Molecular Residual Disease (MRD) in Regional / Locally Advanced NSCLC

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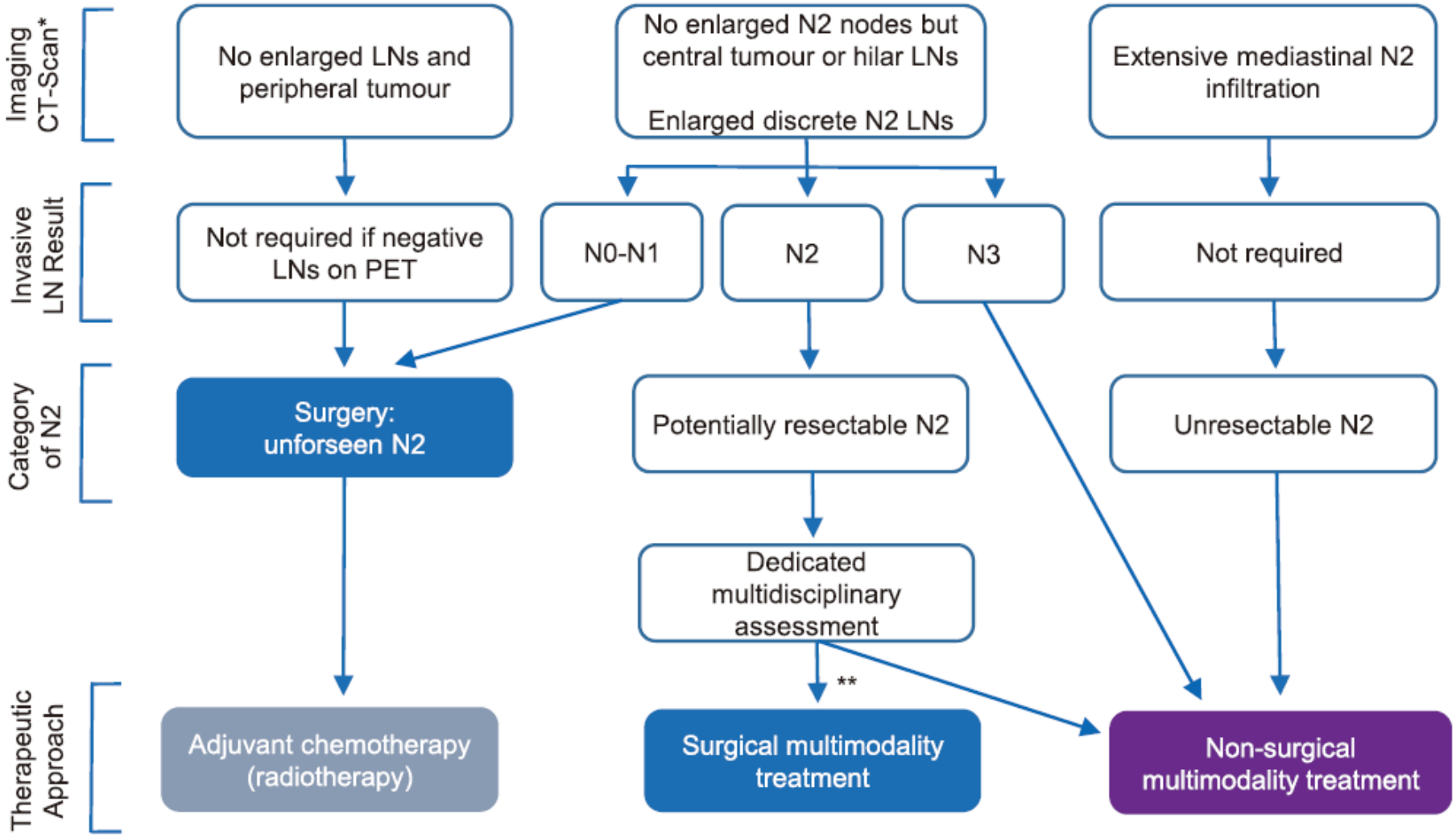
Treatment for Loco-regional NSCLC

Pan-Asian adapted ESMO Clinical Practice Guideline



Ann Oncol 2020;31(2):191-201

Adjuvant Treatment May be Required Based on the Disease Stage and Findings During Surgery: NCCN Guidelines

- Goal of adjuvant treatment: to improve the chance for cure after surgery

Recommendations for adjuvant treatment[a]

Adjuvant chemotherapy and / or RT may be required based on the disease stage and status of the tumor's resected margins[1,2]

Pathologic stage	R0 (complete resection)	R1 / R2 (incomplete resection)
Stage IB / IIA (N0, no lymph nodes)	Observation Chemotherapy for high-risk patients (Stage IB / IIA)	Re-resection (preferred) or RT (+ chemotherapy for Stage IIA)
Stage IIB (N1 lymph nodes)	Chemotherapy	Re-resection + chemotherapy or CRT (R1 sequential / concurrent; R2 concurrent)
Stage IIIA / IIIB (N1 / N2 lymph nodes)	Chemotherapy Sequential chemotherapy + RT (N2 only)	R1: CRT sequential / concurrent R2: CRT concurrent

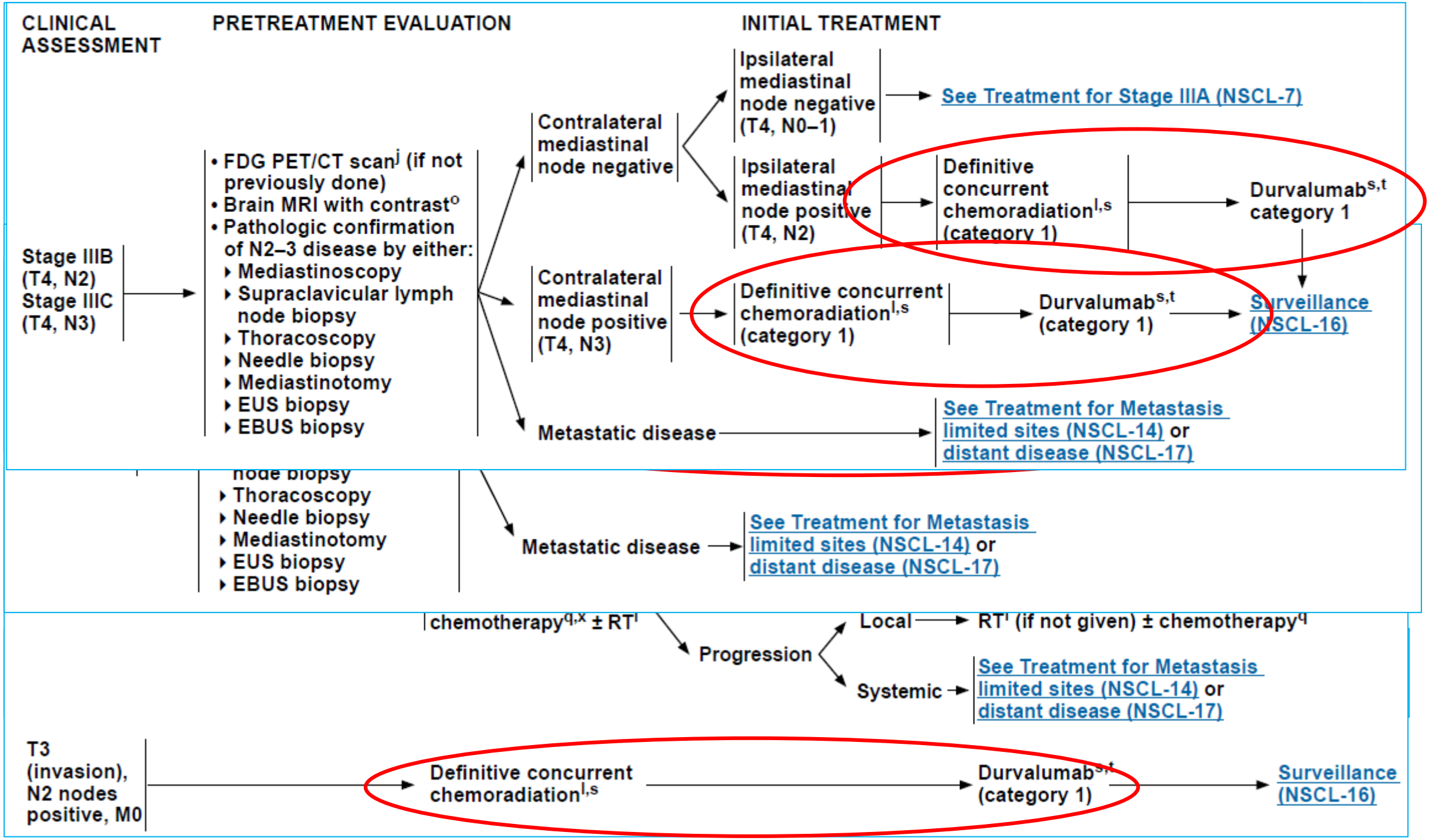
Recommended adjuvant treatment regimens[a]

- Chemotherapy alone or sequential CRT: certain cisplatin-based doublets preferred for 4 cycles
- Concurrent CRT: certain platinum-based doublet chemotherapy preferred for 3–4 cycles

(+) PD tumors, vascular invasion, limited resection or Nx, size >4cm, visceral pleural involvement

NOTE: Staging and nodal status (N0, N1, N2) is per the American Joint Committee on Cancer Staging Manual, 8th Edition. [a]See the NCCN Guidelines for NSCLC for detailed recommendations, including treatment regimens; specific agents or regimens are recommended. Also see the NCCN Guidelines for detailed recommendations for unresectable NSCLC. CRT = chemoradiotherapy; RT = radiotherapy

Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer. V.4.2020. ©National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed May 18, 2020. To view the most recent and complete version of the guideline, go to NCCN.org.


CLINICAL ASSESSMENT
PRETREATMENT EVALUATION
INITIAL TREATMENT
Stage IIIB (T4, N2) Stage IIIC (T4, N3)
• FDG PET/CT scan[j] (if not previously done)
• Brain MRI with contrast[o]
• Pathologic confirmation of N2–3 disease by either:
Mediastinoscopy
Supraclavicular lymph node biopsy
Thoracoscopy
Needle biopsy
Mediastinotomy
EUS biopsy
EBUS biopsy
Contralateral mediastinal node negative
Ipsilateral mediastinal node negative (T4, N0–1)
See Treatment for Stage IIIA (NSCL-7)
Ipsilateral mediastinal node positive (T4, N2)
Definitive concurrent chemoradiation[l,s] (category 1)
Durvalumab[s,t] category 1
Contralateral mediastinal node positive (T4, N3)
Definitive concurrent chemoradiation[l,s] (category 1)
Durvalumab[s,t] (category 1)
Surveillance (NSCL-16)
Metastatic disease
See Treatment for Metastasis limited sites (NSCL-14) or distant disease (NSCL-17)
node biopsy
Thoracoscopy
Needle biopsy
Mediastinotomy
EUS biopsy
EBUS biopsy
Metastatic disease
See Treatment for Metastasis limited sites (NSCL-14) or distant disease (NSCL-17)
chemotherapy[q,x] ± RT[l]
Progression
Local
RT[l] (if not given) ± chemotherapy[q]
Systemic
See Treatment for Metastasis limited sites (NSCL-14) or distant disease (NSCL-17)
T3 (invasion), N2 nodes positive, M0
Definitive concurrent chemoradiation[l,s]
Durvalumab[s,t] (category 1)
Surveillance (NSCL-16)

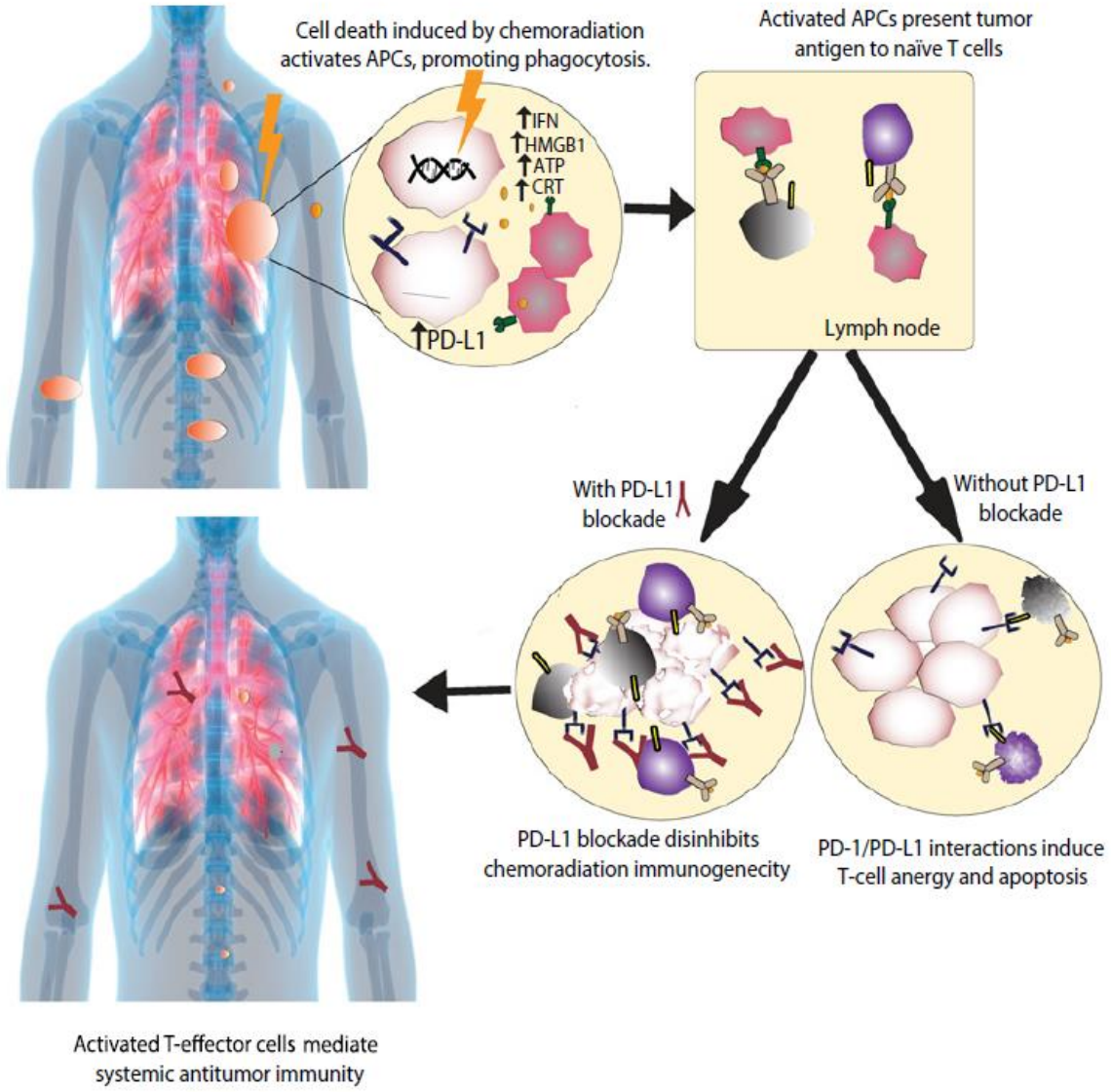
Treatment Landscape for Loco-regional NSCLC

