Precision cancer medicine

Balazs Halmos MD

Precision medicine- what is in it for the surgeon?

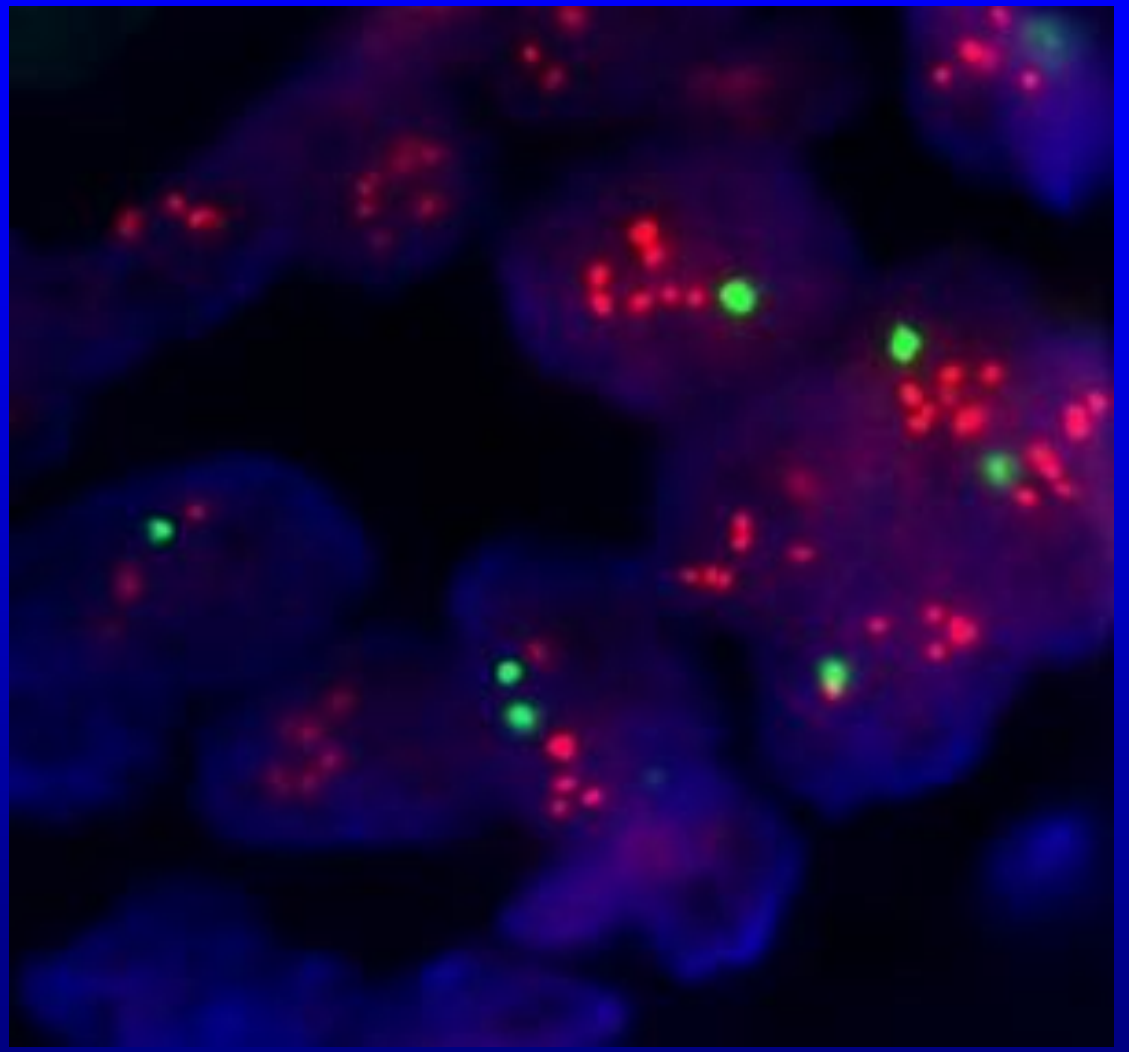
- Biomarkers to test to catch cancer earlier so surgery could be performed
- Biomarkers to test in a cancer patient to define if surgery is meaningful
- Biomarkers to test in a cancer patient to see what treatment they should receive pre-op to increase chance of cure
- Biomarkers to test post-op to define who might not need further therapy
- Biomarkers to test post-op to define what further therapy a patient might need and at what intensity

Breast cancer

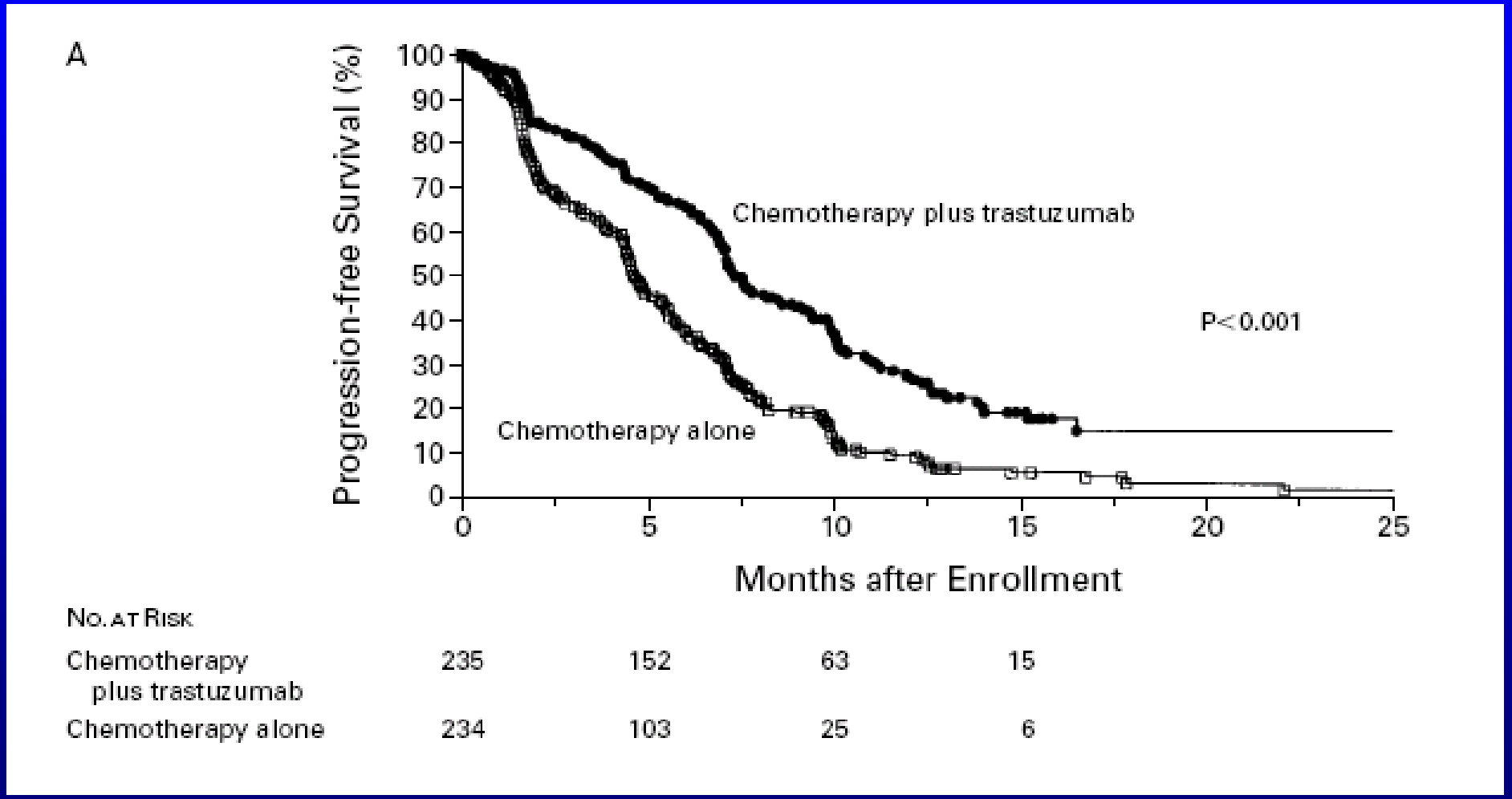
- Most commonly diagnosed cancer in women, 210,000 cases, 40,000 deaths per year in US
- Role of surgery, radiation and chemotherapy unlikely to radically improve
- 15-30% of breast cancer produce a cell surface molecule HER2 (ERBB2) in excess typically secondary to an increase in the number of HER2 gene copies
- The HER2 protein itself plays a critical role in the malignant behavior of these cells
- Such cancers have a worse prognosis and more aggressive behavior than other breast cancers

ErbB2 targeting

- Trastuzumab- molecularly tailored antibody that binds to and thereby blocks the function of HER2
- In early studies it was shown to be overall quite safe with limited activity alone in HER2+ breast cancers
- More significantly it was shown to enhance the activity of chemotherapy when given alongside and thereby led to modest improvements in survival of patients with metastatic breast cancer



Herceptin treatment has modest activity in advanced breast cancer



Herceptin treatment dramatically improves outcomes of patients with ErbB2-positive breast cancer

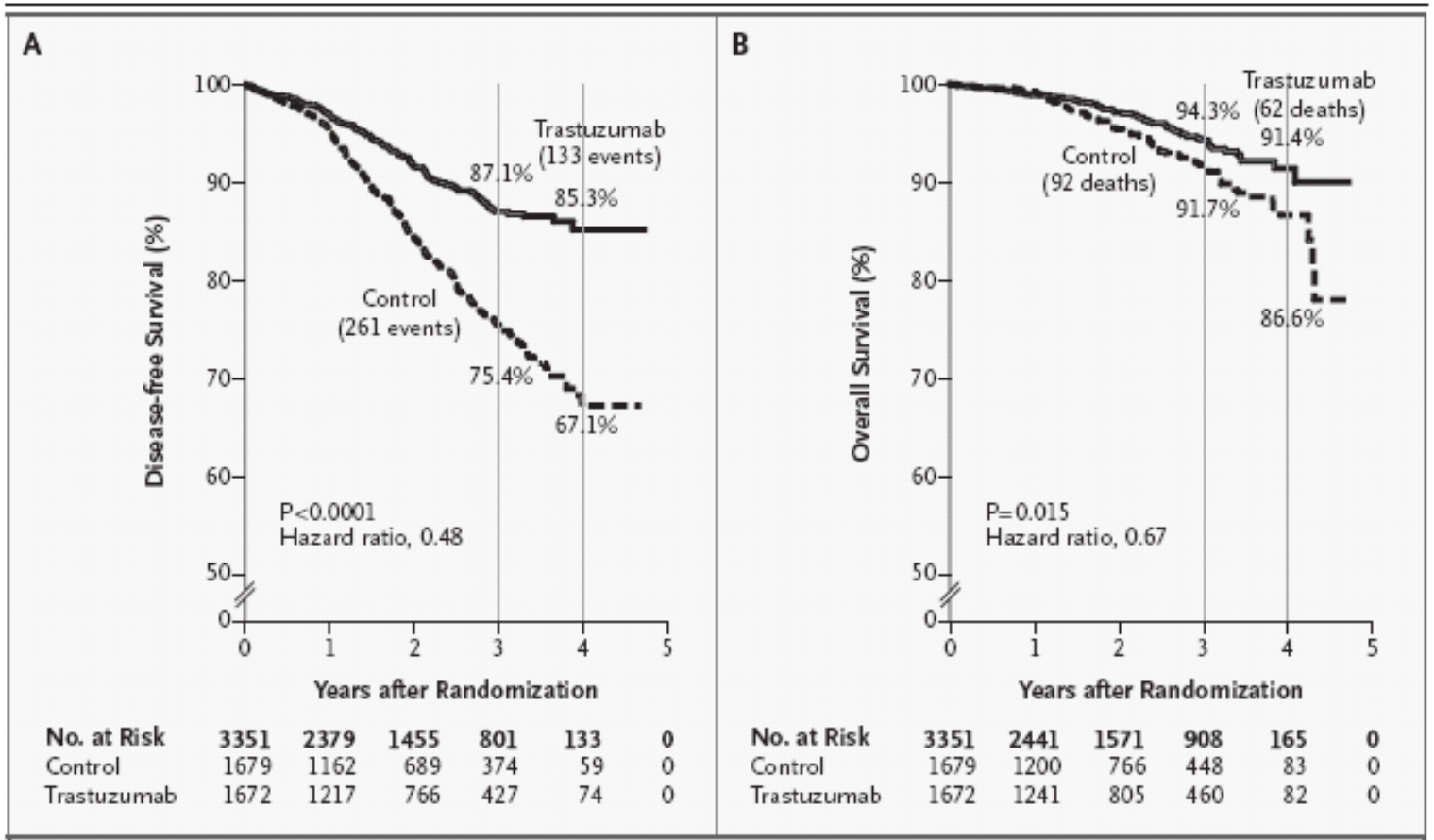


Figure 2. Kaplan–Meier Estimates of Disease-free Survival (Panel A) and Overall Survival (Panel B).
The hazard ratios are for the comparison of the trastuzumab group with the control group.

- Staggering improvements in outcomes (50% reduction in risk of recurrence) in early stage disease leading to many thousands of lives saved per year!!!!

Neosphere study- pathology can guide drug development

Study Eligibility and Objectives

- Eligibility:
  - Operable or locally advanced/inflammatory breast cancer
  - Centrally confirmed HER2-positive (IHC 3+ or FISH positive)
  - Chemotherapy naïve
  - Primary breast tumor >2 cm
  - No metastasis
- Objectives:
  - Primary: pathological CR (pCR) rates
  - Secondary: clinical response, disease-free survival, breast conservation rate, biomarker evaluation

	TH (n = 107)	THP (n = 107)	HP (n = 107)	TP (n = 96)
pCR in breast	29.0%	45.8%	16.8%	24.0%
pCR in breast and node negative at surgery	21.5%	39.3%	11.2%	17.7%
pCR in breast and node positive at surgery	7.5%	6.5%	5.6%	6.3%

The differences between the THP arm and other arms for pCR were statistically significant, with all the *p*-values being <0.05.

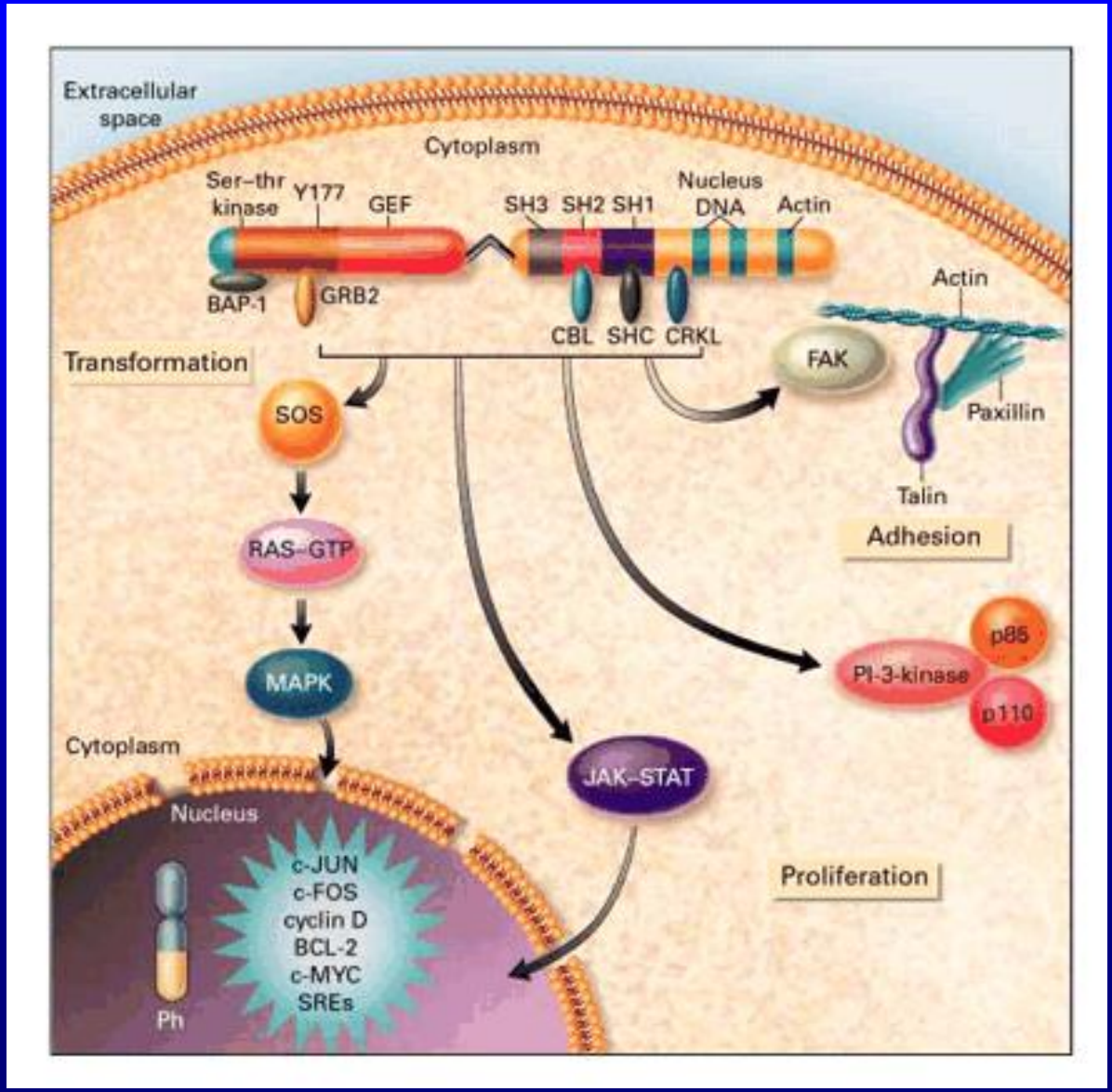
Targeted therapy

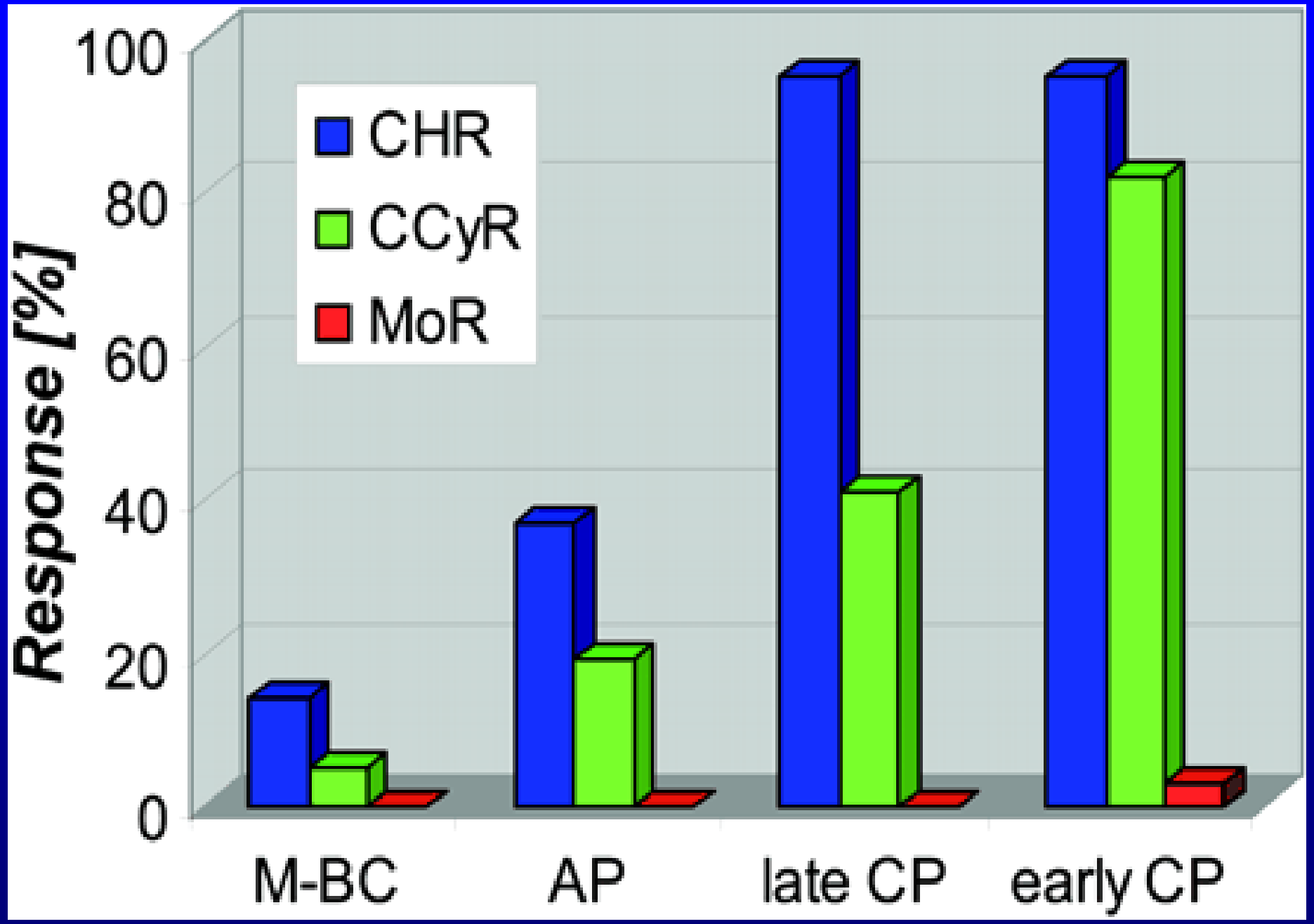
- Definition
  - Drug targets a well-defined molecular pathway
  - Preferably this pathway should be specific to tumor versus normal tissue
  - The activity of the pathway should be critical for the tumor
  - There should be a pharmacological way of inhibiting the target- “druggability”
  - If chosen well, targeted treatments should have low toxicity

Have we been using targeted treatments all along?

- About half of all breast cancers produce hormone receptors for estrogen and/or progesterone hormones
- These tumors are dependent on the activity of these receptors
- Hormone therapy with tamoxifen and other hormones has been the cornerstone of the treatment of such cancers with great success, especially in early-stage cancers- with minimal side effects

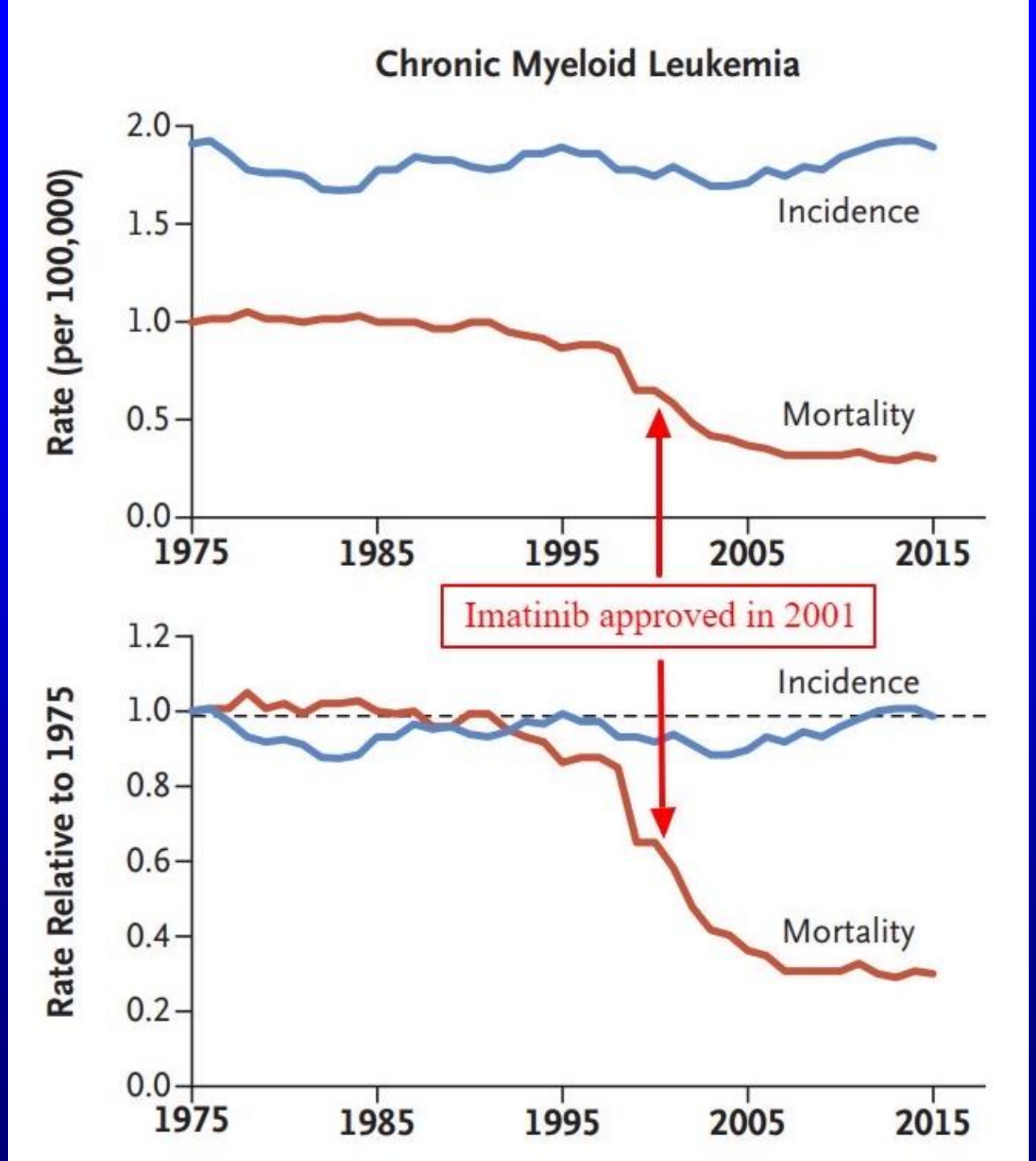
Chronic myeloid leukemia- case example




Response [%]
100
80
60
40
20
0
CHR
CCyR
MoR
M-BC
AP
late CP
early CP

Targeted therapy

- Definition
  - Drug targets a well-defined molecular pathway
    - Close to 100% has BCR-ABL ✓
  - Preferably this pathway should be specific to tumor versus normal tissue
    - Normal cells do not have this fusion product ✓
  - The activity of the pathway should be critical for the tumor
    - Cells depend on its activity ✓
  - There should be a pharmacological way of inhibiting the target- “druggability”
    - Kinase function can be blocked ✓
  - If chosen well, targeted treatments should have low toxicity
    - Indeed, imatinib is fairly non-toxic ✓

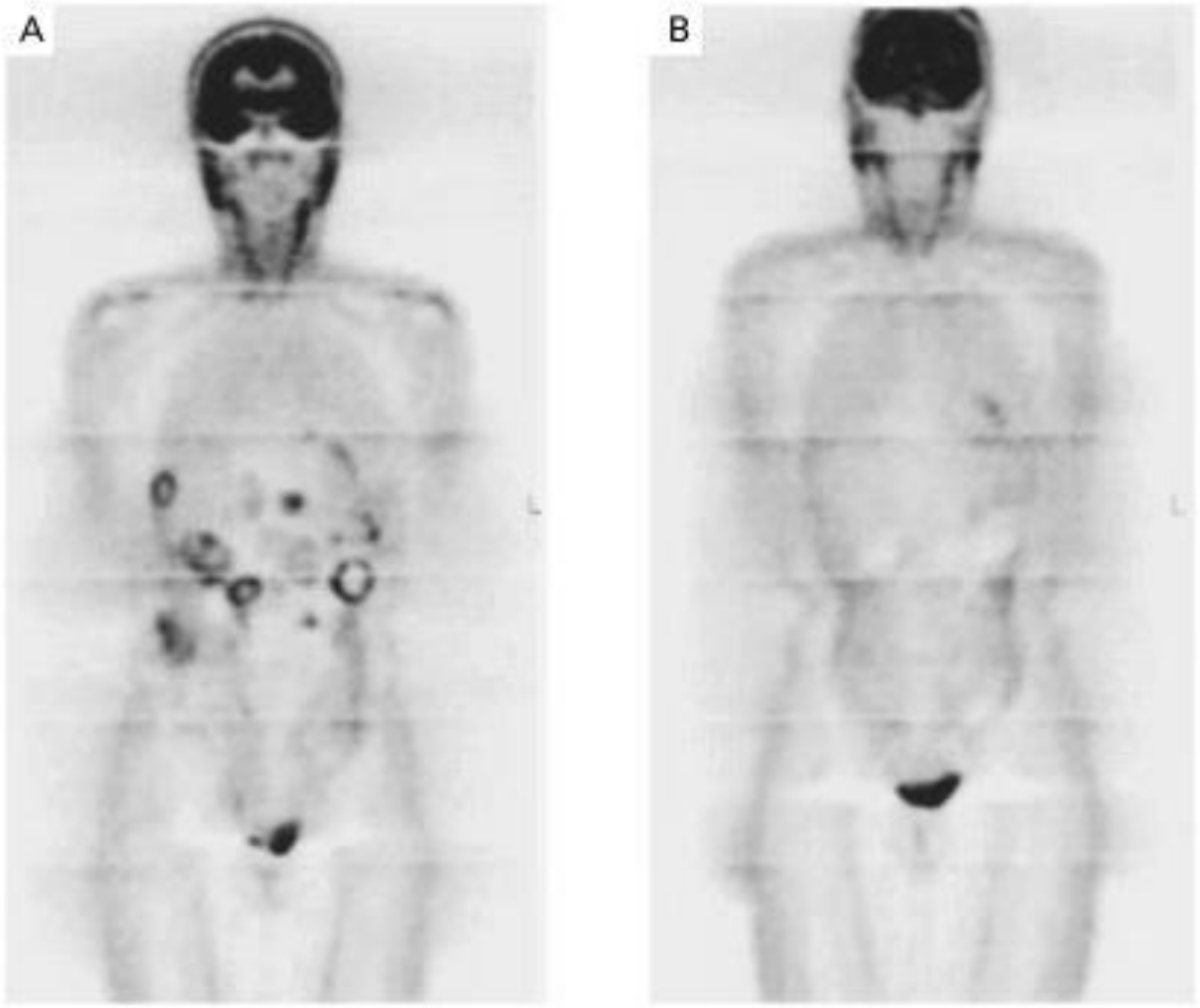

Chronic Myeloid Leukemia
Rate (per 100,000)
2.0
1.5
1.0
0.5
0.0
Incidence
Mortality
1975
1985
1995
2005
2015
Imatinib approved in 2001
Rate Relative to 1975
1.2
1.0
0.8
0.6
0.4
0.2
0.0
Incidence
Mortality
1975
1985
1995
2005
2015

NEJM 2019

"Here's my sequence..."

