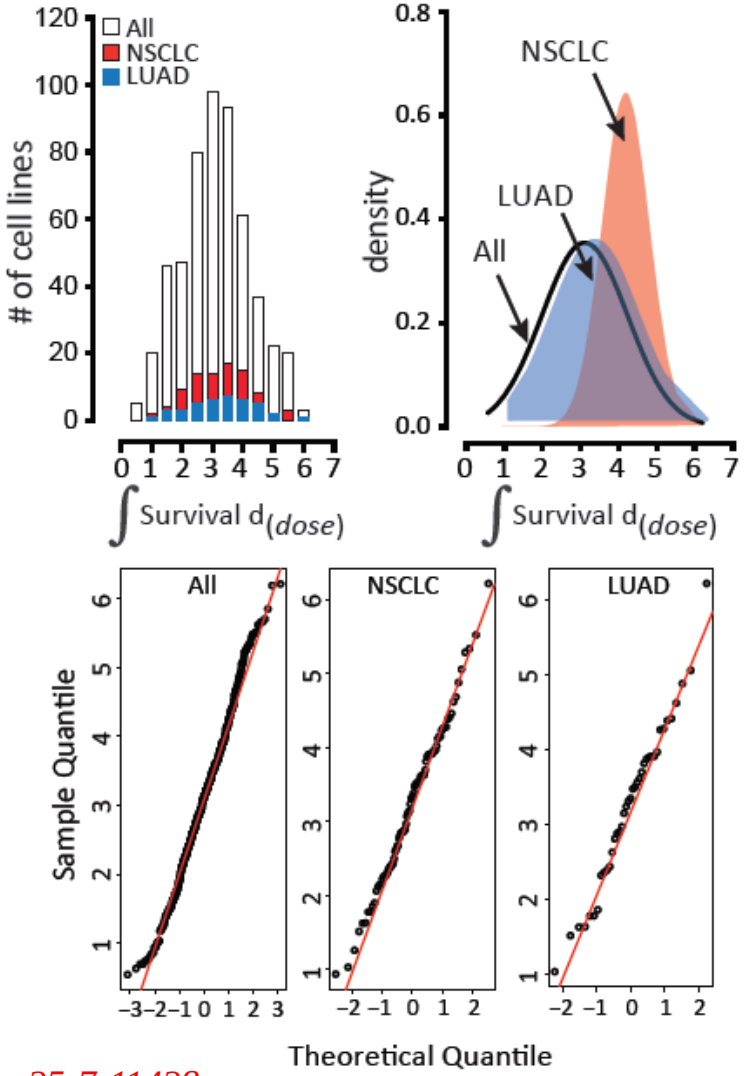
Received 16 Nov 2015 | Accepted 24 Mar 2016 | Published 25 Apr 2016

DOI: 10.1038/ncomms11428 OPEN

A genetic basis for the variation in the vulnerability of cancer to DNA damage

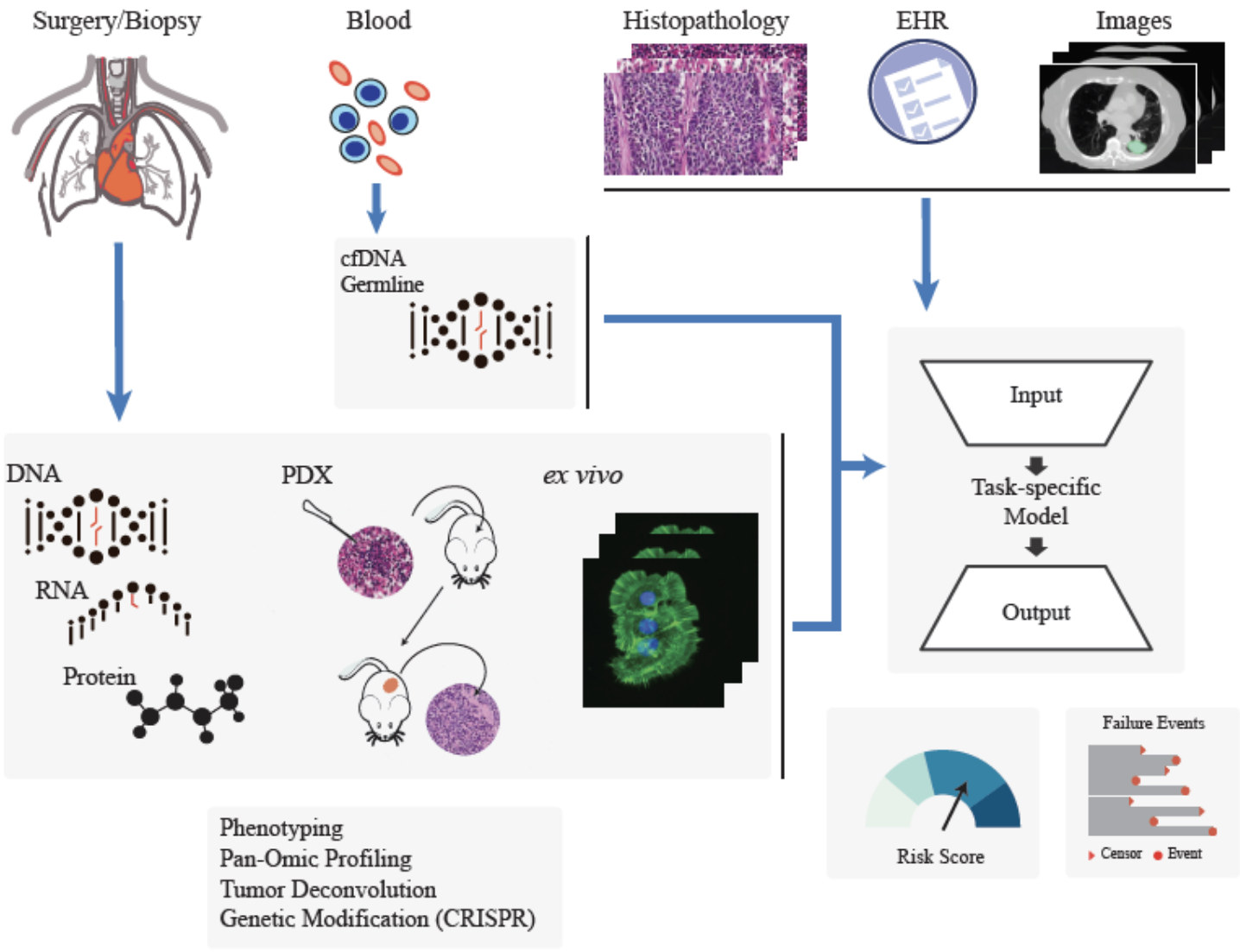
Brian D. Yard[1,*], Drew J. Adams[2,*], Eui Kyu Chie[1,3], Pablo Tamayo[4], Jessica S. Battaglia[1], Priyanka Gopal[1], Kevin Rogacki[1], Bradley E. Pearson[5], James Phillips[1], Daniel P. Raymond[6], Nathan A. Pennell[7], Francisco Almeida[8], Jaime H. Cheah[4,9], Paul A. Clemons[4,9], Alykhan Shamji[4,9], Craig D. Peacock[1], Stuart L. Schreiber[4,9,10,11], Peter S. Hammerman[4,5] & Mohamed E. Abazeed[1,12]





Nat Commun. 2016 Apr 25;7:11428.

Integrated Clinomic Networks: A Platform for Clinical Prediction



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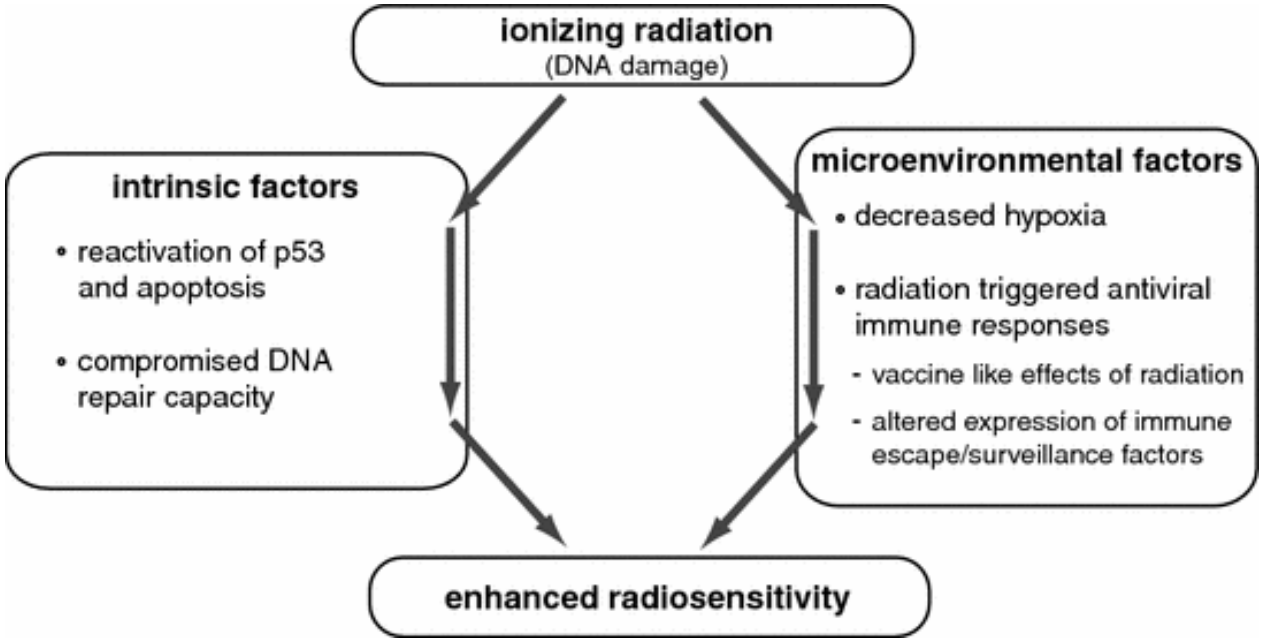
HPV tumors, radiation sensitivity, dose de-escalation

- Patients with human papillomavirus–related oropharyngeal cancers have excellent outcomes but experience clinically significant toxicities when treated with standard chemoradiotherapy (70 Gy).

- Due to the intrinsic and immune-mediated sensitivity of these tumors to radiation, there are ongoing attempts to de-escalate treatments.



De Costa AM., et al. (2015) HPV and Radiation Sensitivity. In: Miller D., Stack M. (eds) Human Papillomavirus (HPV)-Associated Oropharyngeal Cancer. Springer, Cham.