- **Stage-based treatment algorithms**
  - Stage 1 → Surgery
  - Stage 2 → Surgery +/- chemotherapy
  - Stage 3 → Surgery +/- chemotherapy +/- RT

    → Chemoradiation +/- Durvalumab

- **No biomarker driven treatment for Loco-regional NSCLC**

Immunogenic Synergy between CRT and ICI



Clin Cancer Res 2018;24(6):1271-1276

Clinical Trials for Peri-CRT

Table 1. Multi-institutional phase III trials of consolidative or induction systemic therapy after concurrent chemoradiation for unresectable stage III NSCLC

Trial	Induction or consolidative therapy with cCRT	PFS (months) (*P*)	OS (months) (*P*)
CALGB-39801 (5)	Carboplatin + paclitaxel (induction)	7 vs. 8 (NS)	12 vs. 14 (NS)
HOG LU-0124 (6)	Docetaxel (consolidation)	10.8 vs. 10.3 (NS)	24.2 vs. 26.1 (NS)
Korean Cancer Study Group - LU05-04 (2)	Cisplatin + docetaxel (consolidation)	9.1 vs. 8.1 (NS)	21.8 vs. 21.6 (NS)
RTOG-0617 (3)[a]	Cetuximab (consolidation)	10.8 vs. 10.7 (NS)	25 vs. 24 (NS)
SWOG-S0023 (7)	Docetaxel followed by gefitinib (consolidation)	8.3 vs. 11.7 (NS)	23 vs. 35 ($P = 0.013$)
START (8)[b]	Tecemotide (consolidation)	14.2 vs. 11.4 ($P = 0.02$)	30.8 vs. 20.6 ($P = 0.016$)
PACIFIC (28)	Durvalumab (consolidation)	16.8 vs. 5.6 ($P < 0.0001$)	Ongoing

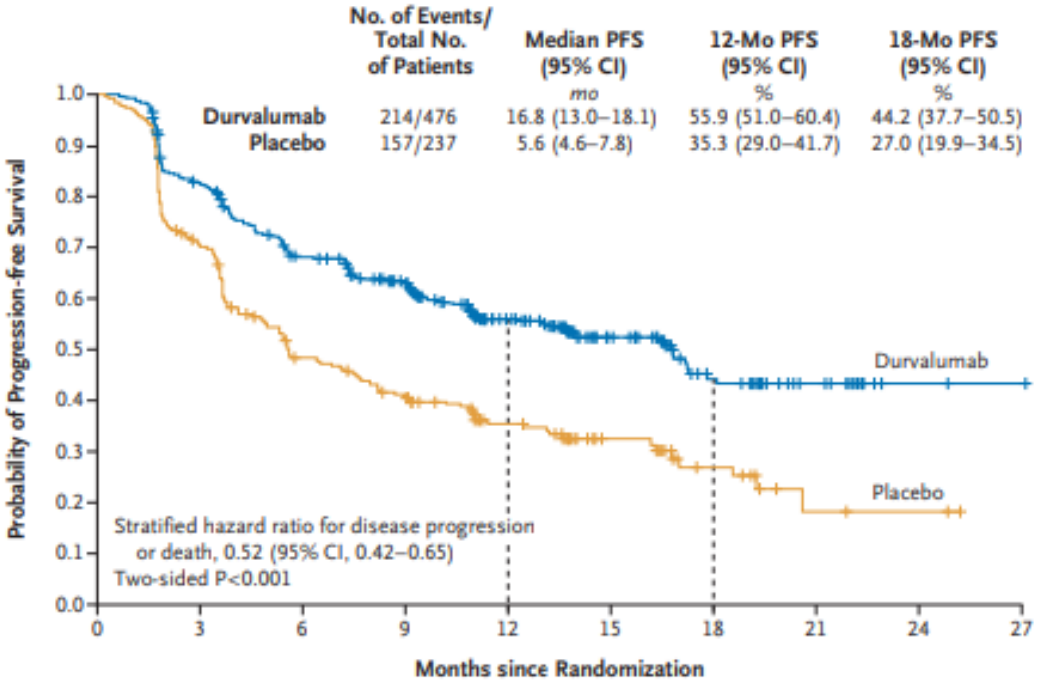
NOTE: All values from clinical trials are presented as experimental arm value versus control arm value.
Abbreviation: NS, not statistically significant.
[a]Data are shown regardless of irradiation to 60 or 74 Gy.
[b]Data from patients who received prior concurrent chemoradiation are shown.

Table 3. Ongoing studies incorporating PD-1/PD-L1 ICIs into cCRT regimens in the treatment of stage III NSCLC

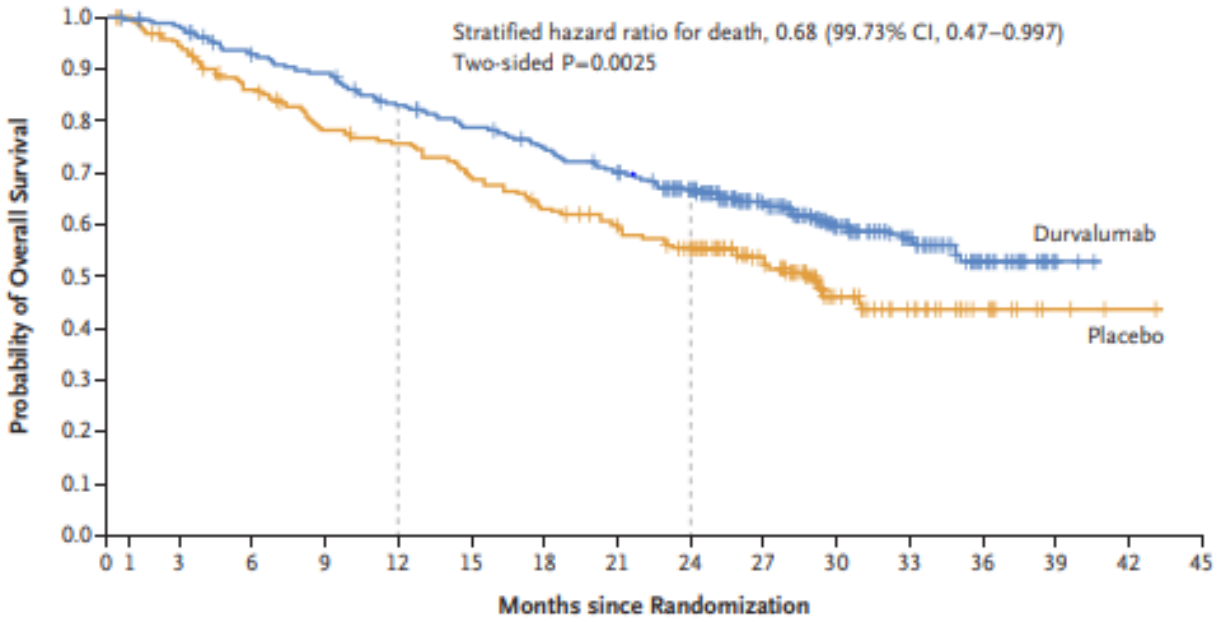
Study	Phase	Study arm(s)	Timing of immunotherapy initiation
RTOG-3505 (30)	III	Nivolumab vs. observation	4–12 weeks after cCRT completion
NCT03285321 (43)	II	Nivolumab + ipilimumab vs. nivolumab alone	28–56 days after cCRT completion
NCT03102242 (45)	II	Atezolizumab (induction and adjuvant)	Induction: 2 or 4 3-week cycles Adjuvant: 3–5 weeks after cCRT completion
NCT02434081 (47)	II	Nivolumab (concurrent and adjuvant)	Within 30 days of first cycle of chemotherapy
NCT02621398 (48)	I	Pembrolizumab (concurrent and adjuvant)	Same day as cCRT initiated