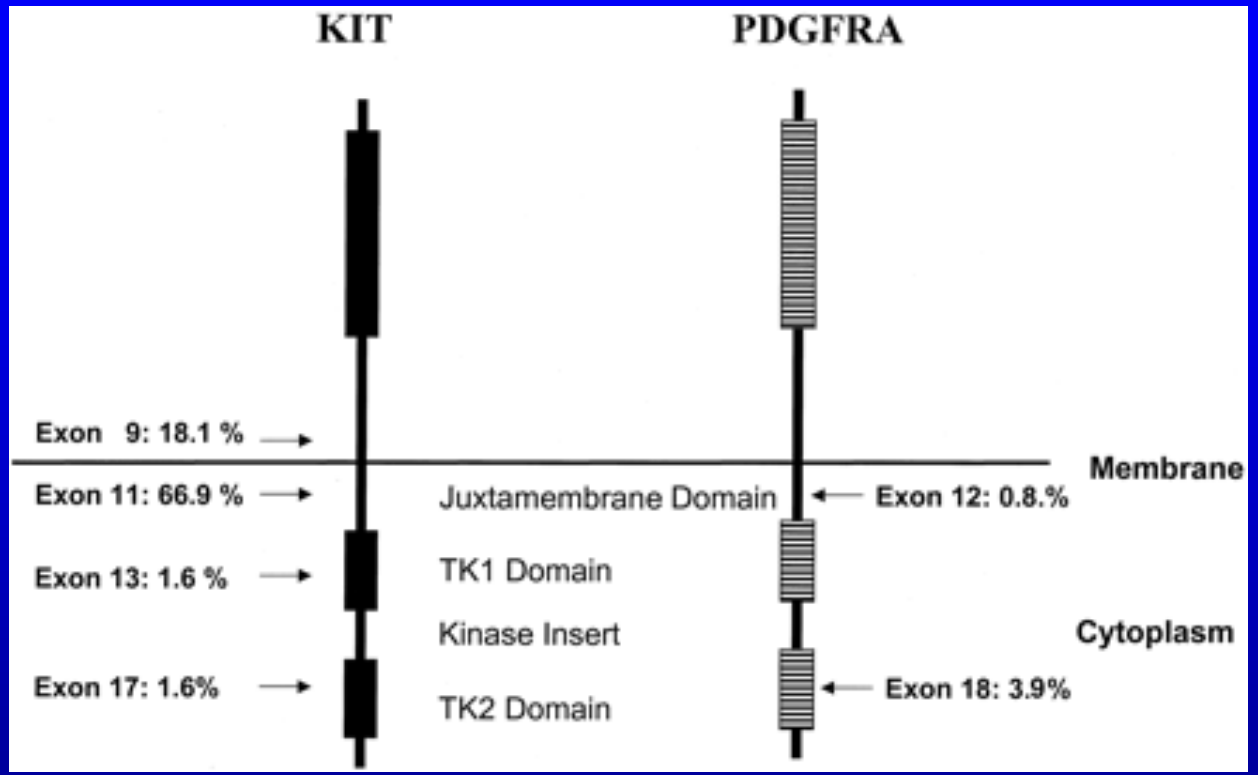
New Yorker, 2000

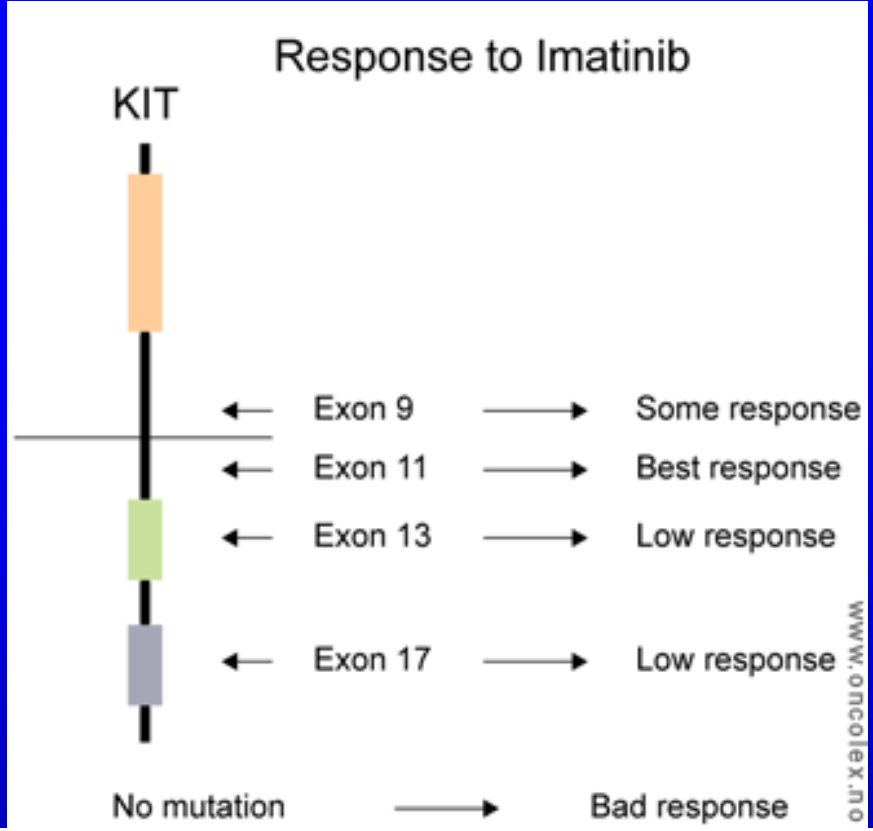
GIST sarcomas

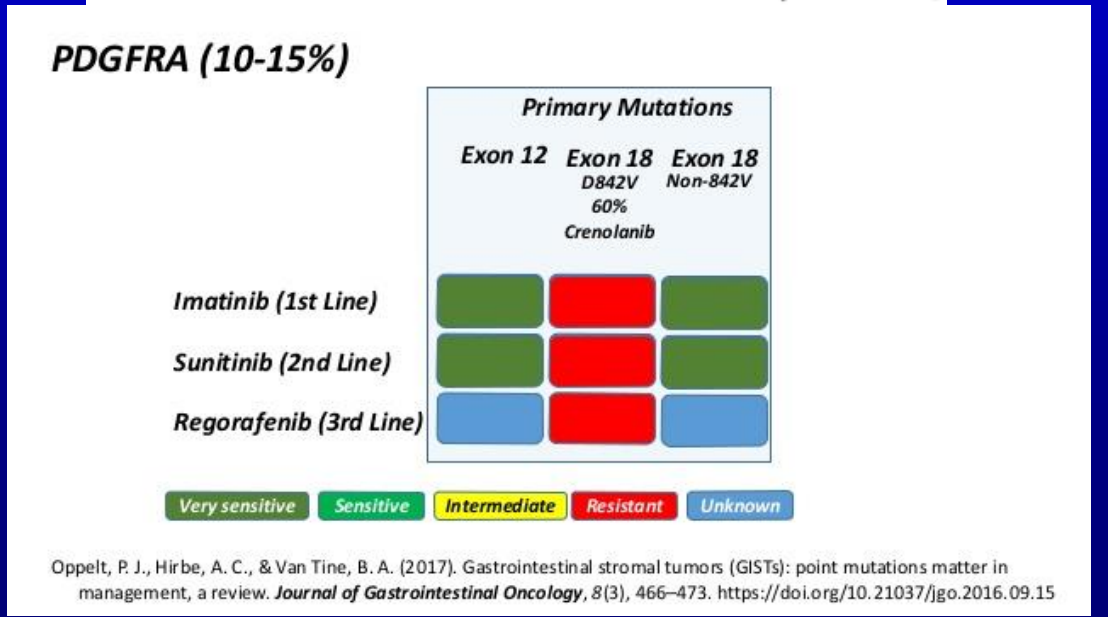


Majority (90%) of GISTs carry oncogenic kit mutations (exons 9 and 11), imatinib highly effective

- 5% carry PDGFR mutations, mostly sensitive to imatinib
- 5% non-mutant- resistant to imatinib
- Interestingly, systemic mastocytosis patients have a D816V kit mutation that is resistant to imatinib

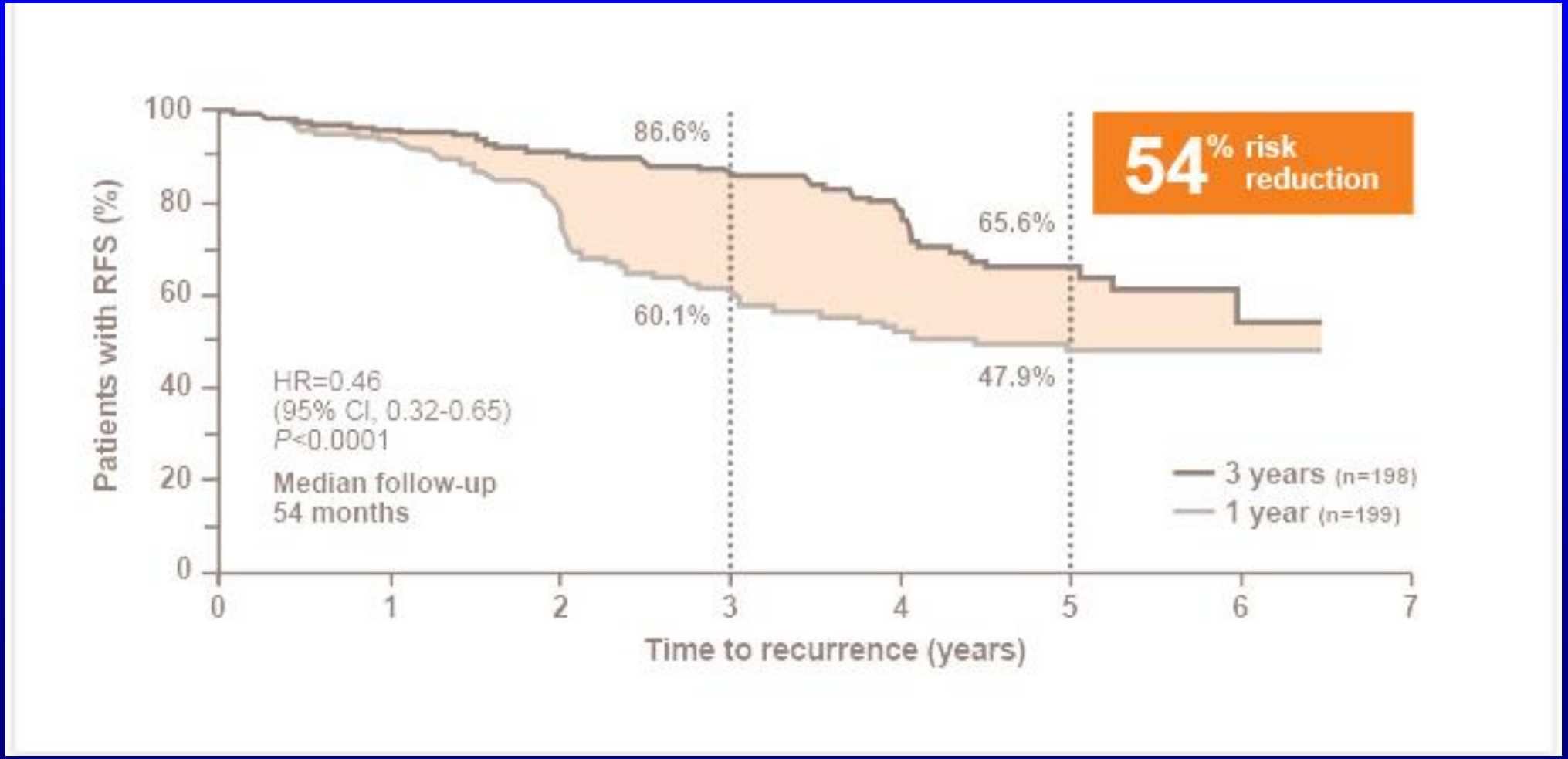






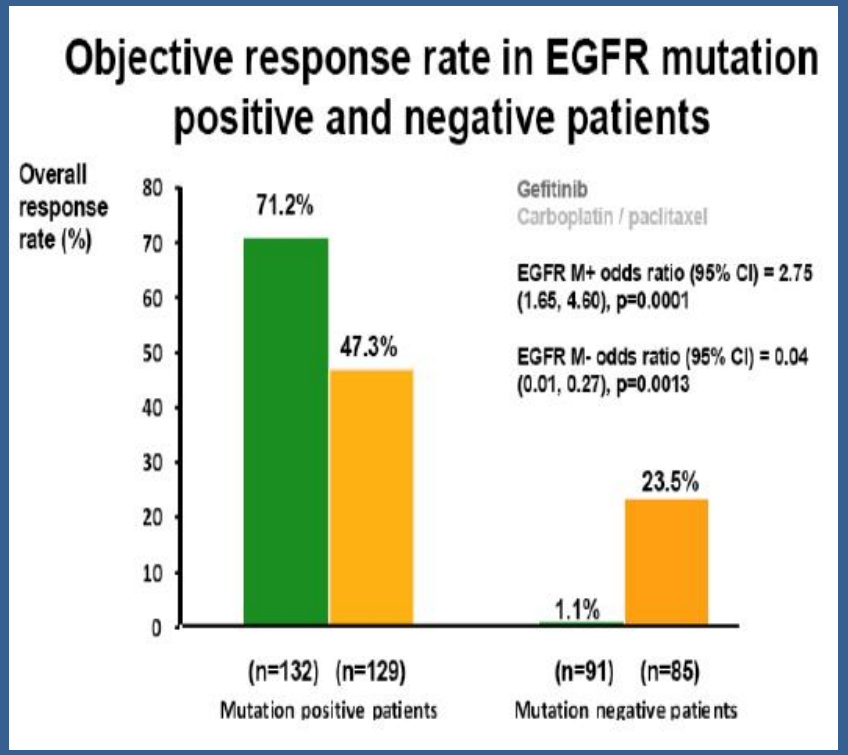
Oppelt, P. J., Hirbe, A. C., & Van Tine, B. A. (2017). Gastrointestinal stromal tumors (GISTs): point mutations matter in management, a review. ***Journal of Gastrointestinal Oncology***, *8*(3), 466–473. https://doi.org/10.21037/jgo.2016.09.15

Benefit of targeted treatment extends into adjuvant setting

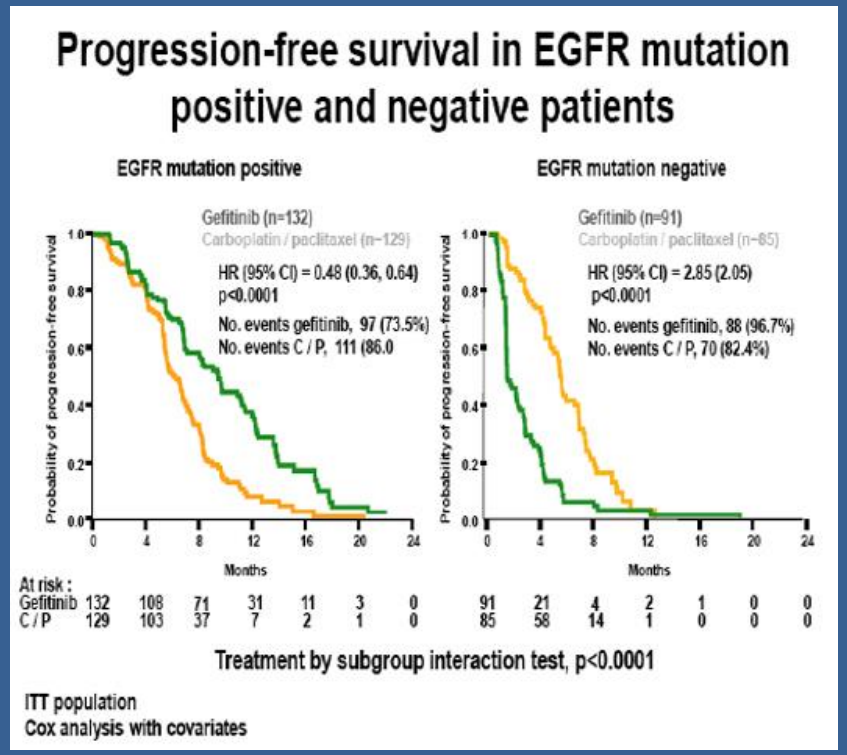


Actionable mutations in non-small cell lung cancer

RESPONSE



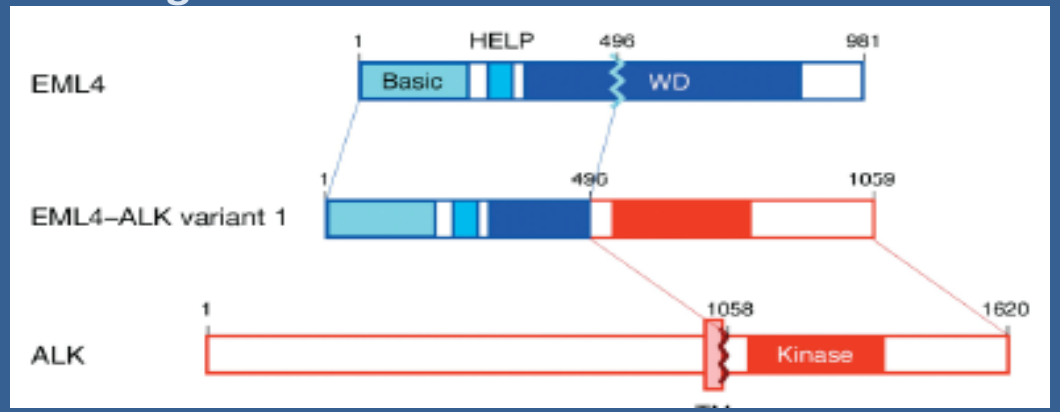
SURVIVAL



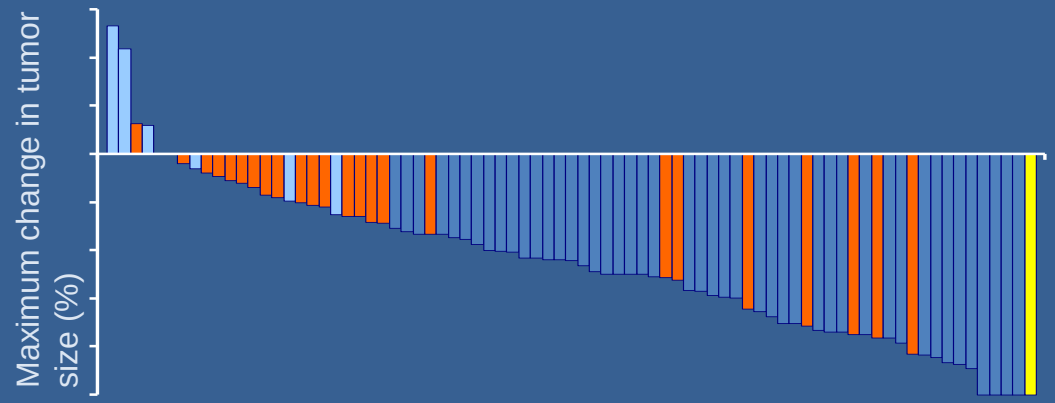
IPASS, Mok et al NEJM

ALK-rearrangement in advanced NSCLC: Dramatic benefit from ALK inhibition

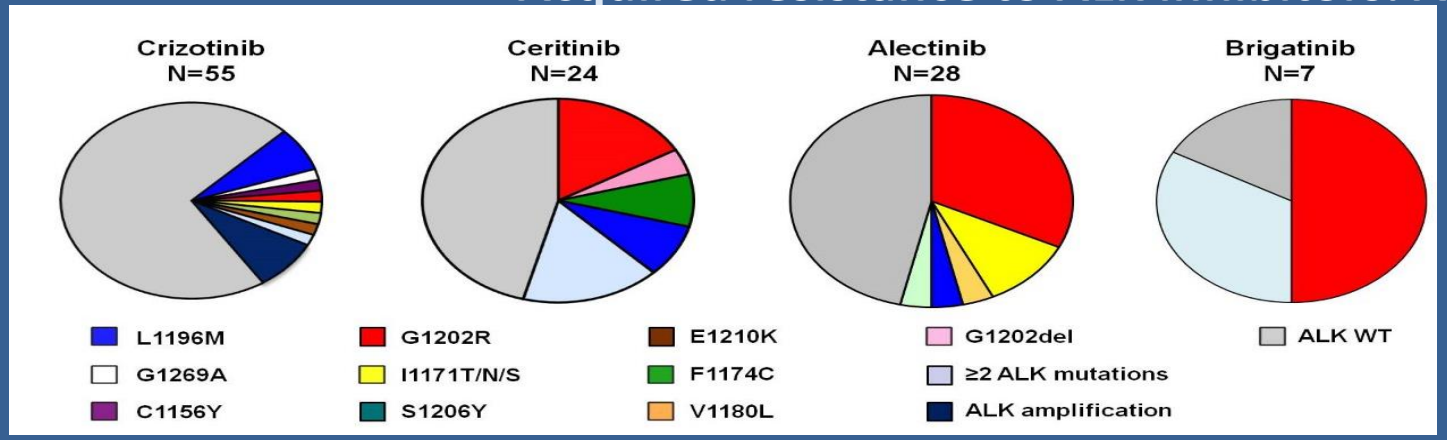
Identification of the transforming *EML4-ALK* fusion gene in NSCLC



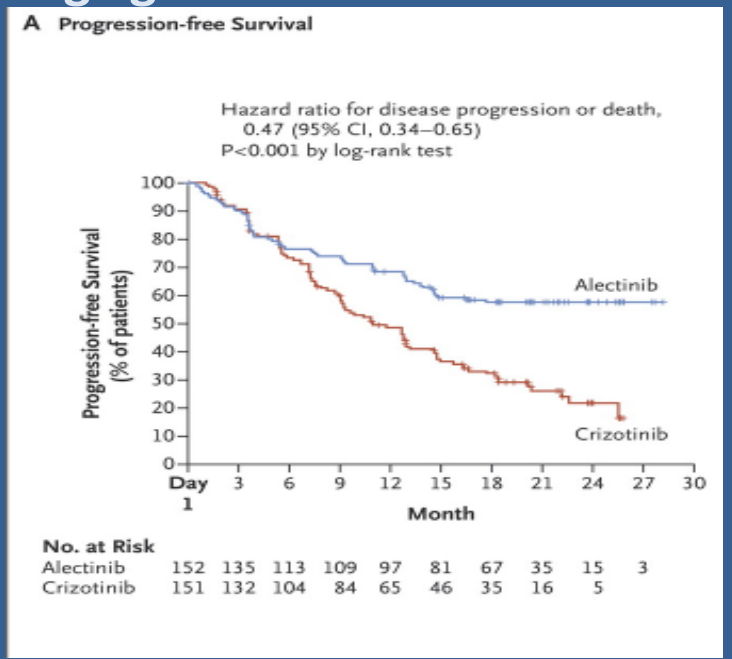
Tumor responses to crizotinib for patients with *ALK*-positive NSCLC



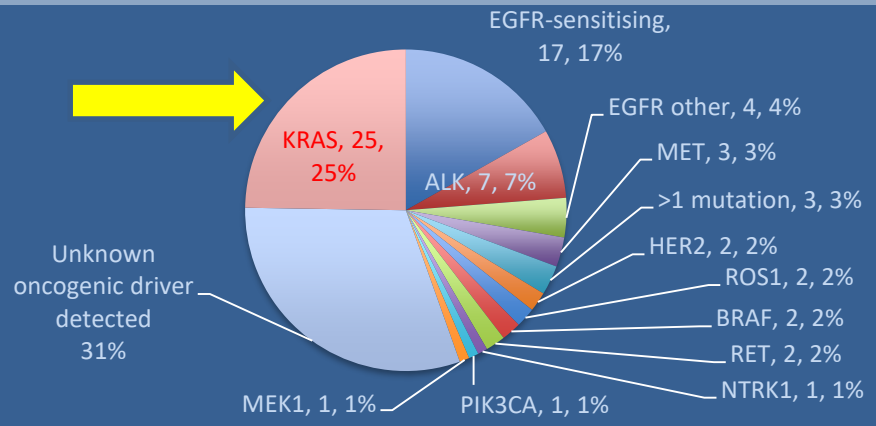
Acquired resistance to ALK inhibitors: A "matching" game



Gainor JF, et al. Cancer Discov. 2016;6(10):1118-33.



The era of multiplex testing is here

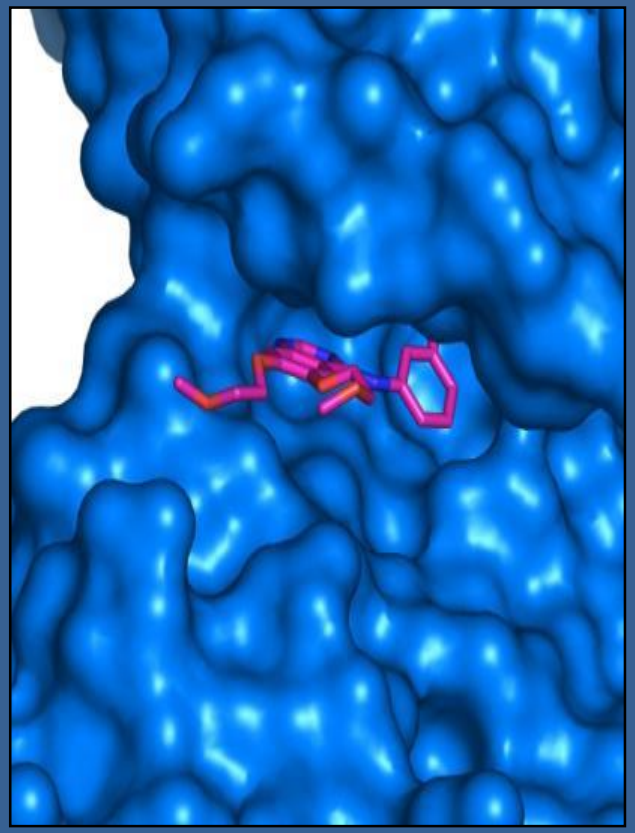


Molecular genotyping for advanced NSCLC

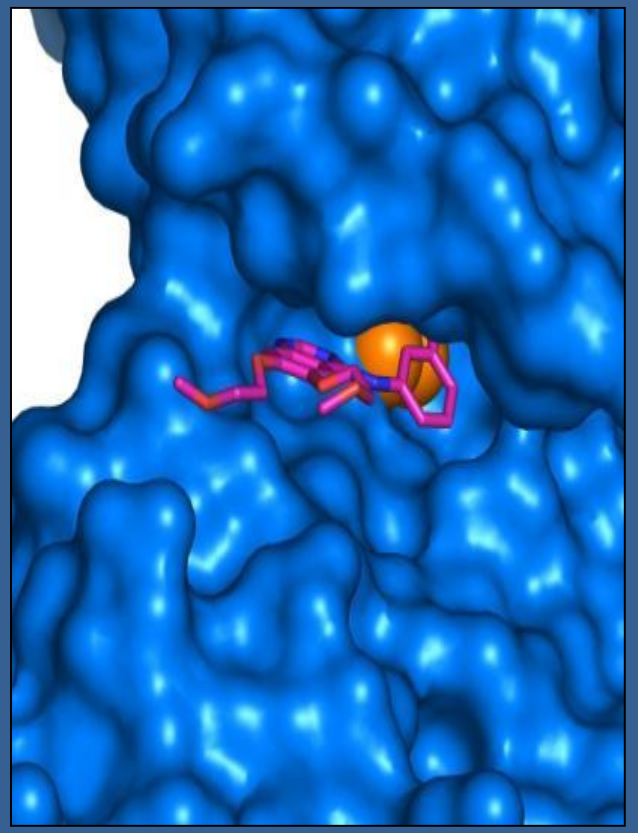
	EGFR	ALK	ROS	MET	B-RAF	NTRK	ErbB2	RET
Level of Evidence	1	1	1	2A	1	3A	2B	2B
1st Line Treatment Options	Erlotinib Gefitinib Afatinib Dacomitinib Osimertinib	Crizotinib Alectinib Ceritinib Brigatinib	Crizotinib Ceritinib Entrectinib	Crizotinib Cabozantinib Capmatinib Glesatinib Tepotinib	Dabrafenib +/- trametinib Vemurafenib	Larotrectinib Entrectinib	T-DM1 Herceptin Afatinib Poziotinib TAE788	Cabozantinib Vandetanib LOXO-292 BIU 667
2nd Line Treatment Options	Osimertinib	Brigatinib Lorlatinib	Lorlatinib					

- **Green: FDA approved drug for indication**
- **Yellow: FDA approved drug for other indications**
- **Red: Experimental agent**

Acquired resistance



Wild-type receptor: erlotinib (chemical structure) snugly fits into the ATP-binding pocket of EGFR blocking its function



T790M mutant receptor: methionine (M) 790 (orange) protrudes into the ATP-binding pocket, leads to steric hindrance disallowing erlotinib to bind

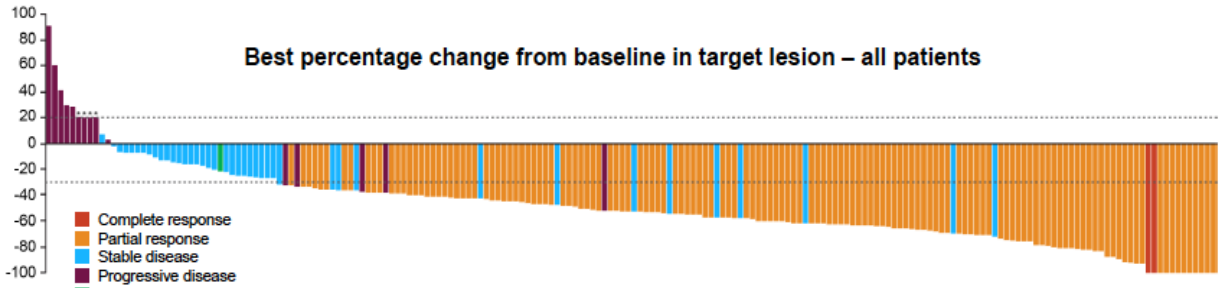
Kobayashi…Halmos, NEJM 2005

Third-generation T790M-targeting TKIs

- These novel and highly promising drugs largely spare EGFR WT signaling and preferentially block mutant/T790M signaling, leading to potentially wider therapeu indices

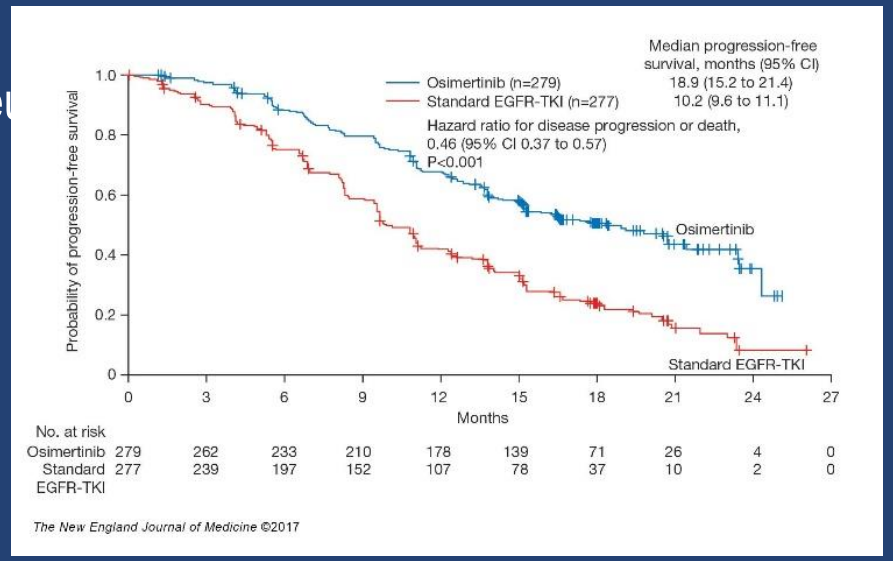
AURA-2: Osimertinib

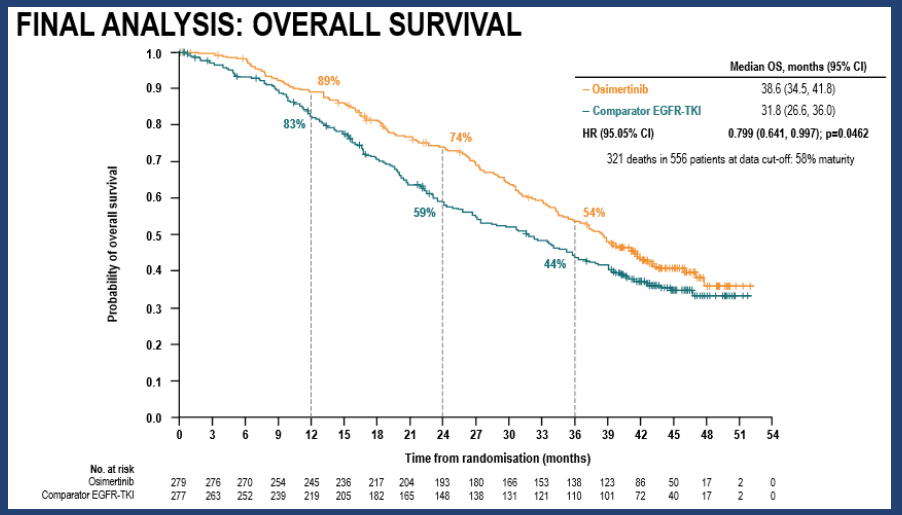
Tumor response by independent central review



Confirmed objective response	Total
ORR,† % (95% CI)	71 (64, 77)
Complete response,‡ n (%)	2 (1)
Partial response,‡ n (%)	139 (70)
Stable disease ≥6 weeks,§ n (%)	41 (21)
Progressive disease, n (%)	15 (8)
DCR, % (95% CI)	92 (87, 95)