NRG Oncology HN002

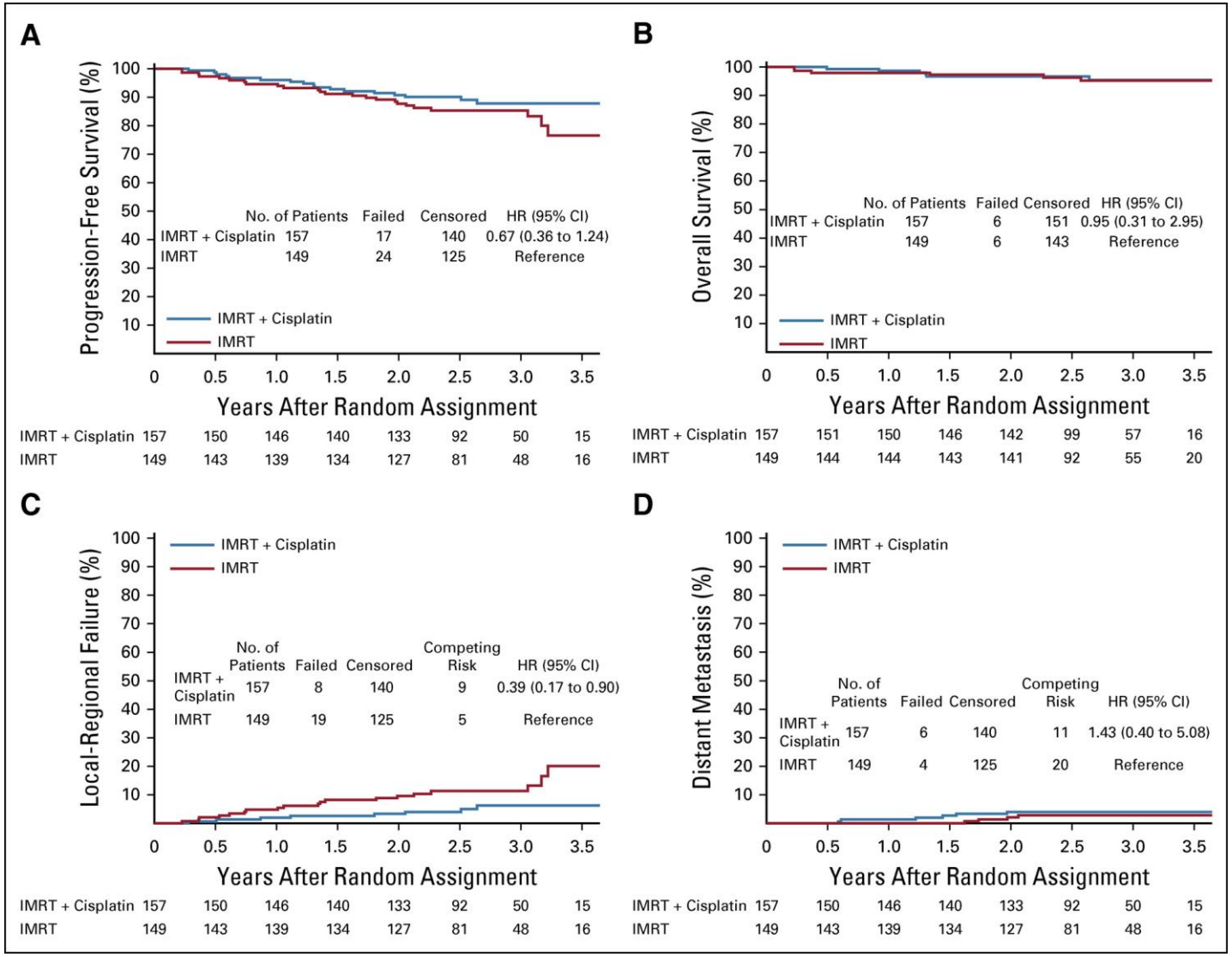
- Randomized, phase II trial, patients with p16-positive, T1-T2 N1-N2b M0, or T3 N0-N2b M0 OPSCC (7th edition staging) with <10 pack-years of smoking received **60 Gy** of intensity-modulated radiation therapy (IMRT) over 6 weeks with concurrent weekly cisplatin or **60 Gy** IMRT over 5 weeks.

- To be considered for a phase III study, an arm had to achieve a 2-year progression-free survival (PFS) rate superior to a historical control rate of 85% and a 1-year mean composite score >60 on the MD Anderson Dysphagia Inventory (MDADI).

NRG Oncology HN002

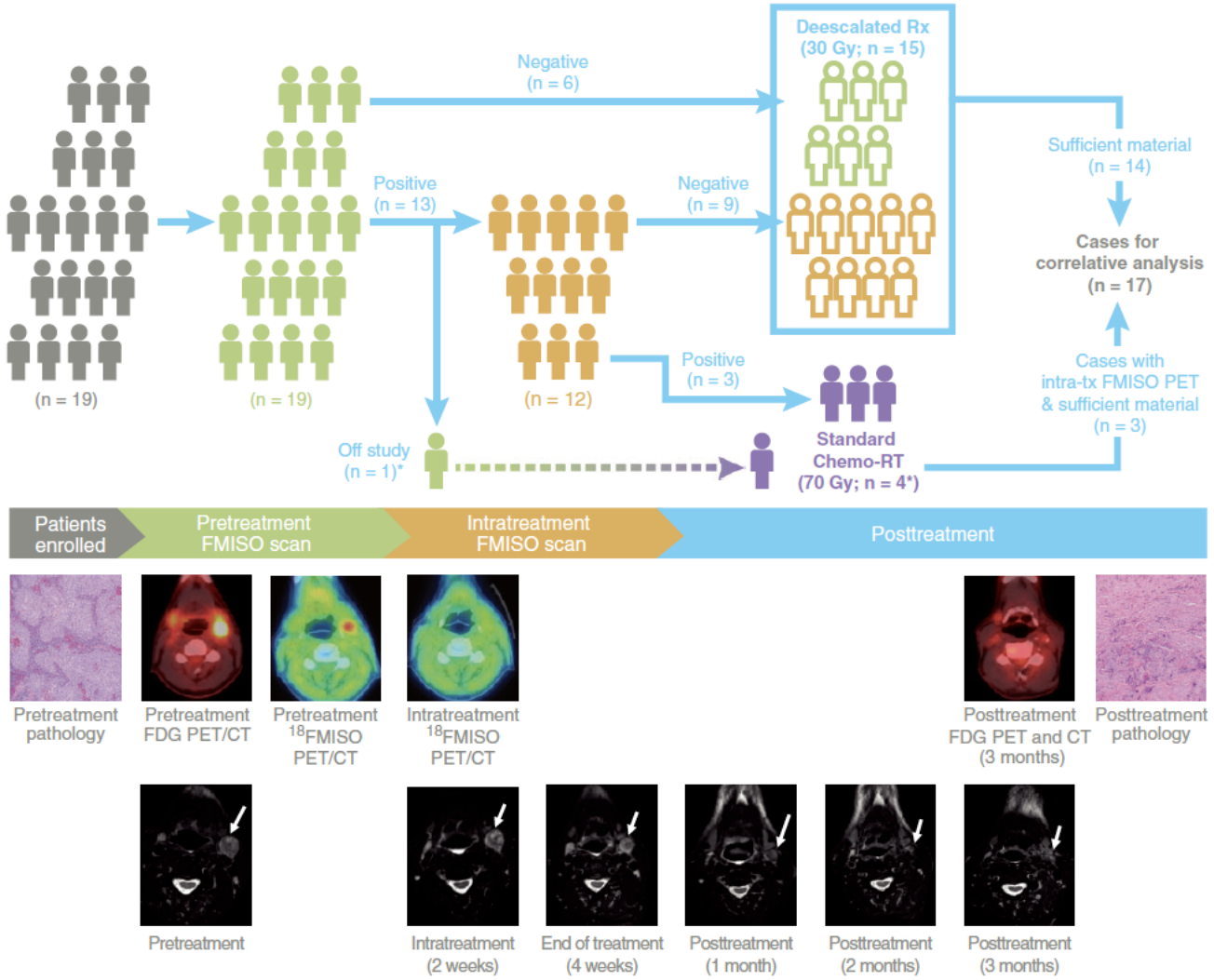
- 306 patients were randomly assigned and eligible.
- Two-year PFS for IMRT + C was 90.5% rejecting the null hypothesis of 2-year PFS < 85% (P = .04).
- For IMRT alone, 2-year PFS was 87.6% (P = .23).
- One-year MDADI mean scores were 85.30 and 81.76 for IMRT + C and IMRT, respectively.

NRG Oncology HN002



30 ROC Trial

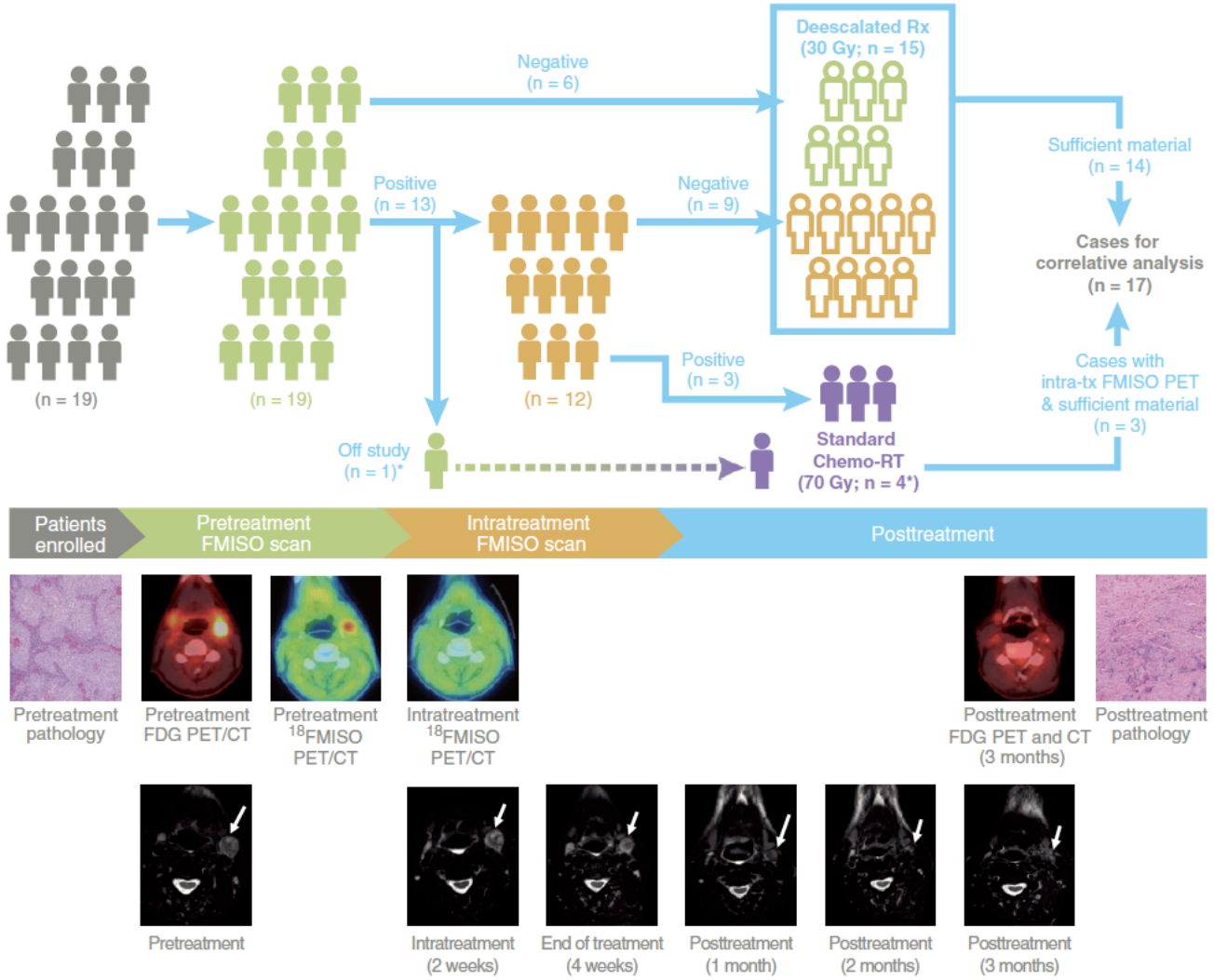
- In 19 patients, pre- and intratreatment dynamic fluorine-18-labeled fluoromisonidazole positron emission tomography (PET) was used to assess tumor hypoxia.
- Patients without hypoxia at baseline or intratreatment received 30 Gy; patients with persistent hypoxia received 70 Gy.
- Neck dissection was performed at 4 months in deescalated patients to assess pathologic response.