Clin Cancer Res 2018;24(6):1271-1276

Benefit of Durvalumab after CRT

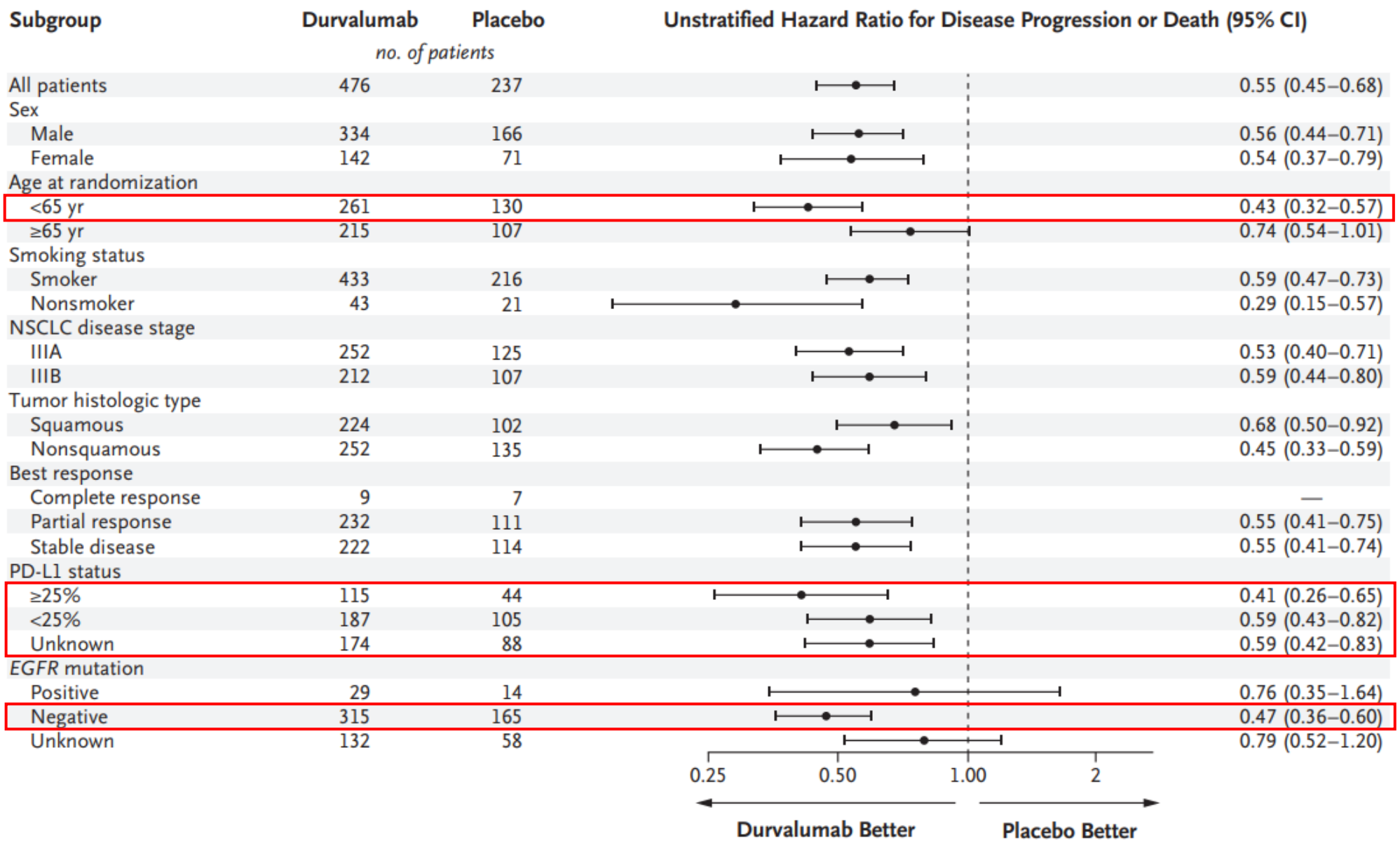


Median PFS 16.8 vs 5.6, HR 0.52, p<0.001



24mo OS 66% vs 56%, HR 0.68, p=0.0025

N Engl J Med 2017;377(20):1919-1929



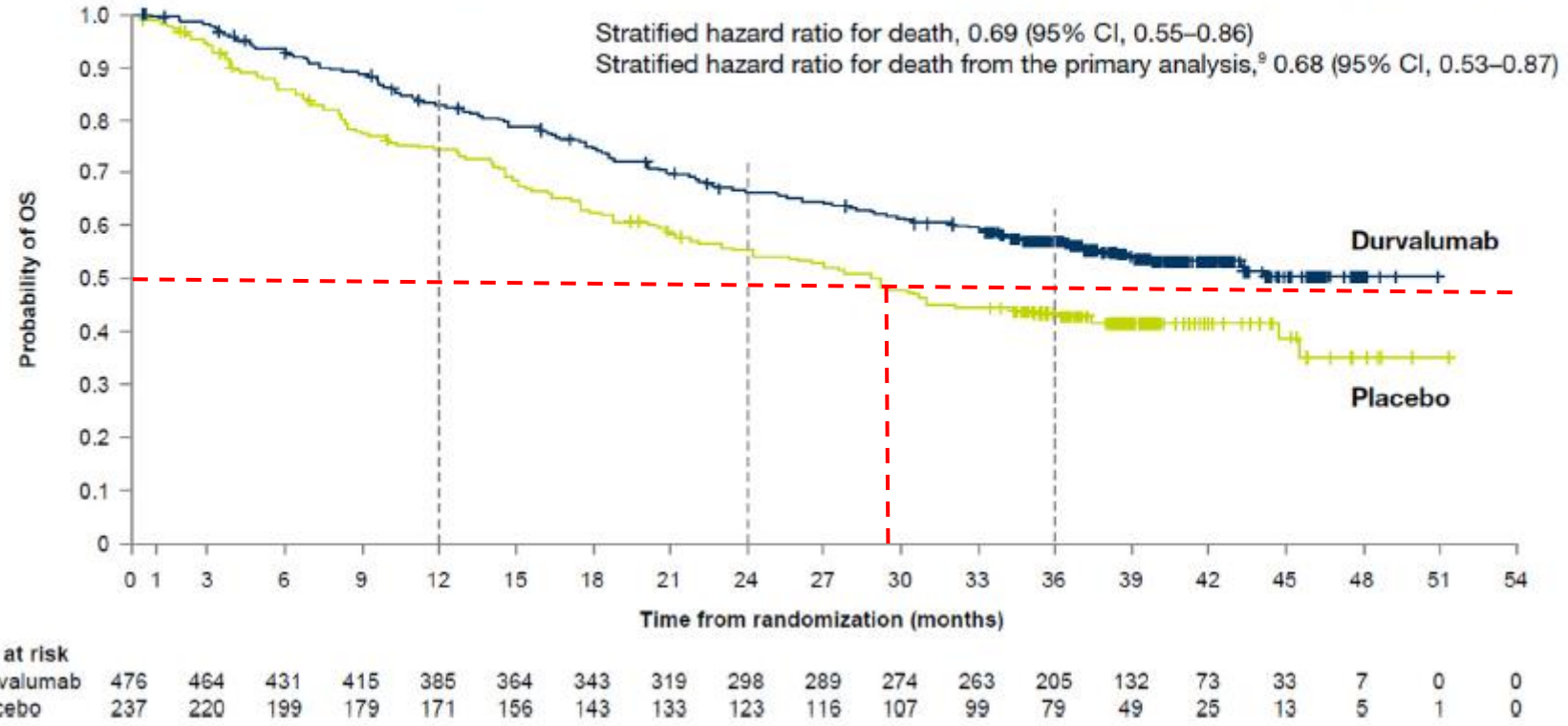
N Engl J Med 2017;377(20):1919-1929

IASLC

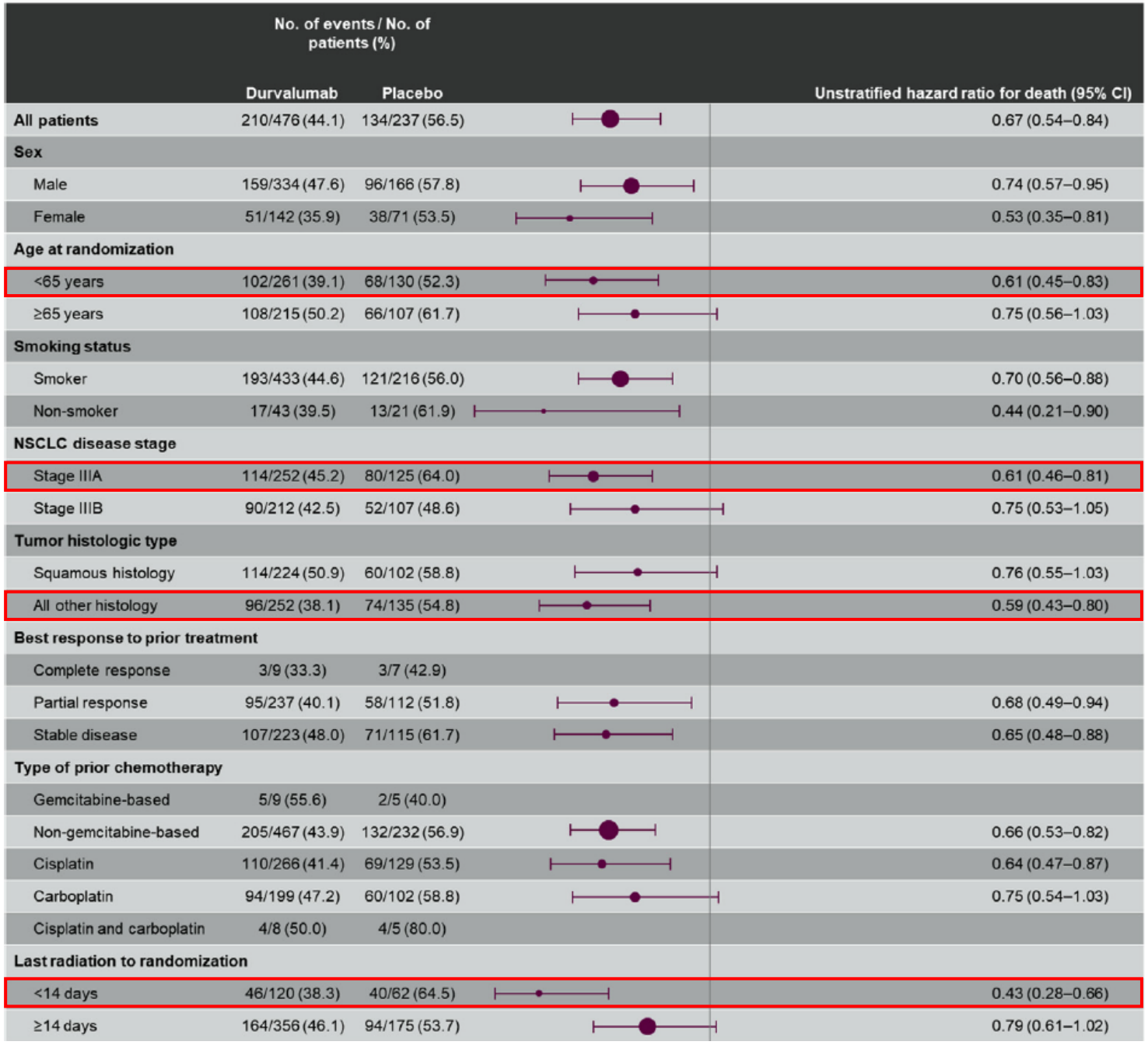
Three-Year Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC—Update from PACIFIC

Check for updates

	No. of events/ total no. of patients (%)	Median OS (95% CI) months	12-month OS rate (95% CI) %	24-month OS rate (95% CI) %	36-month OS rate (95% CI) %
Durvalumab	210/476 (44.1)	NR (38.4–NR)	83.1 (79.4–86.2)	66.3 (61.8–70.4)	57.0 (52.3–61.4)
Placebo	134/237 (56.5)	29.1 (22.1–35.1)	74.6 (68.5–79.7)	55.3 (48.6–61.4)	43.5 (37.0–49.9)

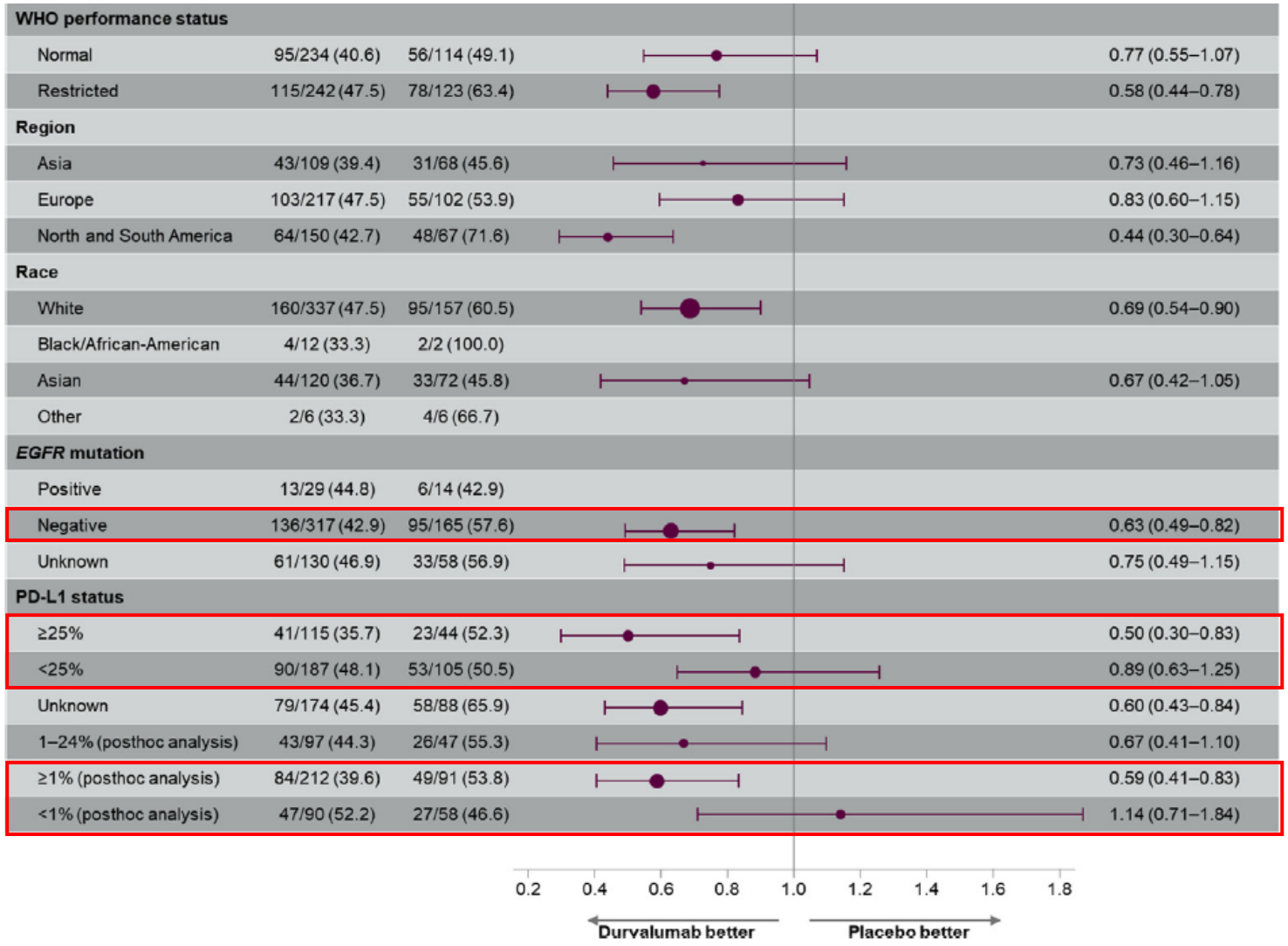


J Thorac Oncol 2020;15(2):288-293



	No. of events / No. of patients (%)		Unstratified hazard ratio for death (95% CI)
	Durvalumab	Placebo	
All patients	210/476 (44.1)	134/237 (56.5)	0.67 (0.54–0.84)
Sex			
Male	159/334 (47.6)	96/166 (57.8)	0.74 (0.57–0.95)
Female	51/142 (35.9)	38/71 (53.5)	0.53 (0.35–0.81)
Age at randomization			
<65 years	102/261 (39.1)	68/130 (52.3)	0.61 (0.45–0.83)
≥65 years	108/215 (50.2)	66/107 (61.7)	0.75 (0.56–1.03)
Smoking status			
Smoker	193/433 (44.6)	121/216 (56.0)	0.70 (0.56–0.88)
Non-smoker	17/43 (39.5)	13/21 (61.9)	0.44 (0.21–0.90)
NSCLC disease stage			
Stage IIIA	114/252 (45.2)	80/125 (64.0)	0.61 (0.46–0.81)
Stage IIIB	90/212 (42.5)	52/107 (48.6)	0.75 (0.53–1.05)
Tumor histologic type			
Squamous histology	114/224 (50.9)	60/102 (58.8)	0.76 (0.55–1.03)
All other histology	96/252 (38.1)	74/135 (54.8)	0.59 (0.43–0.80)
Best response to prior treatment			
Complete response	3/9 (33.3)	3/7 (42.9)	
Partial response	95/237 (40.1)	58/112 (51.8)	0.68 (0.49–0.94)
Stable disease	107/223 (48.0)	71/115 (61.7)	0.65 (0.48–0.88)
Type of prior chemotherapy			
Gemcitabine-based	5/9 (55.6)	2/5 (40.0)	
Non-gemcitabine-based	205/467 (43.9)	132/232 (56.9)	0.66 (0.53–0.82)
Cisplatin	110/266 (41.4)	69/129 (53.5)	0.64 (0.47–0.87)
Carboplatin	94/199 (47.2)	60/102 (58.8)	0.75 (0.54–1.03)
Cisplatin and carboplatin	4/8 (50.0)	4/5 (80.0)	
Last radiation to randomization			
<14 days	46/120 (38.3)	40/62 (64.5)	0.43 (0.28–0.66)
≥14 days	164/356 (46.1)	94/175 (53.7)	0.79 (0.61–1.02)

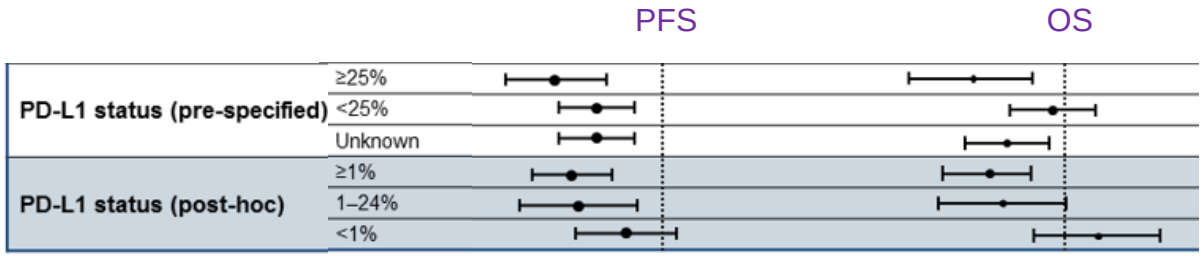
J Thorac Oncol 2020;15(2):288-293



J Thorac Oncol 2020;15(2):288-293

Patient Selection and Biomarkers for Consolidation IO

- **PD-L1**
  - ➢ PACIFIC trial : no selection by PD-L1
  - ➢ Role of PD-L1 in stage III should not yet be discounted or overestimated.
    - ✓ PD-L1 testing was not performed in over 1/3 patients
    - ✓ PD-L1 as binary variable, despite its continuous impact on outcomes



- ✓ Variability in PD-L1 assay (SP263)
- ✓ PD-L1 result based on tissue prior to cCRT (not post-cCRT)

Clin Cancer Res 2018;24(6):1271-1276

Patient Selection and Biomarkers for (Adjuvant or) Consolidation IO

- **Tumor Mutational Burden (TMB)**
  - Can theoretically be affected by previous treatment (esp, cCRT)
  - Need for post-cCRT re-biopsy (Tissue? Blood?)

- **Bim, Soluble PD-L1**
  - Potential blood biomarkers
  - Need to validated in patients receiving operation or cCRT

- **Circulating tumor DNA (ctDNA), Circulating tumor cell (CTC)**
  - Blood biomarkers for Molecular residual disease (MRD) ??