FLAURA





ctDNA- basics

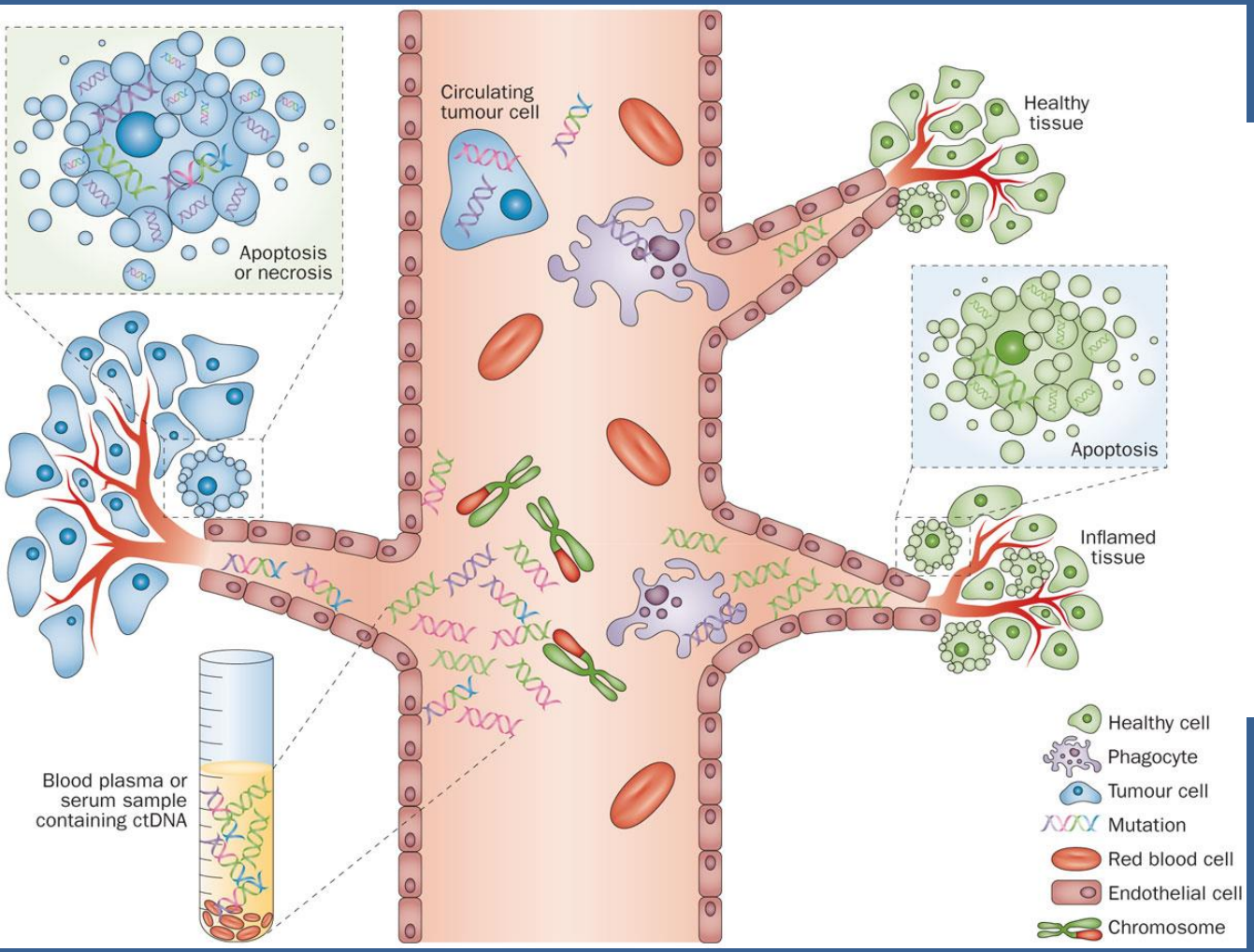
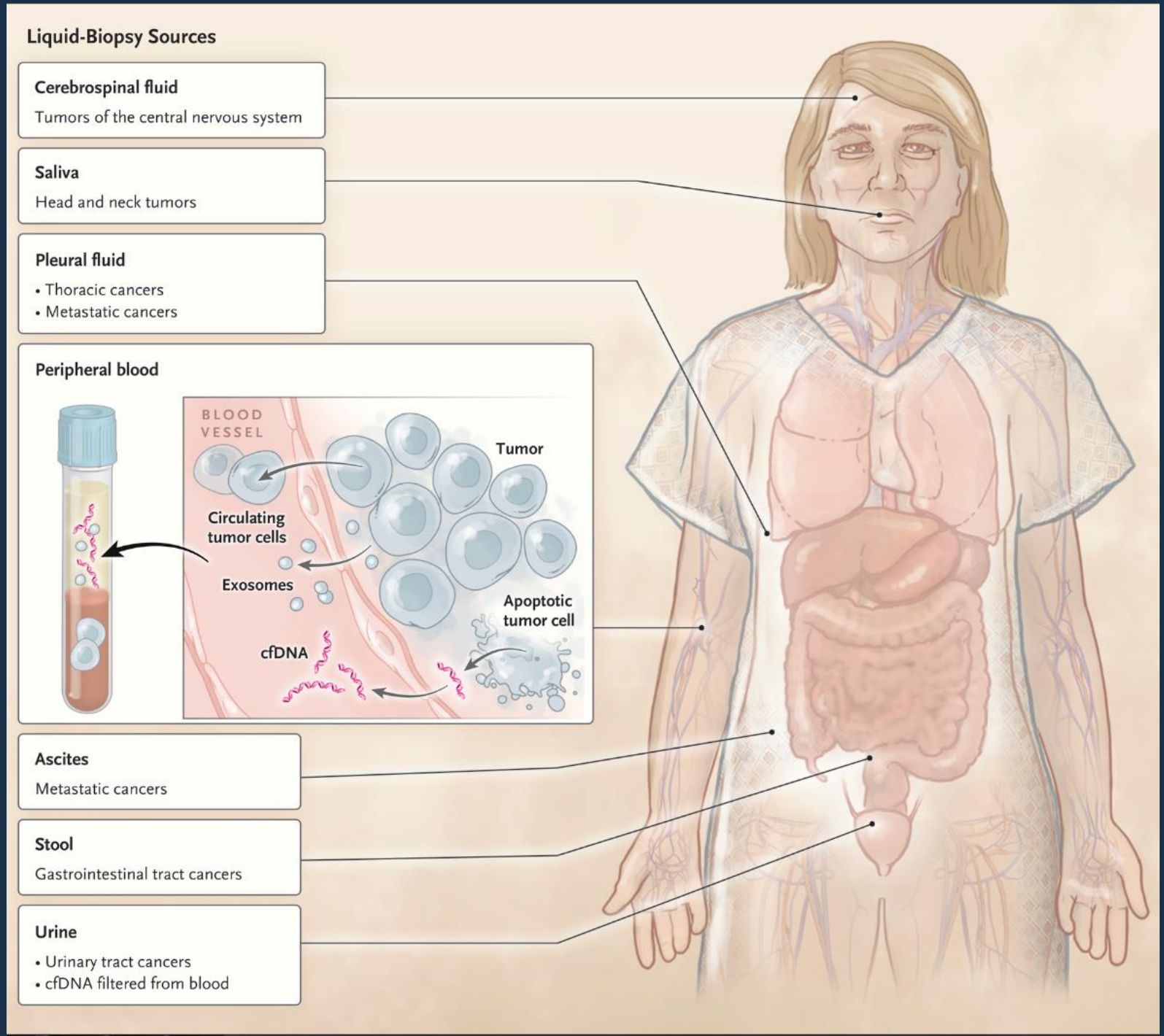


Table. Clinically Available Assays for Genotyping of Plasma Cell-Free DNA (cfDNA)

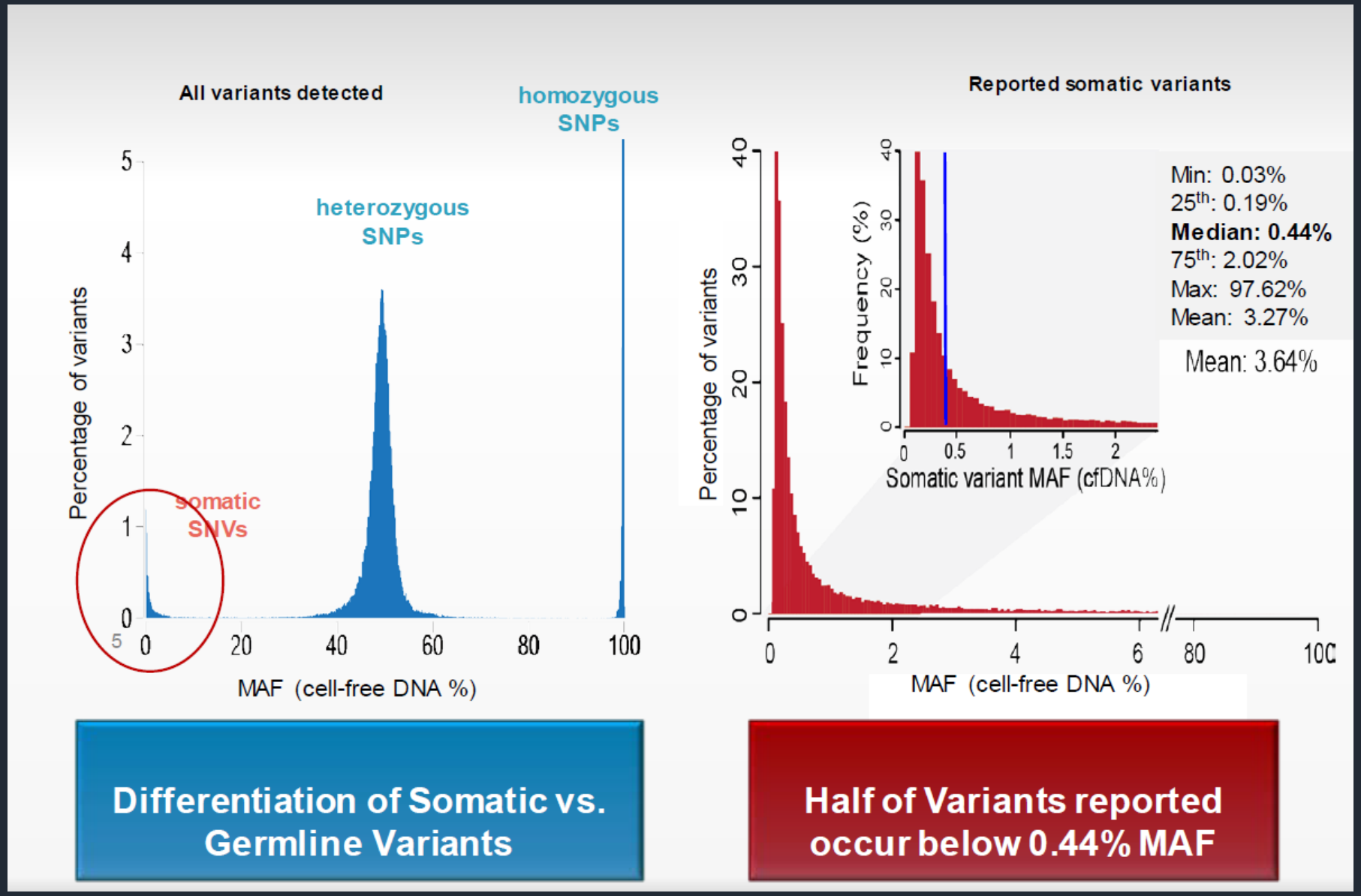
	Assays			
	PCR		NGS	
Characteristic	Allele-Specific	Emulsion	Amplicon-Based Targeted	Capture-Based Targeted
Variants potentially detected	Known recurring mutations	Known recurring mutations	Any exonic mutations, copy number gains	Exonic mutations, intronic gene fusions, copy number gains
Quantitation	Semiquantitative (against standard curve)	Absolute or relative quantitation, wide dynamic range	Quantitation of relative AF, but vulnerable to PCR amplification bias	Quantitation of relative AF
Speed & complexity	Rapid, relatively easy to interpret	Rapid, relatively easy to interpret	Potentially rapid, less complex bioinformatics	Potentially slower, more complex bioinformatics
Examples	Cobas (Roche) therascreen (Qiagen)	Droplet digital PCR (Biorad) BEAMing (Sysmex Inostics)	Tam-seq (Inivata)	Guardant360 (Guardant) cancerselect (Personal Genome Diagnostics)

Oxnard JAMA Onc 2016



Corcoran/Chabner
NEJM 2018

ctDNA usually in low allele frequency



Differentiation of Somatic vs. Germline Variants

Half of Variants reported occur below 0.44% MAF

Lanman PLOS One 2015

Types of assays

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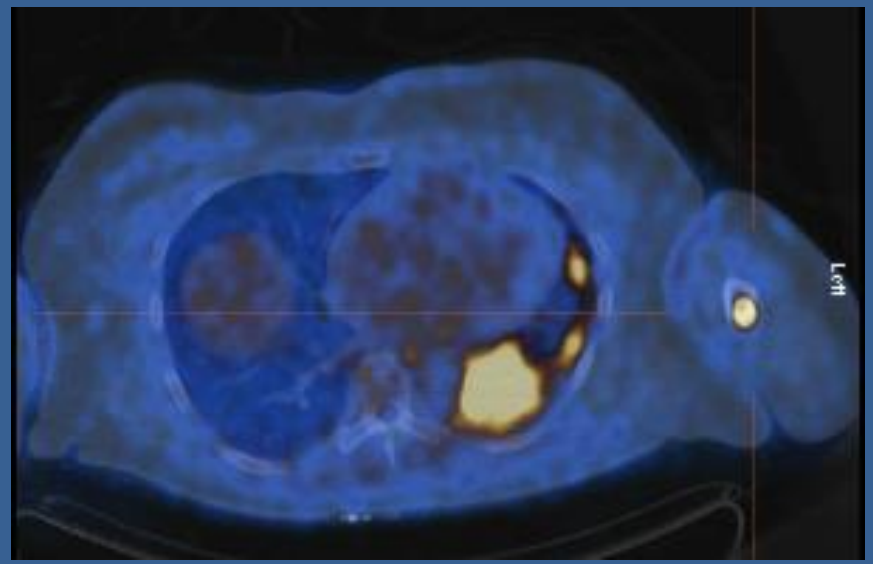
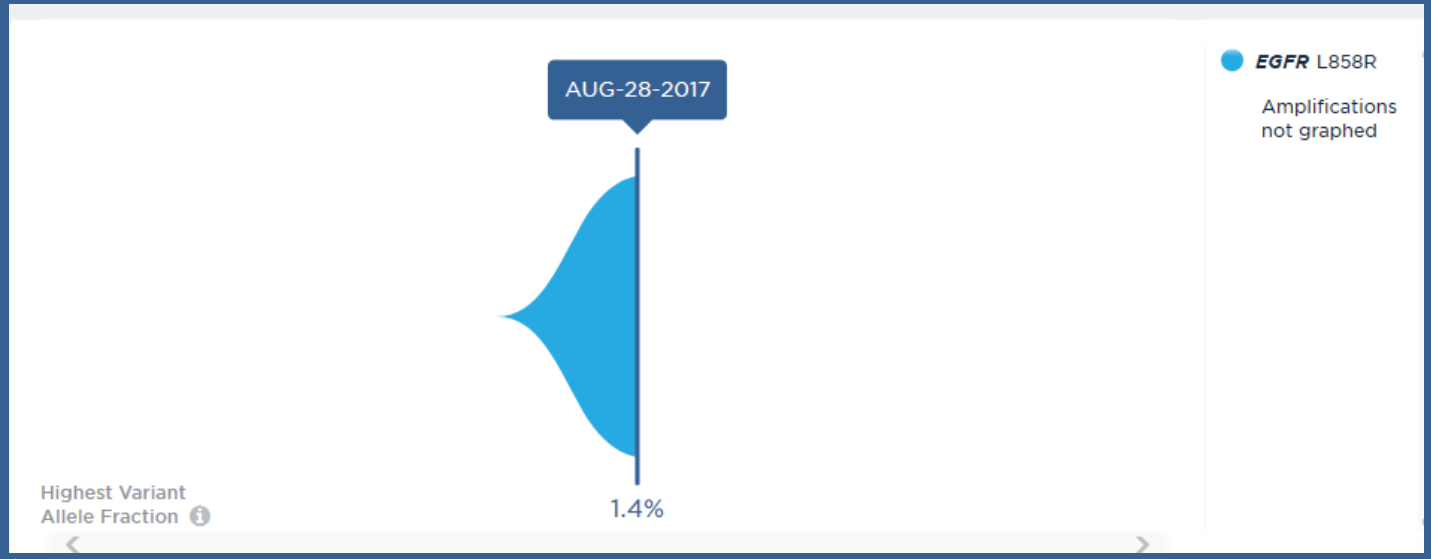
Oxnard JAMA
Onc 2016

Needle in the haystack

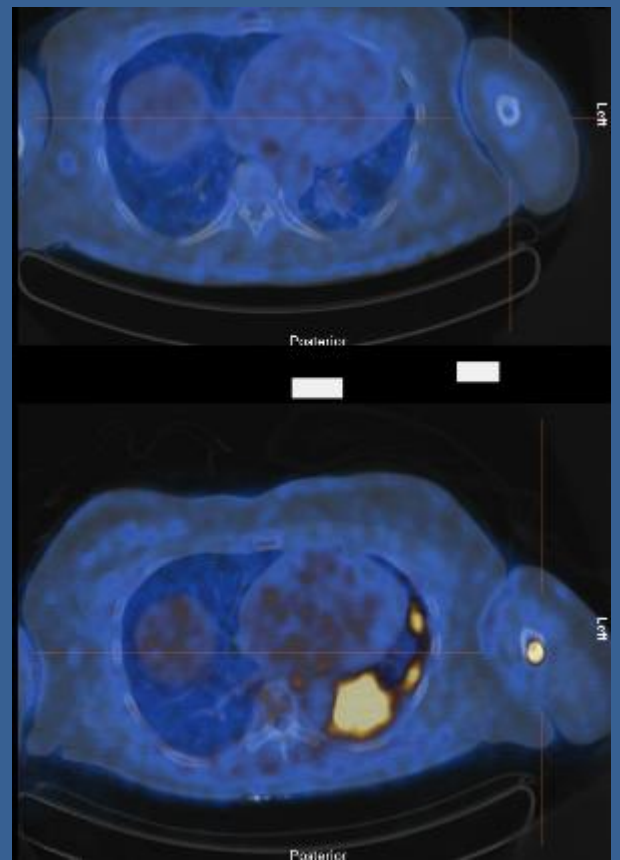
- 64 year old nurse with limited smoking history
- Admitted with massive stroke- found to have hypercoag state of malignancy
- Evaluation showed lung mass and diffuse nodal and bony mets
- EBUS showed adenocarcinoma, no tissue left for further testing
- Patient frail, hemiplegic and extremely discouraged, rebiopsy very difficult due to anticoagulation

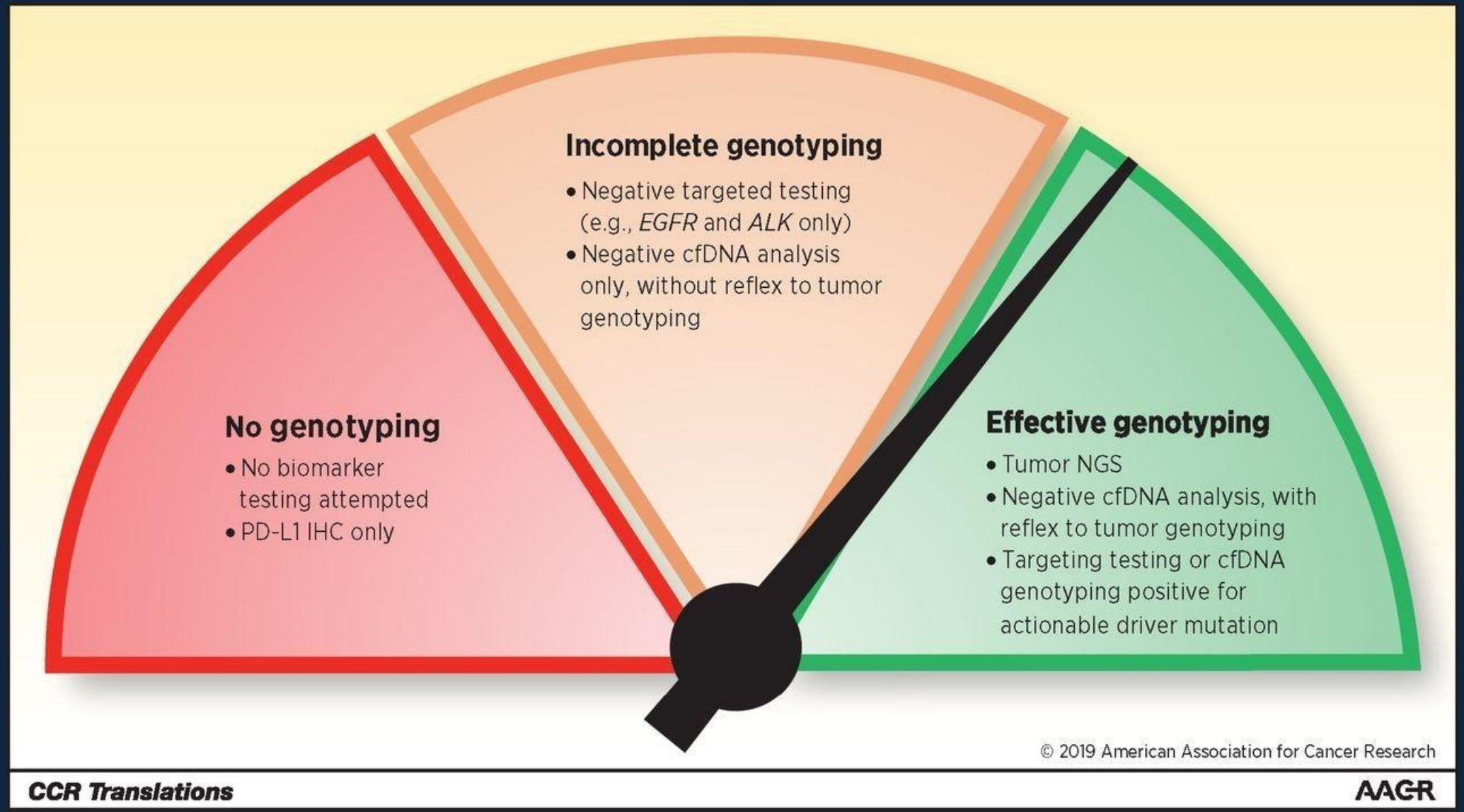




October 2017

August 2017




Incomplete genotyping
• Negative targeted testing (e.g., *EGFR* and *ALK* only)
• Negative cfDNA analysis only, without reflex to tumor genotyping
No genotyping
• No biomarker testing attempted
• PD-L1 IHC only
Effective genotyping
• Tumor NGS
• Negative cfDNA analysis, with reflex to tumor genotyping
• Targeting testing or cfDNA genotyping positive for actionable driver mutation
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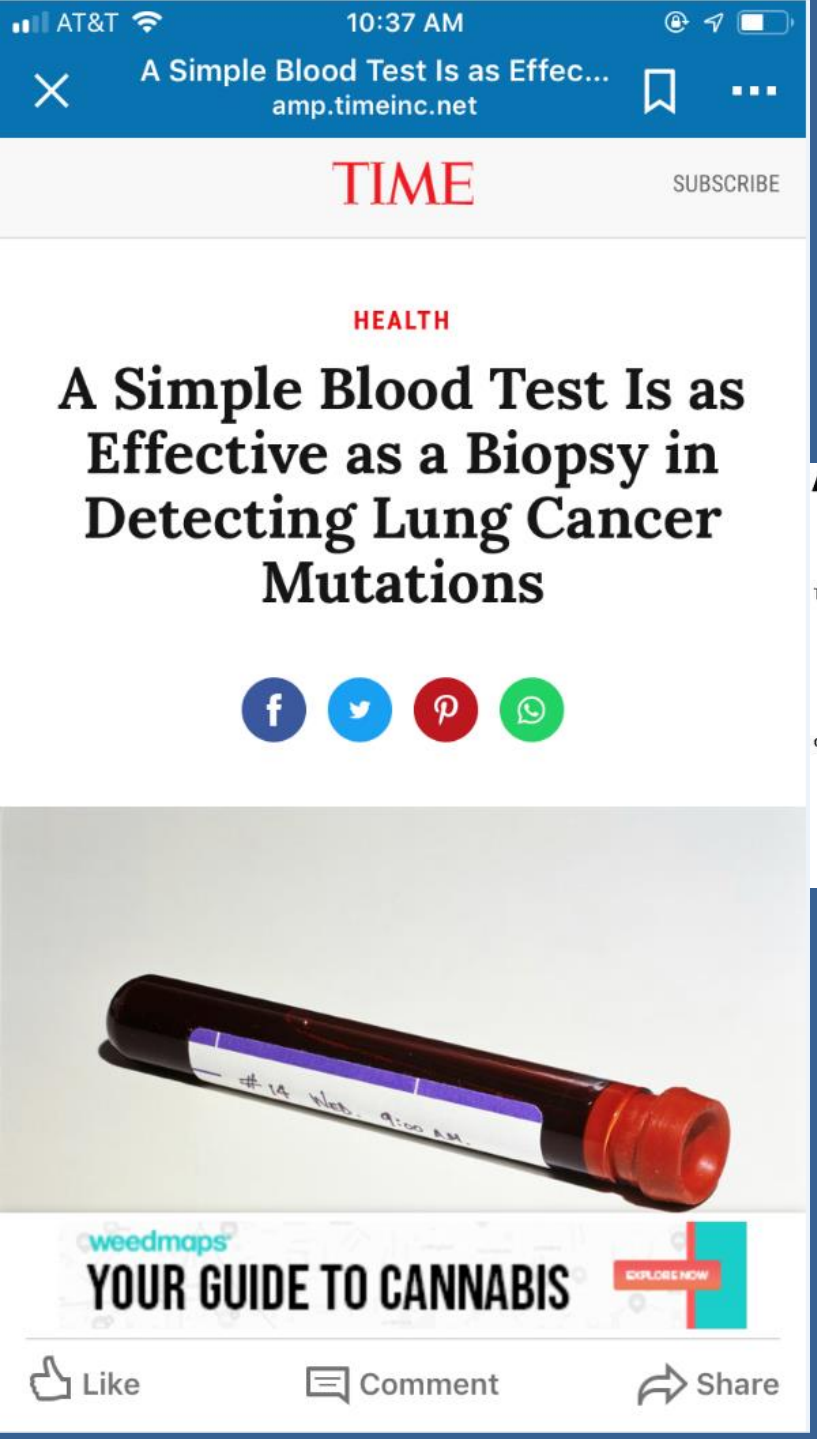
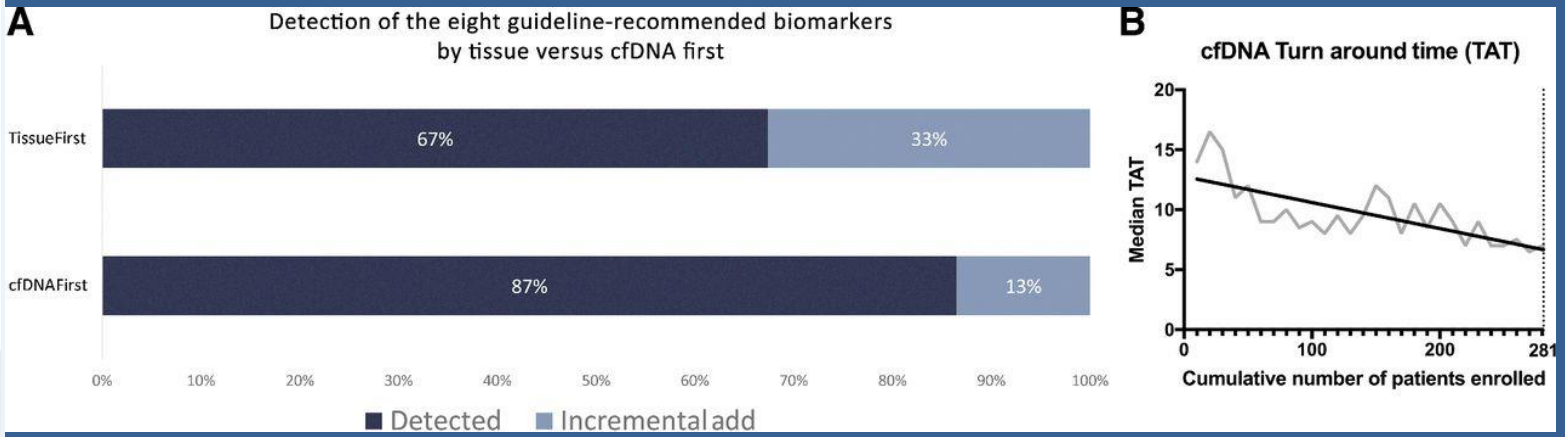
CCR Translations
AACR

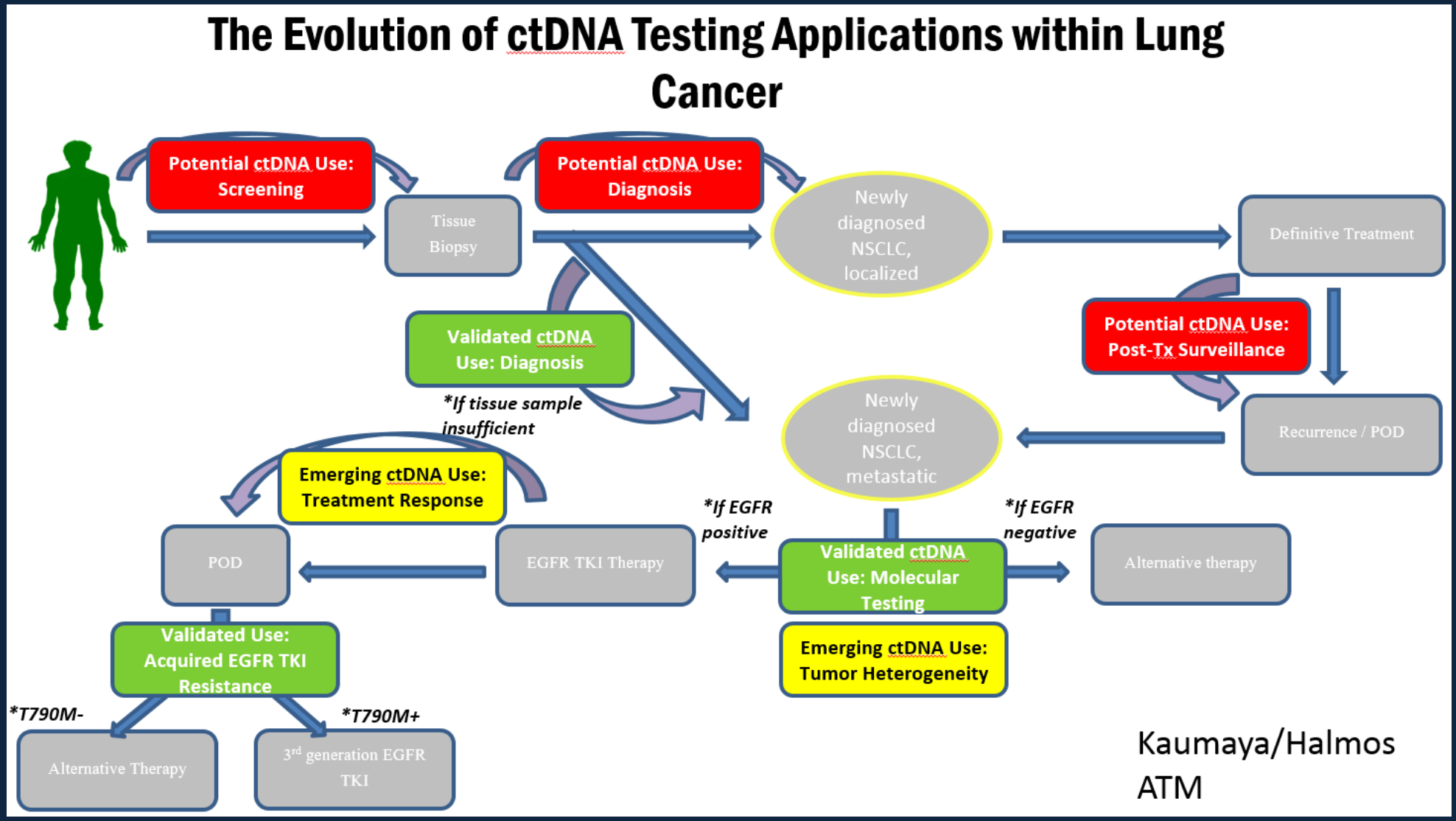
Oxnard, CCR

Blood first?


AT&T
10:37 AM
A Simple Blood Test Is as Effec...
amp.timeinc.net
TIME
SUBSCRIBE
HEALTH
A Simple Blood Test Is as Effective as a Biopsy in Detecting Lung Cancer Mutations
weedmaps
YOUR GUIDE TO CANNABIS
EXPLORE NOW
Like
Comment
Share


A
Detection of the eight guideline-recommended biomarkers by tissue versus cfDNA first
TissueFirst
67%
33%
cfDNAFirst
87%
13%
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%
Detected
Incremental add
B
cfDNA Turn around time (TAT)
Median TAT
20
15
10
5
0
0
100
200
281
Cumulative number of patients enrolled

ctDNA- expanding uses



Eric Topol 
@EricTopol

Testing the liquid biopsy for #cancer outcomes, a step forward for the molecular stethoscope nyti.ms/1alyuQl

Blood Test Shows Promise as Alternative to Cancer Biopsy

19 April 2015

Now the Australian researchers, Dr. Jeanne Tie and Dr. Peter Gibbs of the Walter and Eliza Hall Institute of Medical Research, are starting a study of 450 patients randomly assigned to have the blood test or not. Those who have it will get chemotherapy if the test finds cancer DNA. Those who do not have the blood test will get usual care, whatever their physician prescribes.

"This will be the first real test of whether circulating tumor DNA can be clinically useful," Dr. Vogelstein said.

The New York Times

A Stethoscope for the Next 200 Years

The ability to see 'alien' DNA and RNA in the blood can detect cancers very early.

2 Jan 2015

By **ERIC TOPOL** And **STEPHEN R. QUAKE**

THE WALL STREET JOURNAL.