J Natl Cancer Inst. 2021 Jan 12;djaa184. doi: 10.1093/jnci/djaa184. Online ahead of print.

30 ROC Trial

- 15 of 19 patients had no hypoxia on baseline PET or resolution on intratreatment PET and were deescalated to 30 Gy.
- Of these 15 patients, 11 had a pathologic complete response.
- Two-year locoregional control and overall survival were 94.4% (95% confidence interval 1⁄4 84.4% to 100%) and 94.7% (95% confidence interval 1⁄4 85.2% to 100%), respectively.
- No acute grade 3 radiation–related toxicities were observed.



J Natl Cancer Inst. 2021 Jan 12;djaa184. doi: 10.1093/jnci/djaa184. Online ahead of print.

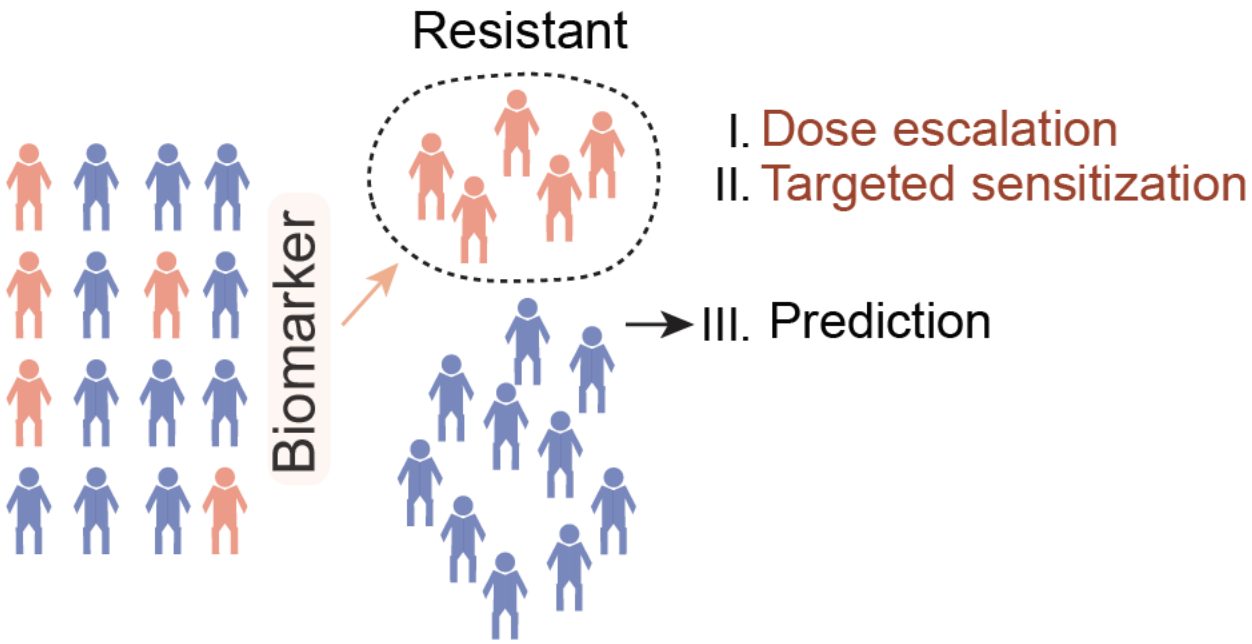
Interim Conclusions

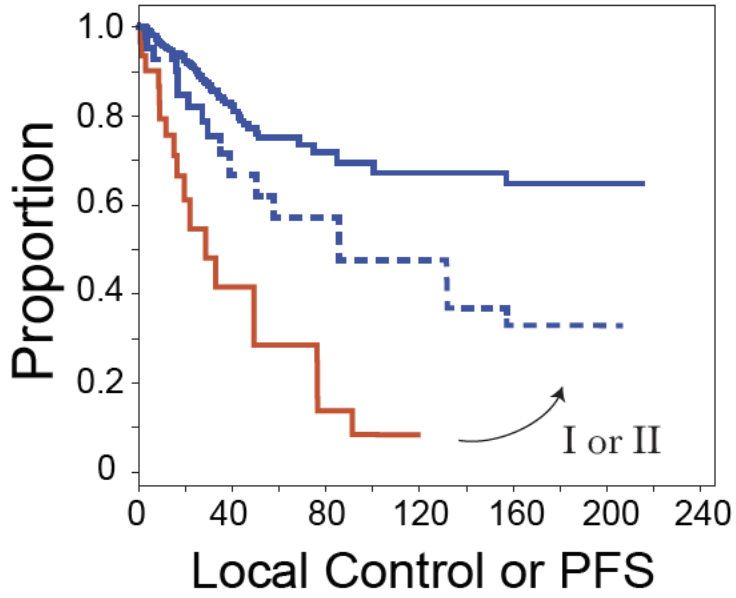
- HPV+ OPSCC are sensitive to radiation and de-escalation studies are warranted/ongoing.

- De-intensification of radiation dose and systemic therapies are likely to result in improved toxicity profiles and improved functional outcomes (e.g. swallowing).

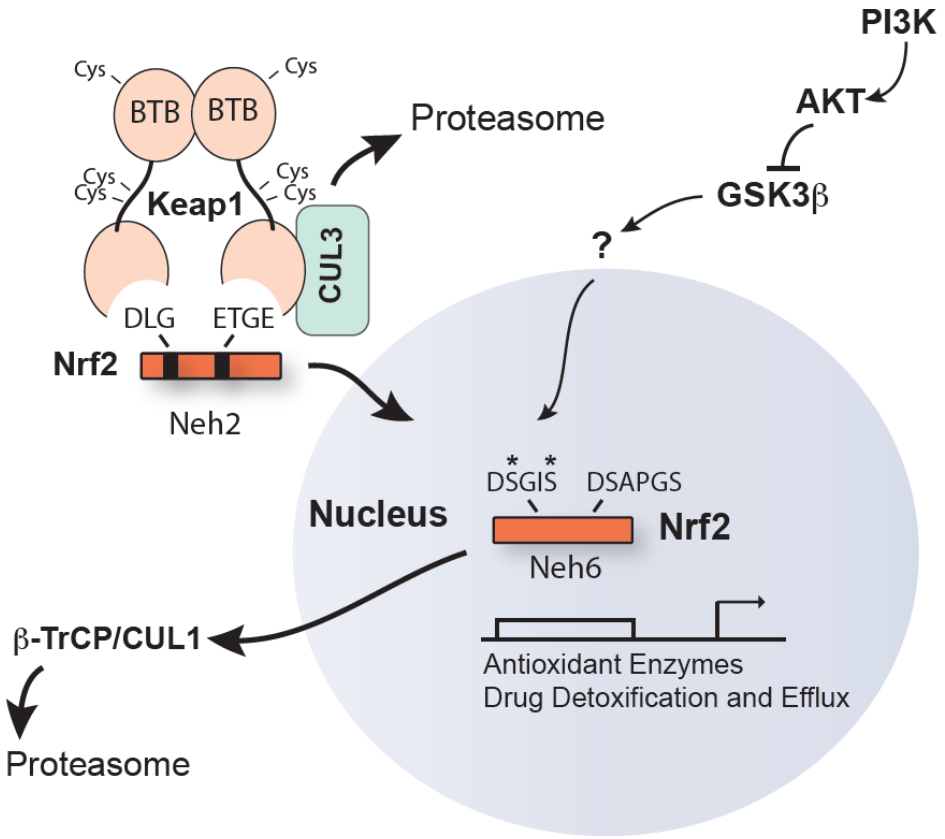
- Biomarkers that can aid in the calibration of radiation dose, thereby significantly altering the clinical paradigm.

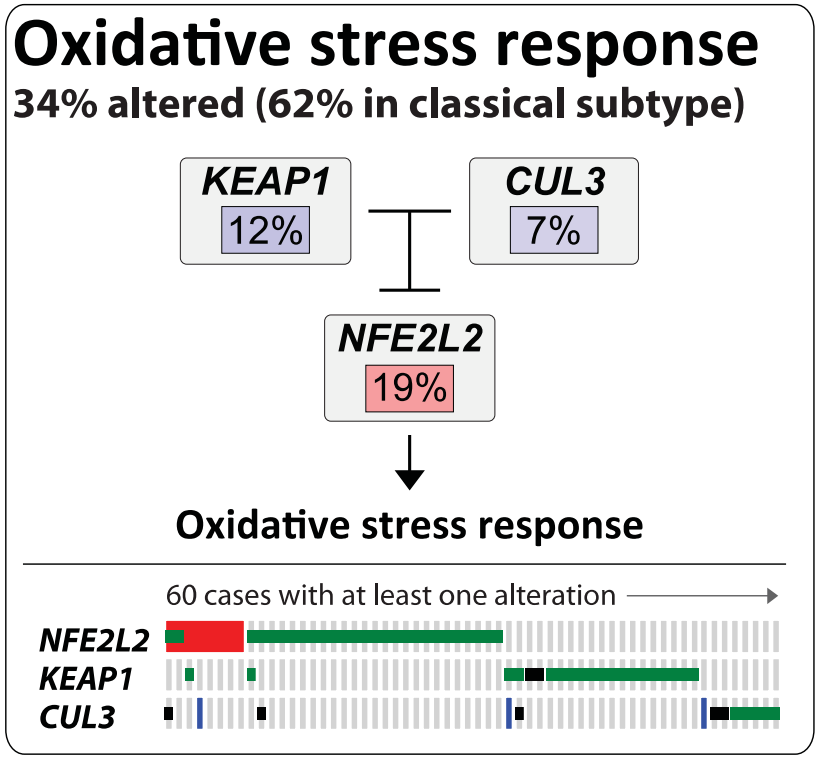
Genetic Mutations that Confer Radiation Resistance





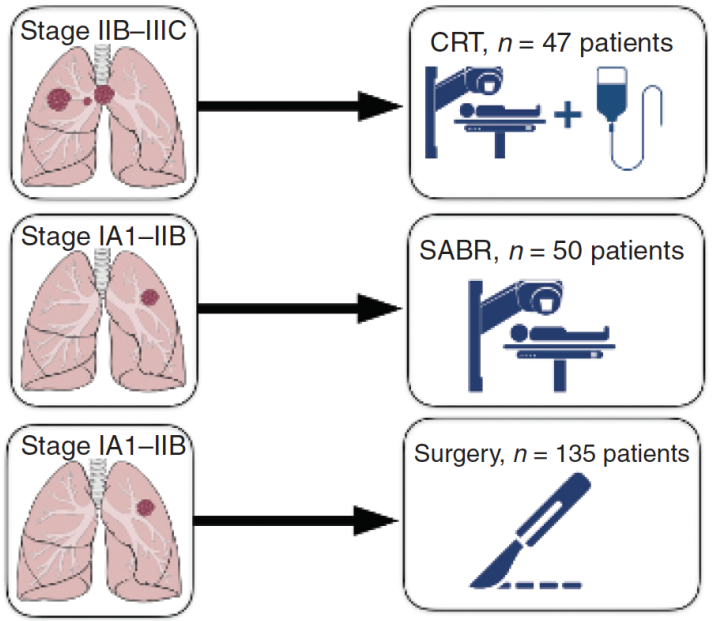
NRF2/KEAP1 Mutants Confer Radiation Resistance