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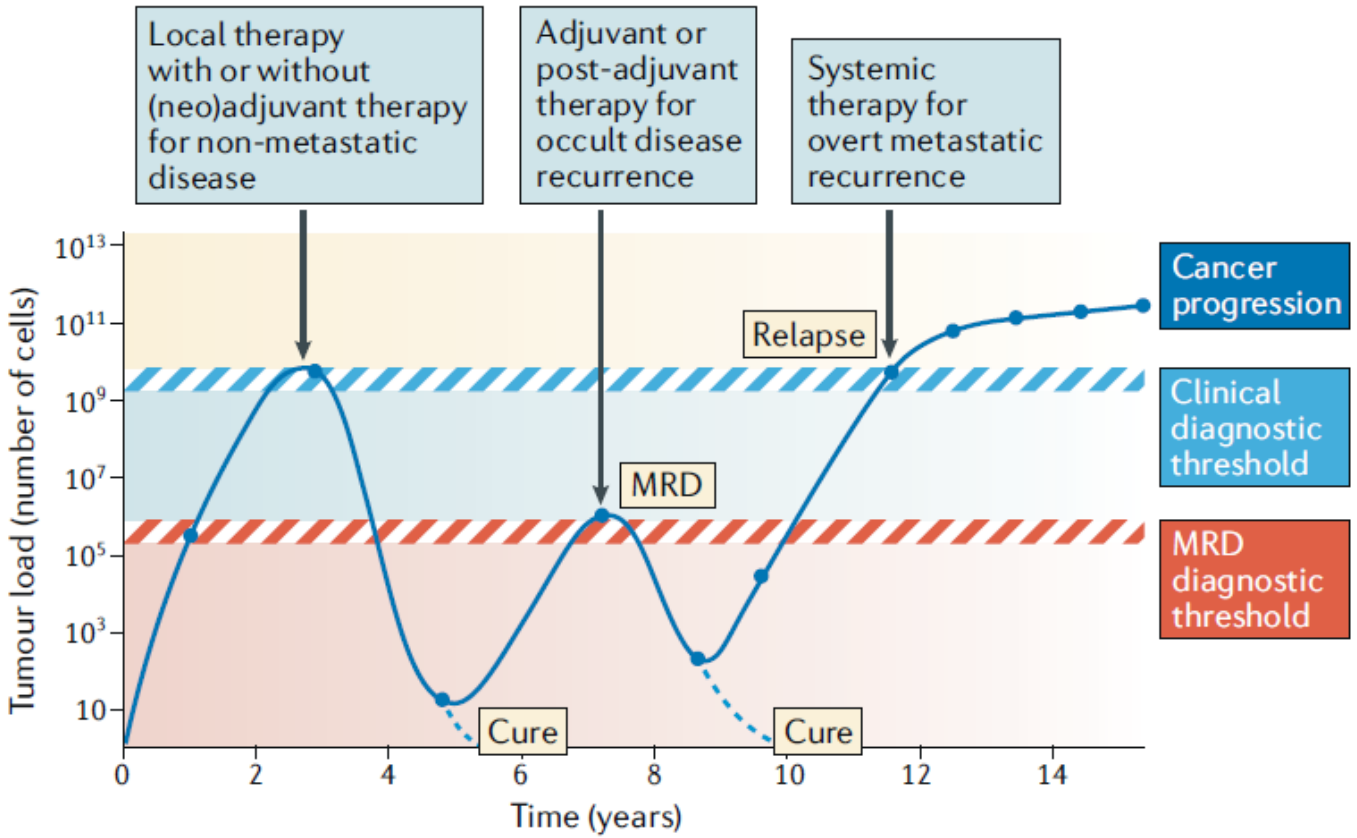
Minimal / Molecular Residual Disease (MRD)

- **MRD =** Cancer persisting in a patient after treatment that cannot be detected with current medical imaging modalities, an occult stage of cancer progression.



Nat Rev Clin Oncol 2019;16:409-424

Rationale of using ctDNA/CTC to assess MRD

- **Post-op adjuvant chemotherapy**
  - Modest improvement in overall survival : 4 to 5.4% benefit at 5 years
  - Potential toxicity & Questionable durability of positive effect

- **Other malignancies**
  - Leukemia, Multiple myeloma : MRD(+) → increased risk of relapse & overall worse prognosis

- **Serial follow-up**
  - Predict relapse earlier before clinical & radiographic changes
  - Declines/Rises in allele frequency or Clearance of relevant mutations

J Thorac Oncol 2019;14(1):16-24

Rationale of using ctDNA/CTC to assess MRD

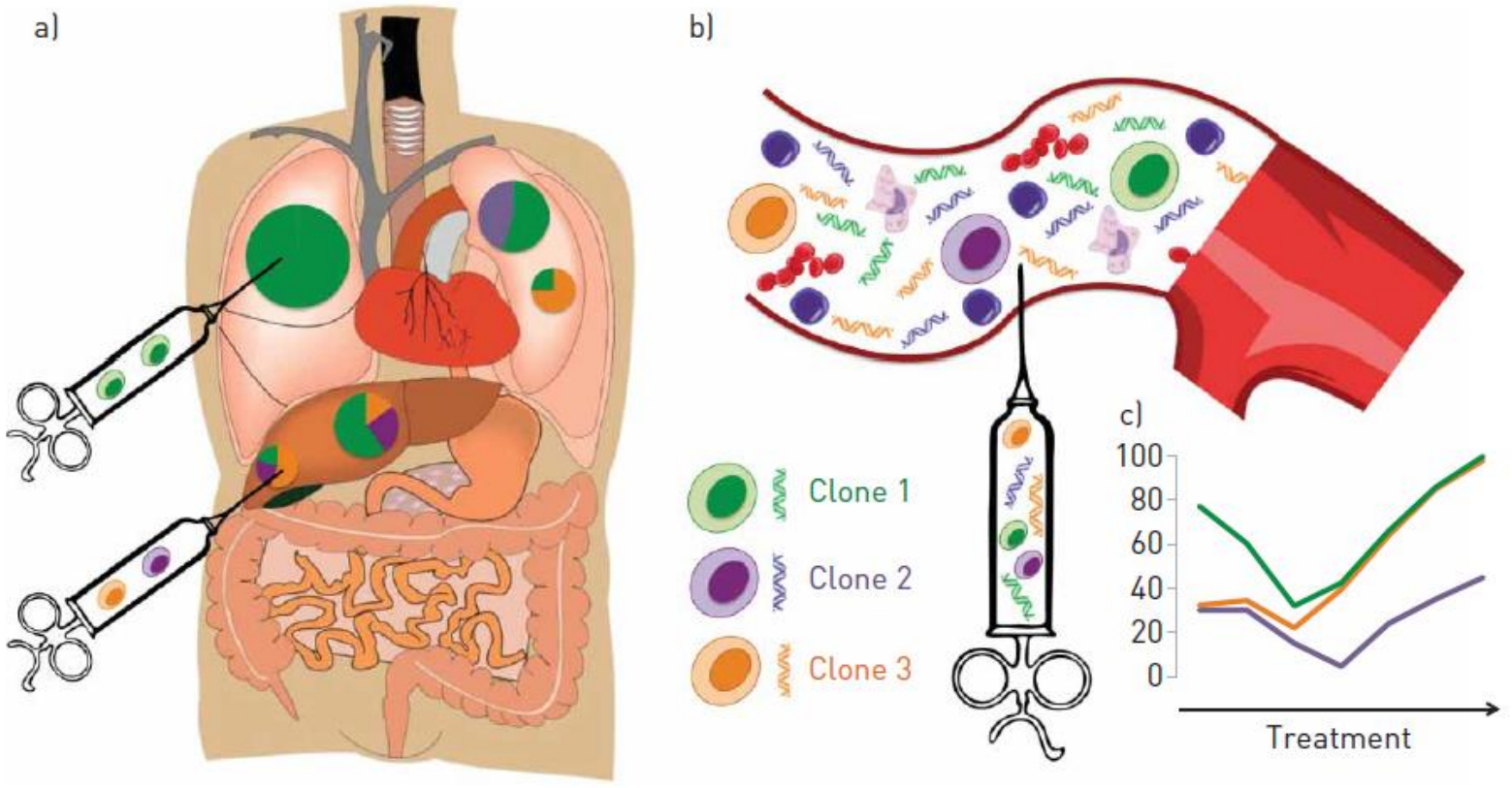
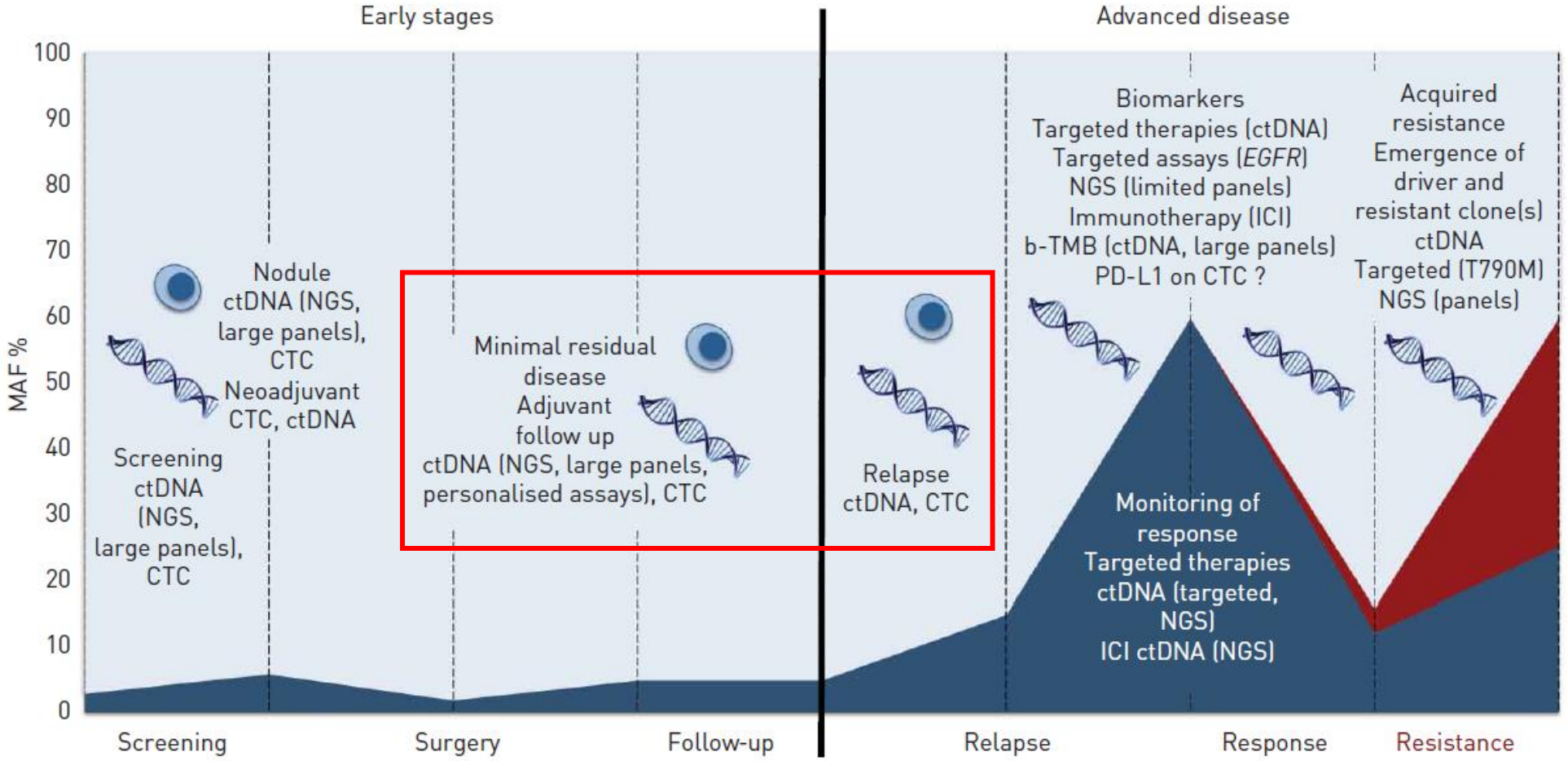


FIGURE 1 Liquid biopsy compared to tissue biopsy can capture both spatial (a *versus* b) and temporal (c) tumour heterogeneity and noninvasively follow the subclonal evolution of the disease through treatment.

Eur Respir Rev 2020;29(155):190052

Rationale of using ctDNA/CTC to assess MRD



Eur Respir Rev 2020;29(155):190052

Table 1. Summary of Clinical Data Supporting Use of ctDNA in Detecting Minimal Residual Disease

Study Population	Assay	ctDNA Detection Rate	Results
NSCLC, stage Ib-II, 3 patients	CAPP-Seq	ctDNA detected before treatment in all 3 patients	3 of 3 patients were ctDNA negative after definitive therapy and did not have recurrence 21-32 mo later
NSCLC, stage I-III, 40 patients	CAPP-Seq	ctDNA detected before treatment in 93% of patients with SCC and 89% with AC	17 of 17 patients who were ctDNA positive after treatment had recurrence, with a mean lead time of 5.2 mo 1 of 15 patients who were ctDNA negative had recurrence
NSCLC, early-stage, 100 patients	SNV detection based on NGS	ctDNA detected before surgery in 97% of patients with SCC and 19% with AC	13 of 14 patients who were ctDNA positive after treatment had recurrence, with a mean lead time of 70 d 1 of 10 patients who were ctDNA negative had recurrence
Breast cancer, localized disease, 20 patients	Digital PCR	ctDNA detected before surgery in 20% of patients	13 of 13 patients who were ctDNA positive after treatment had recurrence, with a mean lead time of 11 mo 1 of 7 patients who were ctDNA negative had recurrence
Breast cancer, stage I-II, 80 patients	1q21.3 amplification detection	Tissue concordance with sensitivity of 93.3%	4 of 4 patients with 1q21.3 detected after treatment had recurrence
Colon cancer, stage II, 231 patients	Safe-SeqS	ctDNA first assessed 4-10 wk after surgery, detected in 7.9% of patients	11 of 14 patients who were ctDNA positive had recurrence 16 of 164 patients who were ctDNA negative had recurrence
Colon cancer, resectable disease, 20 patients	BEAMing	ctDNA first assessed 13-56 d after surgery	15 of 16 ctDNA-positive patients had recurrence 0 of 4 ctDNA-negative patients had recurrence

ctDNA, circulating tumor DNA; Ref., reference; CAPP-Seq, cancer personalized profiling by deep sequencing; SCC, squamous cell carcinoma; AC, adenocarcinoma; SNV, single-nucleotide variation; generation sequencing; *BEAMing*, a term formed from the words beads, emulsion, amplification, and magnetics technique.