Eric Topol 
@EricTopol

Testing the liquid biopsy for #cancer outcomes, a step forward for the molecular stethoscope nyti.ms/1alyuQl

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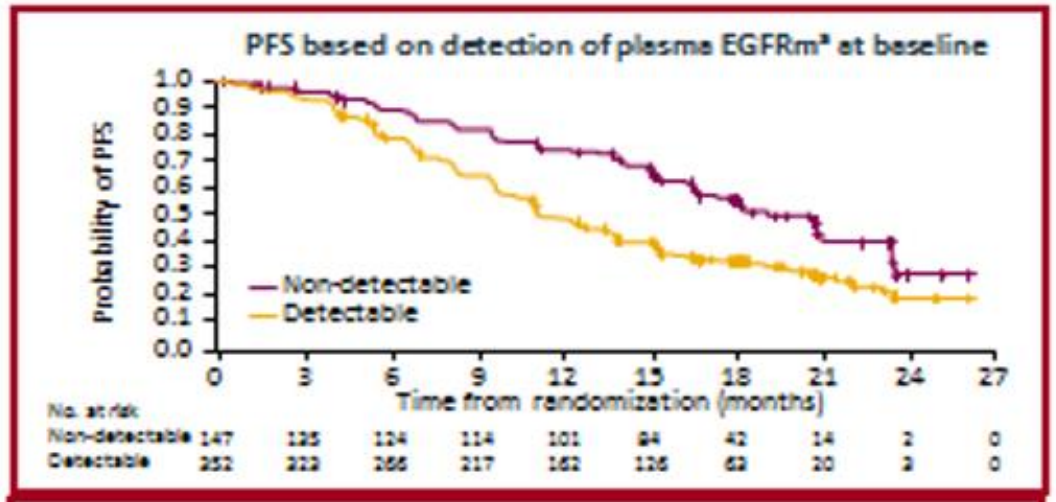
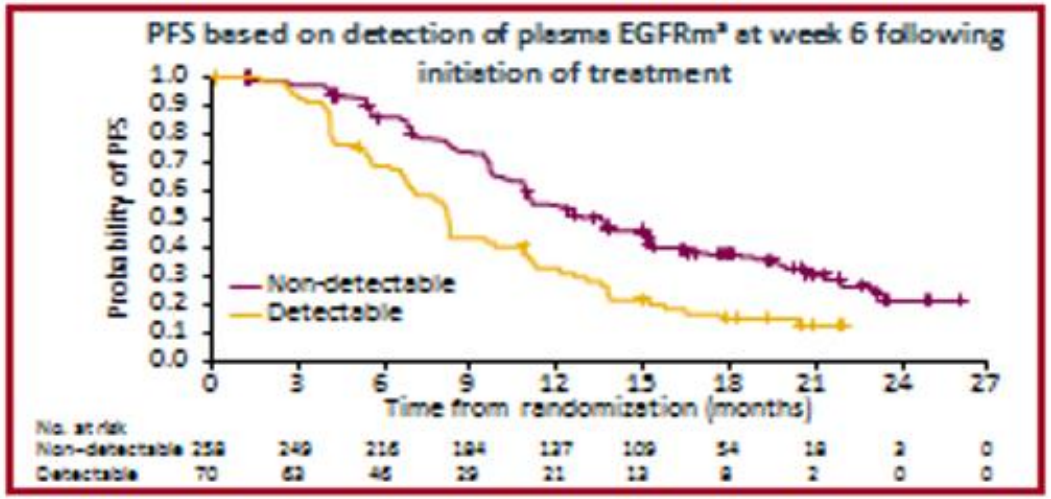
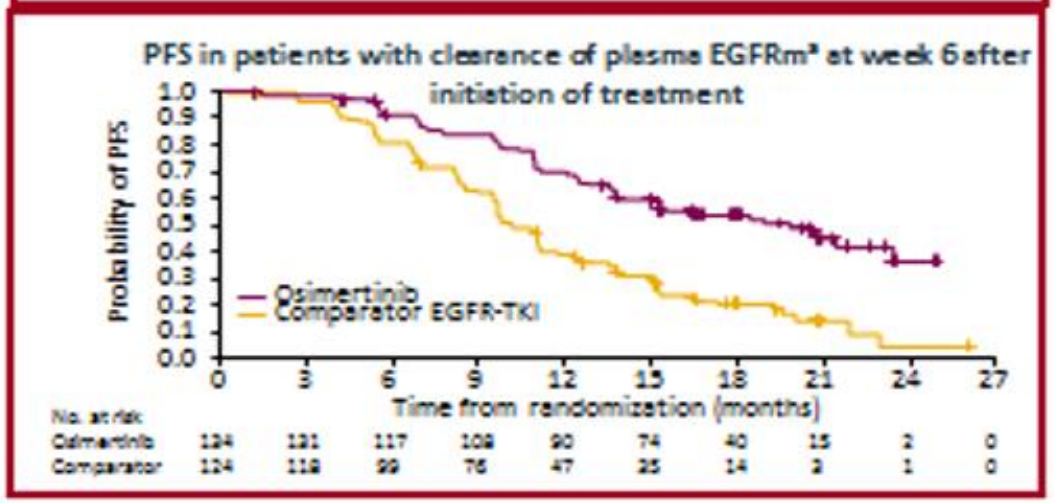
THE WALL STREET JOURNAL.

FLAURA- early ctDNA clearance



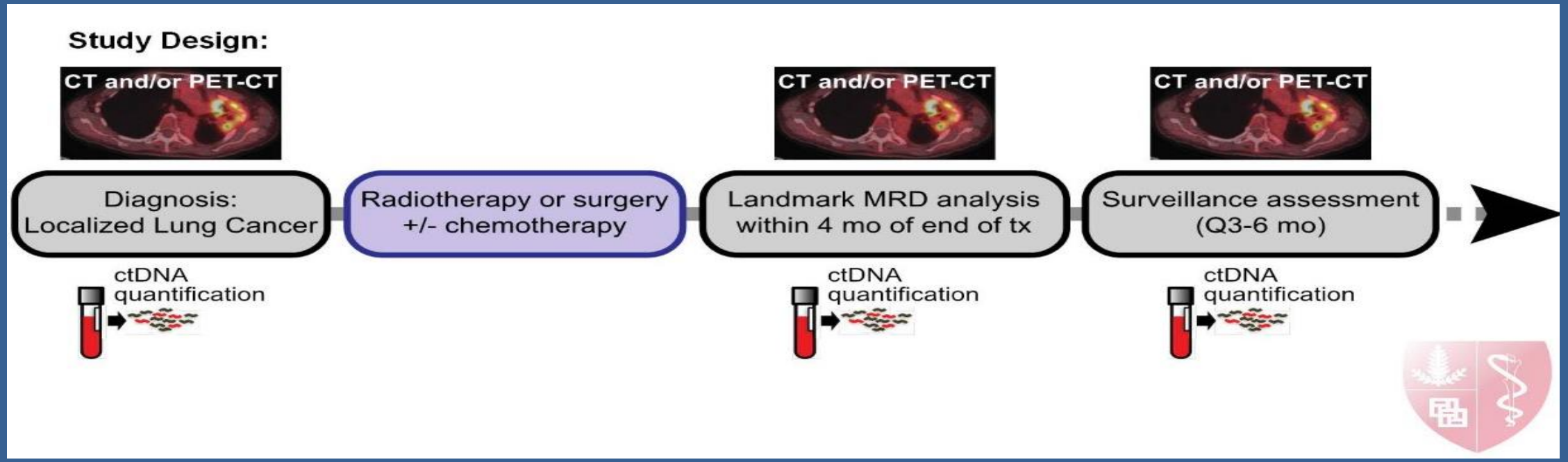


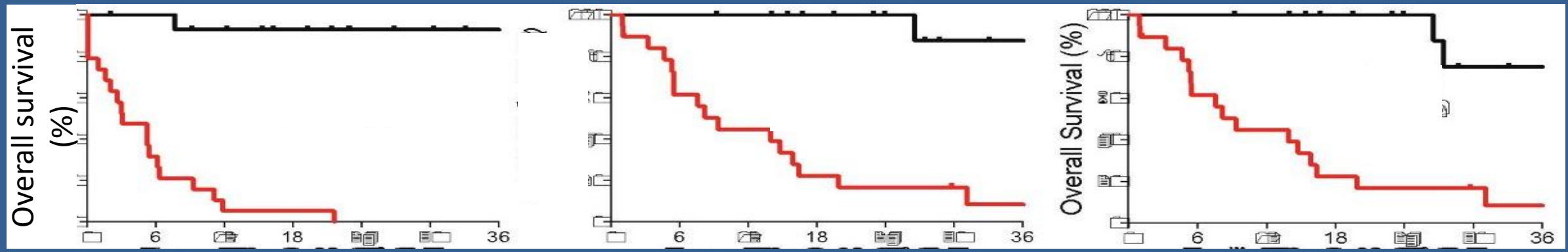


- This analysis of FLAURA confirms prior studies showing that presence of EGFR mutation in plasma ctDNA at baseline is a poor prognostic factor
- Patients with plasma EGFR mutation clearance have improved PFS
- Clearance of EGFR mutation from ctDNA favors osimertinib in PFS

Zhou C. et al, ASCO 2019

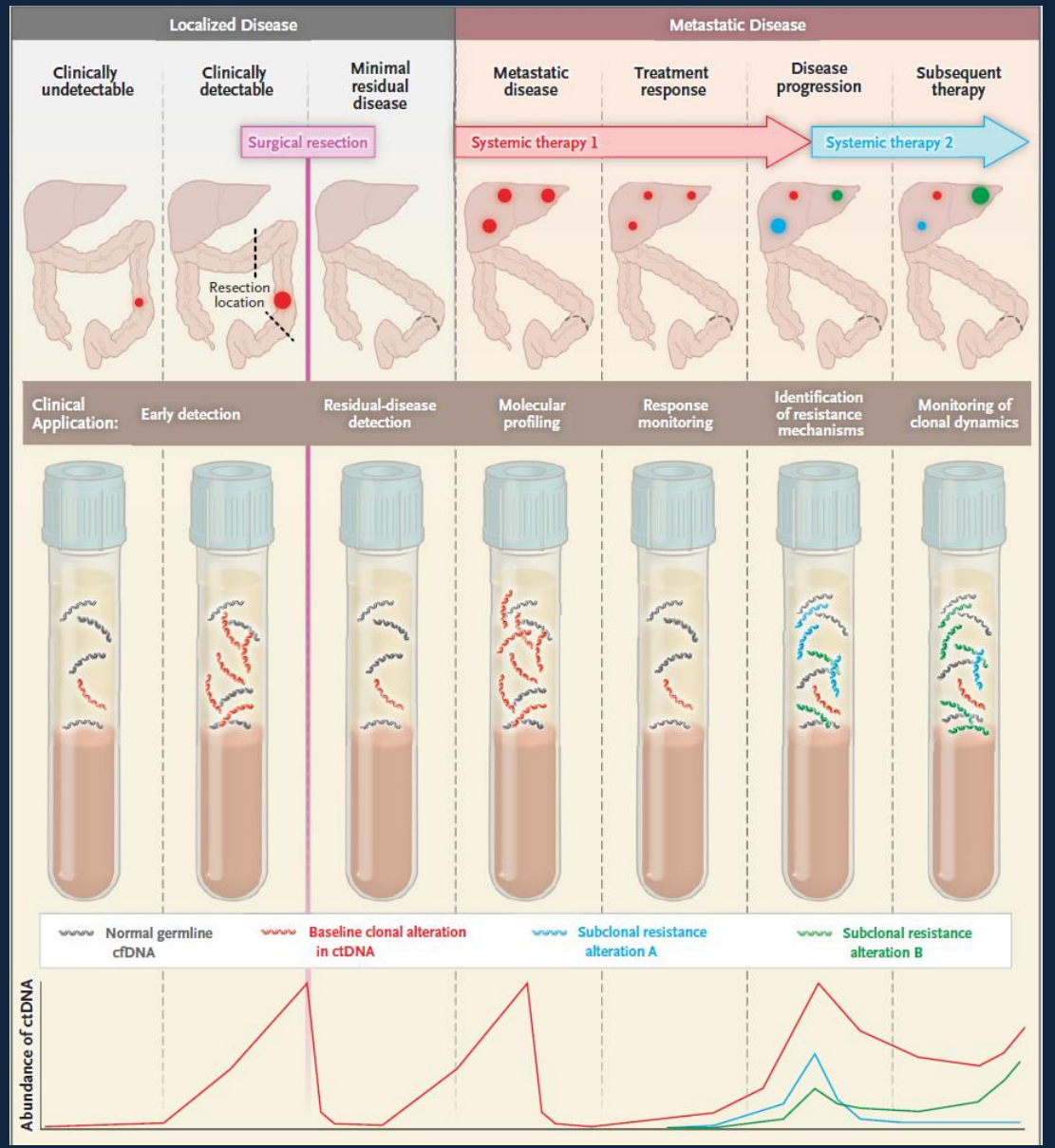
ctDNA for risk stratification

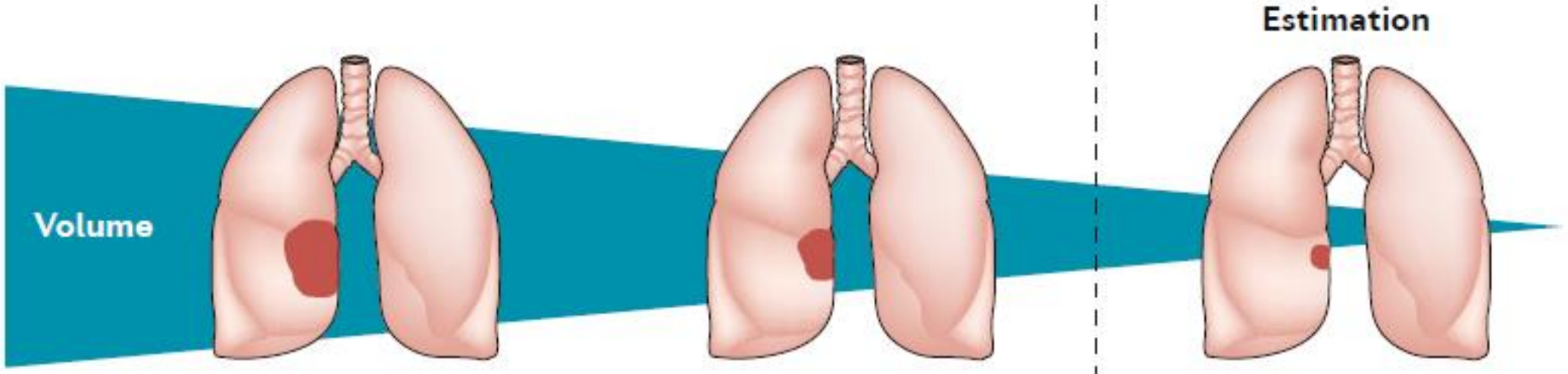




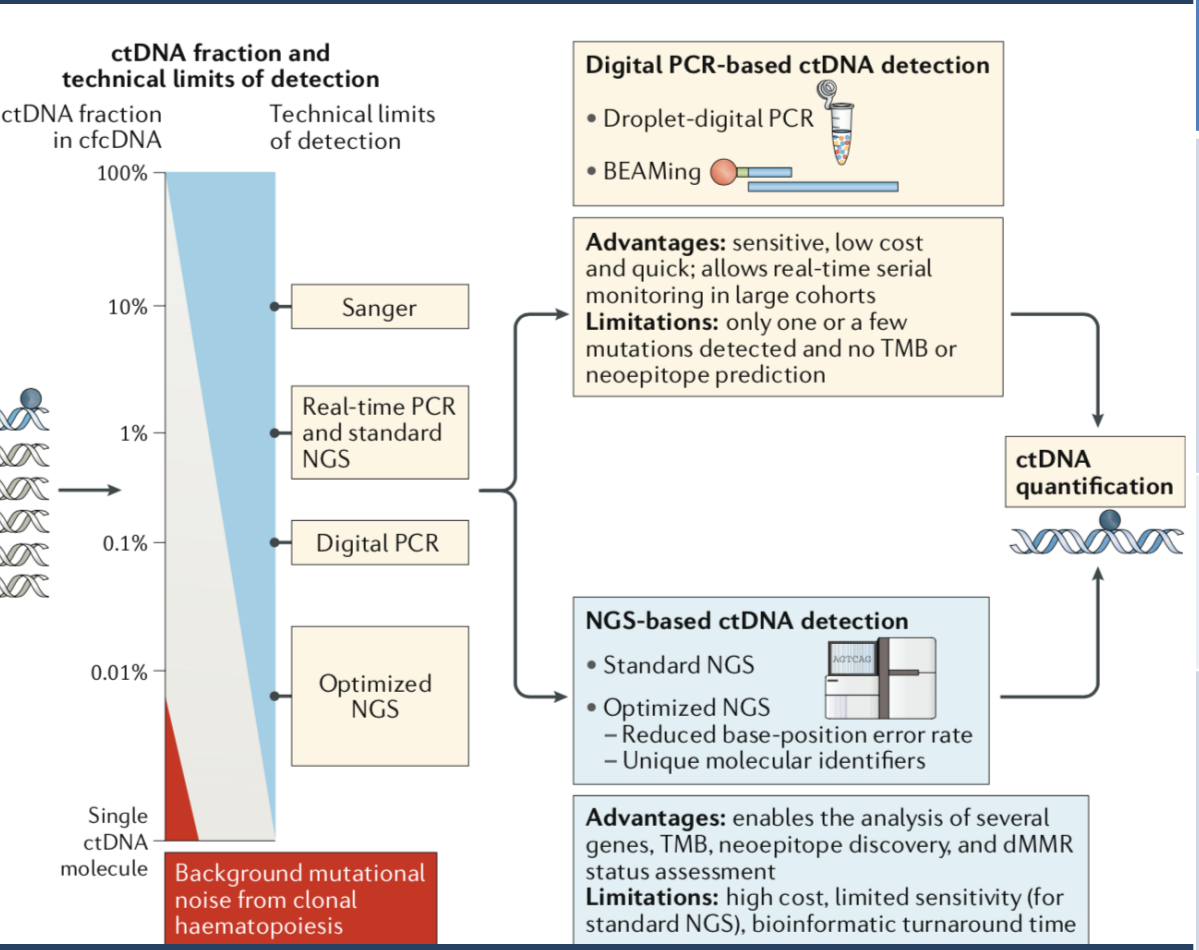
Chaudhuri ASCO 2017

ctDNA- emerging uses





MAF	1.4% (0.62–3.1%)	0.1% (0.06–0.18%)	0.008% (0.002–0.03%)
Nodule diameter	5.8 cm	2.6 cm	1.2 cm
Nodule volume	100 cm^3	10 cm^3	1 cm^3
T stage	T3	T1c	T1b

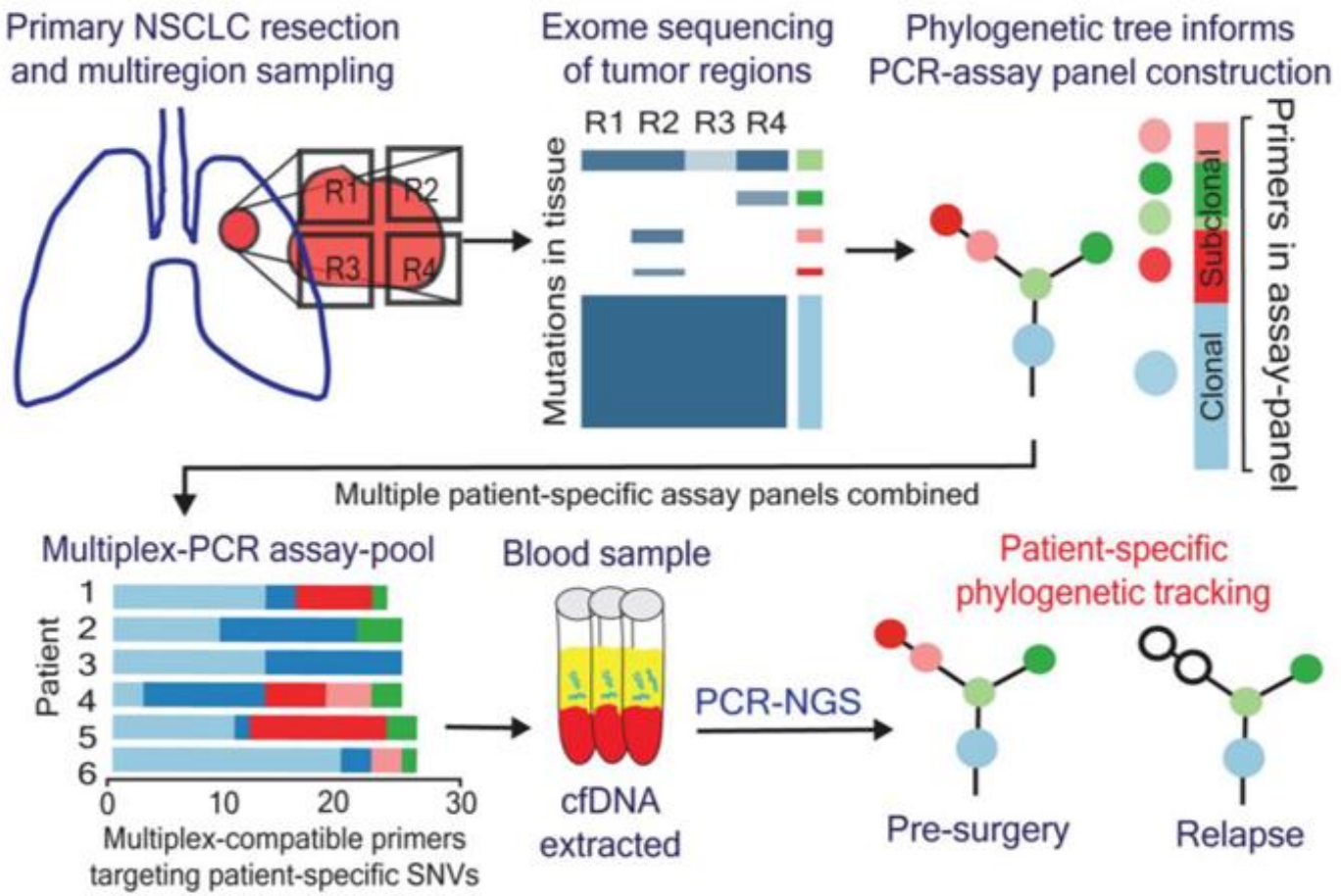


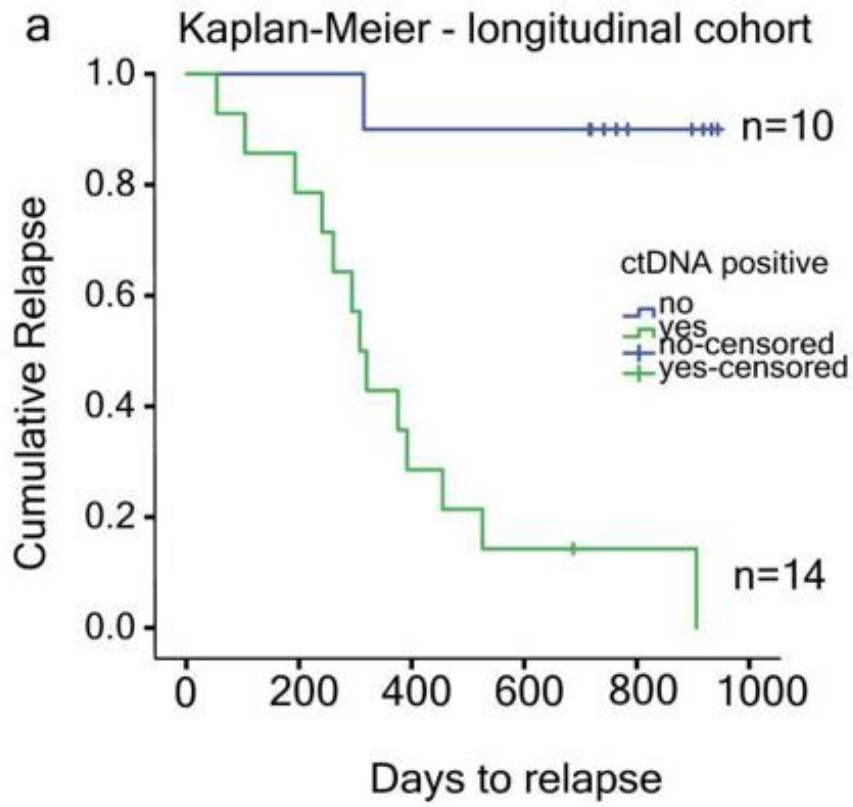
Assay type:	Pre-built assay, tumor agnostic	Pre-built assay, informed by tumor	Personalized “bespoke” assay
Strengths:	- Does not require tumor analysis - Potential to be applied to cancer screening	- Improved sensitivity	- Maximal “on target” sequencing - Maximal sensitivity
Weaknesses:	- Likely less sensitive (~0.2-0.5% AF)	- Tumor information required	- Tumor required - Slowest turnaround time (waiting for assay to be built) -
Examples:	- Existing assays for advanced disease - Cancer screening assays (GRAIL)	- CAPP-seq	- Natera (TRACERx)

Sholl, PeerView

Personalized- bespoke assay

TRACERx approach





Abbosh C, et al. Nature. 2017;545:446-451.

ctDNA in the post-surgical setting- colorectal cancer

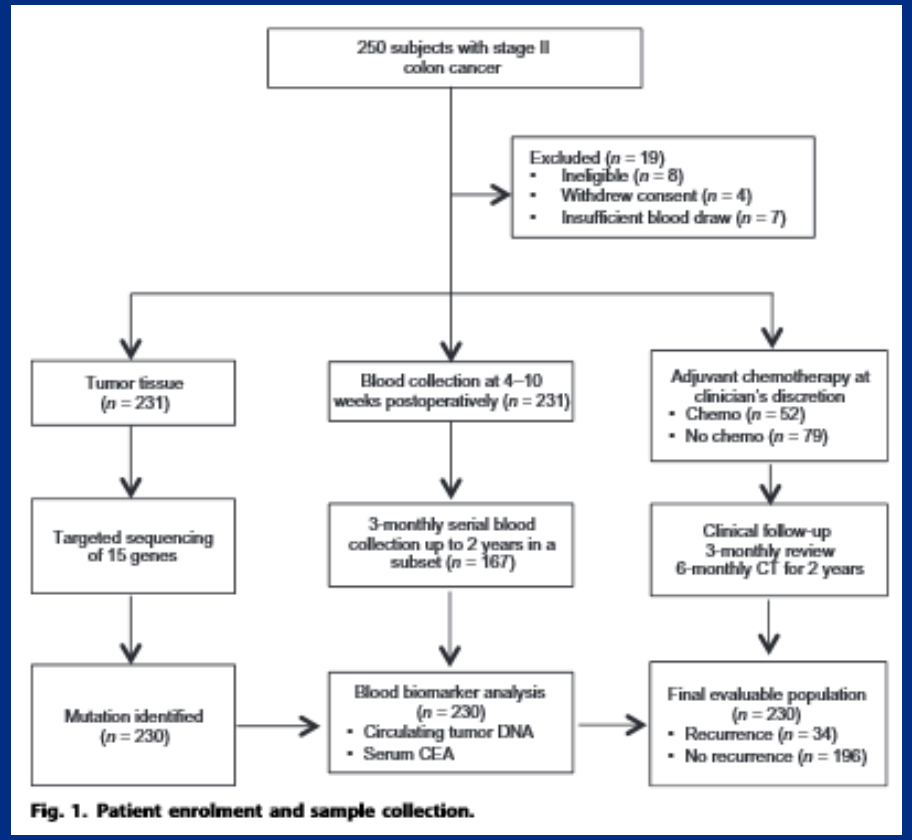
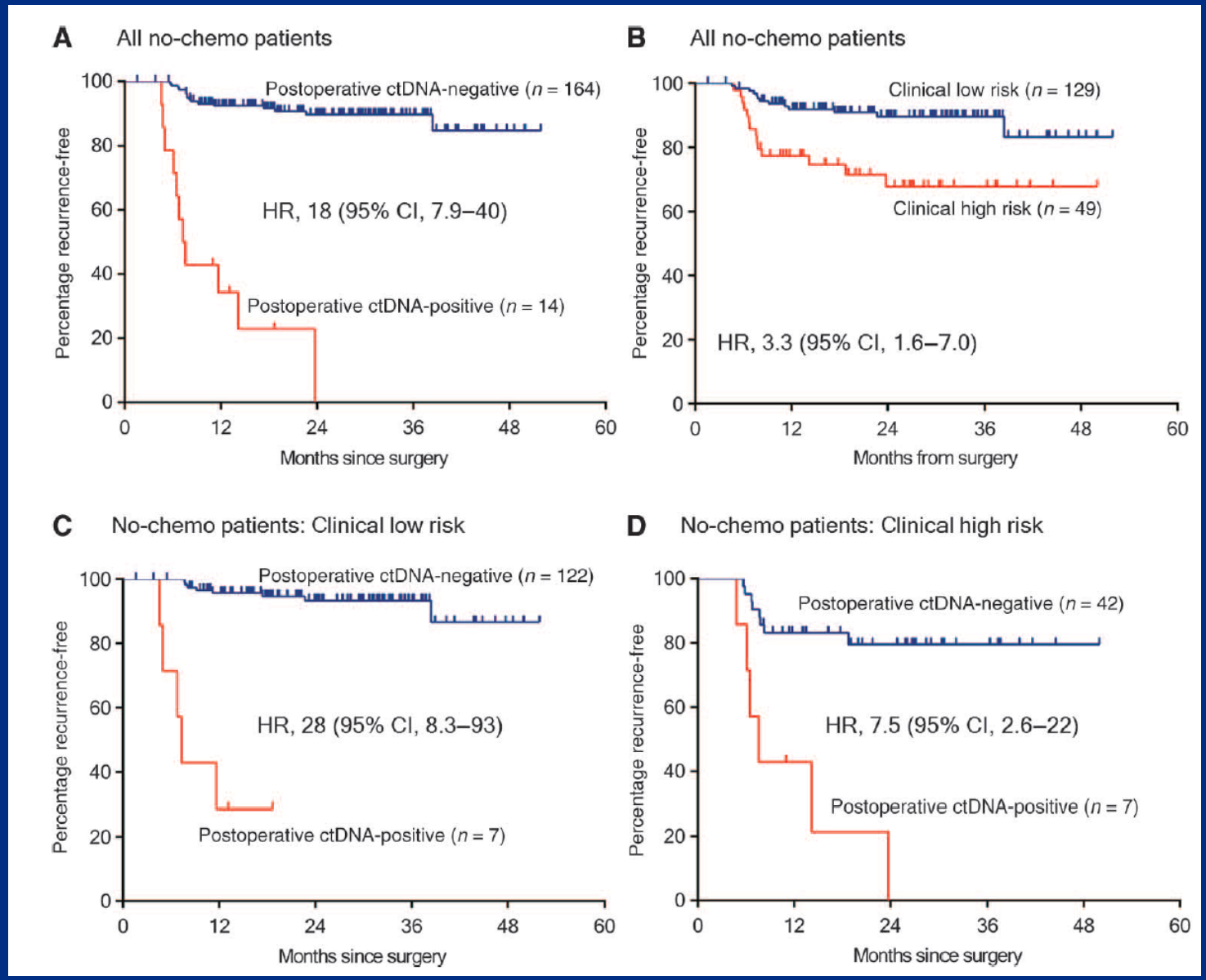
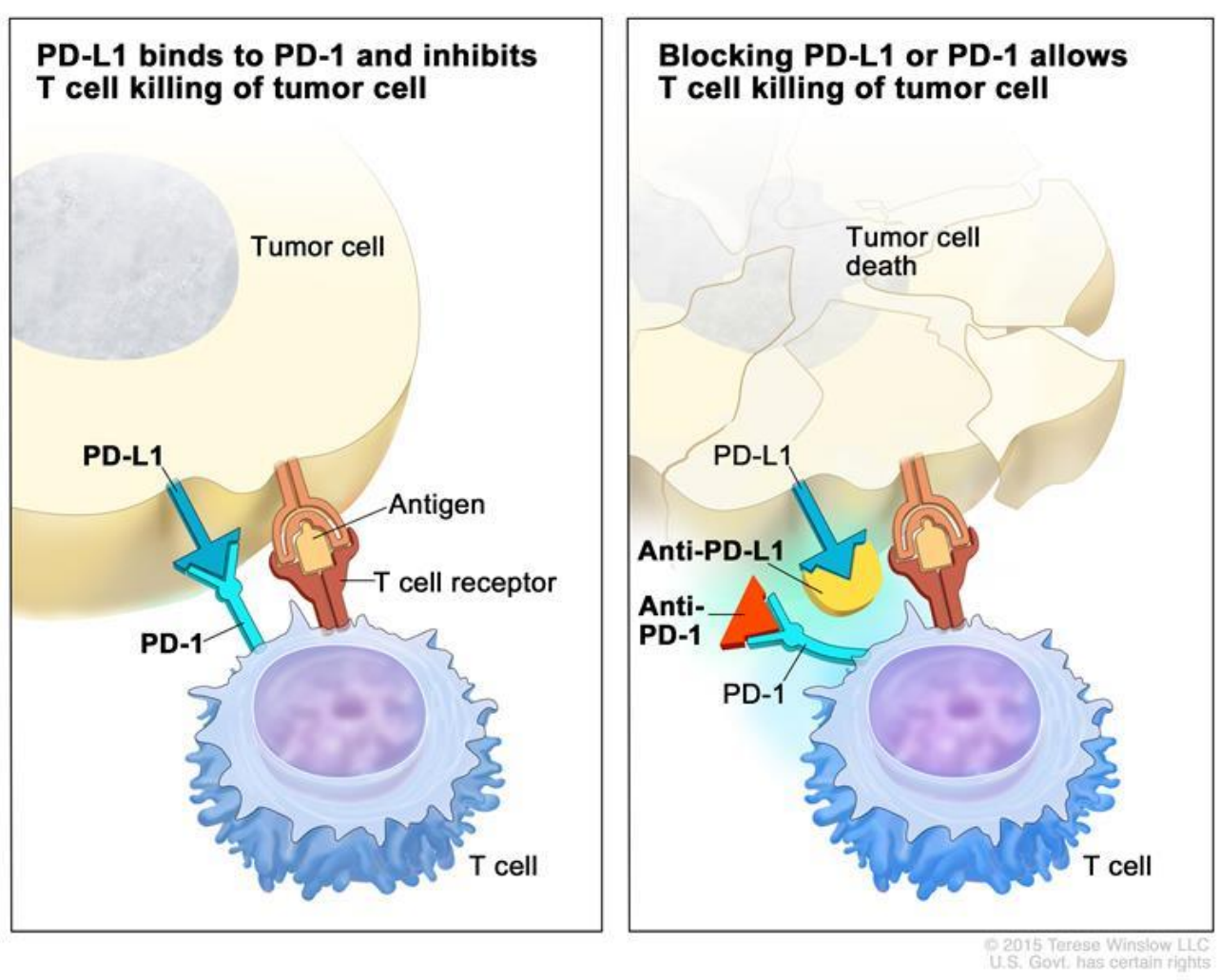


Fig. 1. Patient enrolment and sample collection.