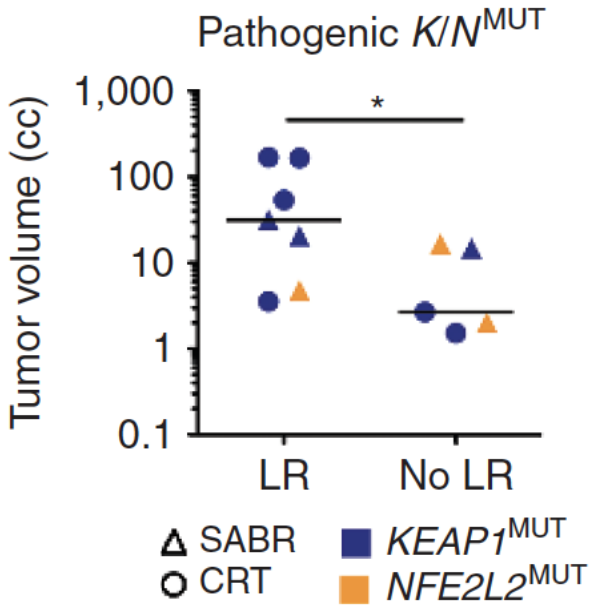


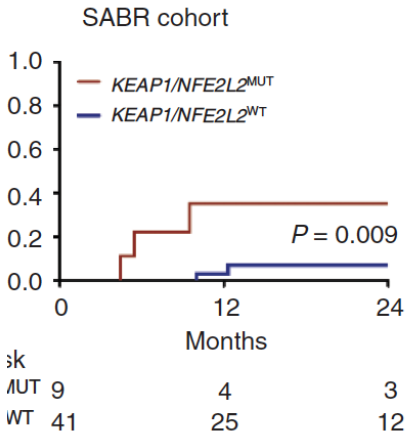


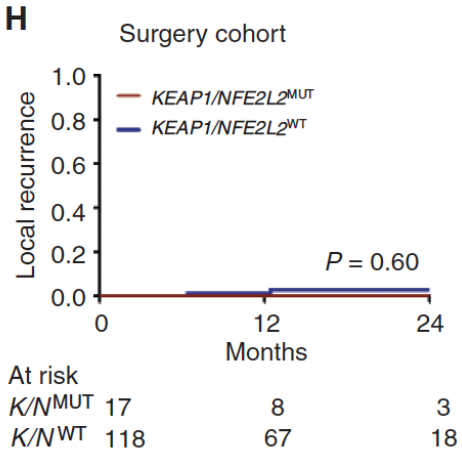
Nature. 2012 Sep 27;489(7417):519-25.

KEAP1 Mutant Tumors and Local Failure after Radiotherapy



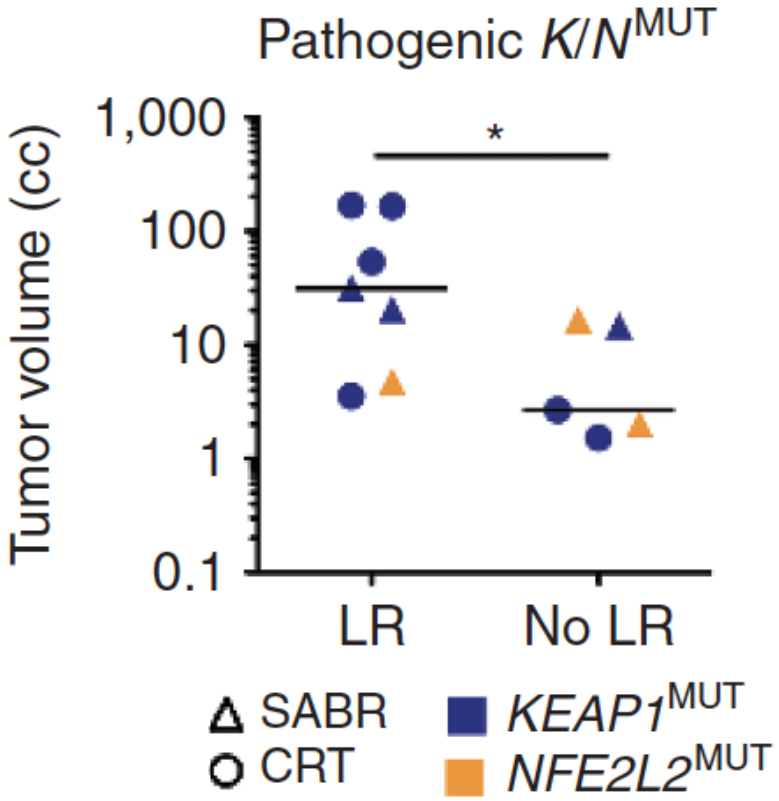






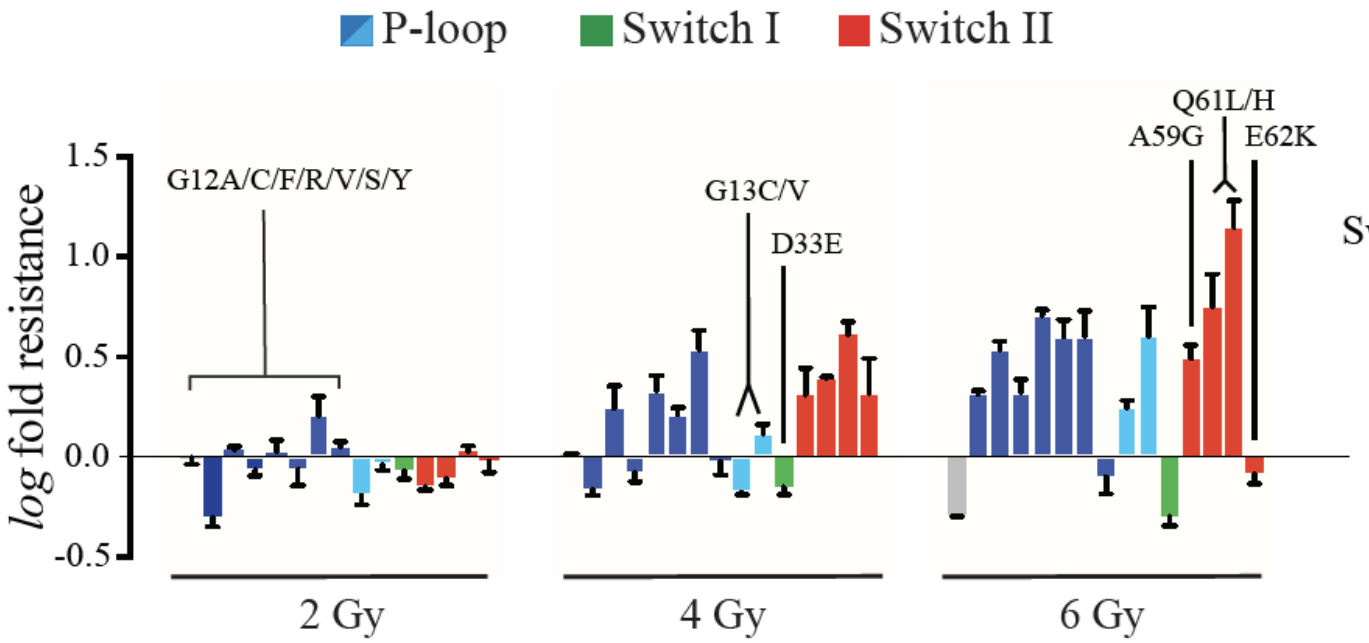
Cancer Discov. 2020 Dec;10(12):1826-1841.

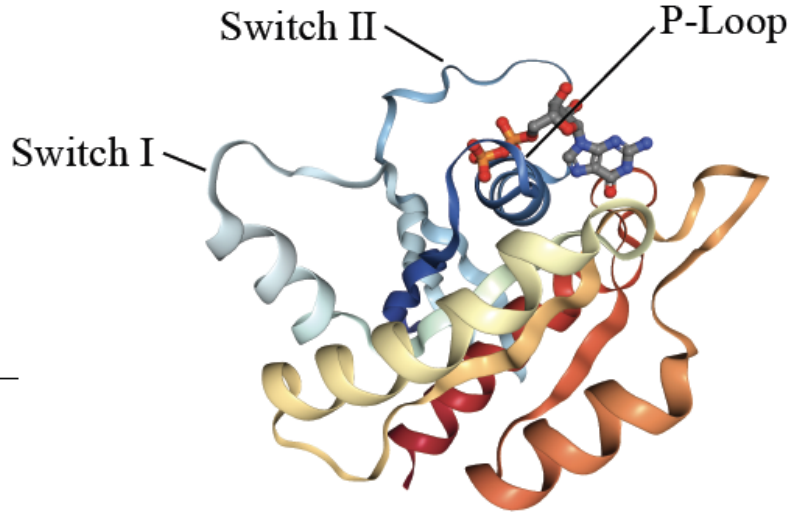
Clinical Variables, Genetic Determinants, and Local Failure after Radiotherapy



Cancer Discov. 2020 Dec;10(12):1826-1841.

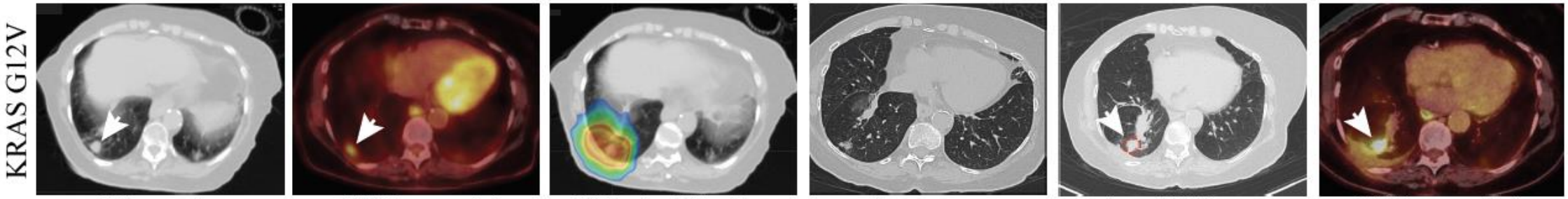
KRAS is a Genetic Determinant of Resistance to Lung SBRT