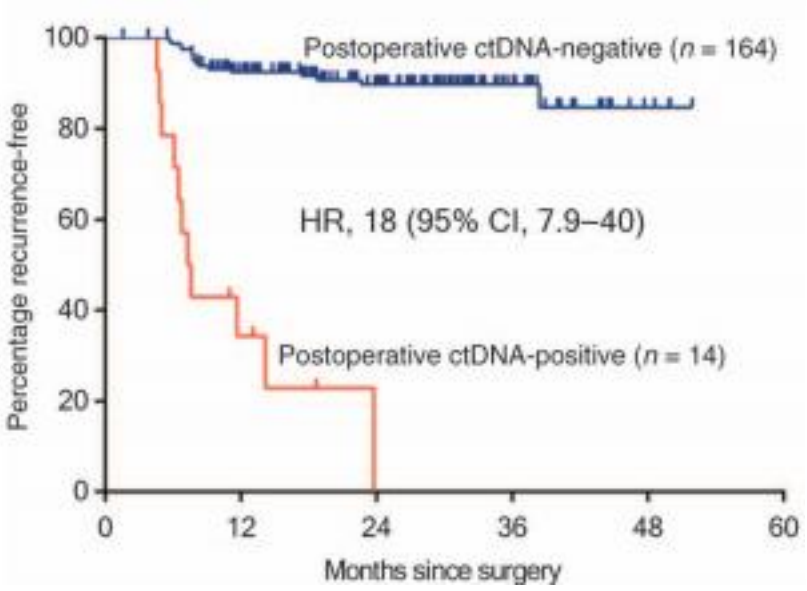
J Thorac Oncol 2019;14(1):16-24

Utilization of ctDNA/CTC as a biomarker for MRD

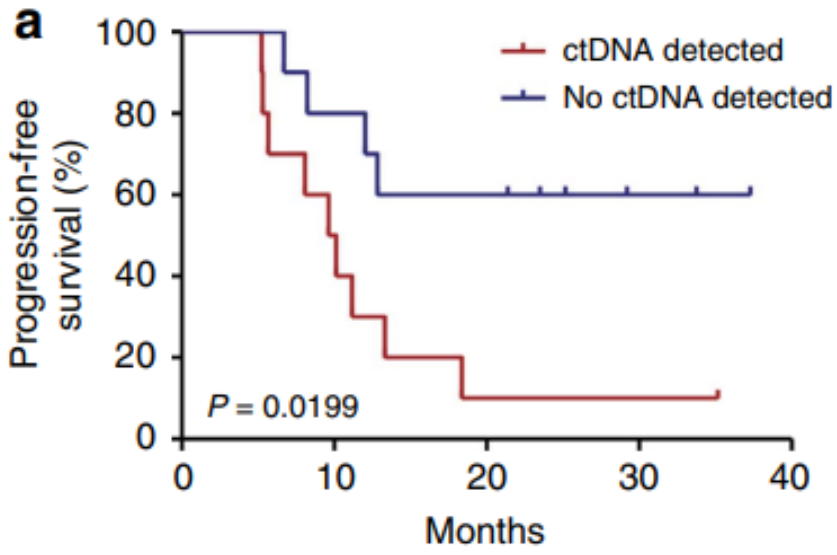
- **Prognosis of ctDNA/CTC(+) NSCLC after Definitive Tx**

- Intervention or Adaptation of treatment during or after Standard therapy
  - ➢ Resume or Change therapy if ctDNA/CTC(+)
  - ➢ Omit or Shorten therapy if ctDNA/CTC(-)

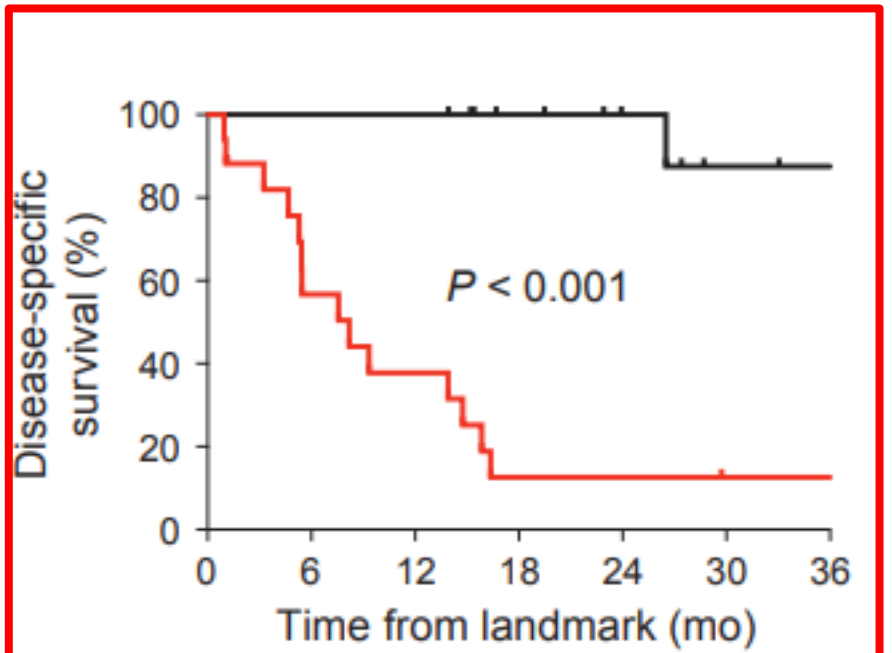
ctDNA clearance predicts recurrence-free survival



Colorectal Cancer



Pancreatic Cancer

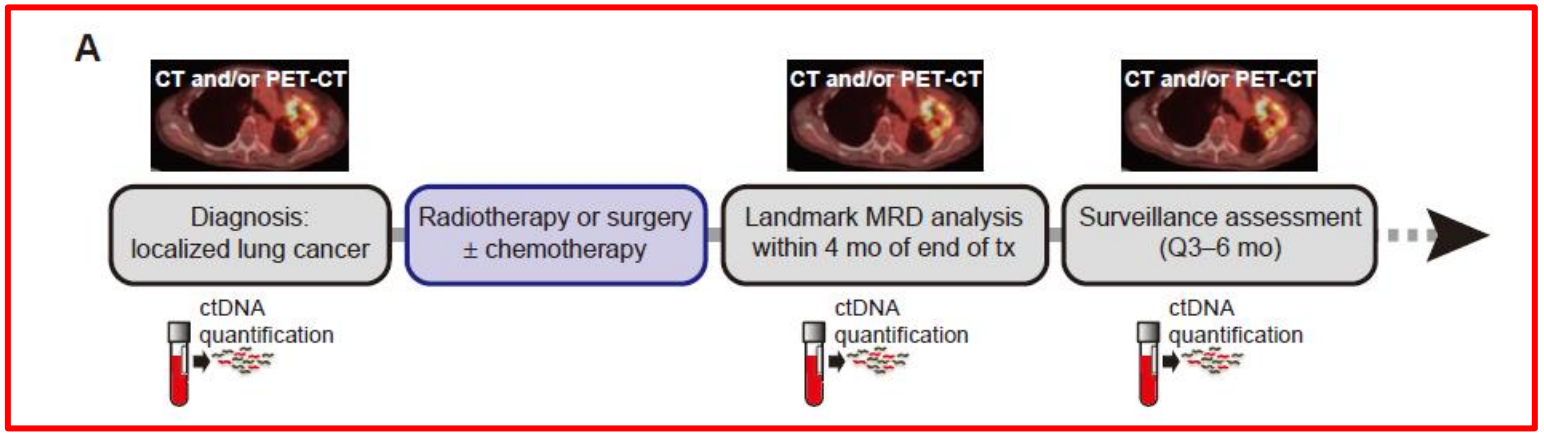


Lung Cancer

RESEARCH BRIEF

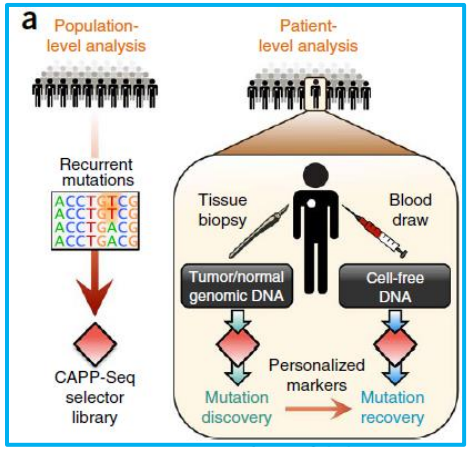
Early Detection of Molecular Residual Disease in Localized Lung Cancer by Circulating Tumor DNA Profiling

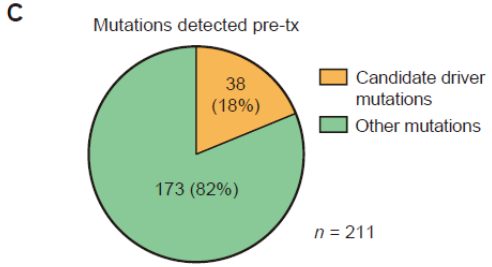
Aadel A. Chaudhuri[1,2], Jacob J. Chabon[2,3], Alexander F. Lovejoy[1,2], Aaron M. Newman[3,4], Henning Stehr[2], Tej D. Azad[2], Michael S. Khodadoust[2,4], Mohammad Shahrokh Esfahani[2], Chih Long Liu[2,4], Li Zhou[2,4], Florian Scherer[2,4], David M. Kurtz[2,4,5], Carmen Say[1], Justin N. Carter[1], David J. Merriott[1], Jonathan C. Dudley[2,6], Michael S. Binkley[1], Leslie Modlin[1], Sukhmani K. Padda[4], Michael F. Gensheimer[1], Robert B. West[6], Joseph B. Shrager[7], Joel W. Neal[4], Heather A. Wakelee[4], Billy W. Loo Jr[1], Ash A. Alizadeh[2,3,4], and Maximilian Diehn[1,2,3]