Immunotherapy – the basics



Checkmate-017: Major survival benefit in squamous NSCLC

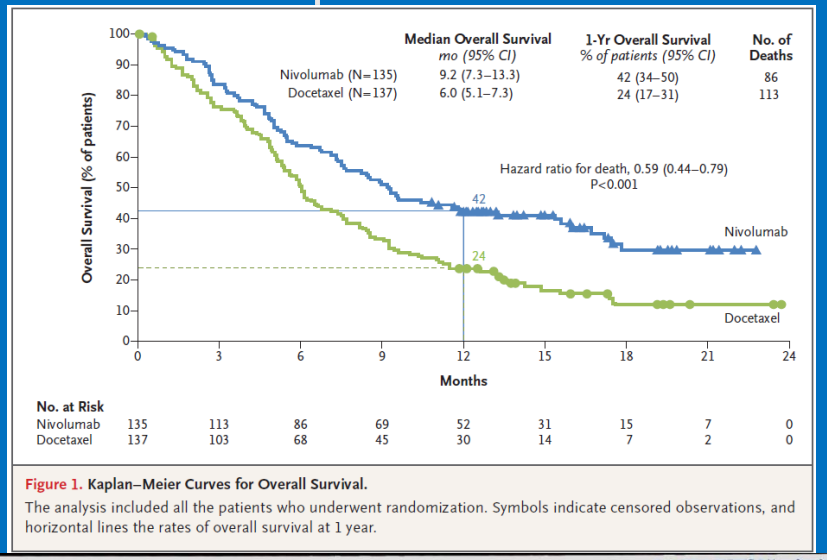
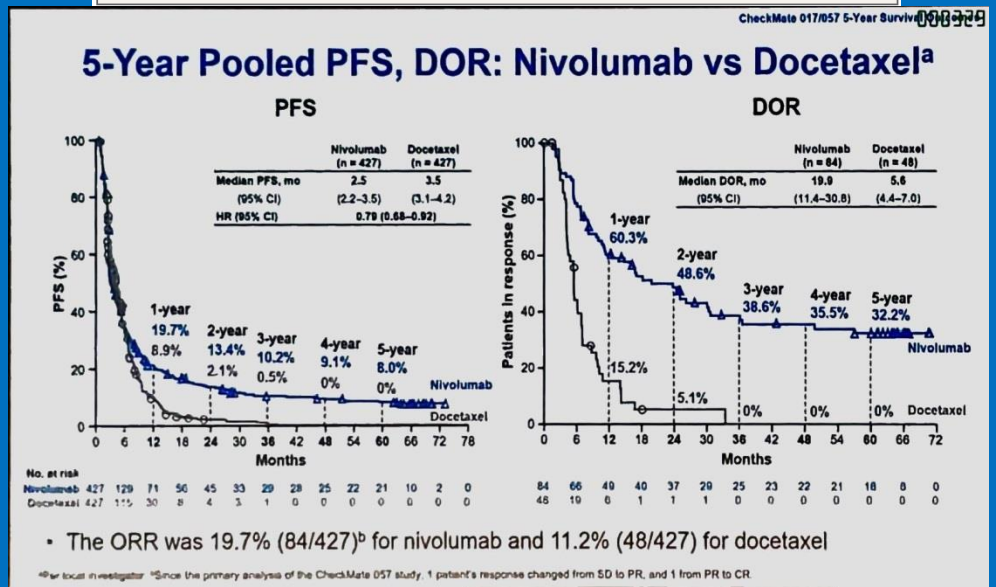


Figure 1. Kaplan–Meier Curves for Overall Survival.
The analysis included all the patients who underwent randomization. Symbols indicate censored observations, and horizontal lines the rates of overall survival at 1 year.



CTLA-4 Checkpoint Inhibition

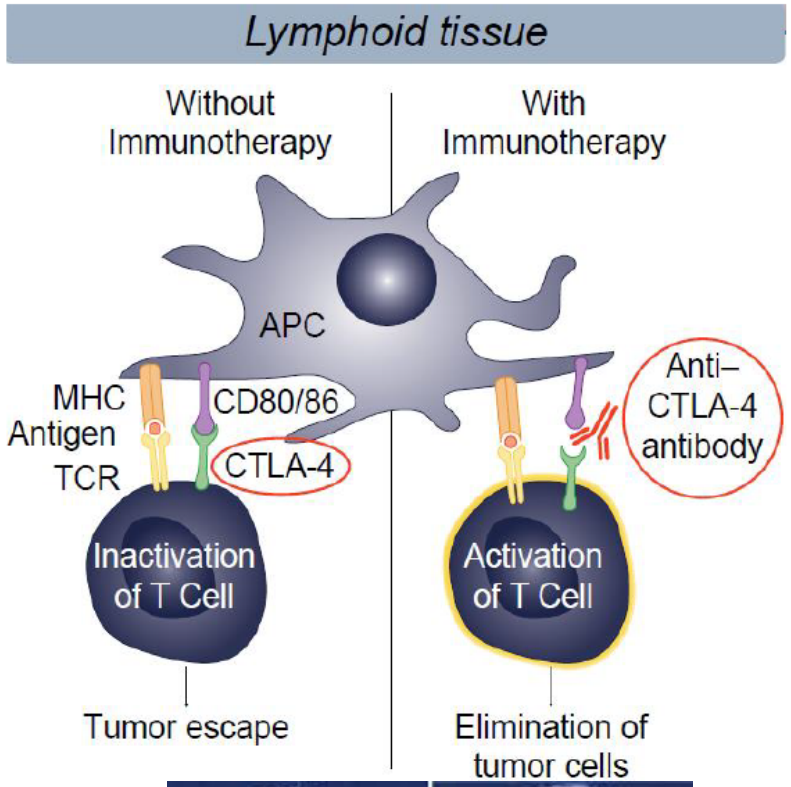
CTLA-4 is a negative regulator of costimulation required for activation of an antitumor T cell in a lymph node upon recognition of tumor antigen

↓

T cell inactivated

↓

Tumor escape



Anti–CTLA-4 monoclonal antibodies block negative regulation by CTLA-4

↓

T cell activated

↓

Tumor attack

Anti–CTLA-4 Therapies → **Ipilimumab**, **Tremelimumab**

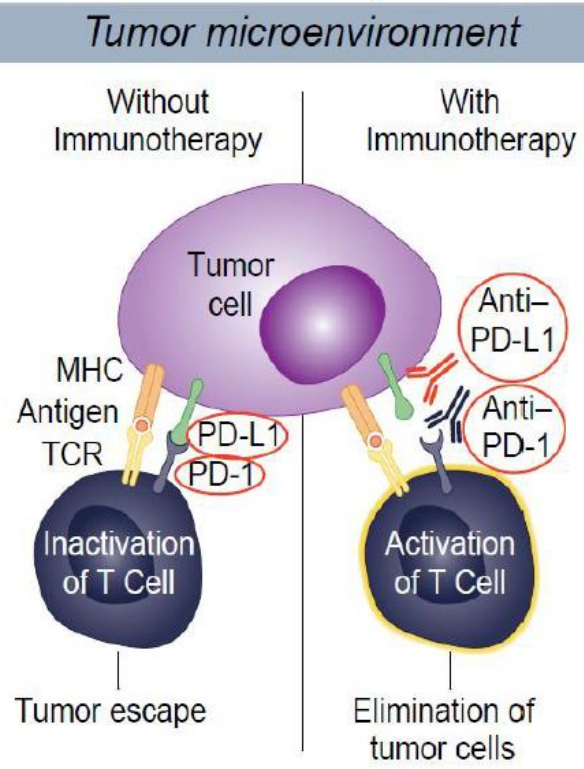
PD-1/PD-L1 Checkpoint Inhibition

PD-1 pathway inhibits signaling downstream of TCR

- **TCR triggered by antigen presented by tumor cell**
- **Negative regulatory receptor PD-1 expressed and PD-L1 reactively expressed**
- **PD-L1 binds to PD-1**

T cell inactivated

Tumor escape



Anti–PD-1 or anti–PD-L1 monoclonal antibodies block the interaction and negative regulation

T cell activated

Tumor attack

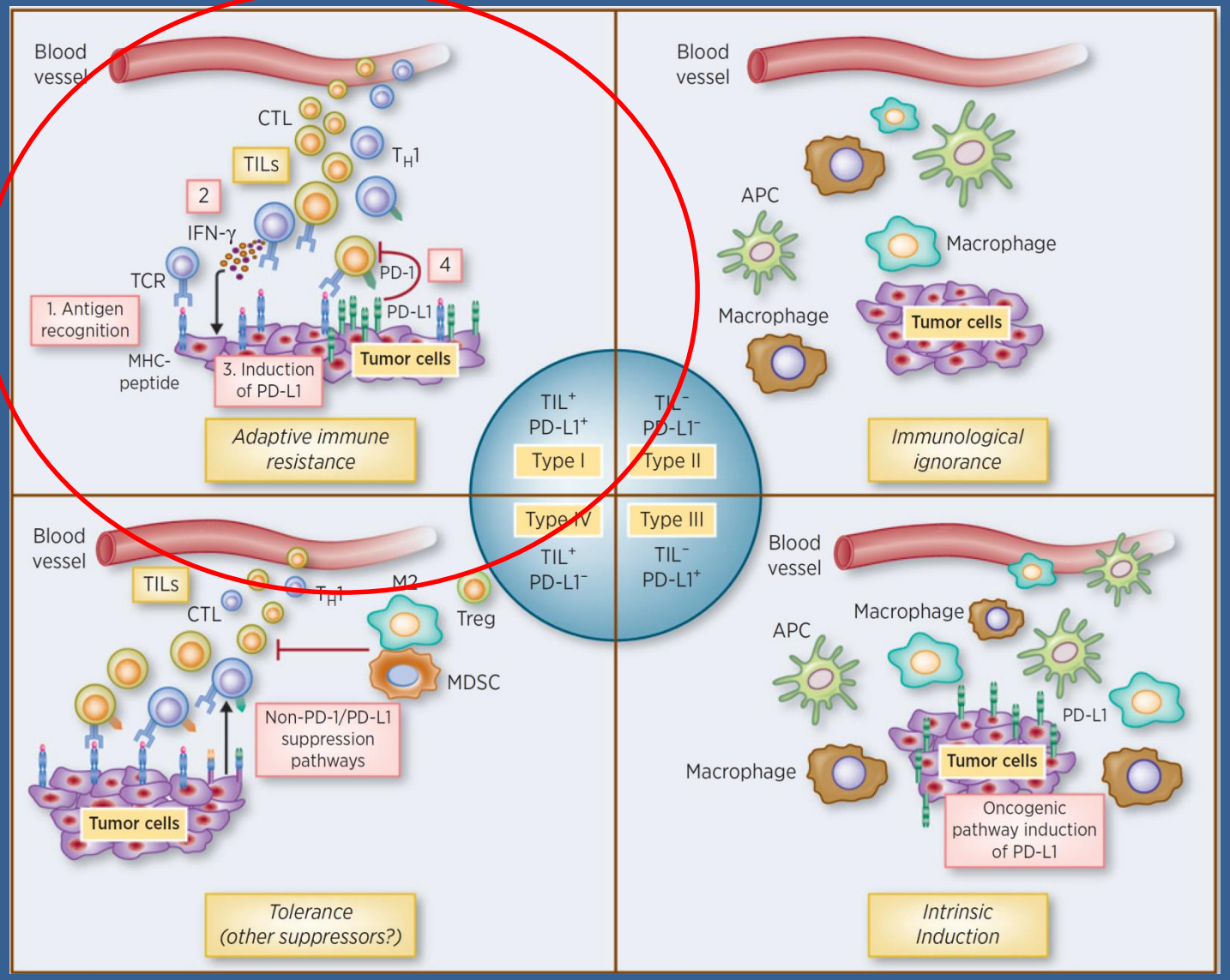
Anti–PD-1 Therapies

Nivolumab
Pembrolizumab
Cemiplimab-rwlc

Anti–PD-L1 Therapies

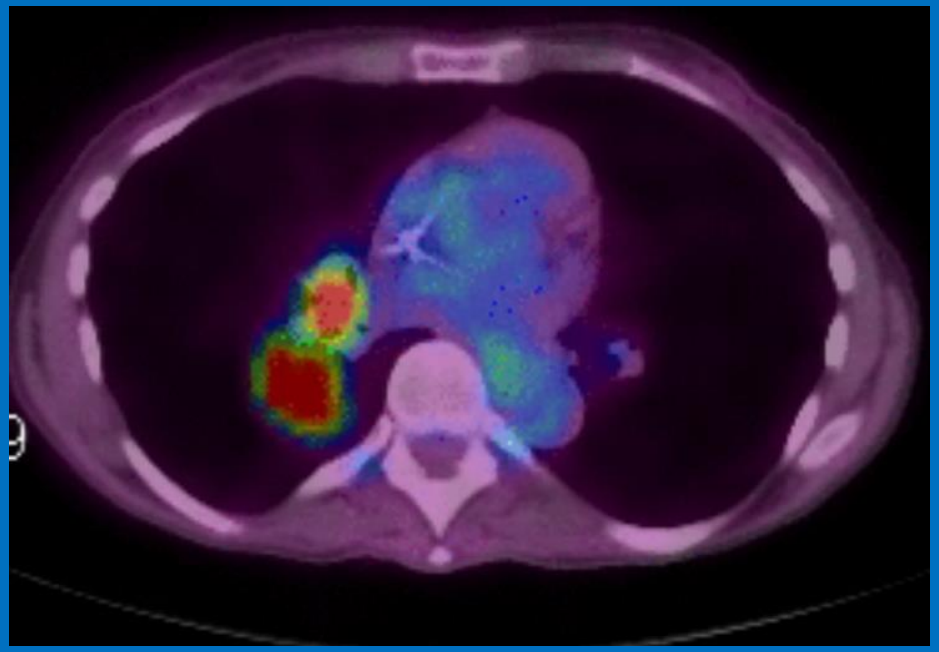
Atezolizumab
Avelumab
Durvalumab

Inflamed versus non-inflamed tumors

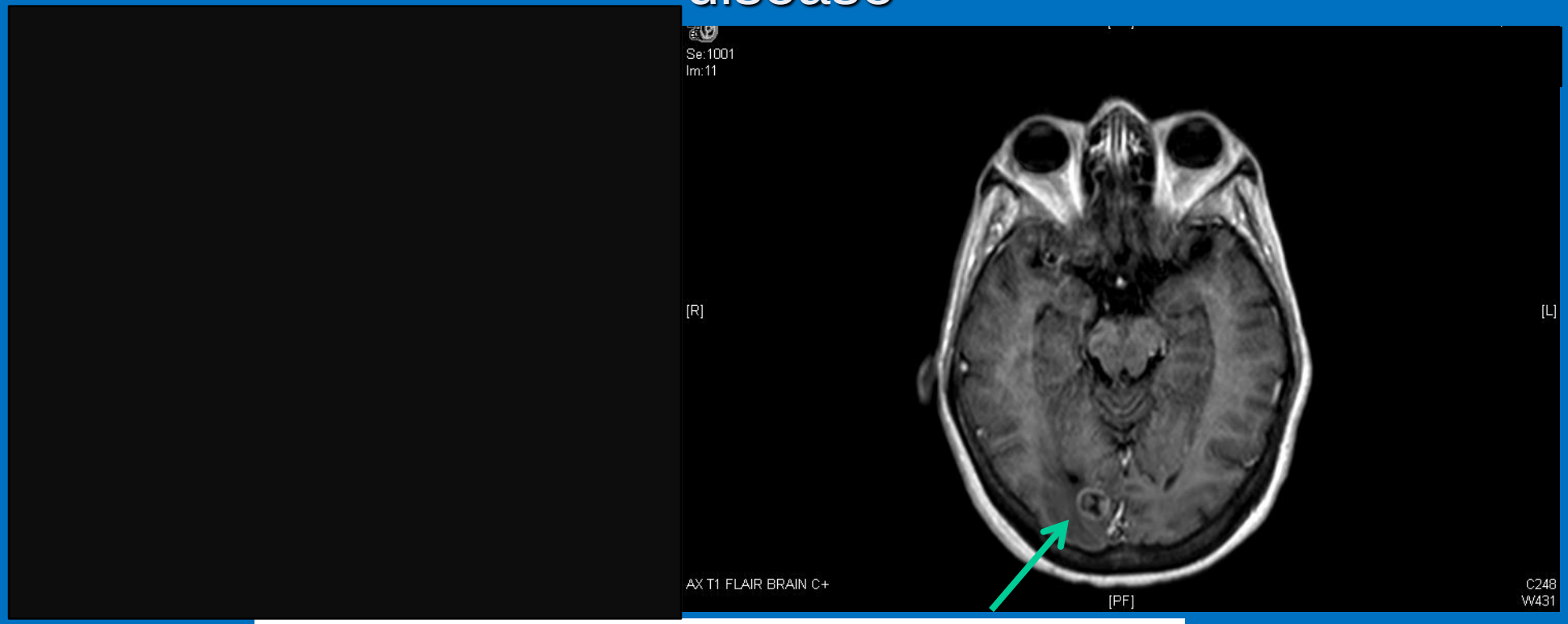


Teng MW et al. *Cancer Res.* 2015;75:2139-2145.

- 74 year old African American lady with heavy smoking history presents in 9/2016 with a supraclavicular mass, evaluation reveals advanced K-ras mutated lung adenocarcinoma



Unfortunately brain MR revealed multiple small CNS mets suggestive of leptomeningeal disease



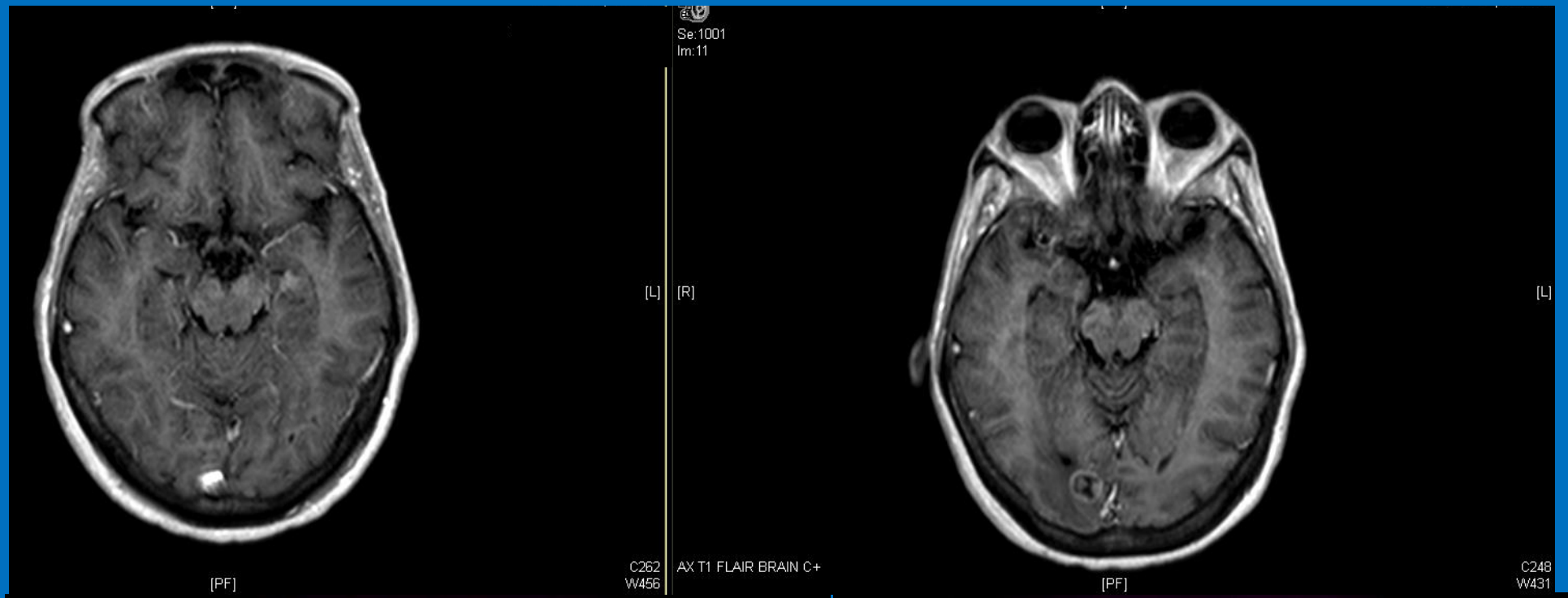
SURGICAL PATHOLOGY ADDENDUM (9/16/2016)

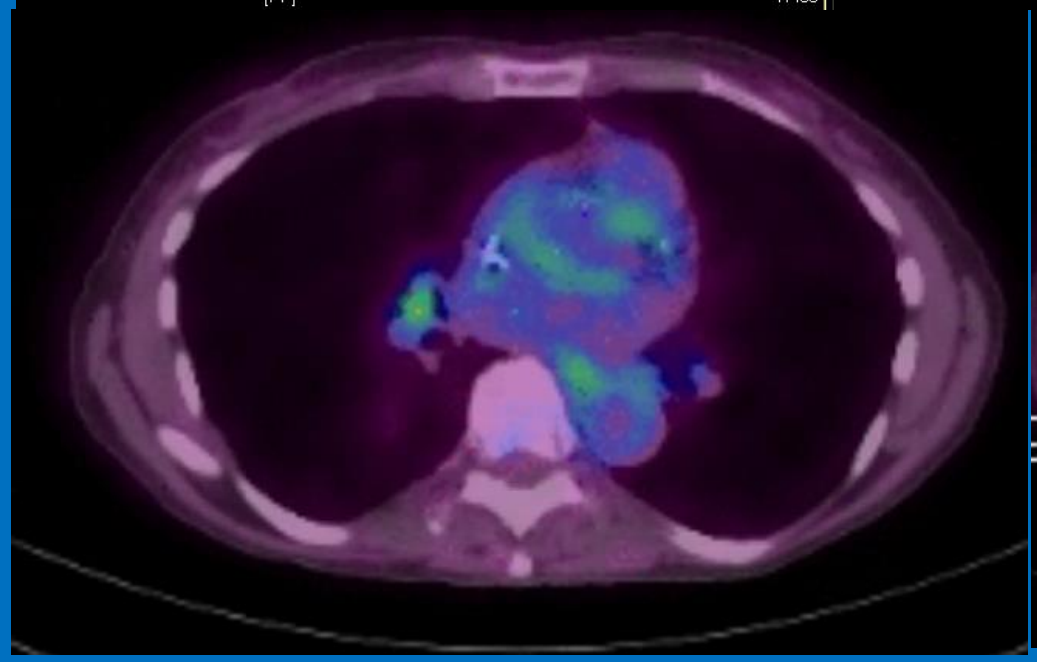
This report is issued to provide results of PD-L1 (22C3) pharmDx immunohistochemical staining, a
companion test to identify tumors for treatment with KEYTRUDA(TM) (pembrolizumab).

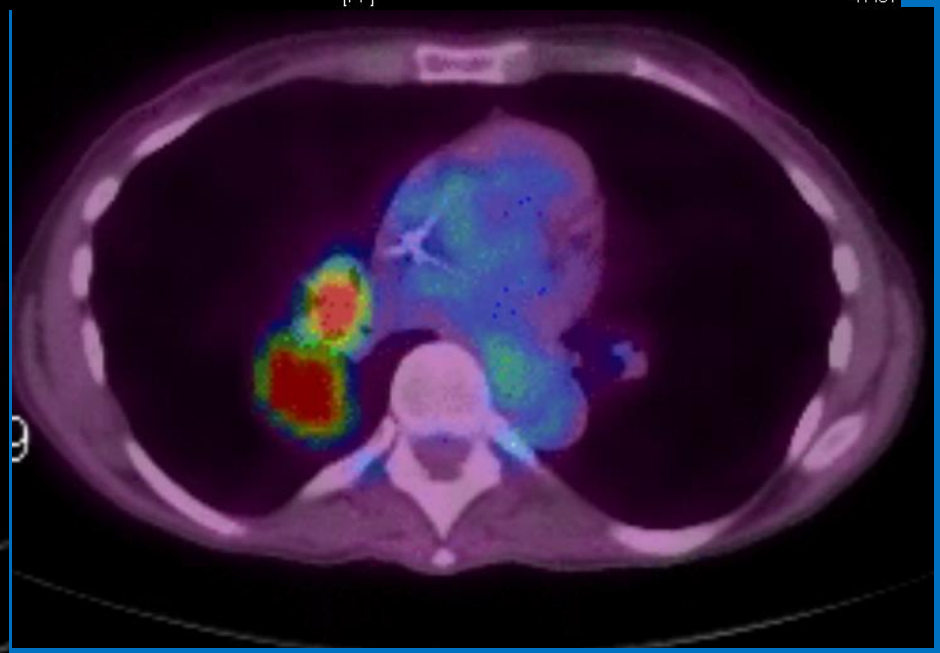
Tissue Block Tested: A1-A

Tumor Proportion Score (TPS): 100%

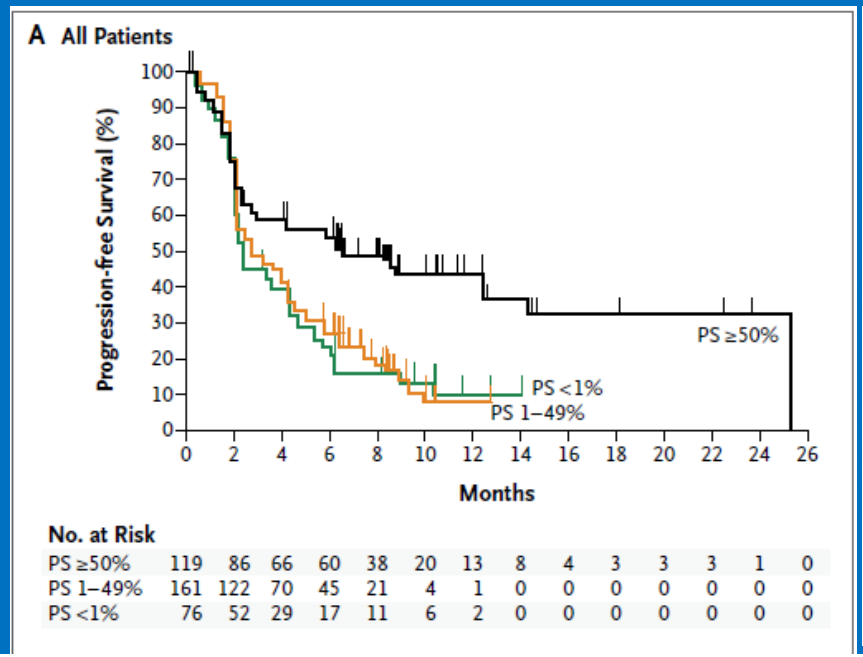
Cell Membrane Stain Intensity: 1 - 3+


Se:1001
Im:11
[L]
[R]
[PF]
C262
W456
AX T1 FLAIR BRAIN C+
[L]
[PF]
C248
W431





PD-L1 as a biomarker



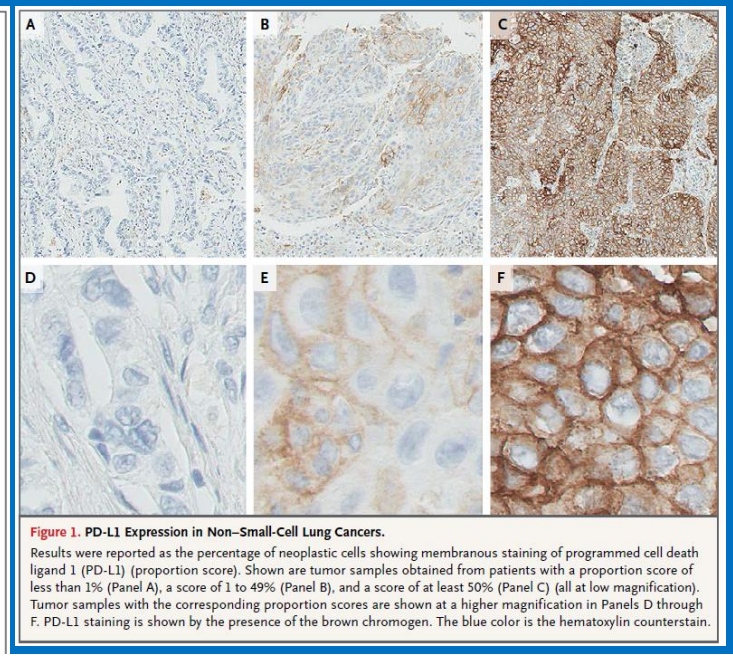
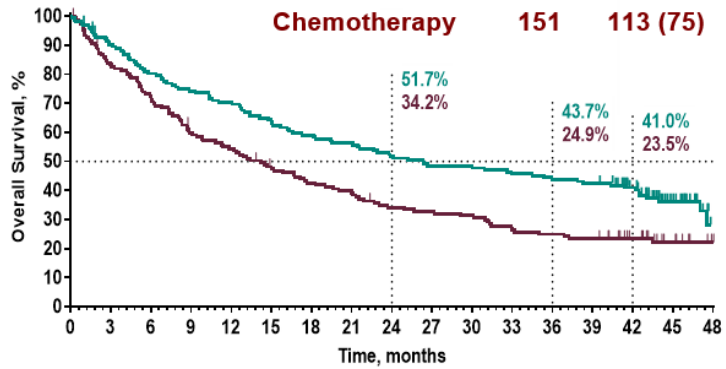


Figure 1. PD-L1 Expression in Non–Small-Cell Lung Cancers.
Results were reported as the percentage of neoplastic cells showing membranous staining of programmed cell death ligand 1 (PD-L1) (proportion score). Shown are tumor samples obtained from patients with a proportion score of less than 1% (Panel A), a score of 1 to 49% (Panel B), and a score of at least 50% (Panel C) (all at low magnification). Tumor samples with the corresponding proportion scores are shown at a higher magnification in Panels D through F. PD-L1 staining is shown by the presence of the brown chromogen. The blue color is the hematoxylin counterstain.