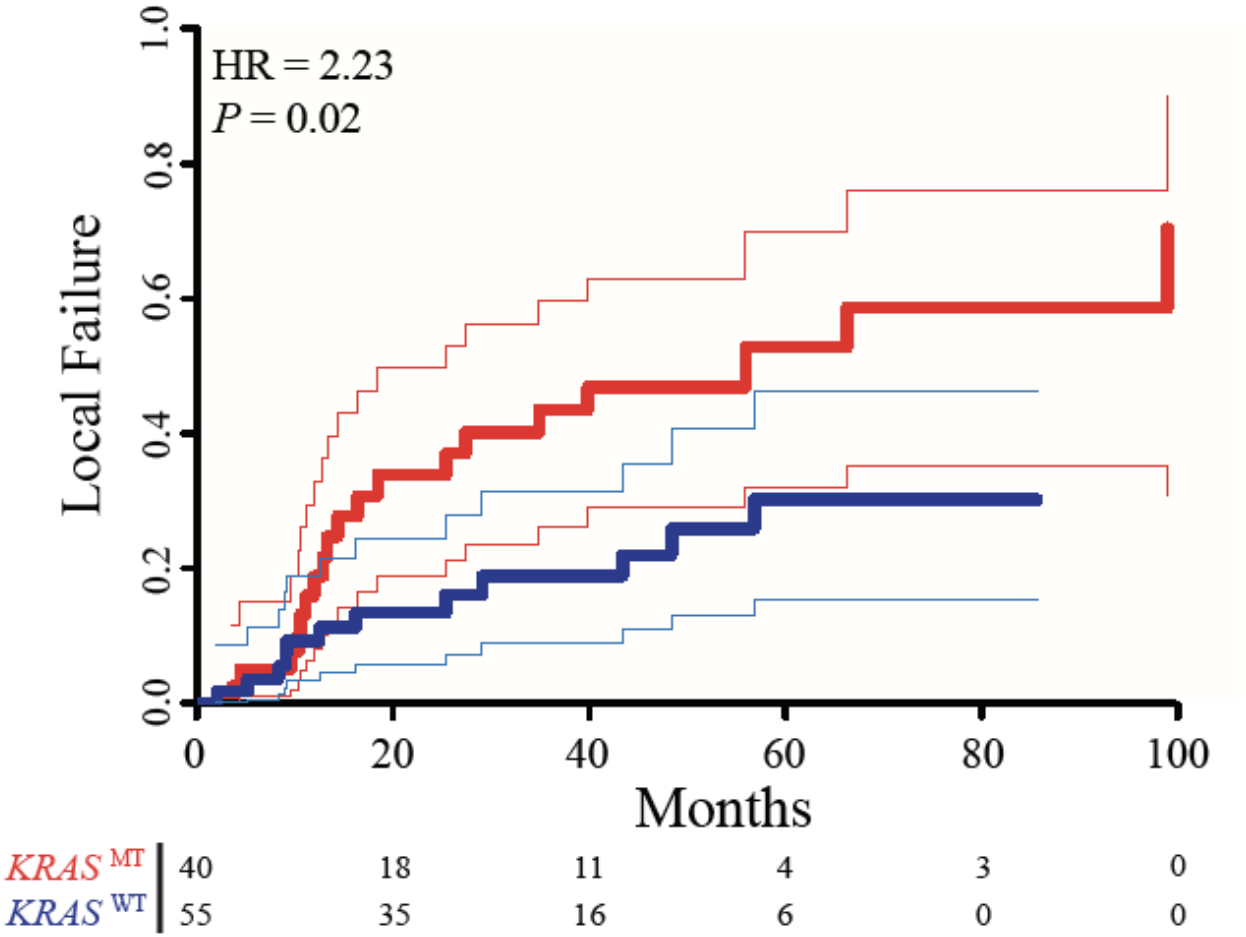
Unpublished.

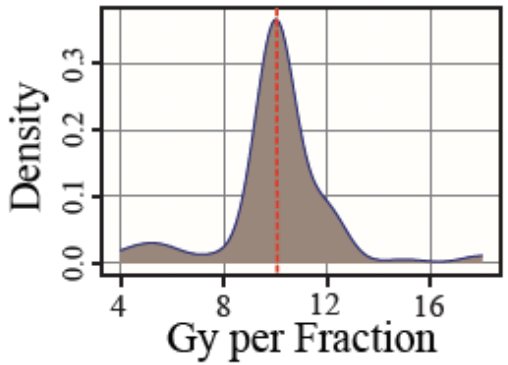
KRAS Mutant Tumors and Local Failure after SBRT

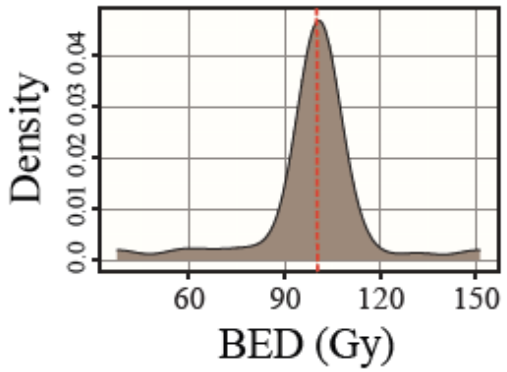


Unpublished.

KRAS Mutant Tumors and Local Failure after SBRT







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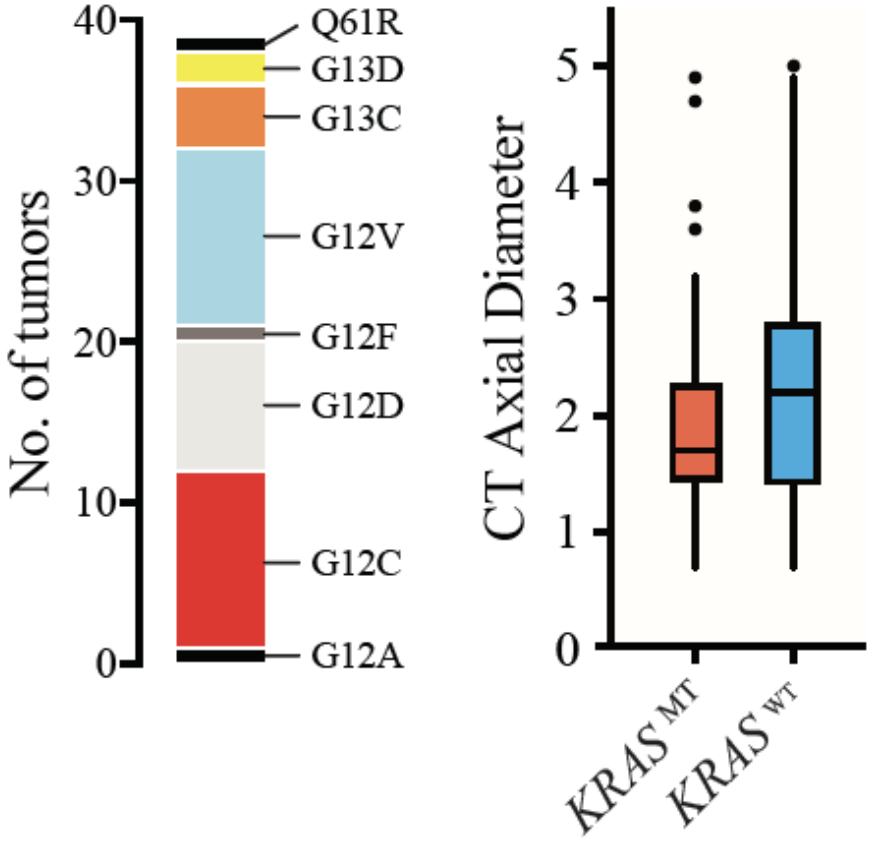
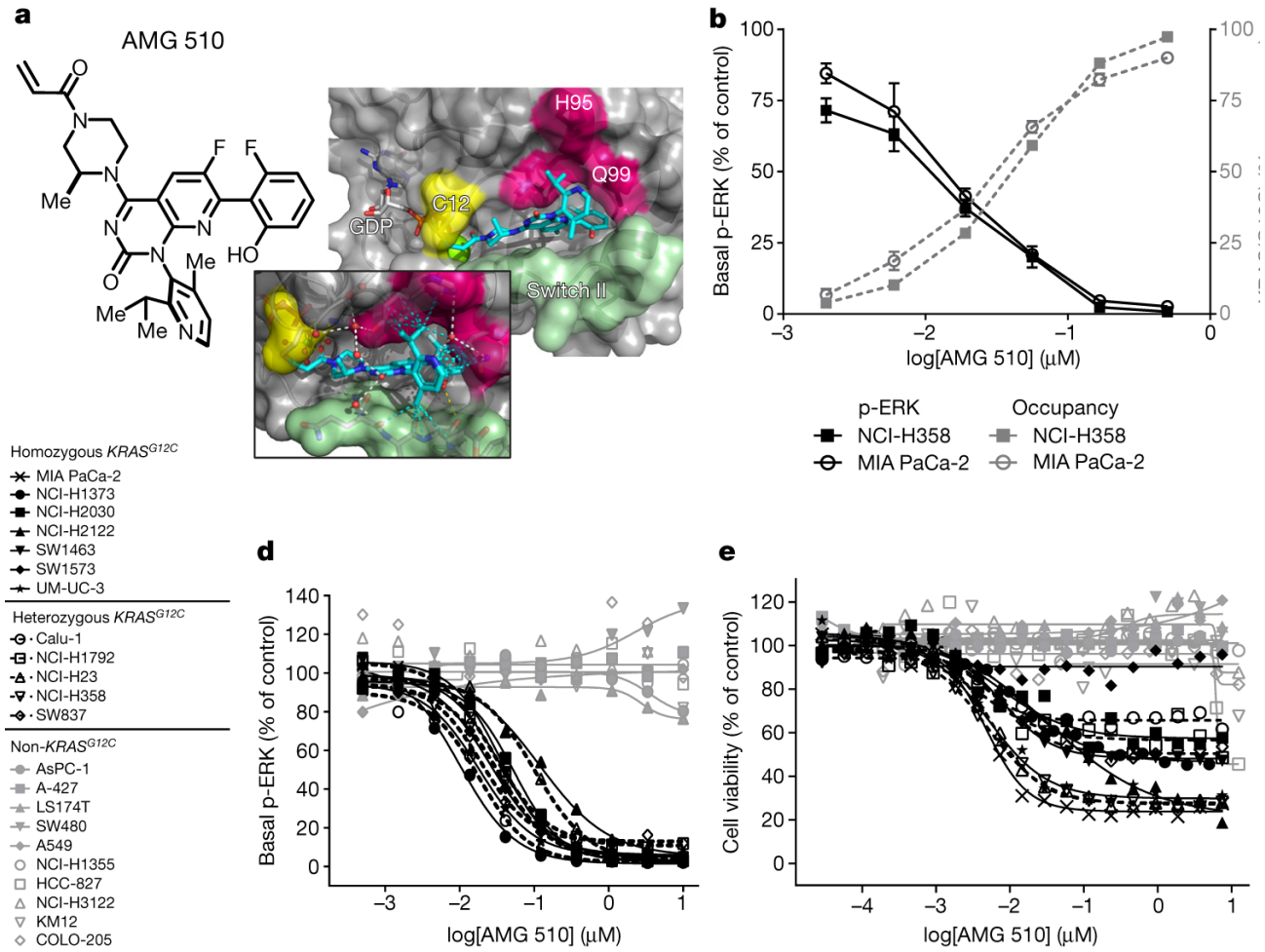
KRAS Mutant Tumors and Local Failure after SBRT



Unpublished.

AMG510 is a Clinical KRAS G12C inhibitor



[*Nature*](#) volume 575, pages217–223(2019)

BEST TUMOR RESPONSE WITH 960 MG DOSE, ALL TUMOR TYPES

Efficacy outcomes	NSCLC, evaluable patients receiving 960mg N = 13	CRC, evaluable patients receiving 960mg N = 12	Other tumor types, evaluable patients receiving 960mg N = 1
Best overall response			
PR – n (%)	7 (54)	1 (8)	0 (0)
SD – n (%)	6 (46)	10 (83)	0 (0)
PD – n (%)	0 (0)	1 (8)	1 (100)[c]
Objective response rate[a]	**54%**	**8%**	**N/A**
Disease control rate[b]	**100%**	**92%**	**N/A**

IASLC, 2021.

Interim Conclusions

- Genetic mutations in the NFE2L2/KEAP1 and KRAS pathways confer resistance to radiation in patients with lung cancer.

- Clinical variables are important to consider when assessing the added benefit of genetic biomarkers.