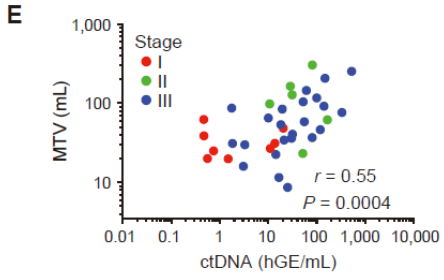


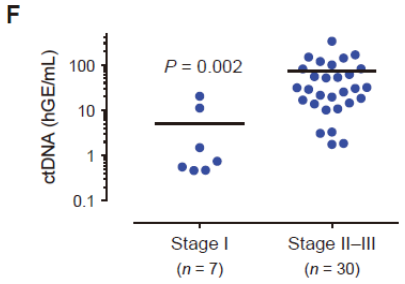
Pre-treatment

CAPP-Seq

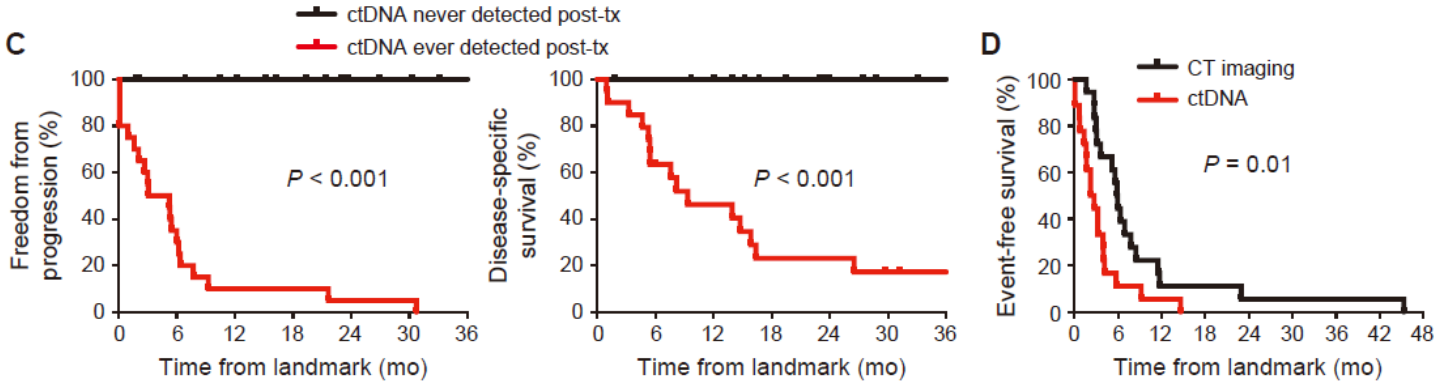


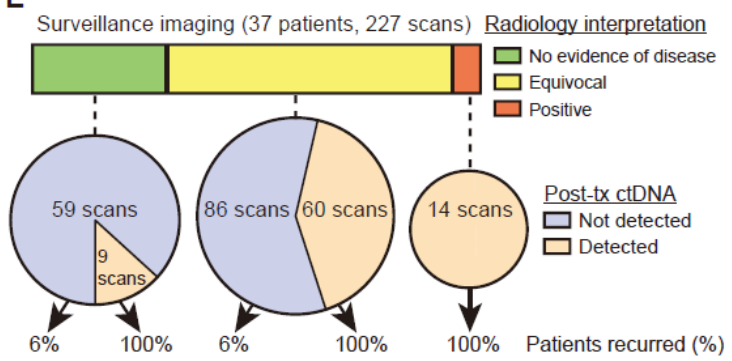


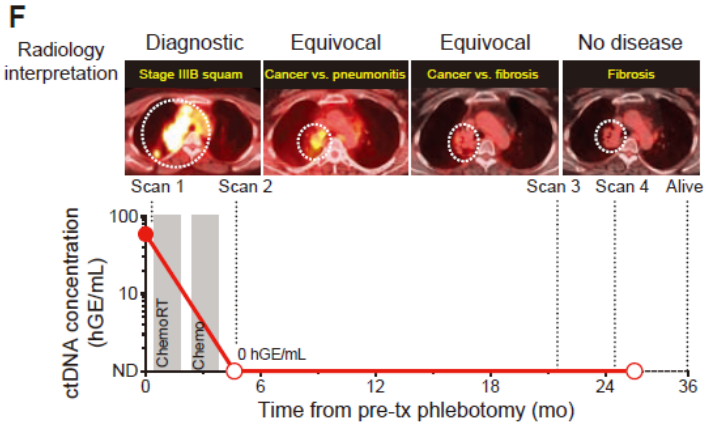




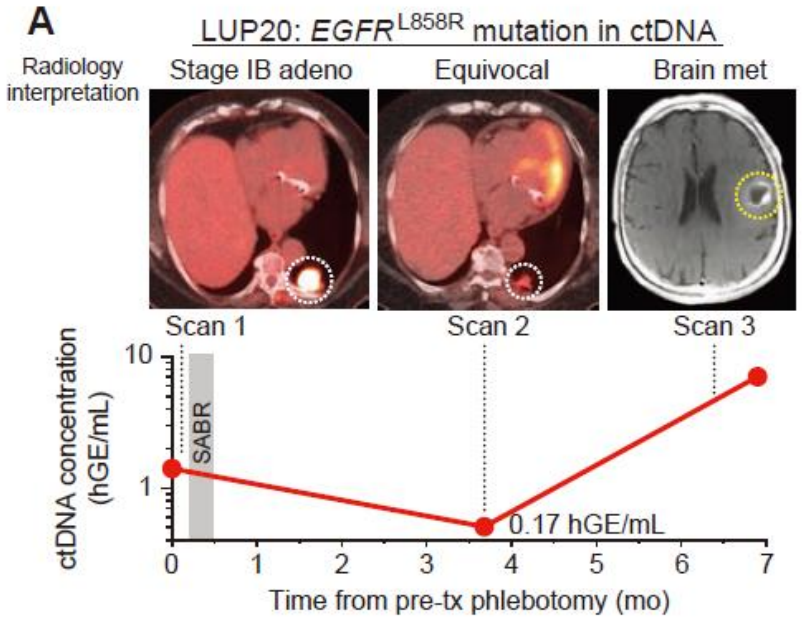
Post-treatment

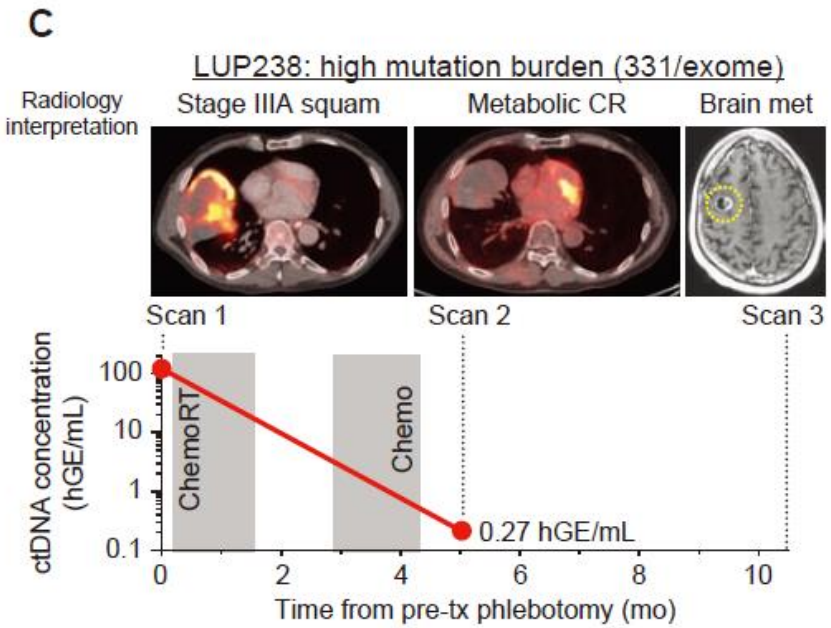




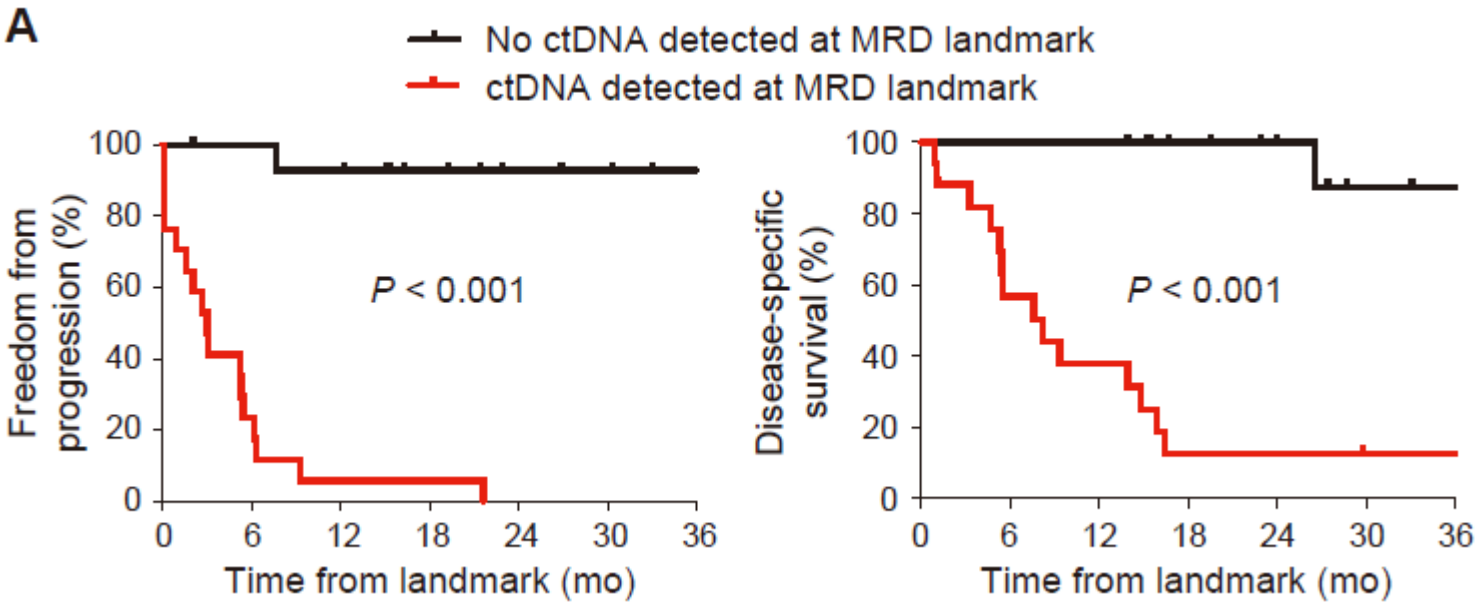


Nat Med 2014;20(5):548-554
Cancer Discov 2017;7(12):1394-1403





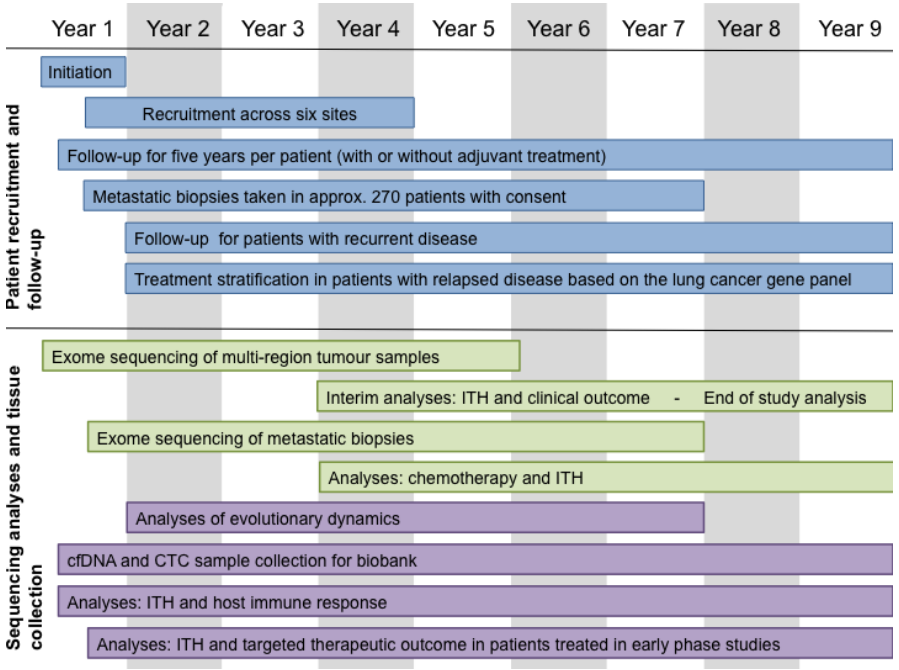
MRD landmark : first post-Tx blood draw within 4 months of Tx completion

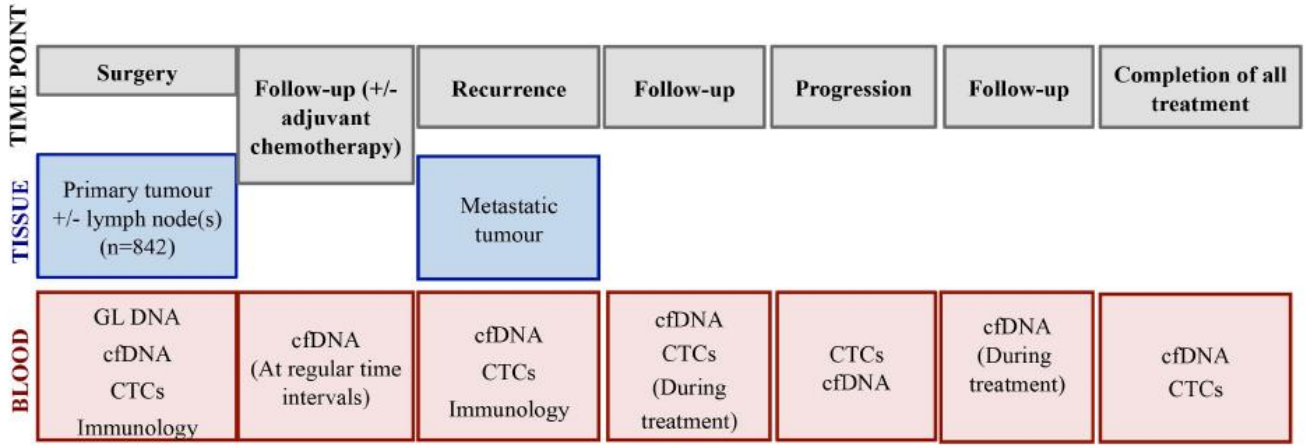


Cancer Discov 2017;7(12):1394-1403

TRACERx Lung

- **Primary objectives**
  - Define the relationship between intratumour heterogeneity and clinical outcome following surgery and adjuvant therapy
  - Establish the impact of adjuvant platinum-containing regimens upon intratumour heterogeneity in relapsed disease compared to primary resected tumor
  - 842 patients, stage I-IIIA NSCLC (PI : prof. Charles Swanton, UCL)