Garon et al NEJM

KEYNOTE 024

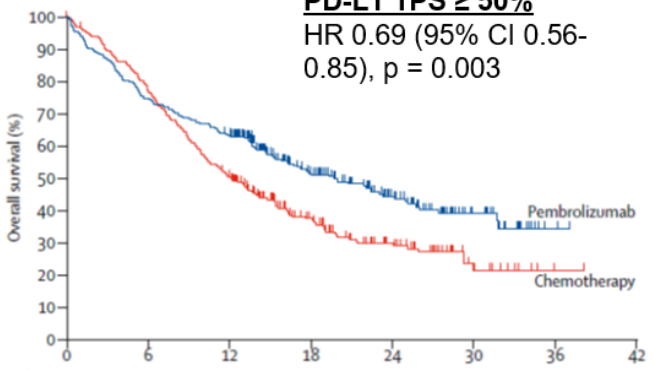
	N	Events, n (%)	HR (95% CI)
Pembrolizumab[a]	154	97 (63)	0.65 (0.50–0.86) *P* = 0.001[b]
Chemotherapy	151	113 (75)	



Median (95% CI)
26.3 mo (18.3–40.4 mo)
14.2 mo (9.8–18.3 mo)

No. at risk
Pembrolizumab 154 136 121 112 106 96 89 85 78 73 73 69 66 64 50 24 5
Chemotherapy 151 124 108 88 80 69 61 56 48 46 44 37 35 33 24 14 6

KEYNOTE 042

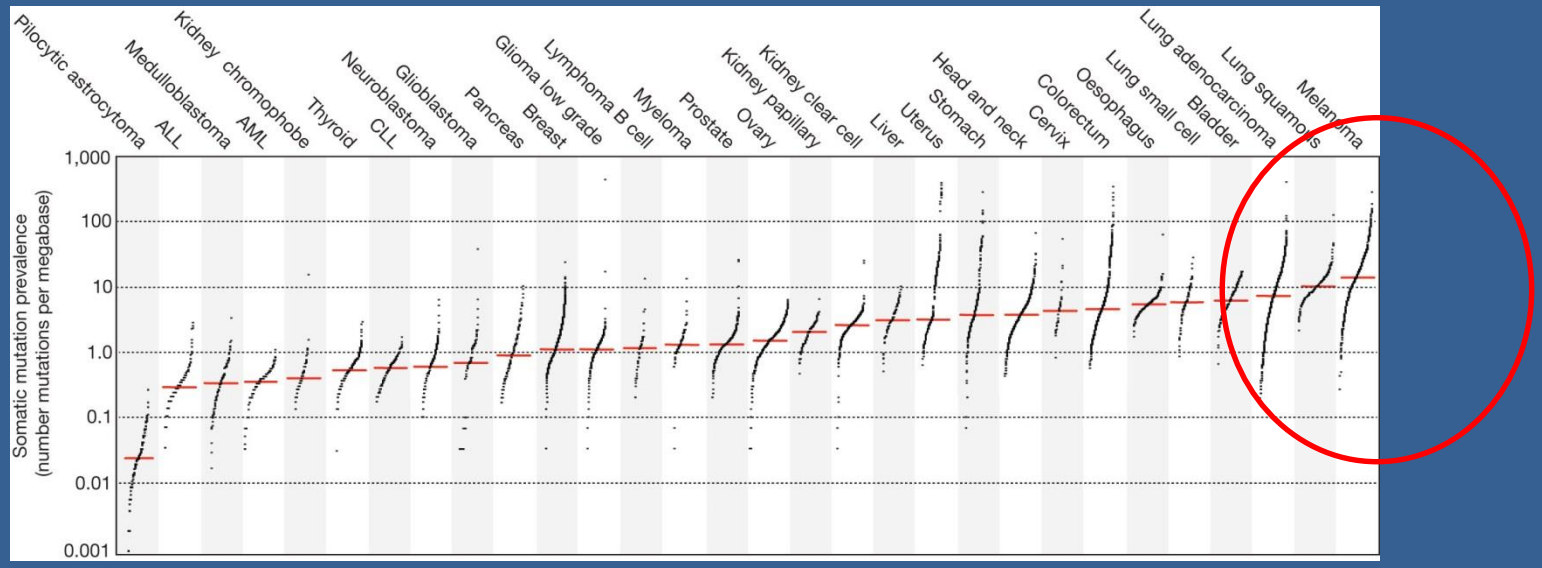


Number at risk (censored)
Pembrolizumab group 299 (0) 224 (0) 189 (1) 107 (55) 59 (91) 22 (122) 2 (140) 0 (142)
Chemotherapy group 300 (0) 231 (2) 149 (4) 75 (46) 40 (67) 11 (90) 1 (100) 0 (101)

Reck et al WCLC 19

Lopes et al ASCO 2019

TMB as a biomarker for IO

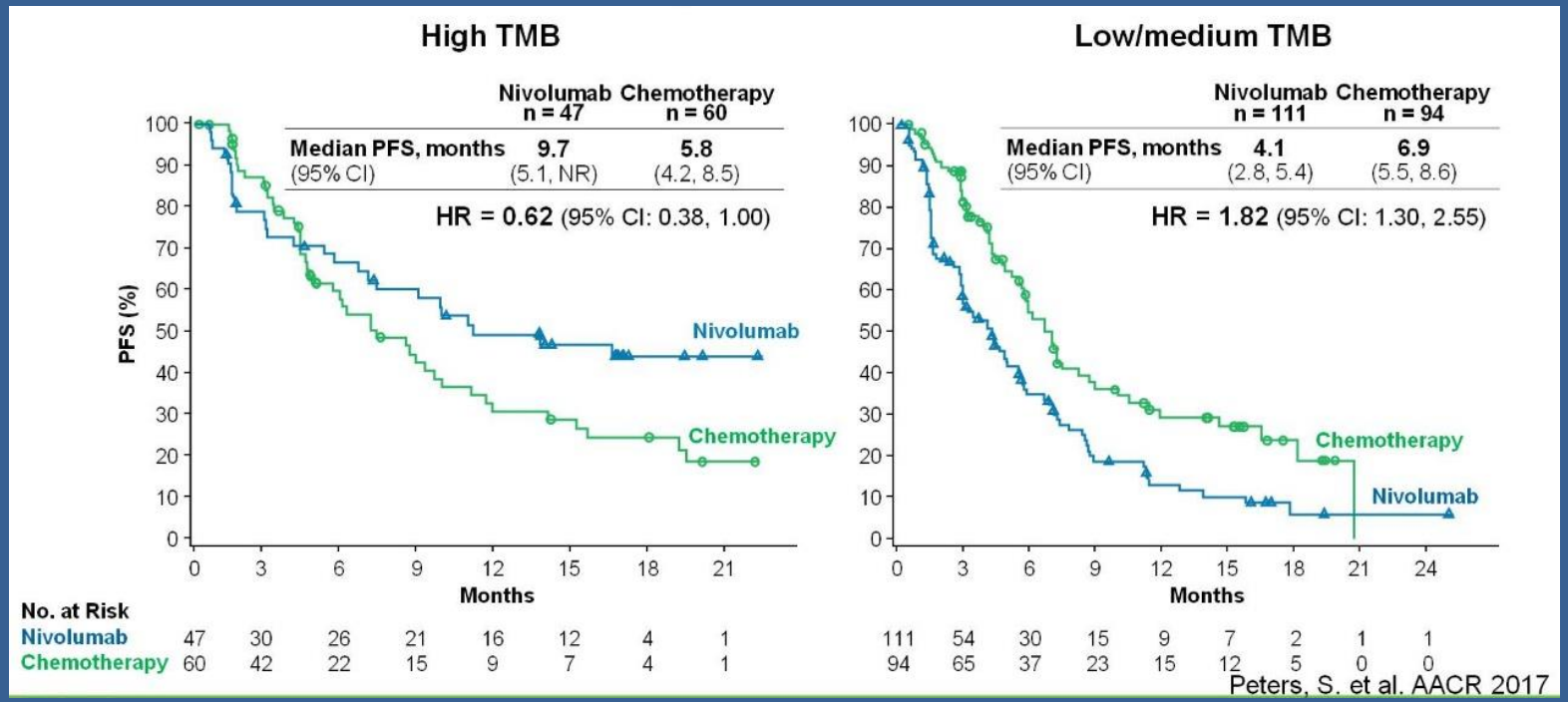


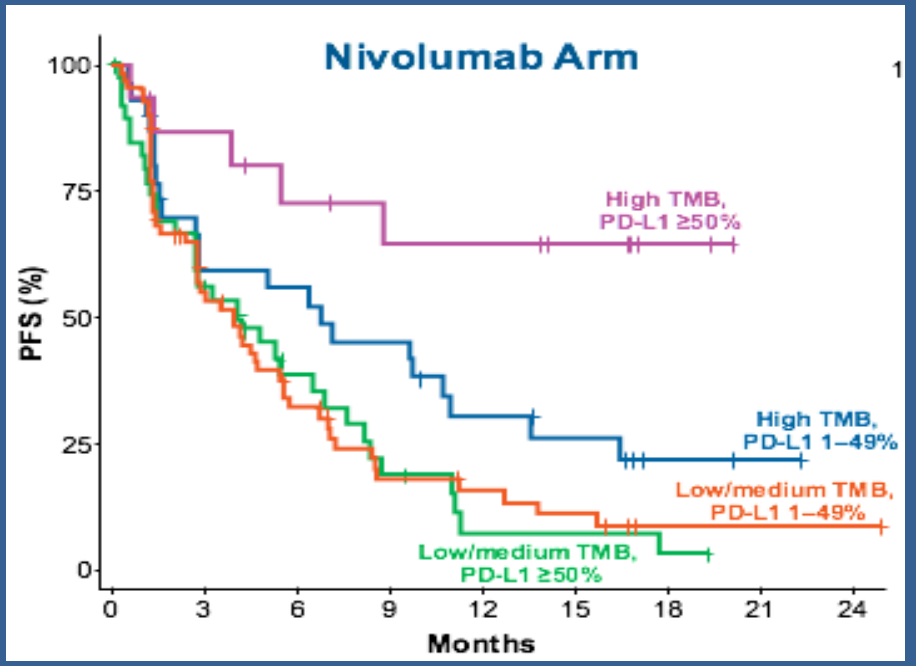
	Whole Exome	Foundation NGS	MSKCC NGS
# Genes	~22,000	324 cancer-related genes	468 cancer-related genes
Coverage	~30 Mb	0.8 Mb	1.22 Mb
Types of mutations	Coding missense mutations	Coding, missense, and indel mutations per Mb	Coding missense mutation per Mb
Germline mutations	Subtracted using germline DNA	Estimated bioinformatically & subtracted	Subtracted using matched blood
TMB Definition	# somatic, missense mutations in the tumor genome	# somatic, coding mutations (synonymous and non-synonymous), short indels per Mb of tumor genome	# somatic, missense mutations per Mb of tumor genome
TAT	At least 4-6 weeks	2 weeks	2 weeks

Alexandrov, LB et al. Nature 2013;500: 415-21

TMB can outperform PD-L1 IHC?

NSCLC: CheckMate 026 (nivolumab)





Peters S, eta al. AACR 2017. Abstract CT082.

Table 1 | **Factors that predict response to immune checkpoint inhibitor therapy**

Factor	Association with favourable clinical outcome	Validated in phase III clinical trial?	Predictive versus prognostic[a]	Cancer type	Tissue type for biomarker assessment[b]	Possible assay type for biomarker assessment
Tumour mutation burden	Positive	Yes	Predictive	Multiple cancer types	Blood or tumour tissue	NGS WES or targeted gene panel sequencing
PDL1 expression	Positive	Yes	Predictive	Multiple cancer types	Tumour tissue	Immunohistochemistry
Copy number variation	Negative	TBD	Prognostic, predictive or both	Multiple cancer types	Tumour tissue	NGS WES or targeted gene panel sequencing
HLA class I diversity	Positive	TBD	Predictive	Melanoma and NSCLC	Blood	NGS WES or PCR-based typing
LOH at HLA class I alleles	Negative	TBD	Predictive	Melanoma	Tumour tissue	TBD
T cell repertoire clonality change	Positive	TBD	Predictive	Melanoma	Tumour tissue or blood	TBD
T cell-inflamed microenvironment	Positive	TBD	Prognostic, predictive or both	Multiple cancer types	Tumour tissue	NGS RNA-seq or immunostaining
SERPINB3 or *SERPINB4* mutations	Positive	TBD	Predictive	Melanoma	Tumour tissue	NGS WES
Gut microbial diversity	Positive	TBD	Predictive	Melanoma	Oral or gut	PCR or NGS
Specific gut microbial species	Positive or negative	TBD	Predictive	Melanoma	Oral or gut	PCR or NGS
TGFβ expression	Negative	TBD	Predictive	Colon cancer and urothelial cancer	Tumour tissue	NGS RNA-seq or expression panel
Mutations in the β-catenin pathway	Negative	TBD	Predictive	Melanoma	Tumour tissue or blood	NGS WES, targeted gene panel sequencing or RNA-seq
JAK2 mutations (rare)[c]	Negative	TBD	Predictive	Melanoma	Tumour tissue or blood	NGS WES or targeted gene panel sequencing
B2M mutations (rare)[c]	Negative	TBD	Predictive	Melanoma	Tumour tissue or blood	NGS WES or targeted gene panel sequencing
STK11 mutations (common)	Negative	TBD	Predictive	NSCLC	Tumour tissue or blood	NGS WES or targeted gene panel sequencing

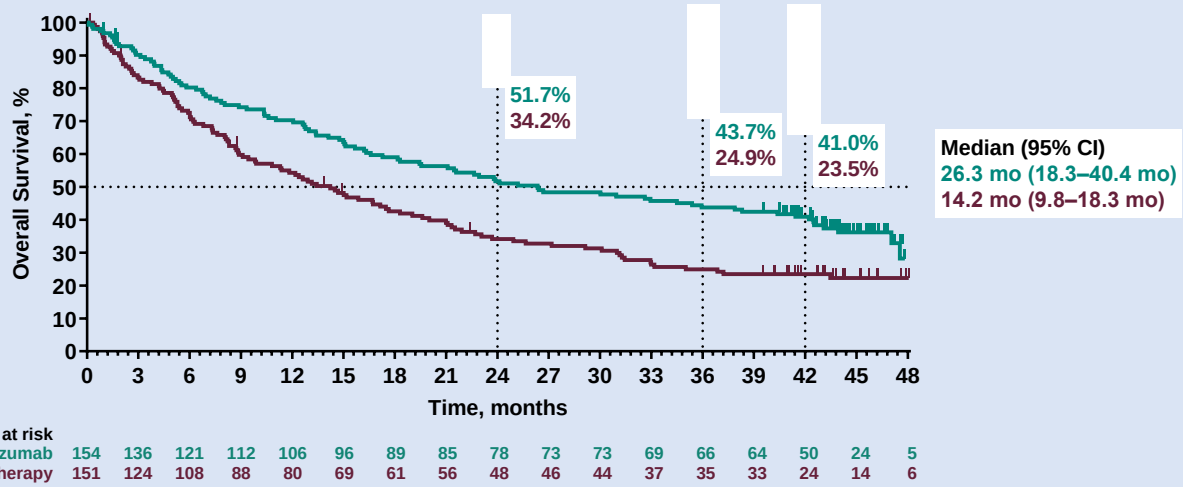
HLA, human leukocyte antigen; LOH, loss of heterozygosity; NSCLC, non-small-cell lung cancer; NGS, next-generation sequencing; PDL1, programmed cell death 1 ligand 1; RNA-seq, RNA sequencing; TBD, to be determined; TGFβ, transforming growth factor-β; WES, whole-exome sequencing. [a]Predictive refers to a given biomarker that has an effect dependent on the immune checkpoint inhibitor therapy, and prognostic refers to a biomarker that has a specific effect independent of the therapy. [b]Blood detection of mutations refers to cell-free DNA analysis. [c]*JAK2* and *B2M* mutations are controversial. Responses have been seen in patients with these mutations. Intratumoural heterogeneity likely needs to be assessed along with these mutations.

Havel et al Nature Rev Cancer


ErbB2
bTMB
NRG
p53
T790M
C797S
B-Raf
SCLC tr
MSI
RET
KRAS
ECOG PS
TILs
TMB
EGFR
ROS
STK11
clonal
PD-L1
Teff
smoking
MET
NTRK
Age
KEAP1
ALK
ctDNA

Keynote 024

	N	Events, n (%)	HR (95% CI)
Pembrolizumab[a]	154	97 (63)	0.65 (0.50–0.86)
Chemotherapy	151	113 (75)	*P* = 0.001[b]



Median (95% CI)
26.3 mo (18.3–40.4 mo)
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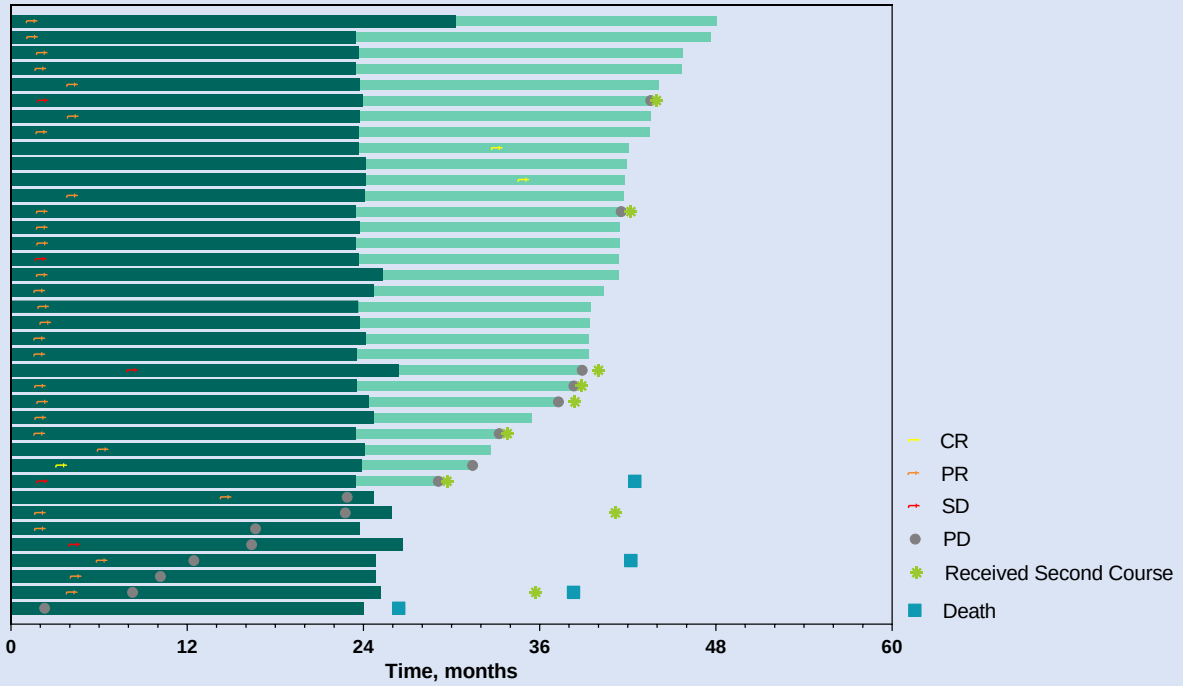
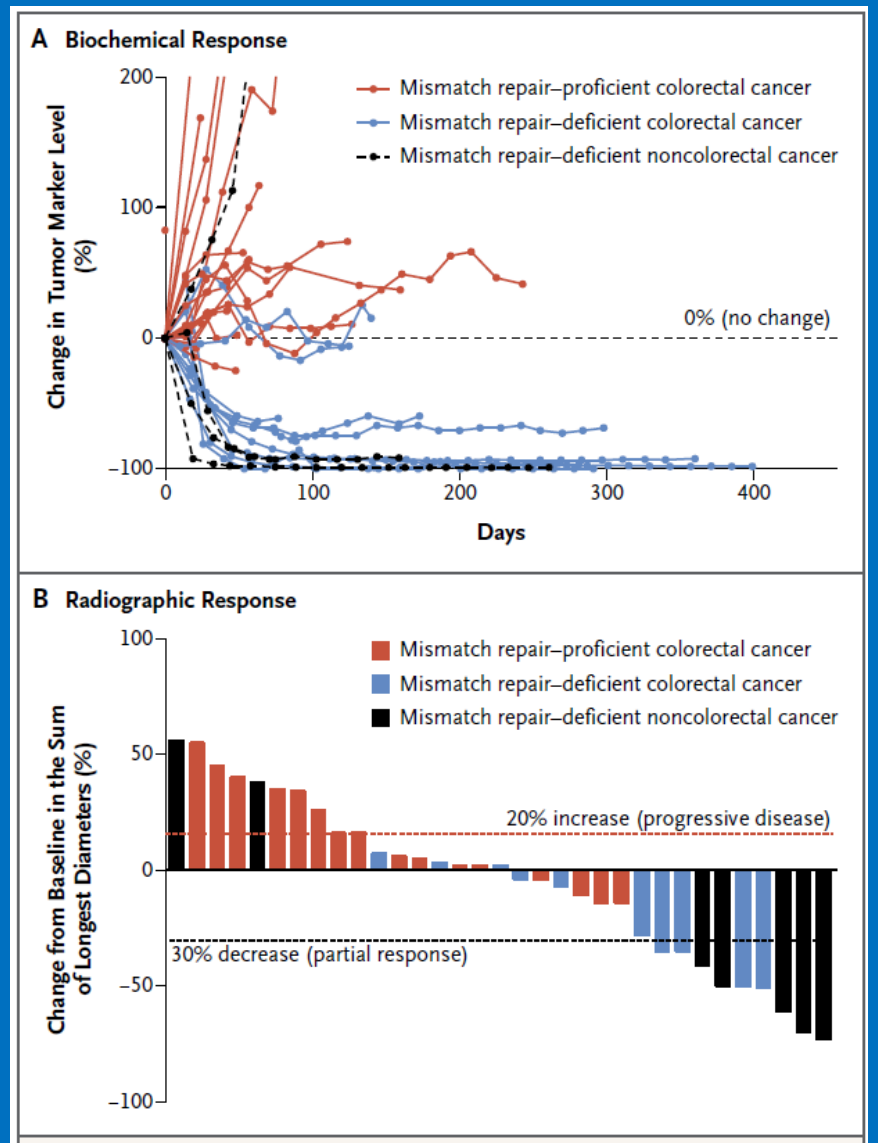


Reck WCLC 2019

[a]Effective crossover rate from chemotherapy to anti–PD-L1 therapy, 64.9% (98 patients in total crossed over to anti–PD-[L]1 therapy: 83 patients crossed over to pembrolizumab during the study, and 21 patients received subsequent anti–PD-L1 therapy outside of crossover; patients may have received >1 subsequent anti–PD-L1 therapy). [b]Nominal *P* value.

Efficacy of immunotherapy in MSI-deficient colorectal cancers



PD-1 Blockade in MSI-H Cancer- a new era of tissue agnostic approaches

Colorectal Cancers

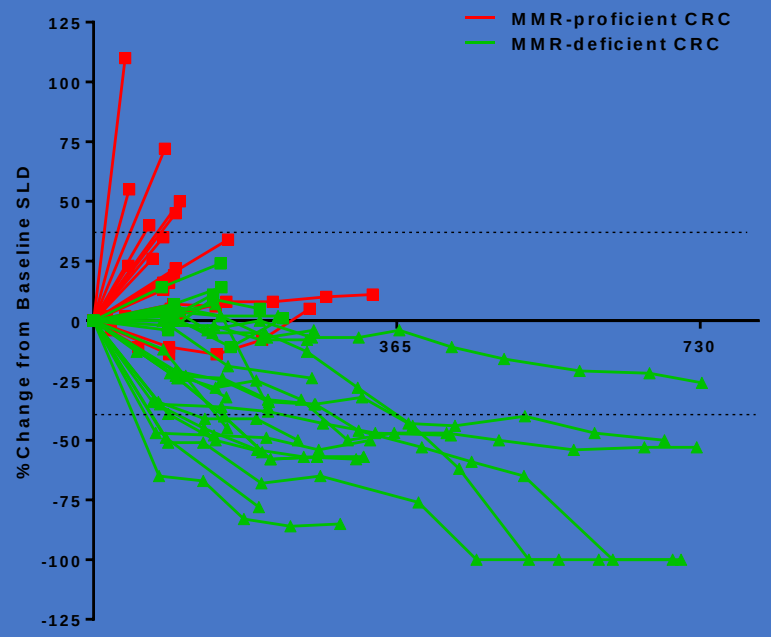
Cohort A
Deficient in Mismatch Repair (MSI-H) (n = 28)

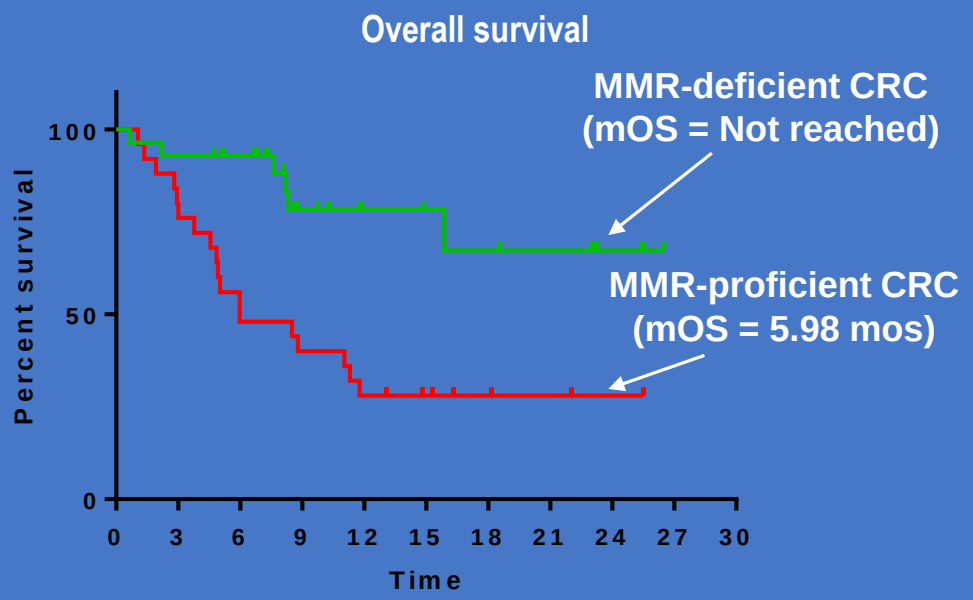
Cohort B
Proficient in Mismatch Repair (n = 25)

Non-Colorectal Cancers

Cohort C
Deficient in Mismatch Repair (MSI-H) (n = 30)

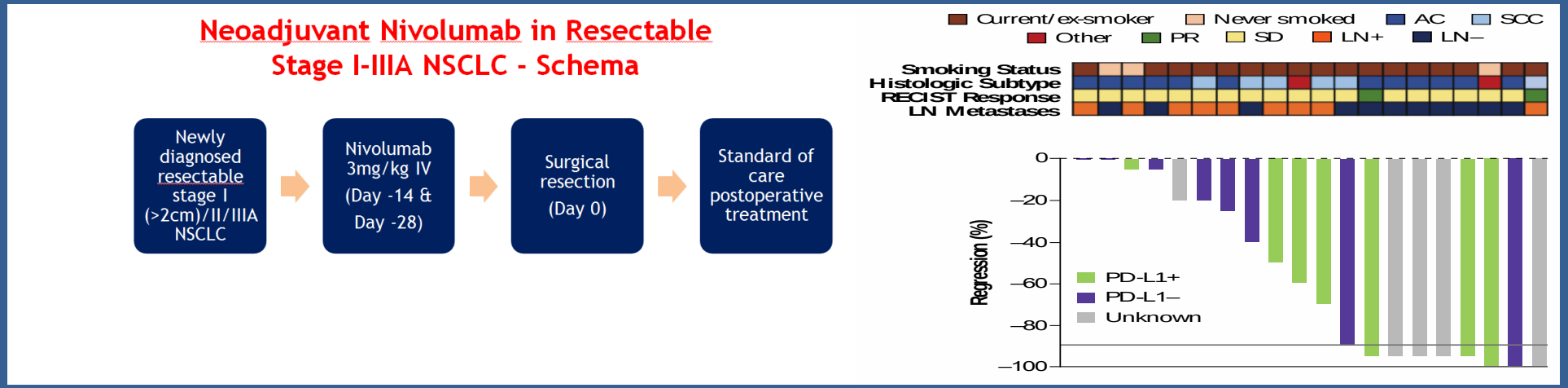
Anti-PD1 (pembrolizumab) – 10 mg/kg every 2 weeks

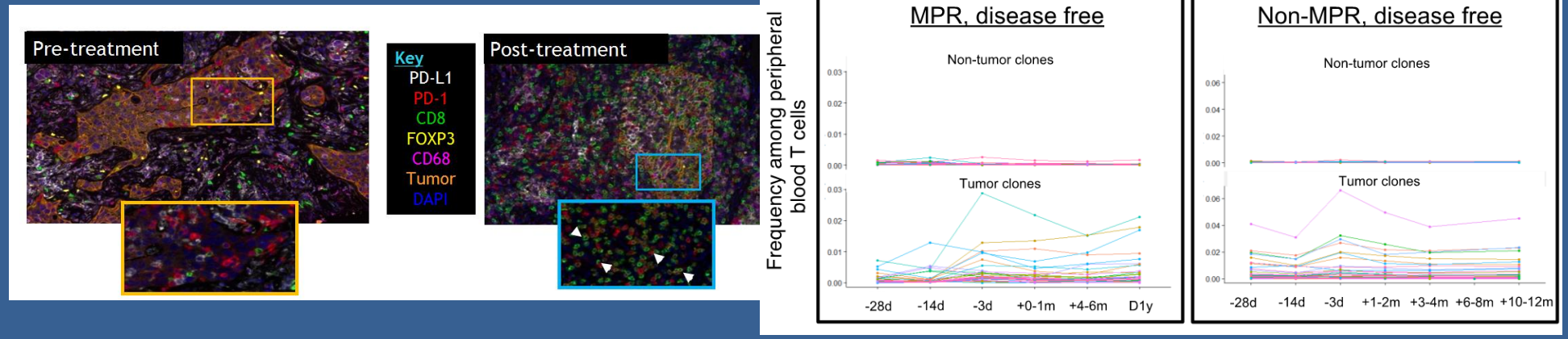




Diaz LA, et al. ASCO 2016. Abstract 3003.

Hopkins/MSKCC study- provocative preliminary/translational results





NADIM study

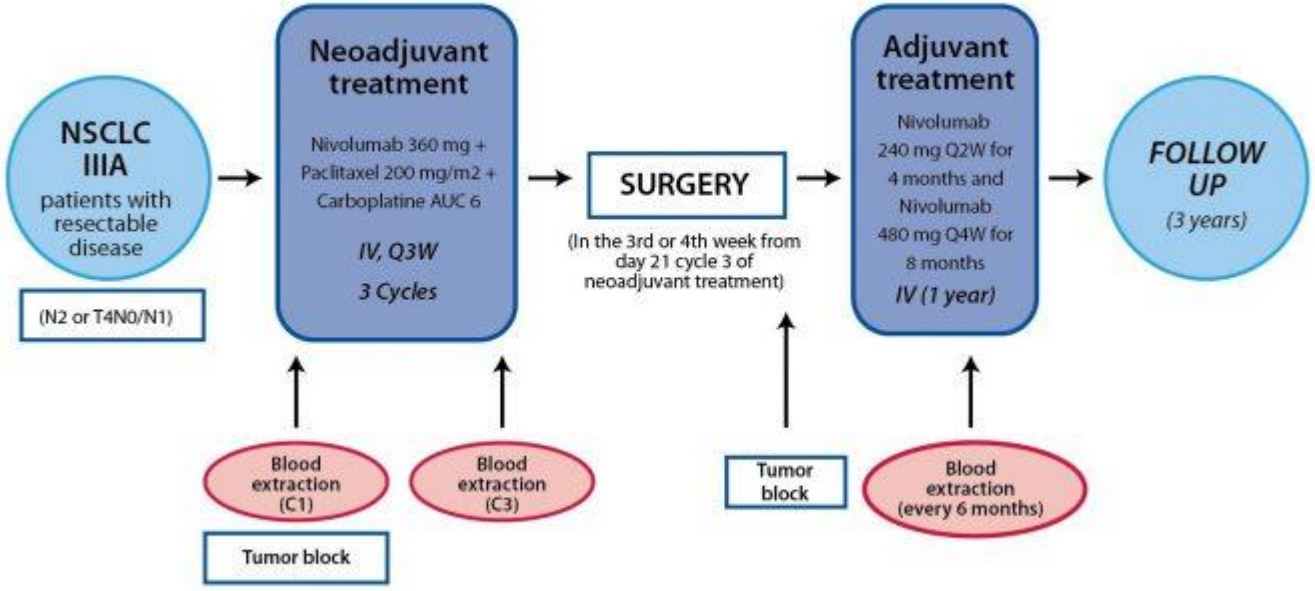
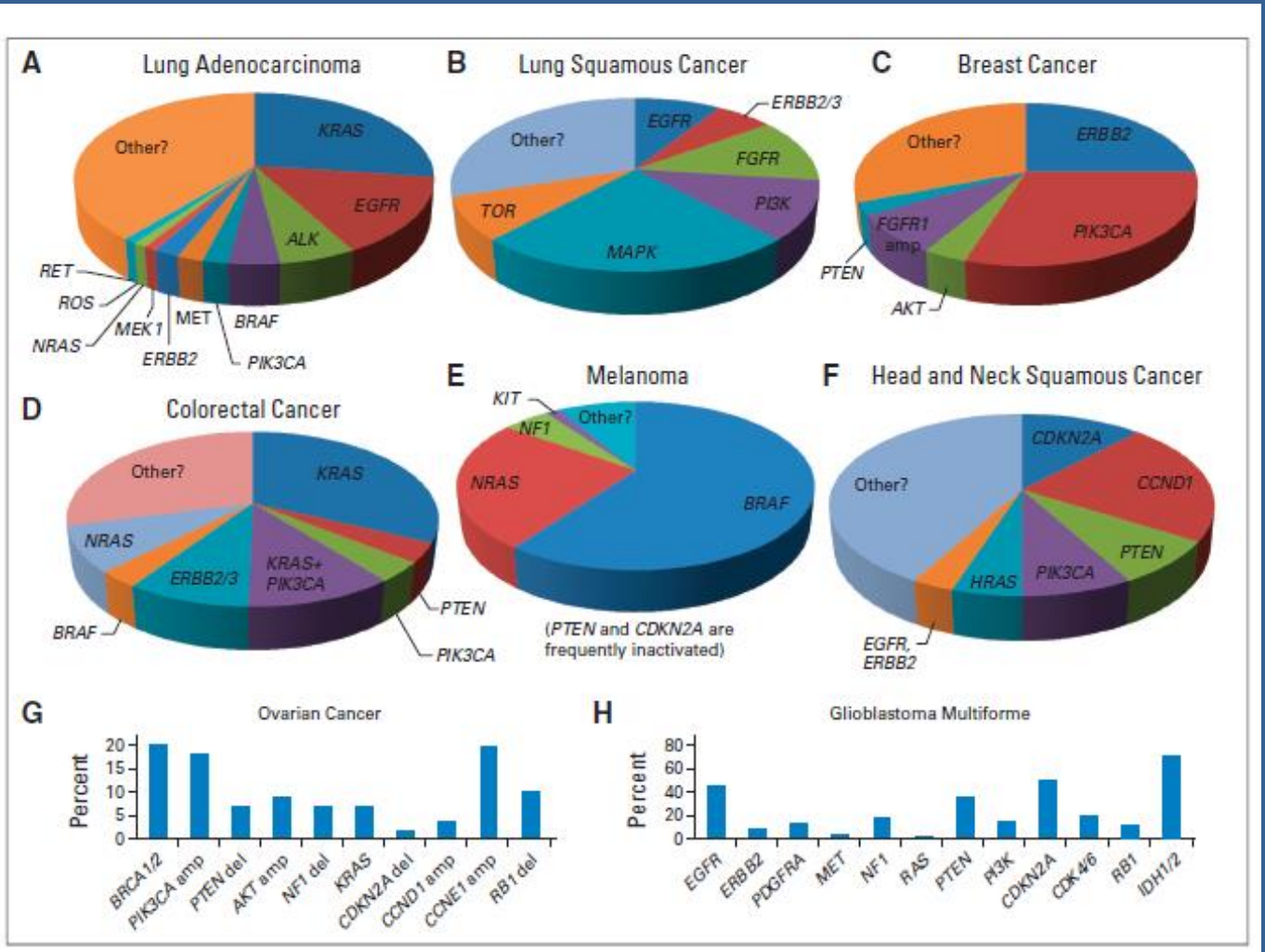


Table 1. Pathologic Response

	N	%
Major response Complete response	24 18	80.0 60.0
Less < 90%	6	20.0
Total	30	100.0

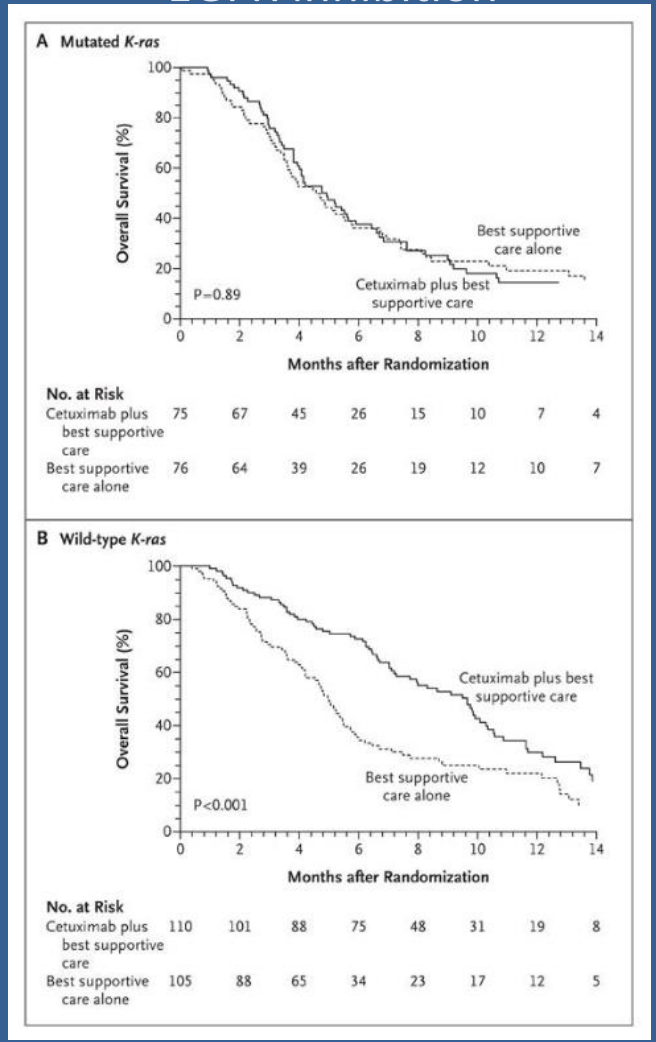
Precision medicine- an enlarging basket

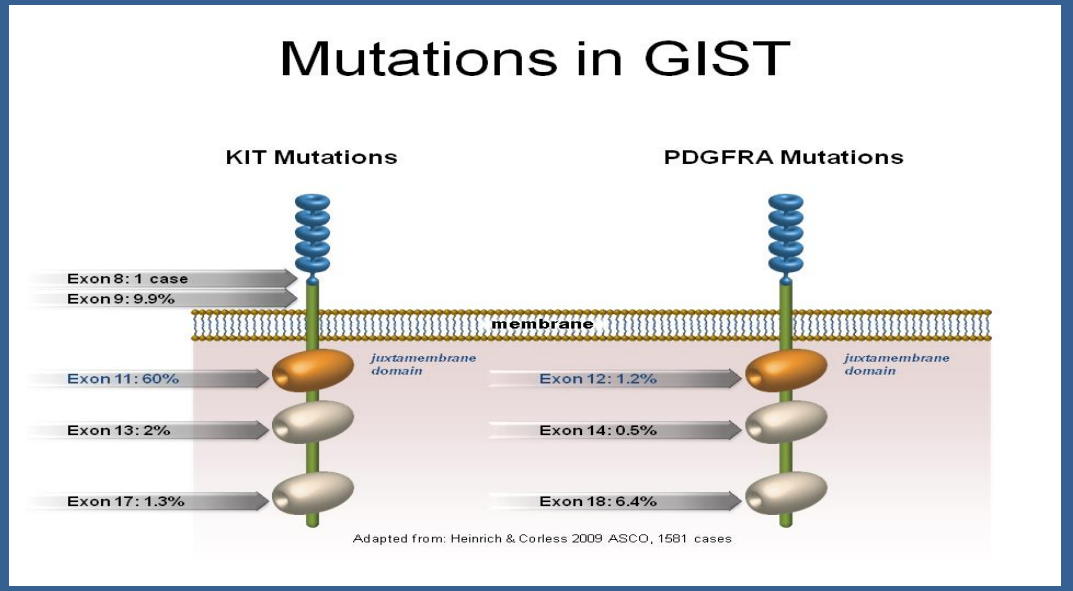


- Non-squamous non-small cell lung cancer
  - EGFR, ALK
  - ROS, RET, B-raf, K-ras, MET, Erbb2
- Metastatic melanoma
  - B-raf
  - KIT, N-ras
- Colorectal cancer
  - K-ras exon 2
  - Extended K-ras, N-Ras, B-raf, PIK3CA, ErbB2
  - MSI testing
- Breast cancer
  - ER, PR, ErbB2
  - BRCA testing
  - PIK3CA
- CNS tumors
  - MGMT promoter methylation
  - IDH1, IDH2, 1p/19q loss, ATRX
- What panel? Single gene? Multiplex platform? NGS?