- The implementation of dose escalation strategies either by selectively increasing radiation dose or the addition of adjuvant systemic therapy post SBRT are areas of active investigation.

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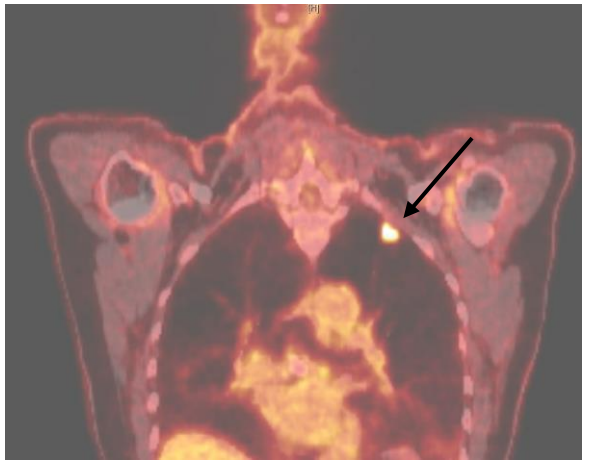
NGS as a Tool for Enhanced Tumor Staging

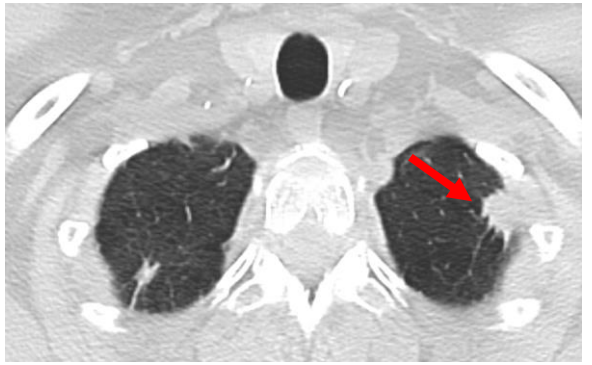
78 yo patient with metachronous and synchronous lung cancers

In 2011, diagnosed with a T1aN0M0 LUAD s/p lingula-sparing lobectomy

In 2019, surveillance imaging showed a spiculated nodule in the LUL. She underwent a LUL segmentectomy.

Pathology showed 2 moderately differentiated LUADs (1.5 & 0.9 cm)





Lung, left lower lob wedge resection (2011):

- Adenocarcinoma
- Molecular studies (PCR): No EGFR mutation; **KRAS G12V mutation**

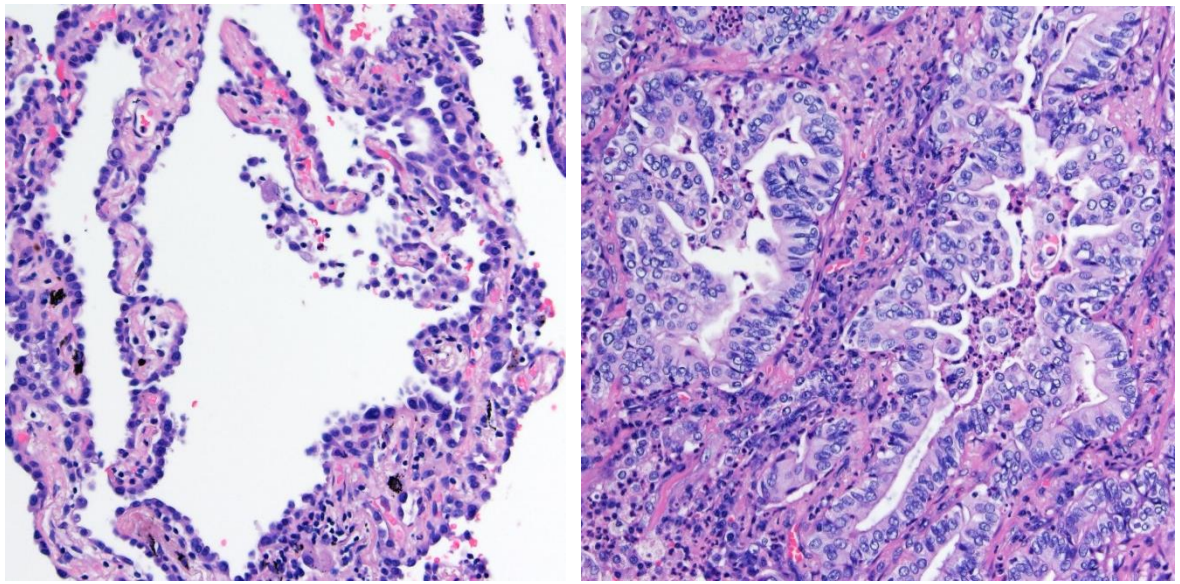
A. Left lung, superior segment, wedge resection (2021):

- Adenocarcinoma moderately differentiated, predominantly acinar with minor lepidic component, measuring 1.5 cm in greatest dimension.

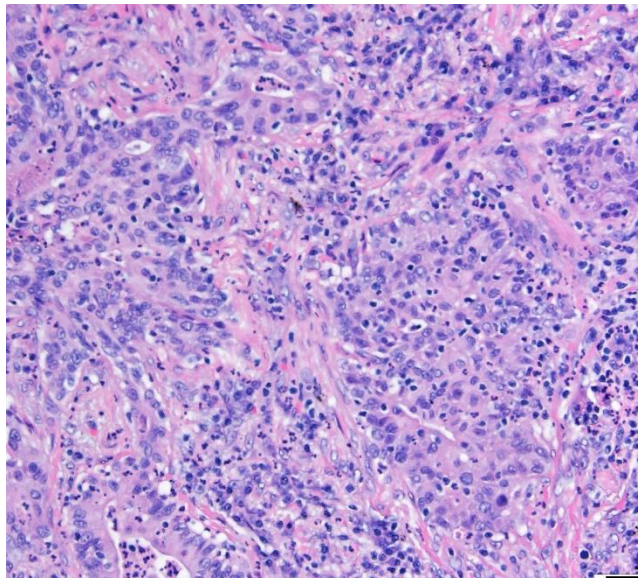
C. Left lung, superior segment mass, biopsy (2021):

- Adenocarcinoma (0.9cm), moderately differentiated

A



C



No two cancers are the same, but some are quite similar, indicating a common ancestor

NGS data strongly suggested that the two lesions shared common truncal mutations

Therefore, they were staged as two nodules of the same cancer in the same lobe T3 v. two separate primaries (T1a and T1b)

A

Variants of possible clinical significance^

Alteration	Variant	Allele Proportion	Drugs Associated with Sensitivity	Drugs Associated with Resistance	Clinical Trials
NF1	NM_001042492.2 c.3315-1G>T	26%	None	None	None
STK11 p.(S283*)	NM_000455.4 c.848_857del	17%	None	None	See Below
ARID1A Loss-of-Function	Deletion	1.06 copies	None	None	None
CDKN2B Loss-of-Function	Deletion	0.52 copies	None	None	None

Variants of unknown clinical significance^

Alteration	Variant	Allele Proportion	Drugs Associated with Sensitivity	Drugs Associated with Resistance	Clinical Trials
MET p.(Q171R)	NM_001127500.1 c.512A>G	7%	None	None	None
NF2 p.(S87*)	NM_000268.3 c.260C>G	9%	None	None	None
NTRK1 p.(A758V)	NM_002529.3 c.2273C>T	13%	None	None	None

C

Variants of known clinical significance^

None

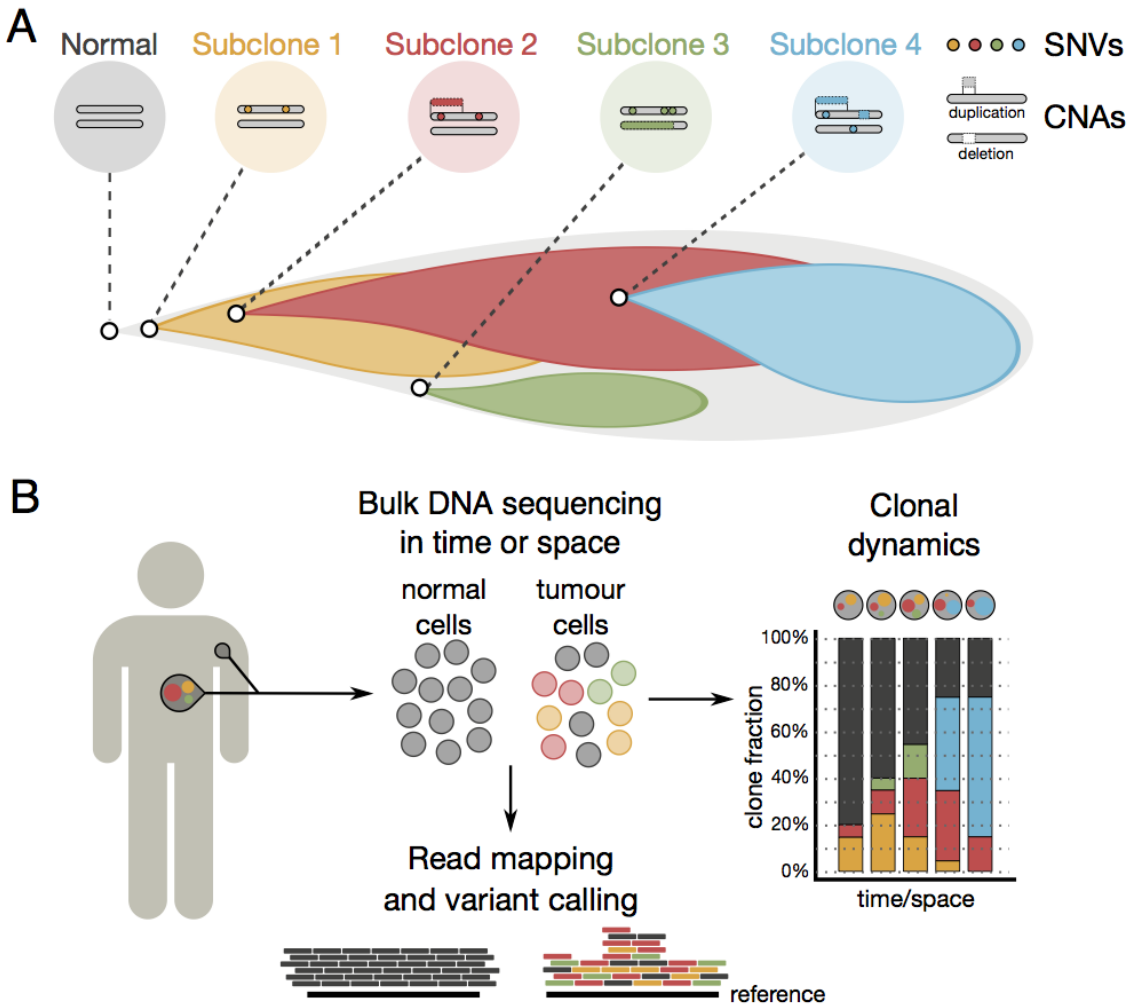
Variants of possible clinical significance^

Alteration	Variant	Allele Proportion	Drugs Associated with Sensitivity	Drugs Associated with Resistance	Clinical Trials
NF1	NM_001042492.2 c.3315-1G>T	10%	None	None	See Below
STK11 p.(S283*)	NM_000455.4 c.848_857del	7%	None	None	See Below

Variants of unknown clinical significance^

Alteration	Variant	Allele Proportion	Drugs Associated with Sensitivity	Drugs Associated with Resistance	Clinical Trials
MET p.(Q171R)	NM_001127500.1 c.512A>G	3%	None	None	None

Clonal Heterogeneity in Cancer and its Implications



Cell Rep. 2014 Jun 12;7(5):1740-1752.