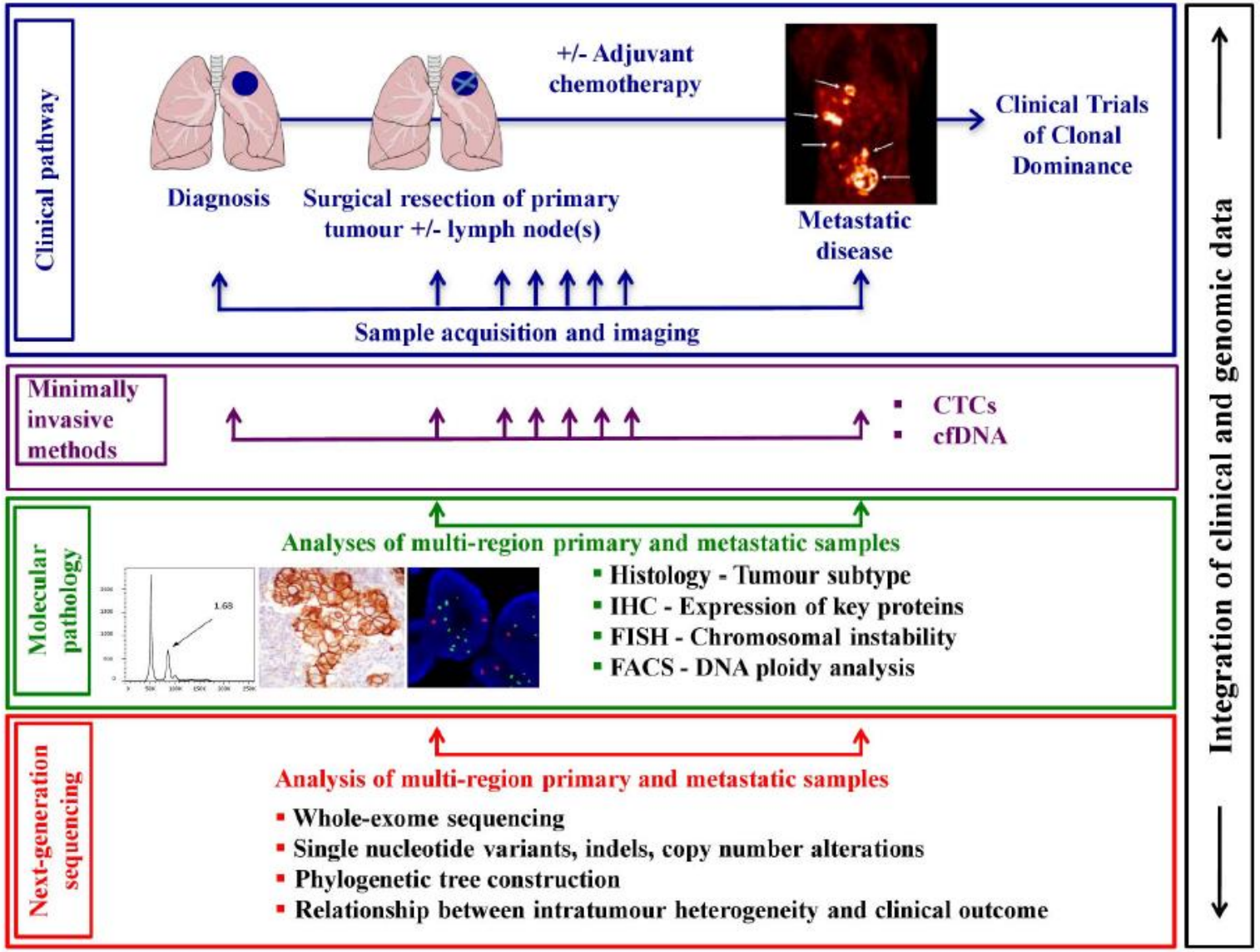




http://www.cruklungcentre.org/Research/TRACERx

PLoS Biol 2014;12(7):e1001906

TRACERx Lung



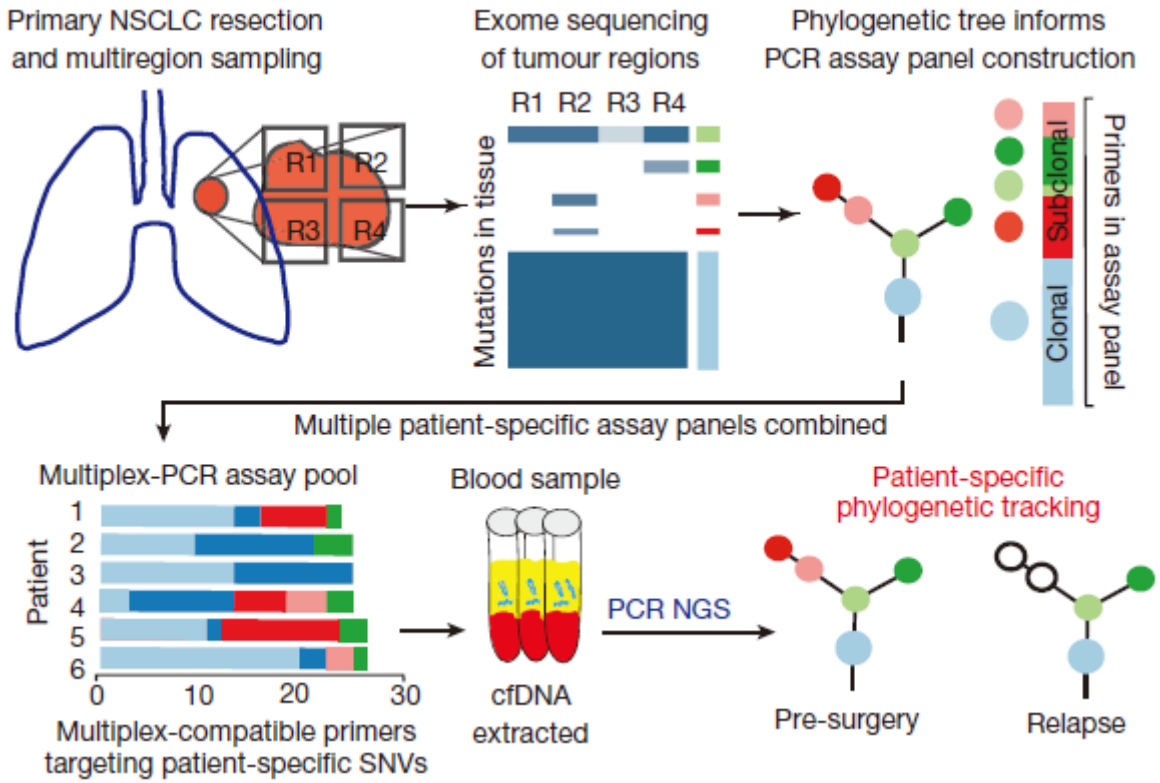
PLoS Biol 2014;12(7):e1001906

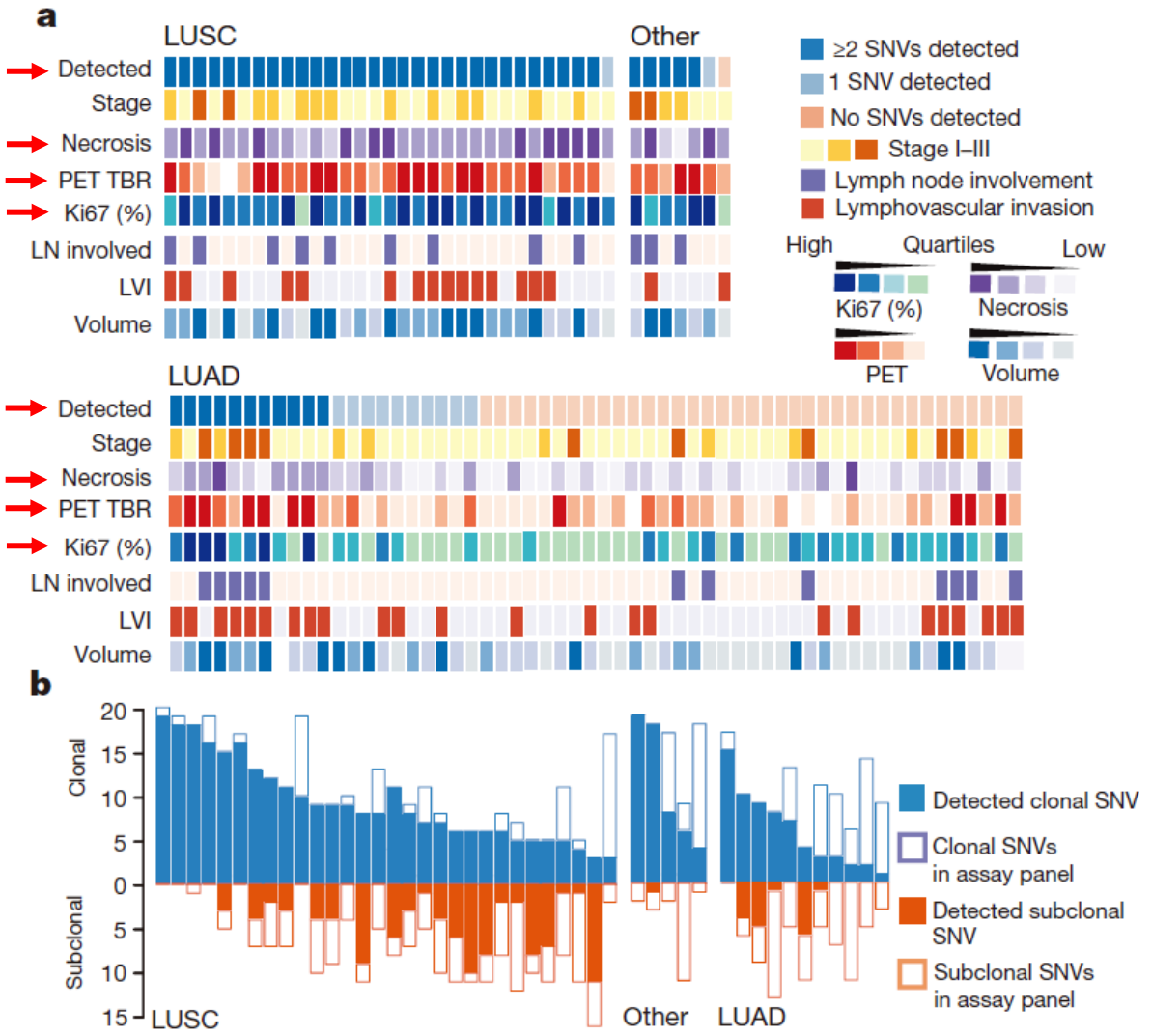
ARTICLE

doi:10.1038/nature22364

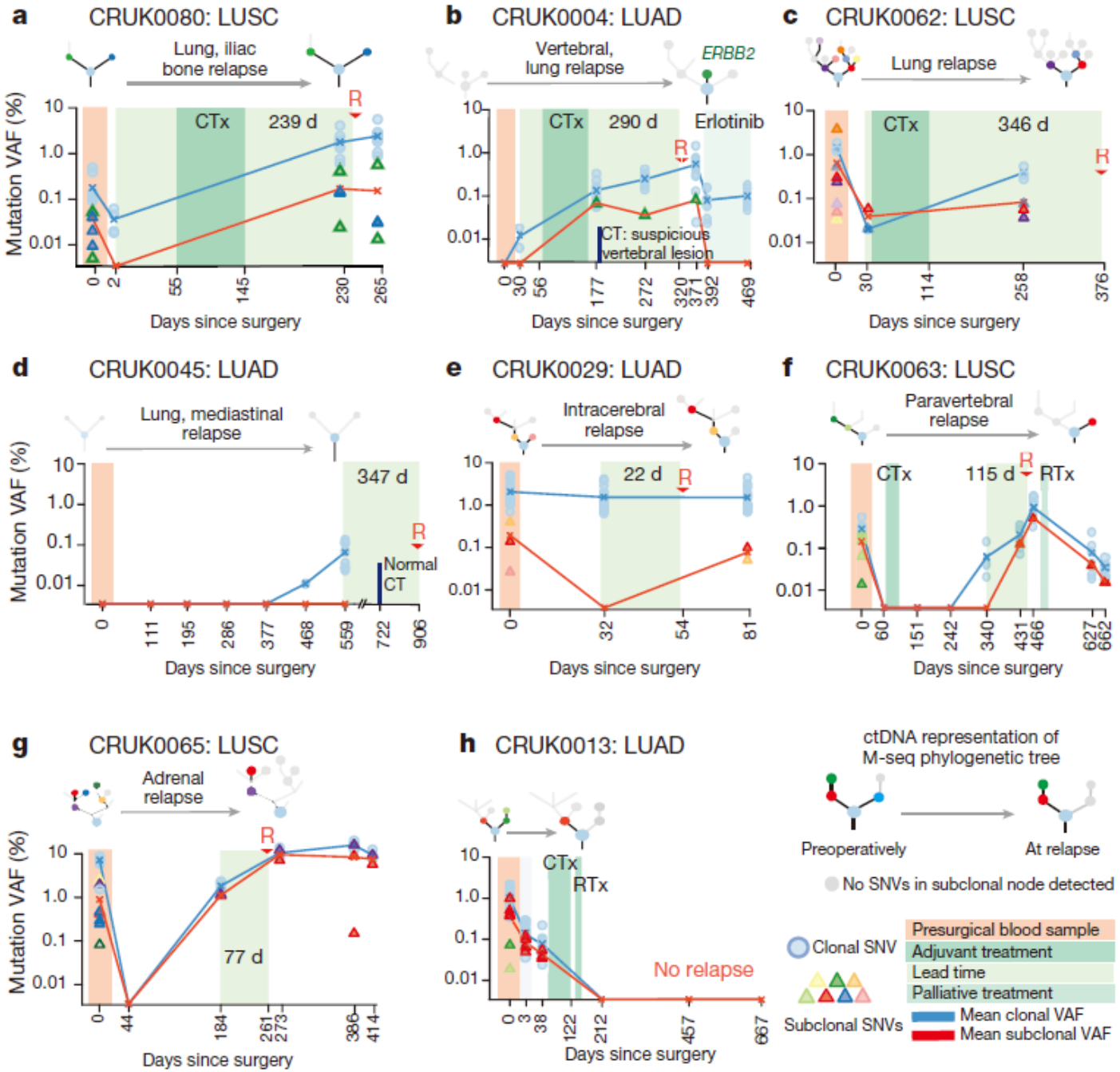
Phylogenetic ctDNA analysis depicts early-stage lung cancer evolution

- **N=100**



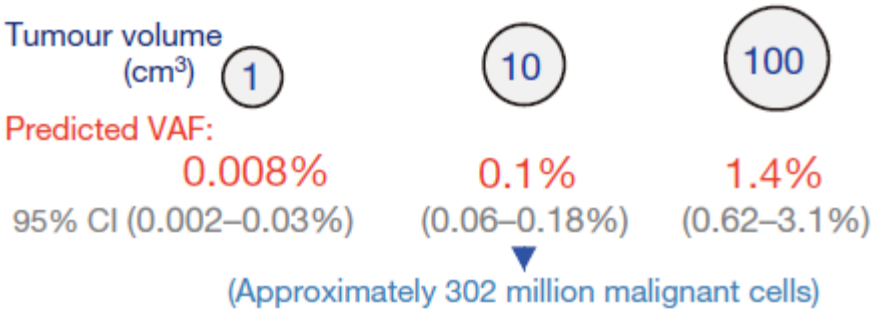


Nature 2017;545(7655):446-451



	Univariable analysis	
	OR (95% CI)	P-value
Clinicopathological variables		
Non-adenocarcinoma histology	49.85 (12.93 -192.19)	<0.001
%Ki67$^+$ cells (10% increase)	1.72 (1.40 - 2.12)	<0.001
Lympho-vascular invasion	2.53 (1.10 - 5.80)	0.028
Necrosis (10% increase)	2.16 (1.58 - 2.97)	<0.001
Path tumour size (10mm increase)	1.45 (1.13 - 1.86)	0.004
Lymph-node involvement	3.60 (1.33 - 9.77)	0.012
Male gender	1.80 (0.78 - 4.16)	0.172
Age (years)	0.96 (0.92 - 1.01)	0.115
Technical variables		
cfDNA input (ng)	1.01 (1.00 - 1.03)	0.028
Ubiquitous SNVs in assay-panel	0.96 (0.88 - 1.05)	0.341

Ubiquitous SNVs (SNVs present in all tumour regions sequenced).

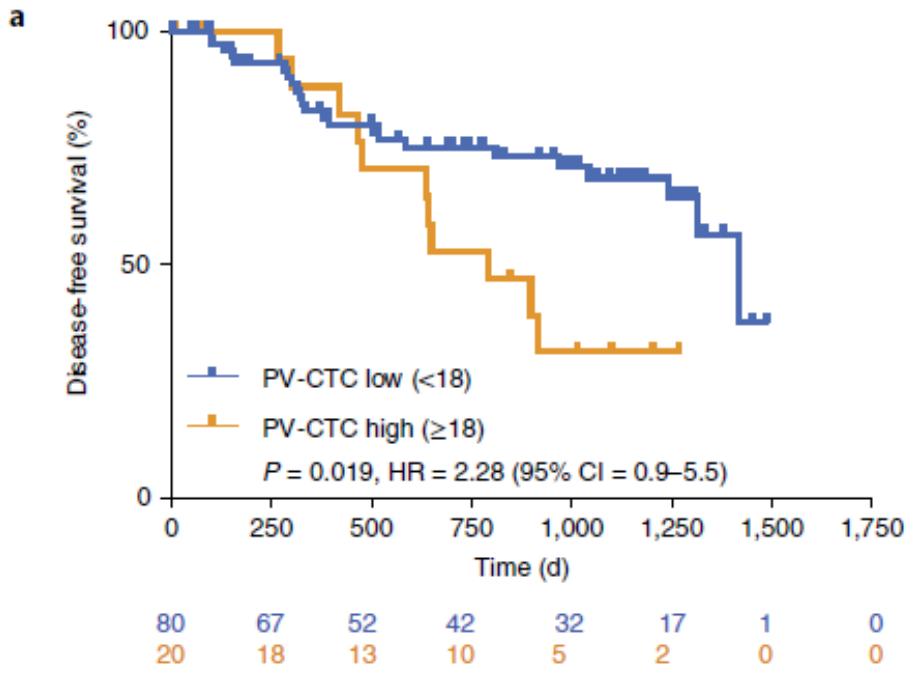


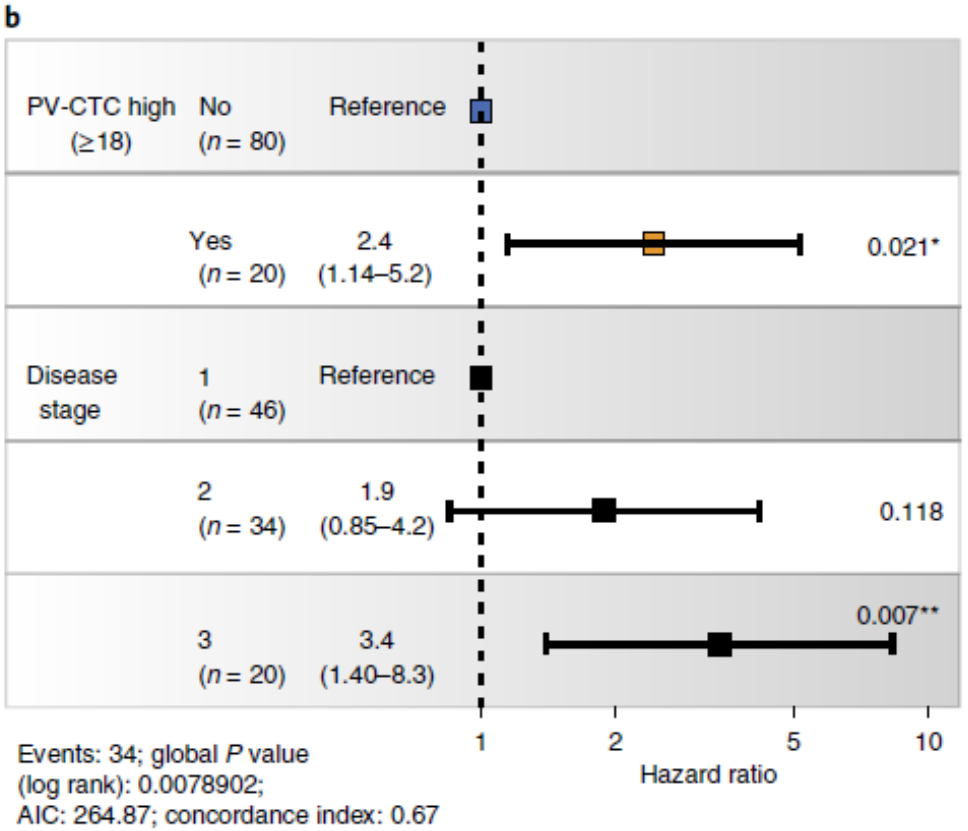
Nature 2017;545(7655):446-451

LETTERS
https://doi.org/10.1038/s41591-019-0593-1
nature medicine

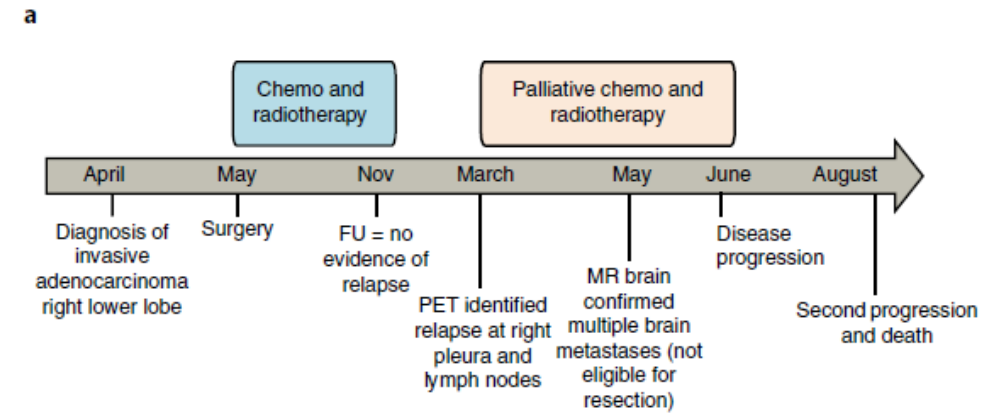
There are amendments to this paper

Pulmonary venous circulating tumor cell dissemination before tumor resection and disease relapse