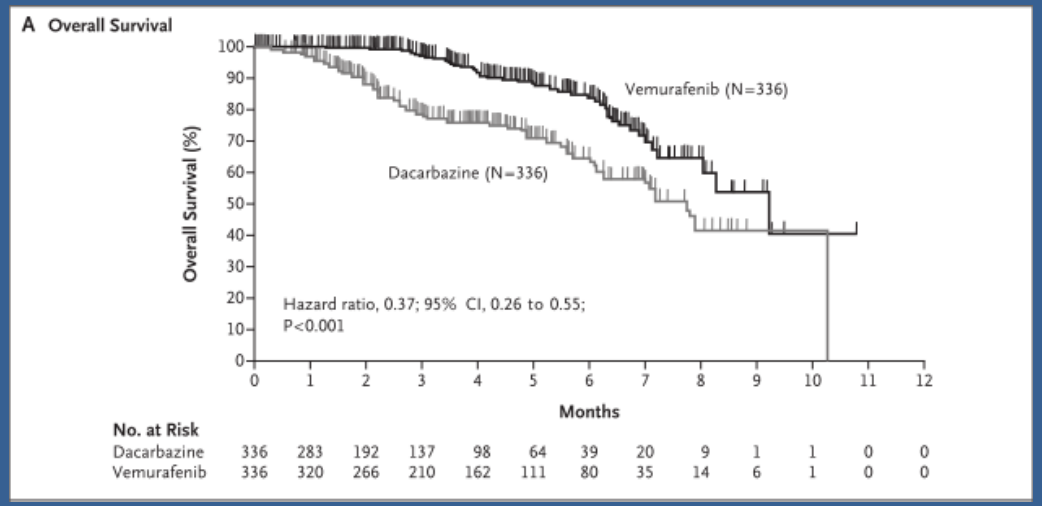
Tumor types showing success with genomic testing

CRC: K-Ras as a negative selection marker for EGFR inhibition

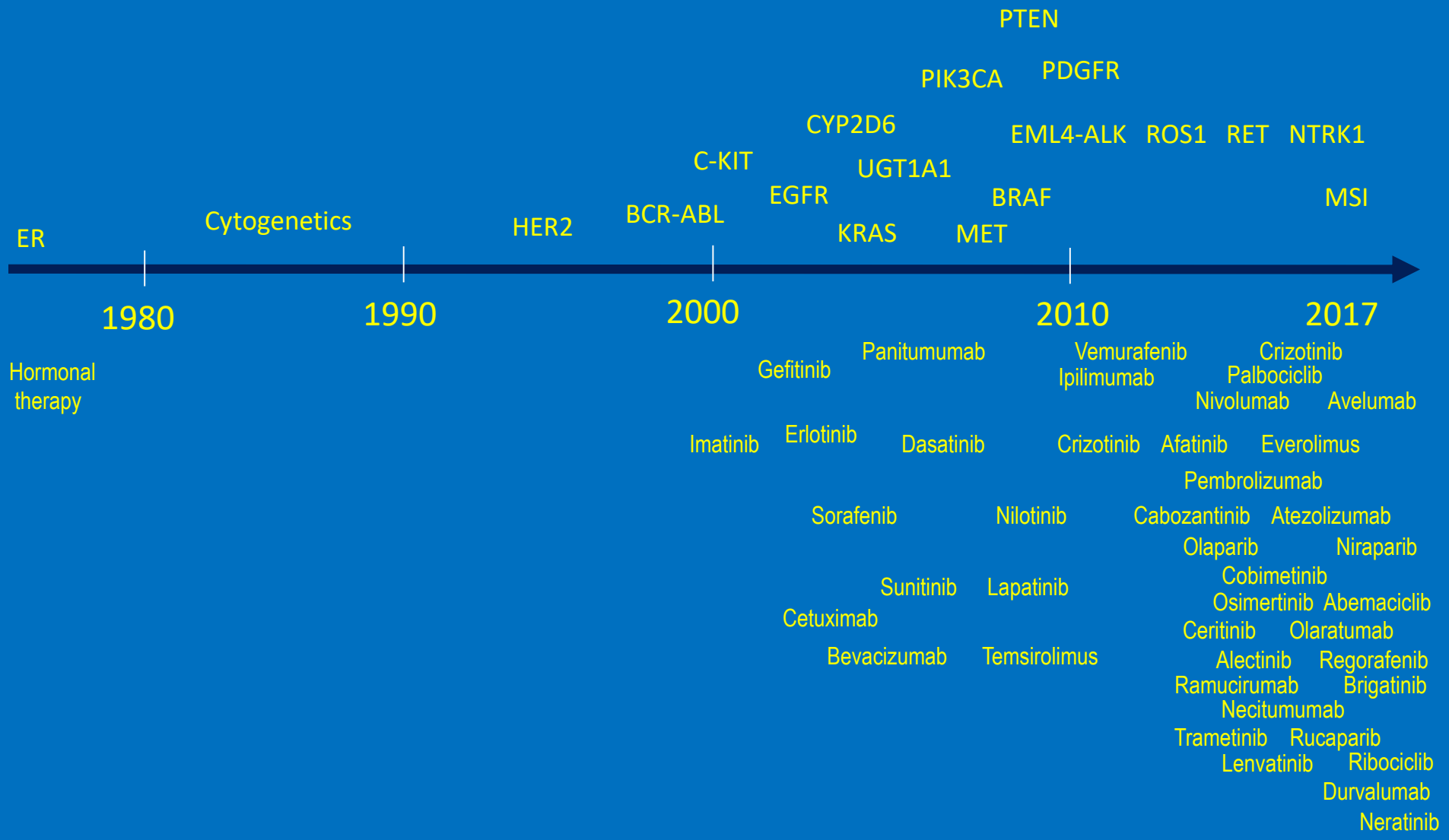


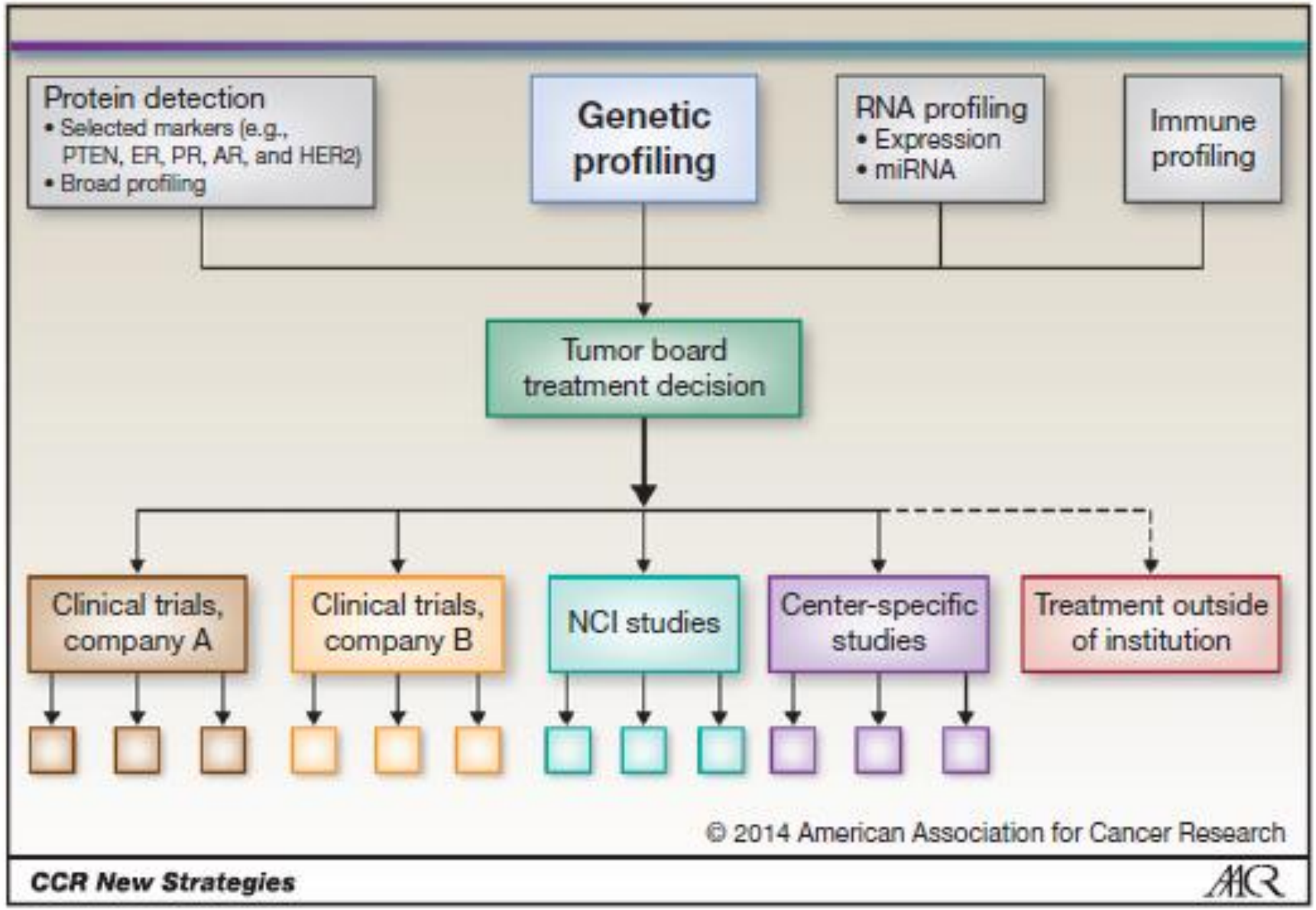


Melanoma: Braf V600E



Genomic Mechanisms (and Targeted Drugs) in Cancer





Jurgensmeier et al, CCR 2014

NTRK as a tissue agnostic treatment biomarker

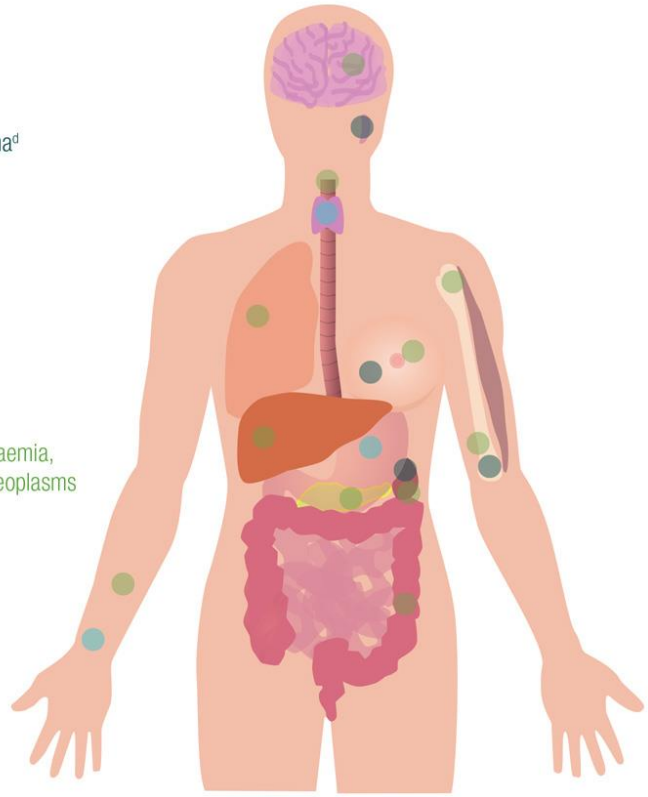
Cancers enriched for TRK fusions

Frequency >90%
MASC
Secretory breast carcinoma[b]
Cellular and mixed congenital mesoblastic nephroma[d]
Infanfile fibrosarcoma

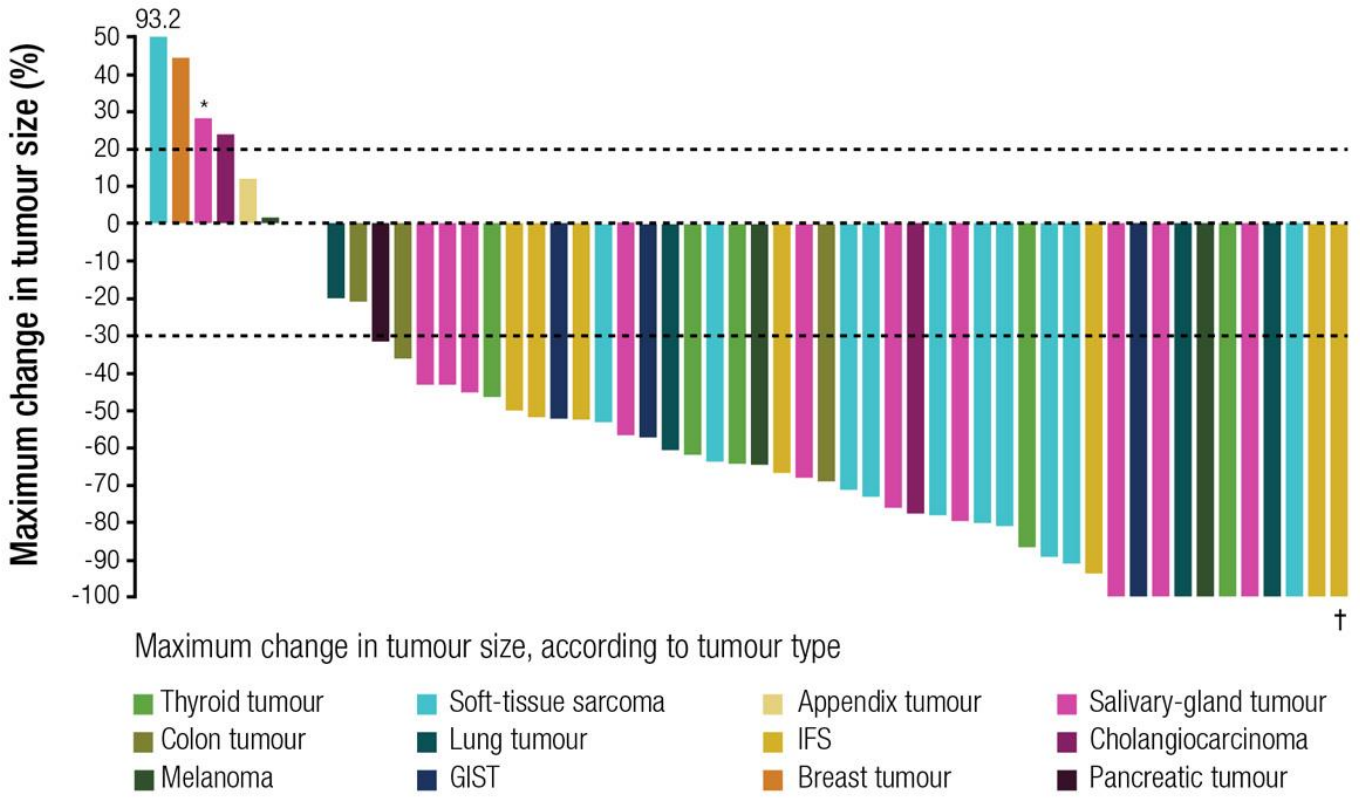
Cancers harbouring TRK fusions at lower frequencies

Frequency 5% to 25%
Gastrointestinal stromal tumour (pan-negative)
Thyroid cancer[c]
Spitzoid tumours

Frequency <5%
Acute lymphoblastic leukaemia, acute myeloid leukaemia, histiocytosis, multiple myeloma and dendritic cell neoplasms
Infantile sarcoma[d]
Breast cancer
Colorectal cancer
Cholangiocarcinoma
High-grade glioma[b]
Head and neck cancer
Lung cancer
Pancreatic cancer
Melanoma
Renal cell carcinoma[a]
Sarcoma

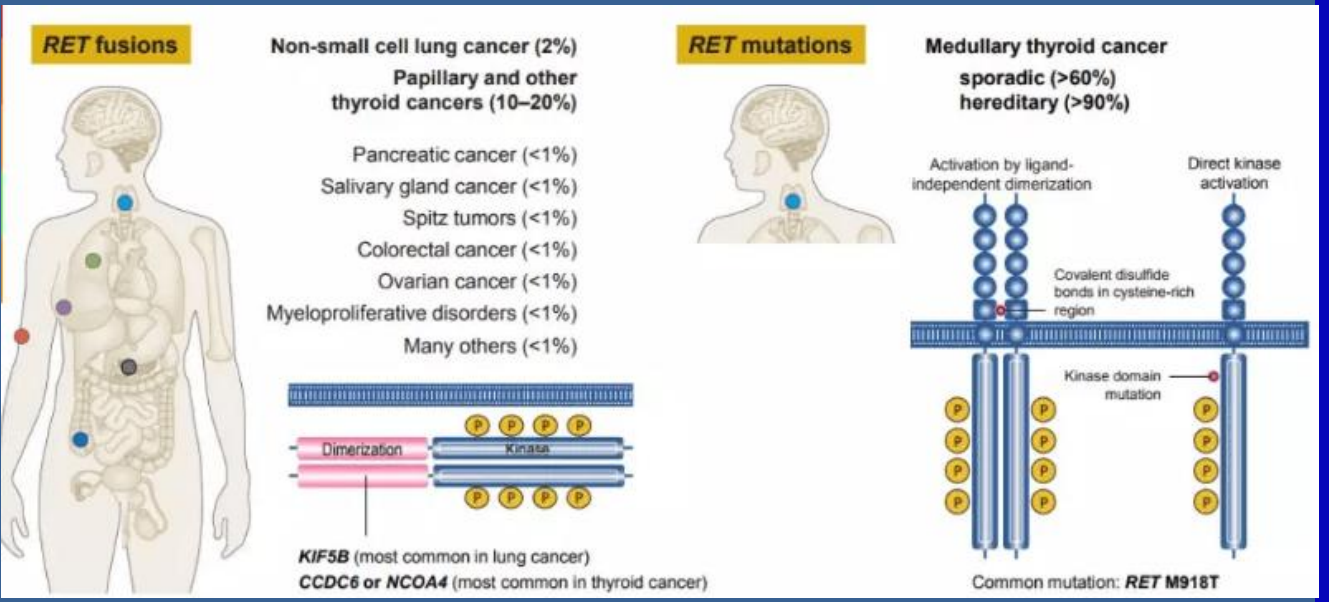


Maximum change in tumour size, according to tumour type

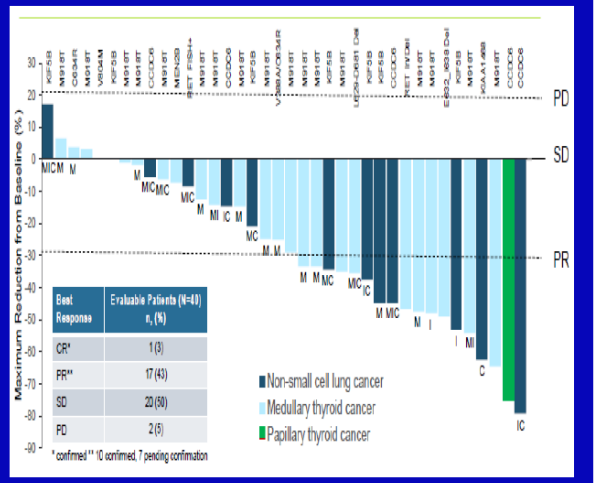


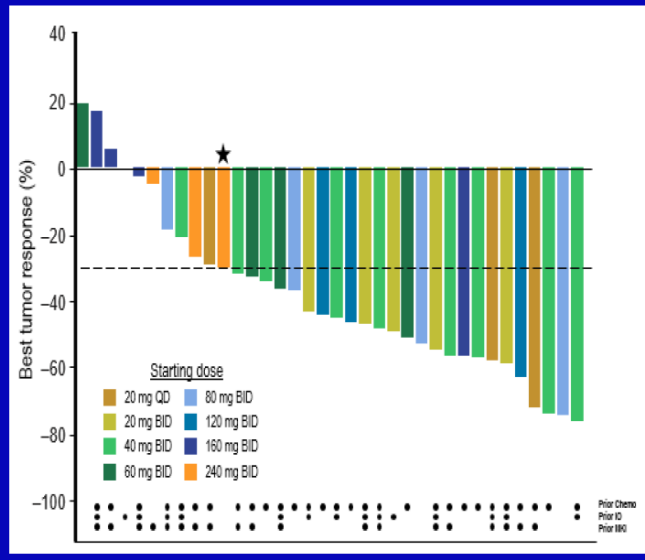
*One patient had a TRK solvent front resistance mutations (NTRK3 G623R) at baseline owing previous therapy;
†One patient had a pathological complete response.
GIST, gastrointestinal stromal tumour; IFS, infantile sarcoma.

RET targeting- thyroid/lung



Newer RET inhibitors appear highly effective



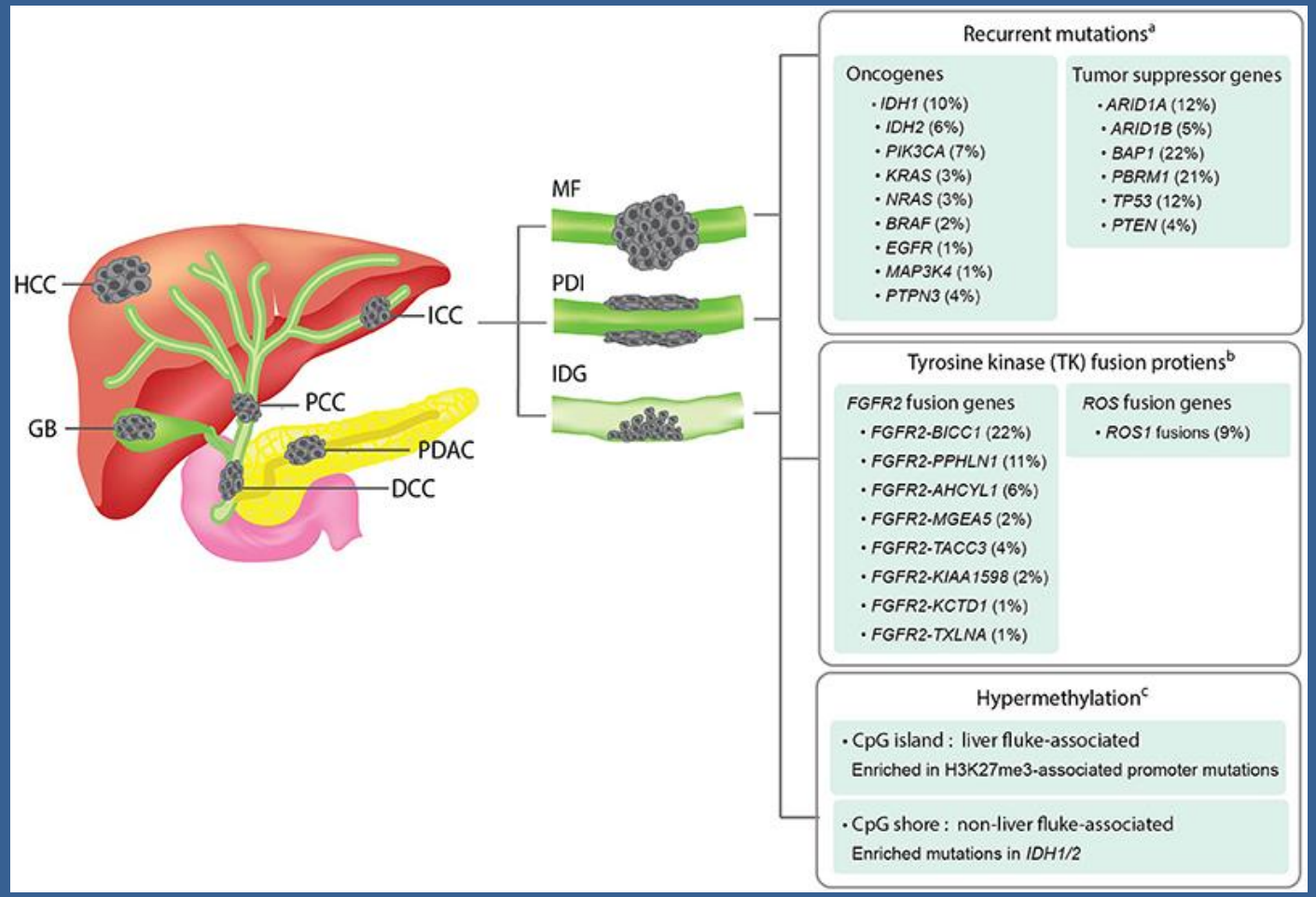


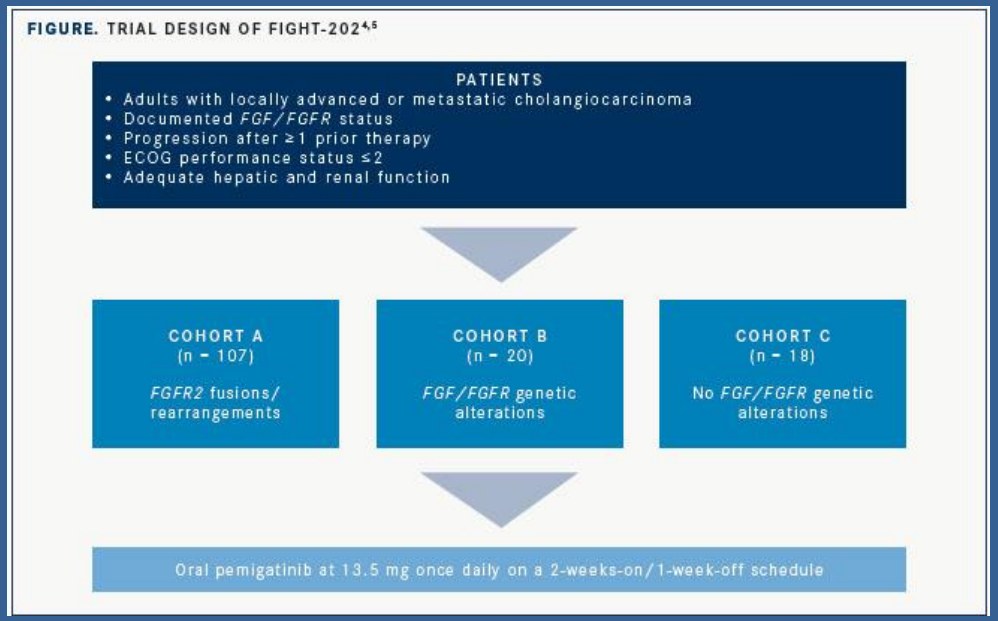
BLU-667
n = 12
ORR 50%

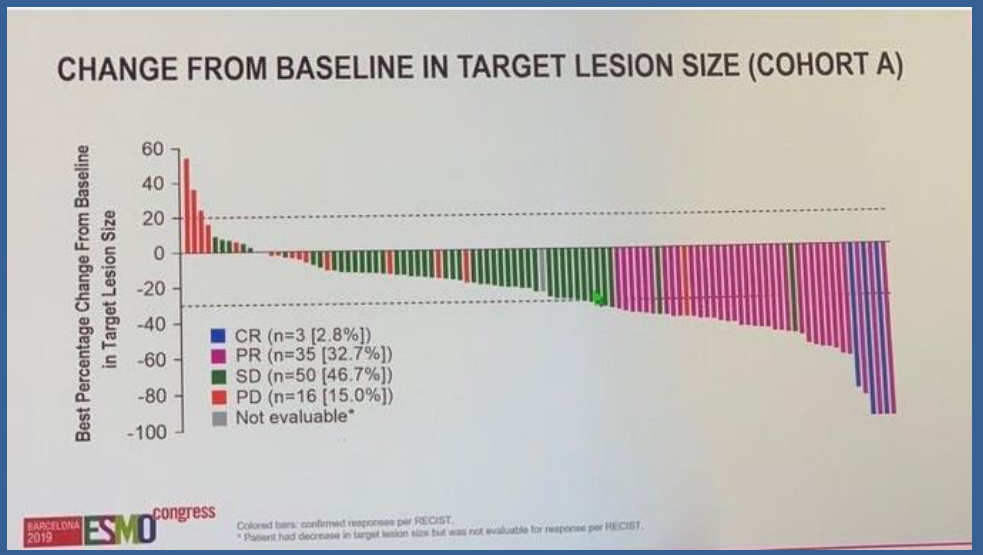
LOXO-292
n = 38
ORR 68%
4/4 CNS responses