Interim Conclusions

- It is frequently difficult to distinguish synchronous or metachronous primaries v. metastatic disease.

- Assessment of NGS data and clonal or truncal mutations can provide definitive clarification of the phylogenic trees of tumors.

- This enhanced staging information can significantly alter clinical management.

Learning Objectives

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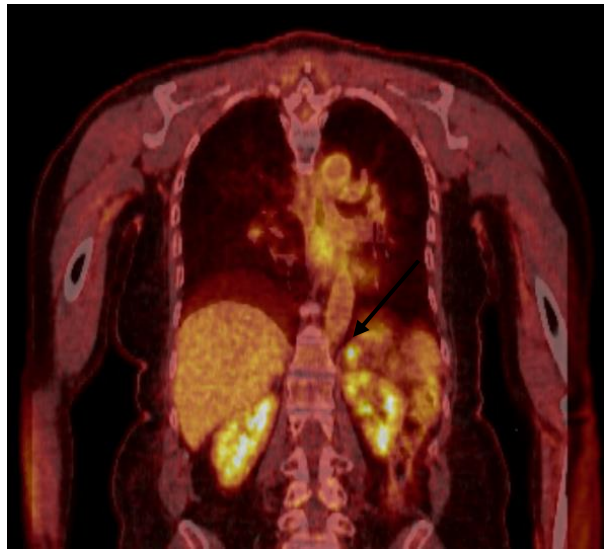
Liquid Biopsy and Systemic Disease Status

- 63 yo diagnosed with locally-advanced adenocarcinoma with an EGFR exon 19 del in 2017
- Received chemoradiation to the chest c/b pneumonitis
- Solitary brain mets in 2018 & 2019 s/p SRS
- Initiated TKI in 2018, transitioned to osimertinib
- Without evidence of disease until 10/2020, p/w L adrenal mass (+PET)



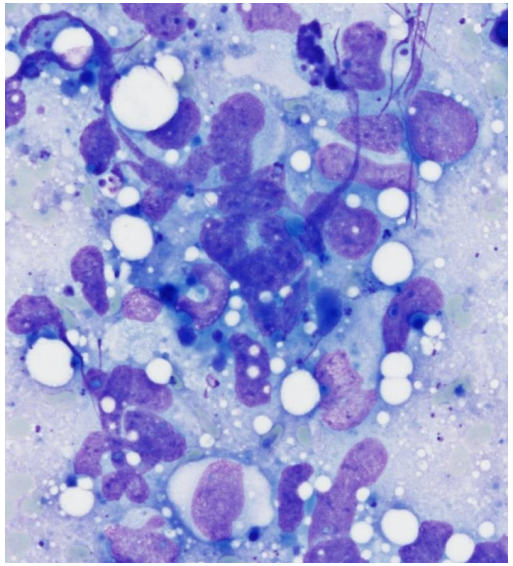
Lung, left lower lobe, bronchial biopsies (2017, outside diagnosis):

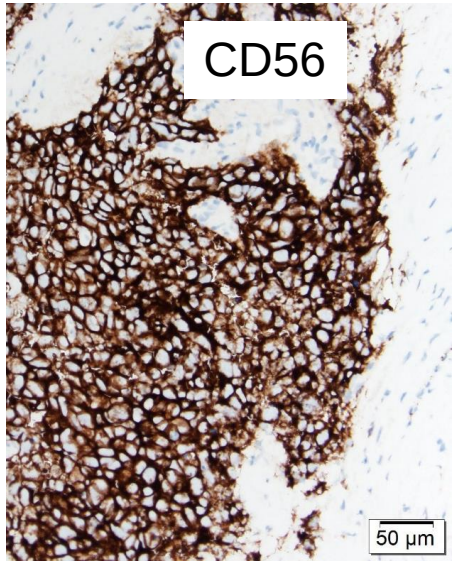
- Adenocarcinoma.
- PDL1: 90% of tumor cells +

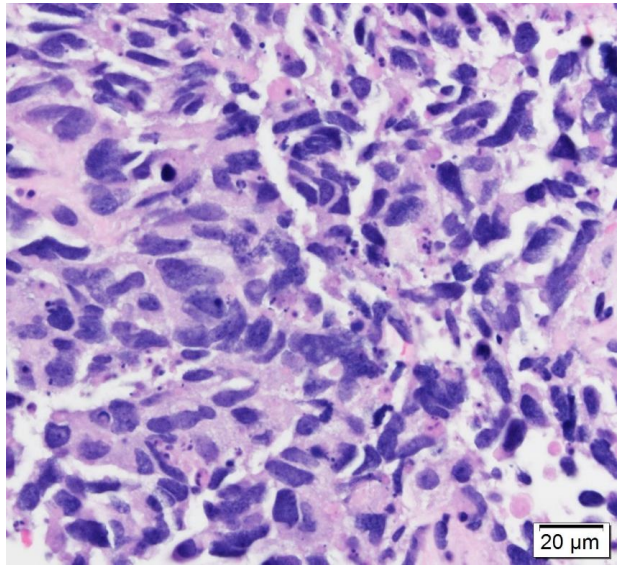
Adrenal biopsy (10/23/2020)

Stain Name	Result
Synaptophysin	Positive
Chromogranin	Negative
CD56	Positive
Ki-67 proliferation index	80-90%
Cam 5.2	Positive
TTF-1	Positive
GATA3	Negative

What is your diagnosis?







Diagnosis

High-grade neuroendocrine carcinoma

Variants of known clinical significance^

Alteration	Variant	Allele Proportion	Drugs Associated with Sensitivity	Drugs Associated with Resistance	Clinical Trials
EGFR p.(E746_A750del)	NM_005228.3 c.2235_2249del	64%	Erlotinib Gefitinib Dacomitinib Afatinib	None	See Below
MET Gain-of-Function	Amplification	20.74 copies	Crizotinib	None	See Below

Variants of possible clinical significance^

Alteration	Variant	Allele Proportion	Drugs Associated with Sensitivity	Drugs Associated with Resistance	Clinical Trials
TP53 p.(L111fs)	NM_000546.5 c.331_332delCT	73%	None	None	None
MSH6 Loss-of-Function	Deletion	1.09 copies	None	None	See Below
PTEN Loss-of-Function	Deletion	1.15 copies	None	None	See Below

Variants of unknown clinical significance^

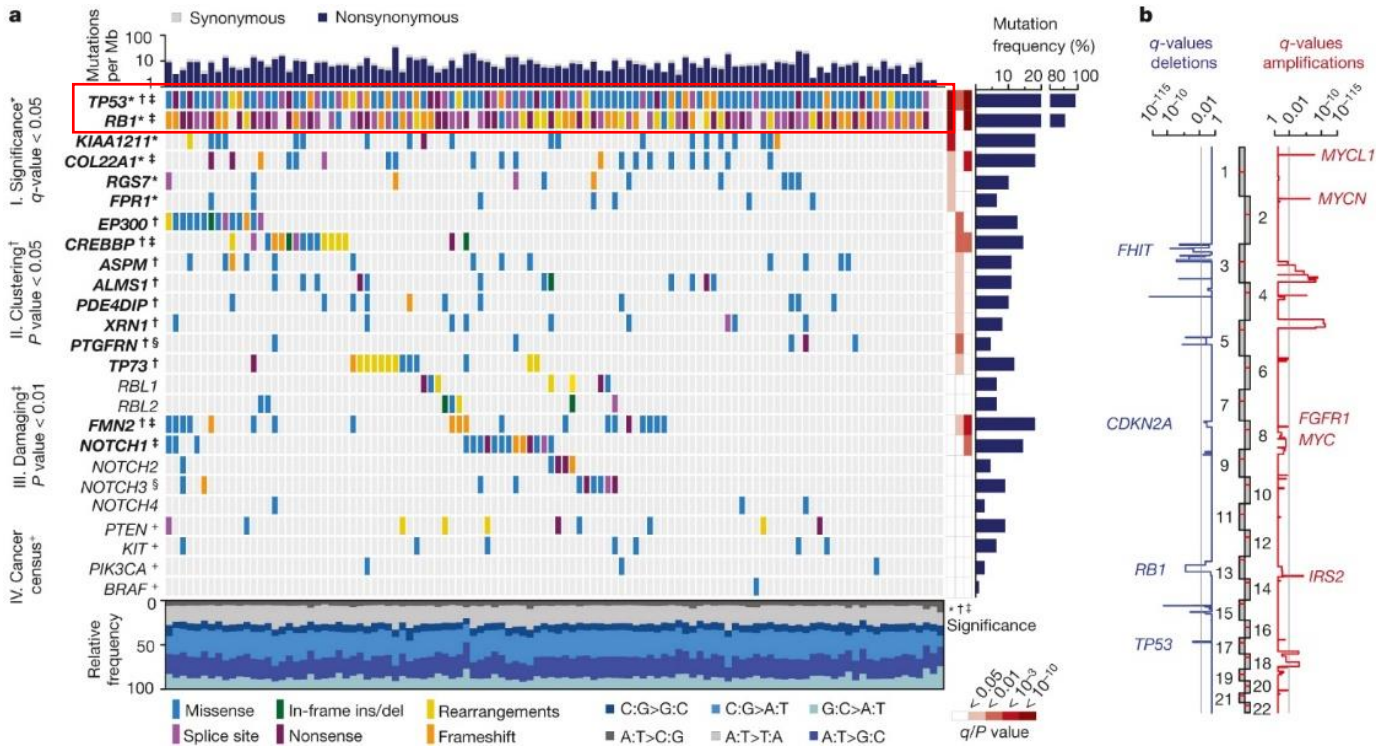
Alteration	Variant	Allele Proportion	Drugs Associated with Sensitivity	Drugs Associated with Resistance	Clinical Trials
CDKN1B Loss-of-Function	Deletion	0.83 copies	None	None	None

Reflection Question

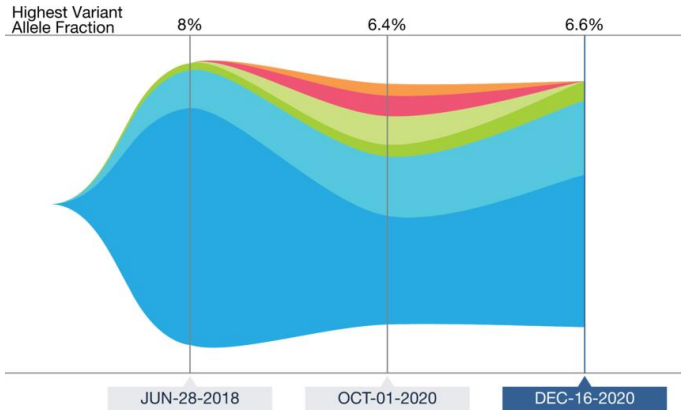
- Which two genes are frequently mutated in small cell carcinoma?