Proc AACR, Chicago 14-18 April 2018; Oxnard WCLC Toronto 2018 OA12.07

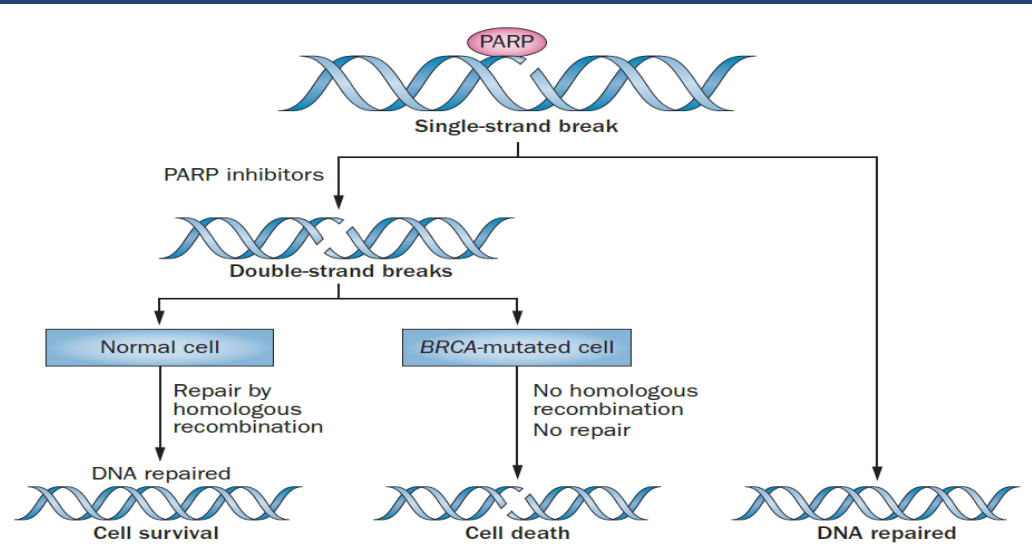
FGFR targeting- cholangiocarcinomas



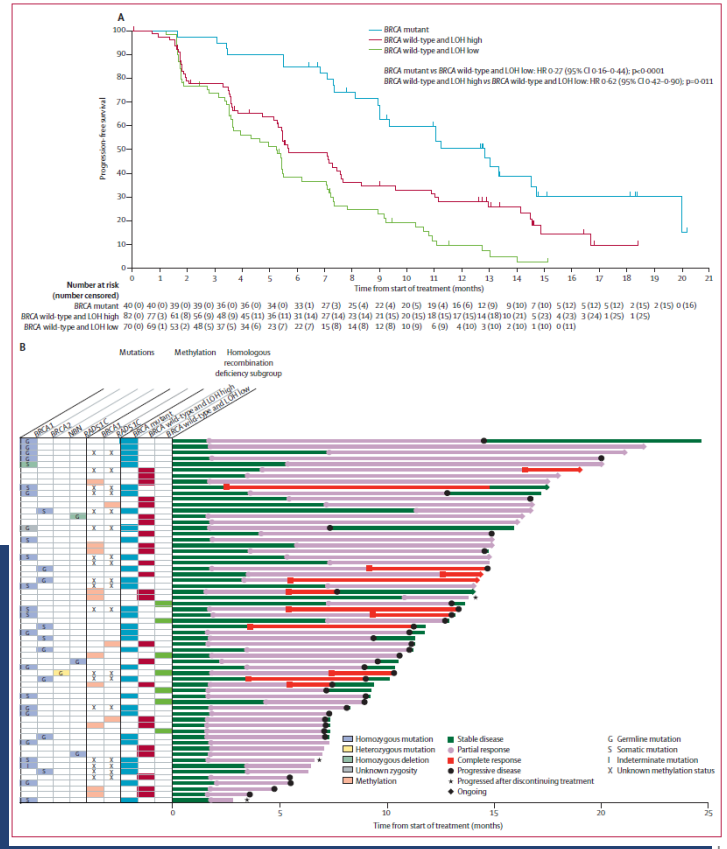




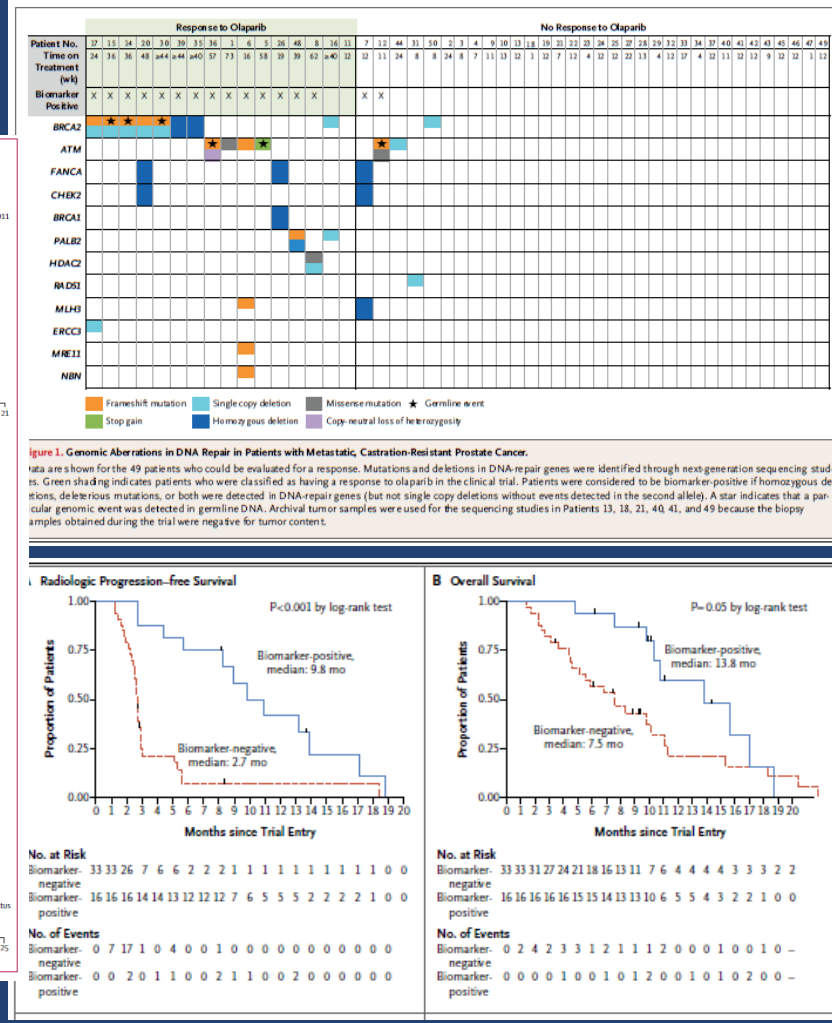
Finding the Achilles heel- PARP inhibition in advanced ovarian/prostate cancer



Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): an international, multicentre, open-label, phase 2 trial

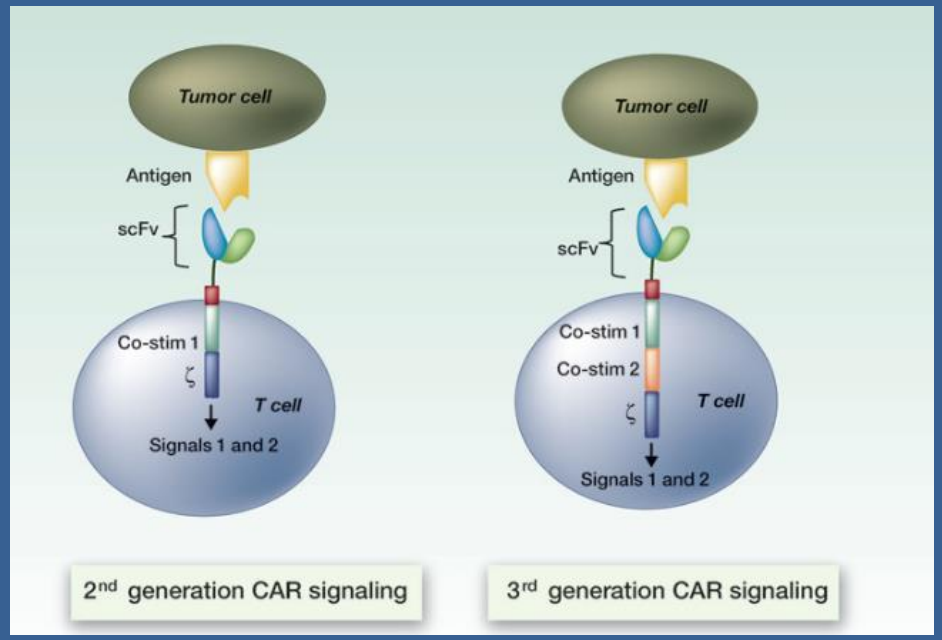


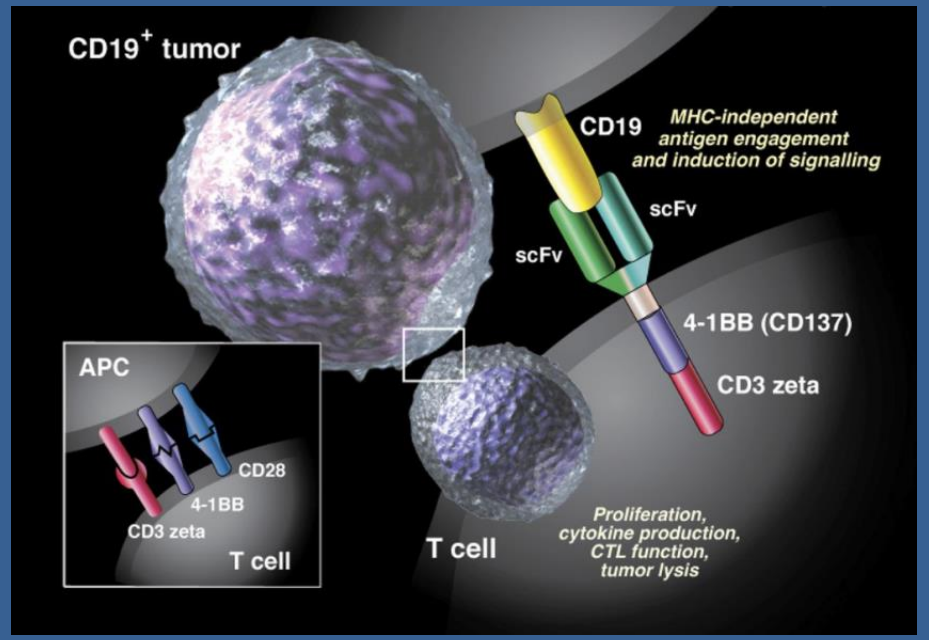
Prostate cancer

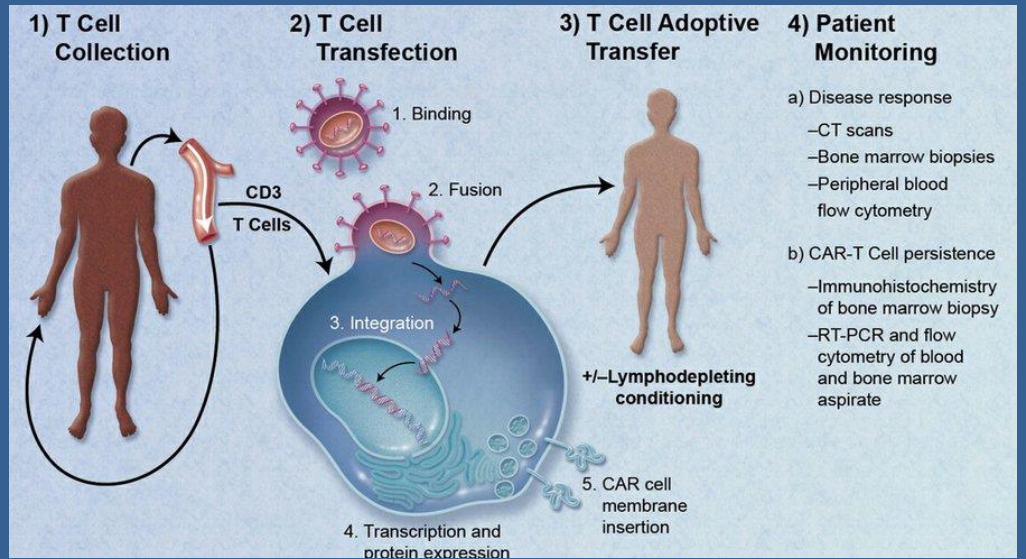


Swisher E et al. *Lancet Oncol.* 2017;18(1):75-87.

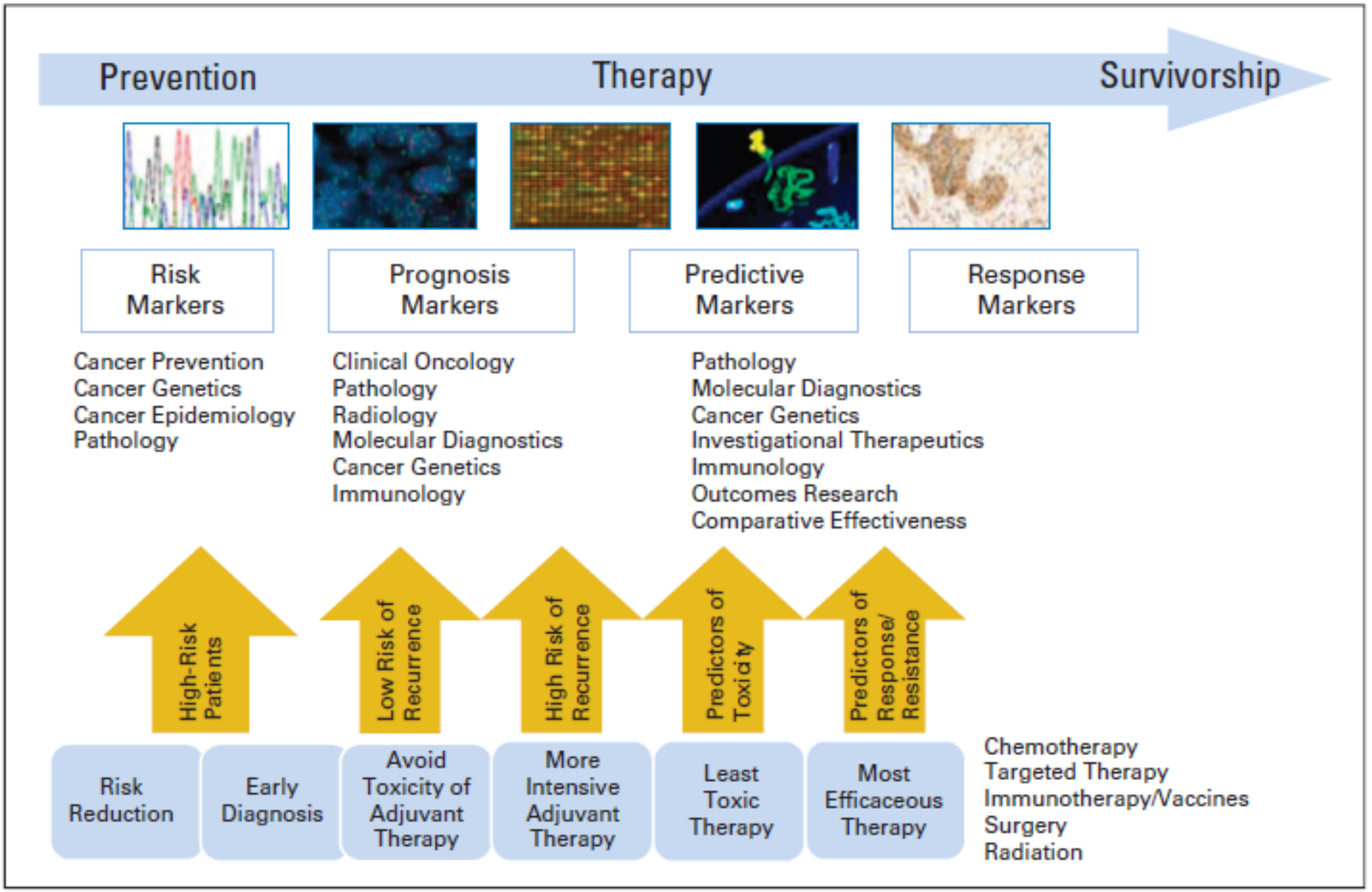
Personalizing immunotherapy- the next frontier



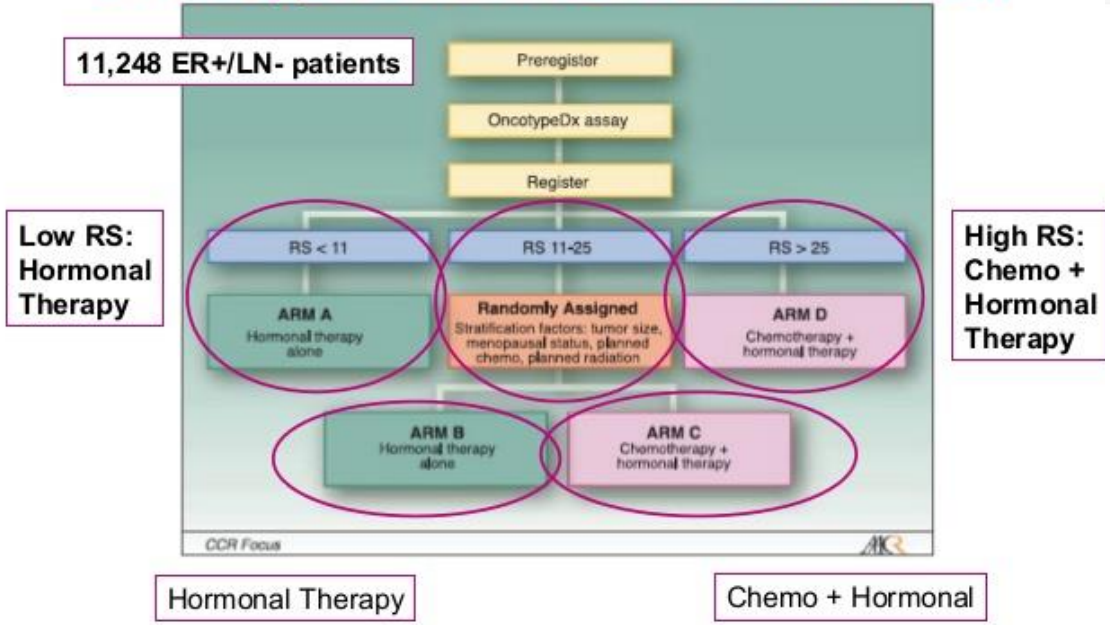




Precision cancer medicine



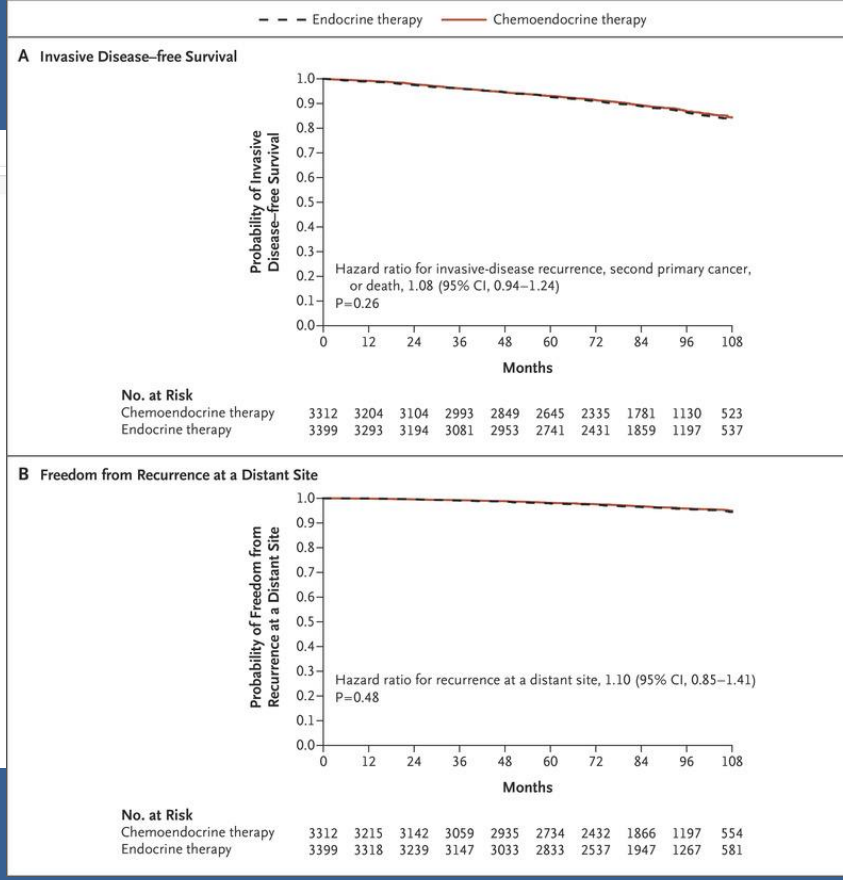
Prospective Validation of Oncotype DX: The TAILORX Trial

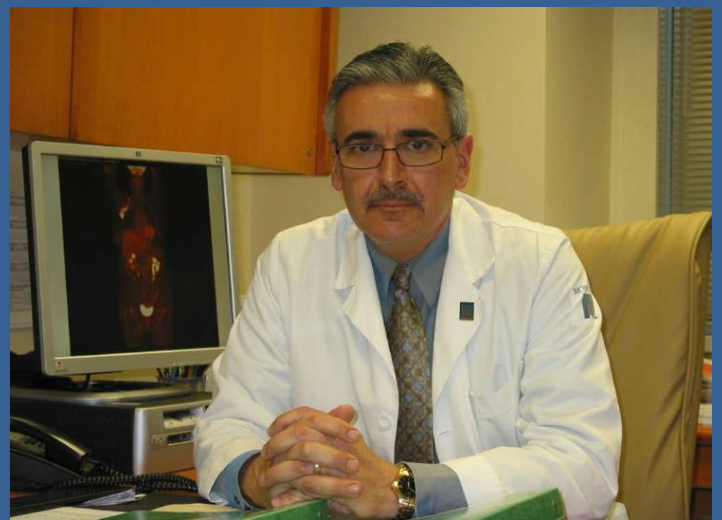


Dowsett, M. & Dunbier, A. Clin Cancer Res, 2008.

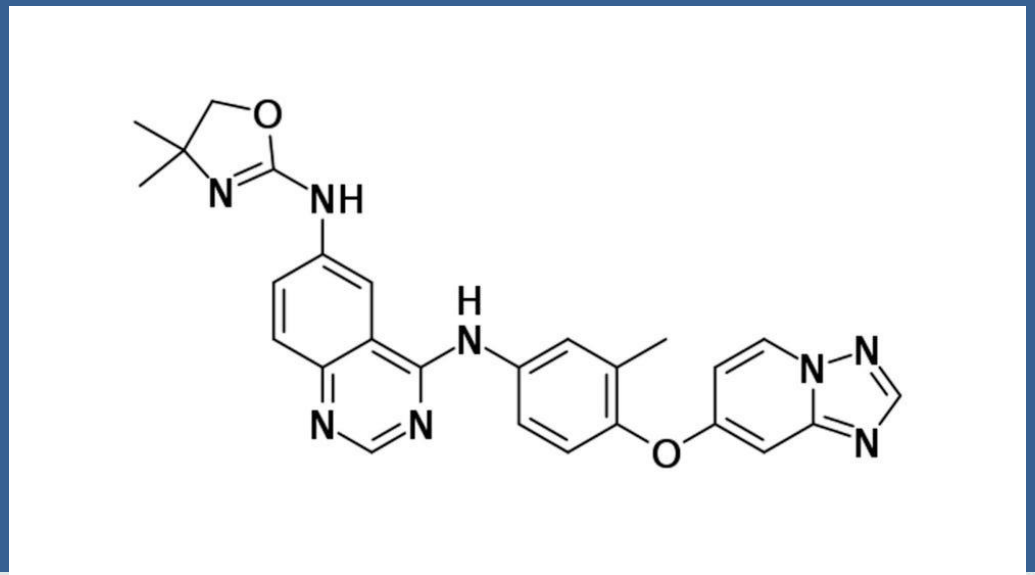
The New York Times

Good News for Women With Breast Cancer: Many Don't Need Chemo





SABS update



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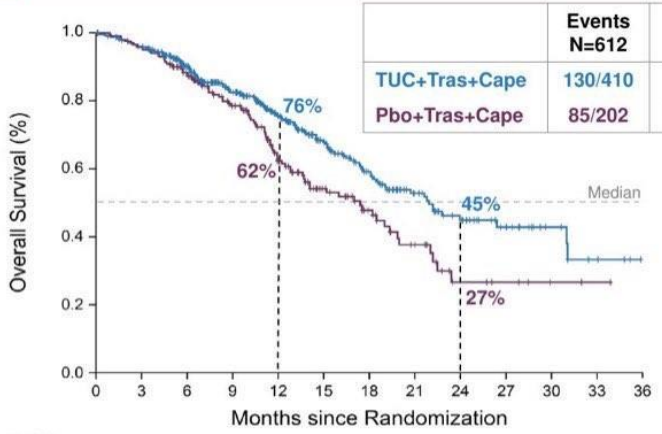
Overall Survival in the Total Study Population



	Events N=612	HR (95% CI)	P Value
TUC+Tras+Cape	130/410	0.66 (0.50, 0.88)	0.00480
Pbo+Tras+Cape	85/202		

Risk of death was reduced by 34% in the total population

Two-year OS (95% CI):	
TUC+Tras+Cape 45% (37, 53)	Pbo+Tras+Cape 27% (16, 39)
Median OS (95% CI):	
21.9 months (18.3, 31.0)	17.4 months (13.6, 19.9)

Prespecified efficacy boundary for OS (P=0.0074) was met at the first interim analysis.
Data cut off: Sep 4, 2019

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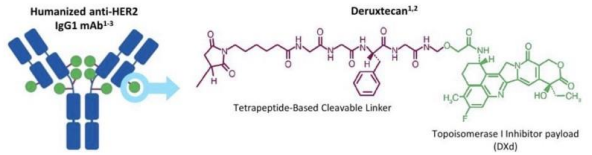
Trastuzumab Deruxtecan (DS-8201) is a Novel ADC Designed to Deliver an Optimal Antitumor Effect

Trastuzumab deruxtecan is an ADC composed of 3 components:

- A humanized anti-HER2 IgG1 mAb with the same amino acid sequence as trastuzumab
- A topoisomerase I inhibitor payload, an exatecan derivative
- A tetrapeptide-based cleavable linker



- Payload MOA: topoisomerase I inhibitor
- High potency of payload
- High drug to antibody ratio ≈ 8
- Payload with short systemic half-life
- Stable linker-payload
- Tumor-selective cleavable linker
- Membrane-permeable payload

The clinical relevance of these features is under investigation.
ADC, antibody-drug conjugate; MOA, mechanism of action.
1. Nakada T, et al. Chem Pharm Bull (Tokyo). 2019;67(3):173-185. 2. Ogitani Y, et al. Clin Cancer Res. 2016;22(20):5097-5108. 3. Trail PA, et al. Pharmacol Ther. 2018;181:126-142. 4. Ogitani Y, et al. Cancer Sci. 2016;107(7):1039-1046.

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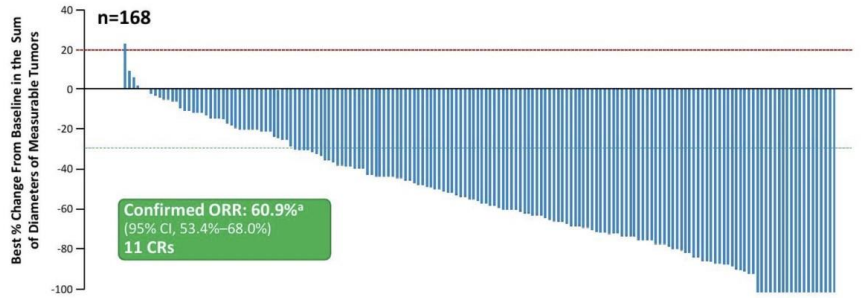
Best Change in Tumor Size



By independent central review.
The line at 20% indicates progressive disease; the line at −30% indicates partial response.
[a]Includes all patients who received T-DXd 5.4 mg/kg (intent-to-treat analysis; N=184).

Keynote -522

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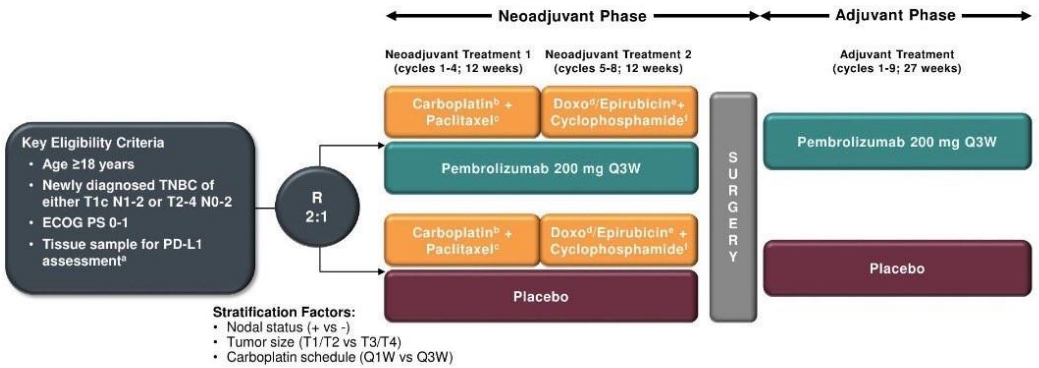
KEYNOTE-522 Study Design (NCT03036488)



Stratification Factors:
- Nodal status (+ vs -)
- Tumor size (T1/T2 vs T3/T4)
- Carboplatin schedule (Q1W vs Q3W)

Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (post treatment included)

Adjuvant phase: starts from the first adjuvant treatment and includes radiation therapy as indicated (post treatment included)

[a]Must consist of at least 2 separate tumor cores from the primary tumor.
[b]Carboplatin dose was AUC 5 Q3W or AUC 1.5 Q1W.
[c]Paclitaxel dose was 80 mg/m² Q1W.
[d]Doxorubicin dose was 60 mg/m² Q3W.
[e]Epirubicin dose was 90 mg/m² Q3W.
[f]Cyclophosphamide dose was 600 mg/m² Q3W.

T

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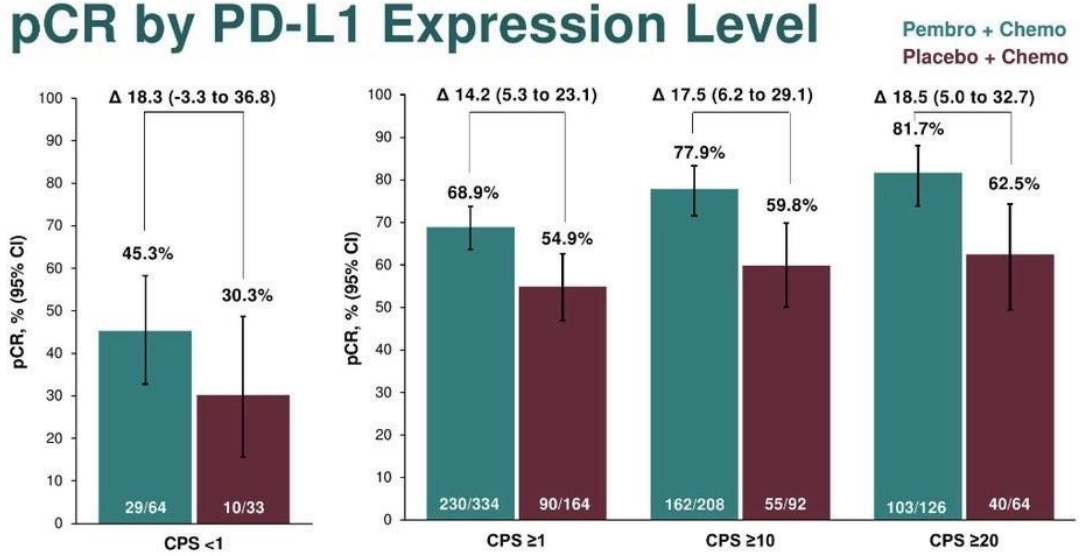
pCR by PD-L1 Expression Level



Pre-specified analysis. PD-L1 assessed at a central laboratory using the PD-L1 IHC 22C3 pharmDx assay and measured using CPS; number of PD-L1–positive tumor cells, lymphocytes, and macrophages divided by total number of tumor cells x 100); PD-L1–positive = CPS ≥1. Estimated treatment difference based on Miettinen & Nurminen method stratified by nodal status (positive vs negative), tumor size (T1/T2 vs T3/T4) and choice of carboplatin (Q3W vs QW). Data cutoff date: September 24, 2018.

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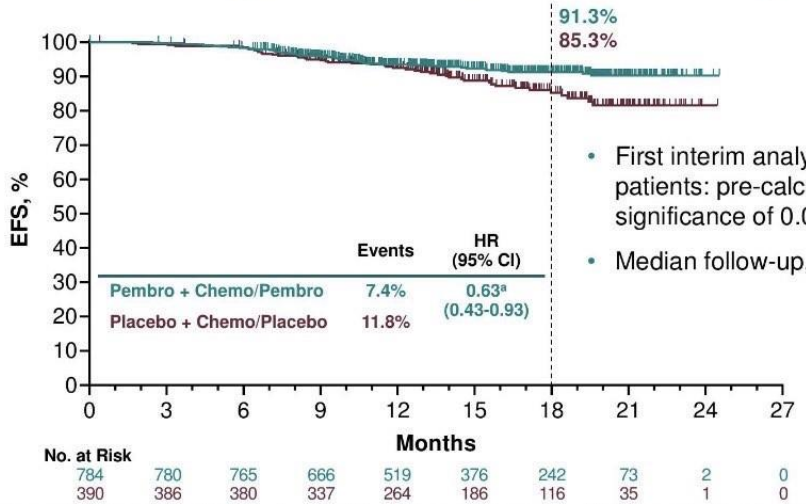
First Pre-planned Interim Analysis for EFS



- First interim analysis of EFS based on 1174 patients: pre-calculated P value boundary for significance of 0.000051 (HR <0.4)
- Median follow-up, 15.5 months

[a]Pre-specified P value boundary of 0.000051 not reached at this analysis (the first interim analysis of EFS). Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. Data cutoff April 24, 2019.


I'M WORRIED THAT HEALTH CARE HAS BECOME TOO IMPERSONAL, DOC.
NONSENSE... JUST RELAX AND LIE BACK ON THE BAR CODE SCANNER.
2229701655