RB1* and *TP53

In nearly all 110 small cell lung cancers (SCLC) analyzed, authors found bi-allelic inactivation of *TP53* and *RB1,* sometimes by complex genomic rearrangements.



ctDNA

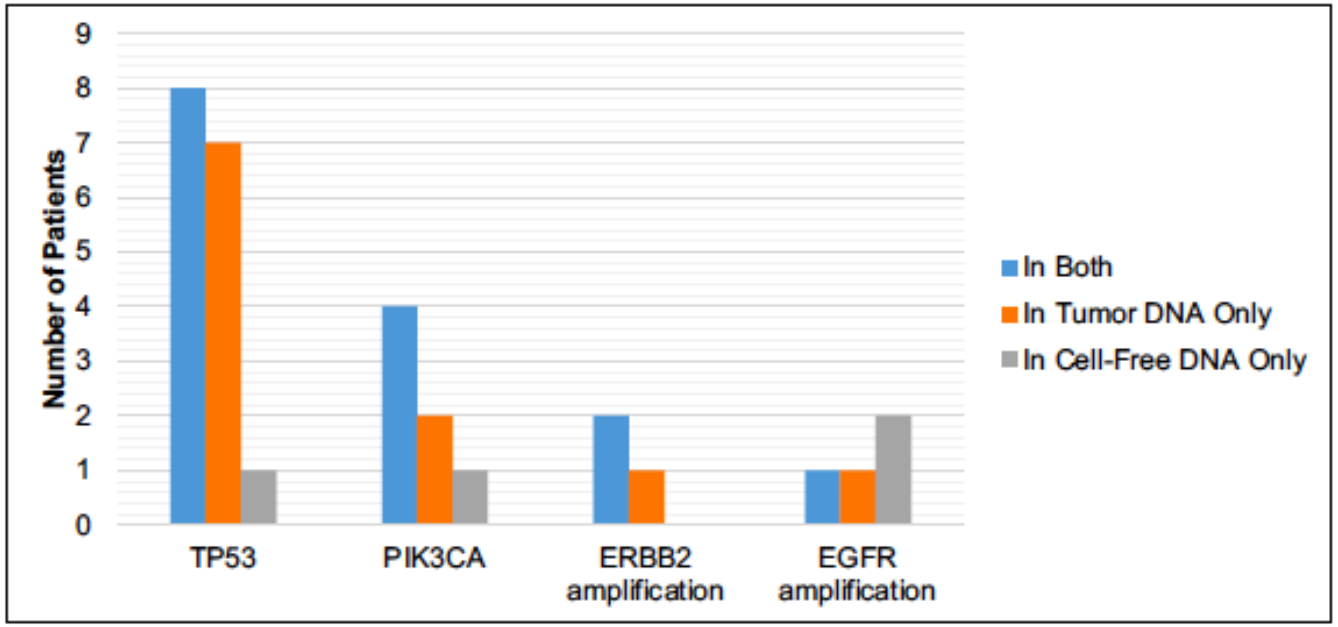


Detected Alteration(s) / Biomarker(s)	% cfDNA or Amp	Alteration Trend
GNAS R201H	6.6%	8% 6.4% 6.6%
MPL W515L	2.7%	0.8% 3% 2.7%
TP53 I254N	0.5%	0.1% 0.4% 0.5%
MET Amplification	ND	ND 2.2 ND
EGFR E746_A750del	ND	ND 1.2% ND
TP53 L111fs	ND	ND 0.8% ND
RB1 R787fs	ND	ND 0.4% ND

RB1 and TP53 mutations in neuroendocrine tumors of lung

ctDNA vs. Tissue NGS Discrepancy

- Concordance: >90%
- Discordance may be due to:
  - The intra-tumor heterogeneity
  - Changes in the tumor genomic profile during disease progression/ metastasis
  - Different neoplasms (?)
    - CHIP mutations (e.g. TET2, DNMT3A)
    - Hematopoietic neoplasm
    - Rarely different primary solid tumor

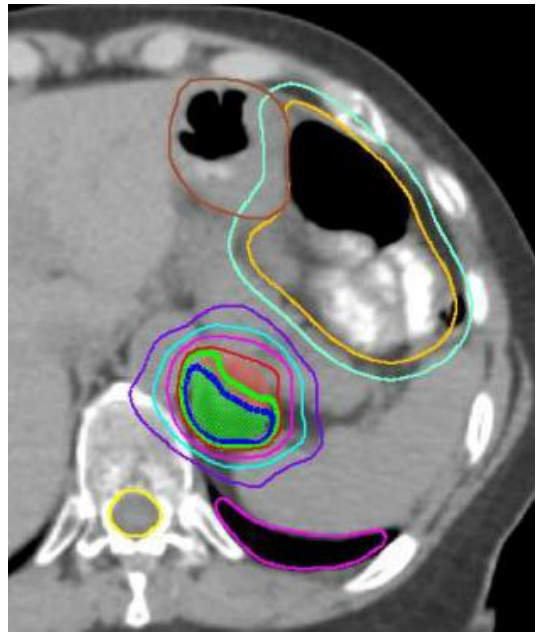


Y. K. Chae, et al. Mol Cancer Ther. 2017(7):1412–1420.
D. Liang et al. Breast Cancer Res Treat. 2016(155):139–149.

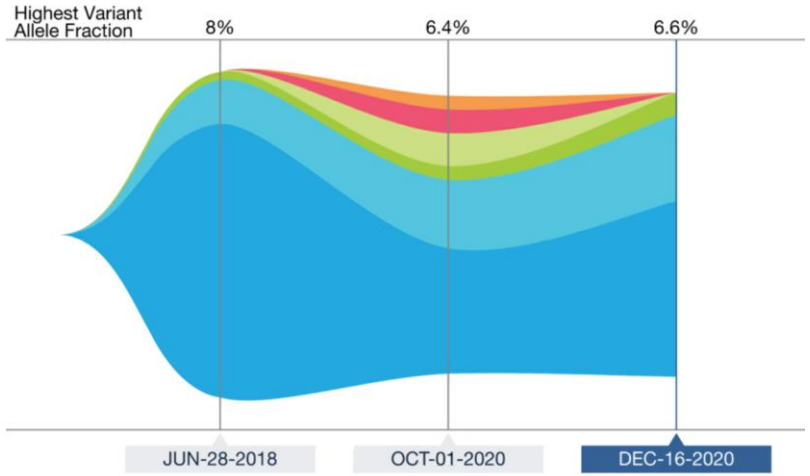
Additional Molecular Studies

Completed SBRT to the L adrenal lesion on 12/1/2020

Guardant360 pre and post therapy…

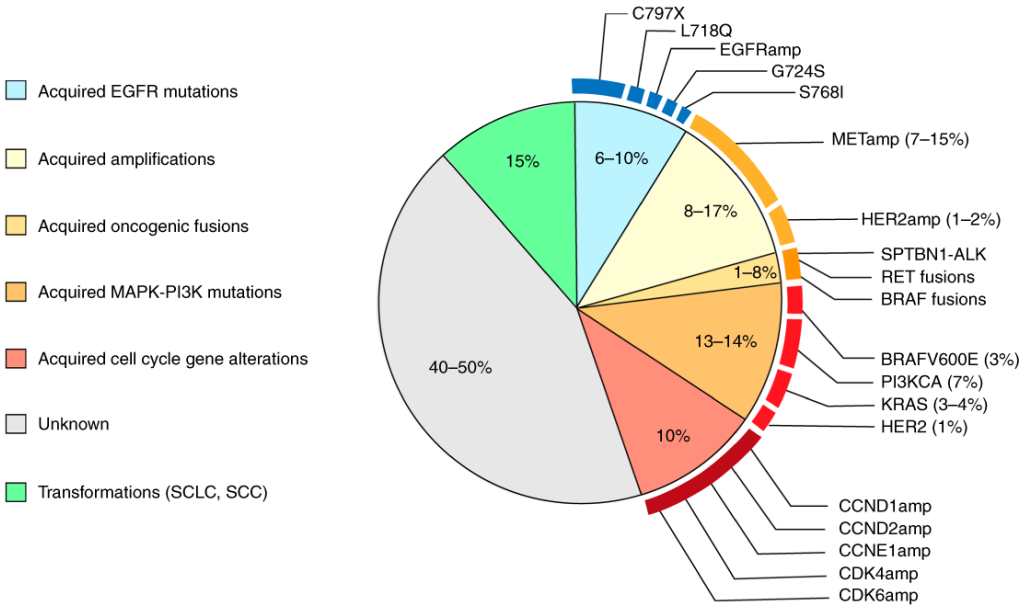


GNAS R201H	6.4%	8% → 6.4%
MPL W515L	3.0%	0.8% → 3%
EGFR E746_A750del	1.2%	ND → 1.2%
TP53 L111fs	0.8%	ND → 0.8%
TP53 I254N	0.4%	0.1% → 0.4%
RB1 R787fs	0.4%	ND → 0.4%

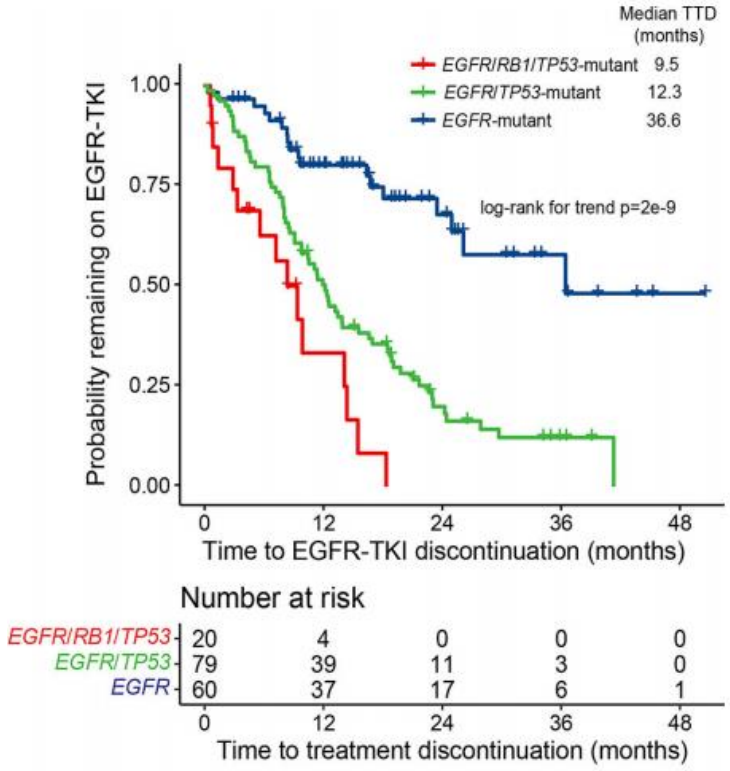


RB1 Loss and Small Cell Transformation

RB1 loss predisposes to small cell transformation and poorer outcomes



British Journal of Cancer volume 121, pages725–737(2019)



J Thorac Oncol. 2019 Oct;14(10):1784-1793. doi: 10.1016/j.jtho.2019.06.002.

Interim Conclusions

- There is high concordance (>90%) between liquid and tissue biopsy NGS.

- Liquid biopsy can be a good surrogate marker of systemic disease burden.

- Liquid biopsy can help identify disease transformation (*e.g.* lung adenocarcinoma to neuroendocrine differentiation), thereby guiding systemic treatment strategies.

Overall Conclusions

1. Cancer is genetically heterogeneous.
2. Cancers respond to radiotherapy in a manner reflected by genetic subtypes.
3. Several genetic biomarkers are being tested for treatment de-escalation (e.g. HPV+ OPSCC) or escalation of radiation dose or the addition of systemic adjuvant treatments (e.g. *KRAS* mutant tumors).
4. NGS is frequently used for stratifying patients for systemic and, increasingly, radiotherapy treatments.
5. NGS can be used as a tool for enhanced tumor staging (metastases v. new primaries).
6. New clinical radiotherapy biomarkers are actively being translated into clinical practice.