Nat Med 2019;25(10):1534-1539



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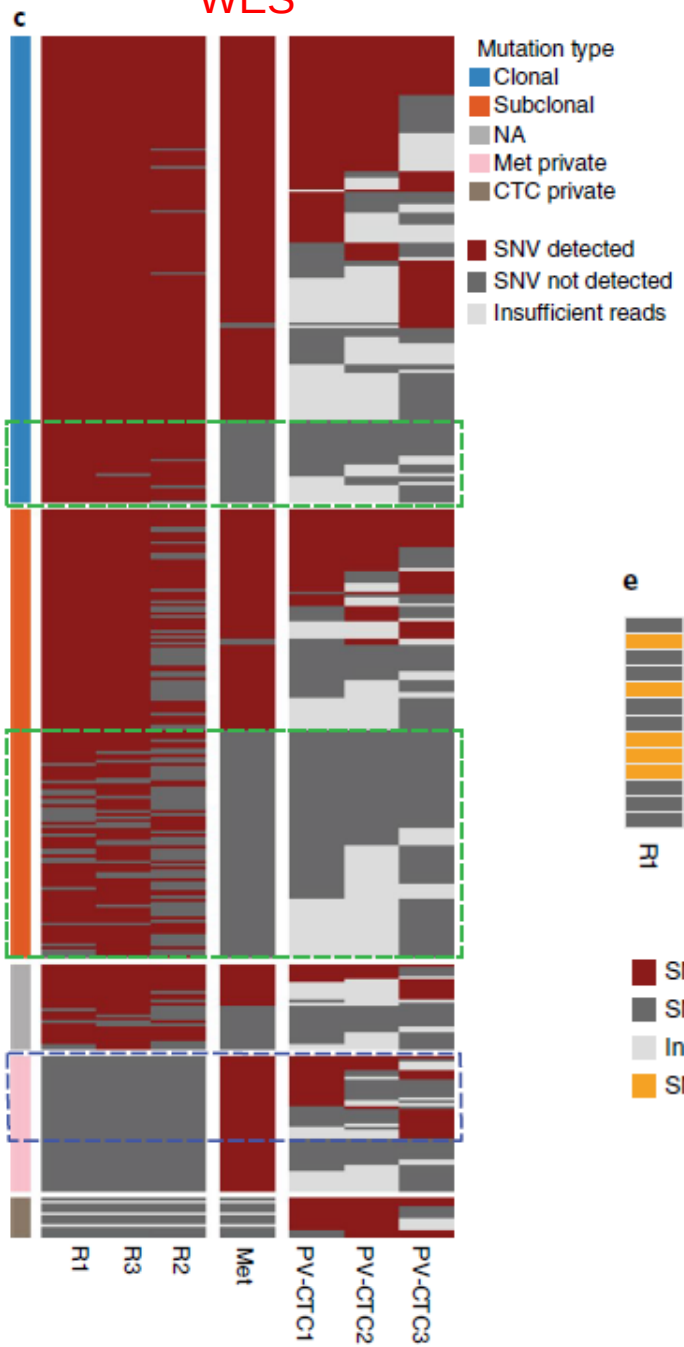
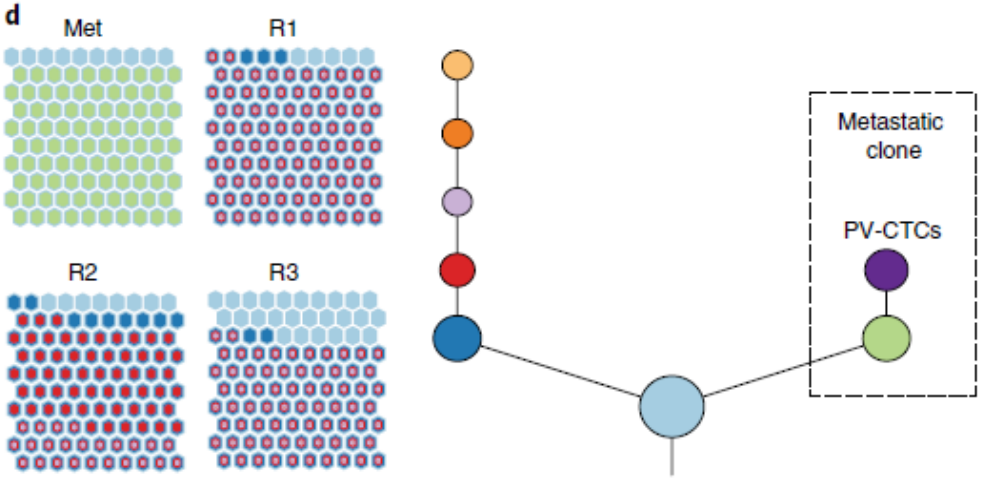
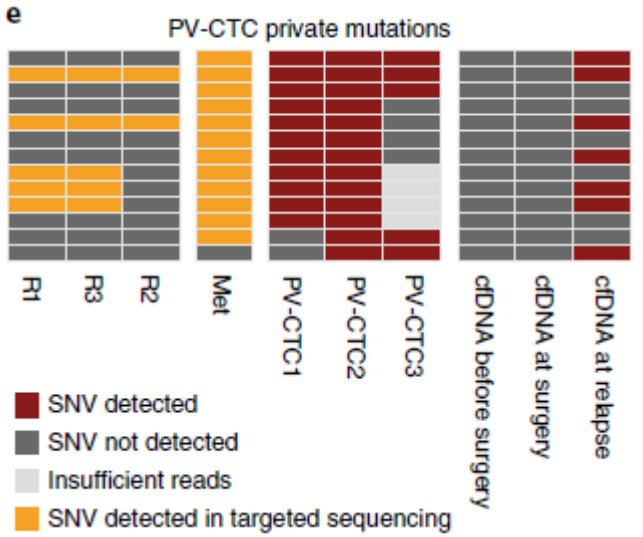






Nat Med 2019;25(10):1534-1539

Utilization of ctDNA/CTC as a biomarker for MRD

- Prognosis of ctDNA/CTC(+) NSCLC after Definitive Tx

- **Intervention or Adaptation of treatment during or after Standard therapy**
  - **Resume or Change therapy if ctDNA/CTC(+)**
  - **Omit or Shorten therapy if ctDNA/CTC(-)**

Editorial

Targeting minimal residual disease after surgery with molecular targeted therapy: the real path to a cure?

Katsuhiro Masago, Shiro Fujita, Yasushi Yatabe

Table 1 Ongoing randomized phase III trial of an EGFR-TKIs as adjuvant treatment for patients with NSCLC harboring *EGFR* activating mutations (12)

Clinical trial	Region	Stage, planned accrual, EGFR mutation	Study design	Primary end-point
NCT02125240 (ICWIP)	China	II–IIIA, 300, ex19del and L858R	Rand. to icotinib ×2 years *vs.* placebo ×2 years (platinum-based chemotherapy ×4 cycles)	DFS
NCT01996098 (ICTAN)	China	II–IIIA, 300, ex19del and L858R	Rand. to icotinib ×12 months *vs.* icotinib ×6 months *vs.* observation (platinum-based chemotherapy ×4 cycles)	DFS
NCT02193282 (ALCHEMIST)	U.S.	IB (≥4 cm) –IIIA, 450, ex19del and L858R without T790M	Rand. to erlotinib ×2 years *vs.* placebo ×2 years (after standard adjuvant chemotherapy)	OS
NCT02201992 (ALCHEMIST)	U.S.	IB (≥4 cm)–IIIA, 378, ALK-positive	Rand. to crizotinib ×2 years *vs.* placebo for 2 years (after standard adjuvant chemotherapy)	OS
WJOG6401L	Japan	II–IIIA, 230, ex19del and L858R without T790M	Rand. to gefitinib ×2 years *vs.* cisplatin/vinorelbine ×4 cycles	5-year DFS
NCT02448797 (EVIDENCE)	China	II–IIIA, 320, ex19del and L858R	Rand. to icotinib ×2 years *vs.* cisplatin/vinorelbine ×4 cycles	DFS
NCT02518802	China	II–IIIA (N1, N2), 220, ex19del and L858R	Rand. to cisplatin/pemetrexed ×4 cycles + gefitinib ×2 years *vs.* cisplatin/pemetrexed ×4 cycles	DFS
NCT01996098 (ICTAN)	China	II–IIIA, 477, ex19del and L858R	Rand. to icotinib ×12 months *vs.* icotinib ×6 months *vs.* observation (platinum-based chemotherapy ×4 cycles)	DFS
NCT02511106 (ADAURA)	International	IB–IIIA, 700, ex19del and L858R ± other EGFR mutation*	Rand. to osimertinib ×2 years *vs.* placebo ×2 years (standard adjuvant chemotherapy allowed)	DFS

*, including T790M. NSCLC, non-small cell lung cancer; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; Rand., randomization; *vs.*, versus; DFS, disease-free survival; OS, overall survival.

J Thoracic Dis 2018;10:S1982-S1985

A meta-analysis of adjuvant EGFR-TKIs for patients with resected non-small cell lung cancer

Hua Cheng, Xiao-Jian Li, Xiao-Jin Wang, Zuo-Wen Chen, Rui-Qi Wang, Hong-Cheng Zhong, Tian-Chi Wu, Qing-Dong Cao*

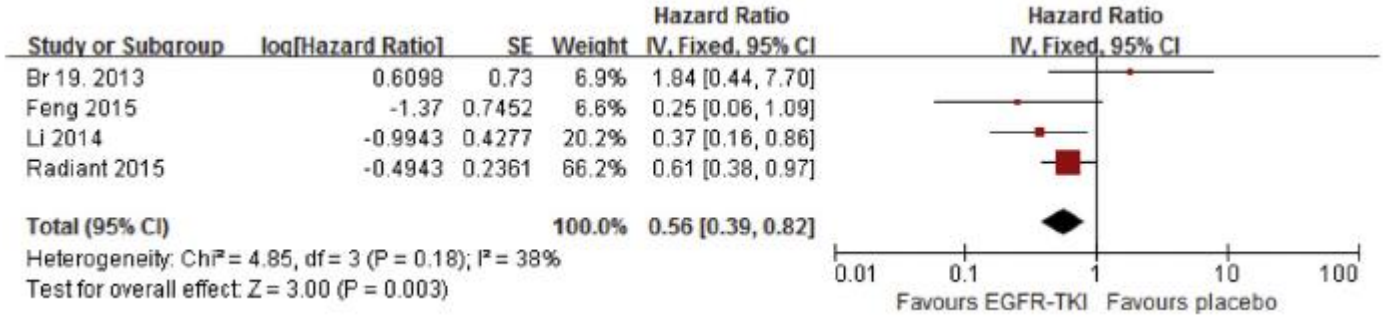
Department of Thoracic Surgery, The Fifth Affiliated Hospital of Sun Yat-Sen University, China

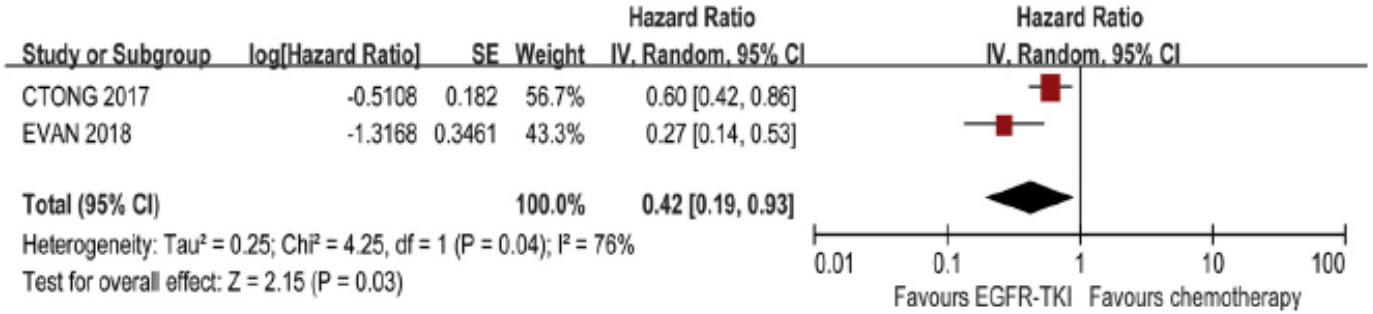
Table 1
Baseline characteristics of included studies. *NA, not assessable.

Trials	Intervention	No.	AgeMedian	Stage (No.)	Adjuvant chemotherapy		Primary endpoint	EGFR mutation positive patients	Median follow up(year)	Median TKI treatment duration (month)
					Yes	No				
RADIANT [10]	erlotinib	N=623	62	IB to IIIA	315(50.6%)	308(49.4%)	DFS	N=102	3.9	11.9
	Placebo	N=350	62	IB to IIIA	200(57.1%)	150(42.9%)	DFS	N = 59		
Br.19 [11]	gefitinib	N=251	66	IB to IIIA	43(17%)	208(83%)	OS and DFS	N=7	4.7 (range, 0.1–6.3)	4.8
	placebo	N=252	67	IB to IIIA	44(17%)	208(83%)	OS and DFS	N = 8		
Li [9]	chemotherapy-gefitinib	N = 30	59.5	IIIA N2	30	0	DFS	N = 30	2.5 (range, 0.3–4.39)	6
	chemotherapy	N = 30	54.6	IIIA N2	30	0	DFS	N = 30		
Feng [8]	Chemotherapy-Icotinib	N=21	57	IB to IIIA	21	0	DFS	21	2	NA*(Range, 4–8)
	chemotherapy	N=20	55	IB to IIIA	18	2	DFS	20		
CTONG1104 [12]	gefitinib	N = 111	58	II–IIIA (N1–N2)	0	0	DFS	N = 111	3.04(IQR 1.98–3.73)	21.9
	Vinorelbine plus cisplatin	N = 111	60	II–IIIA (N1–N2)	111	0	DFS	N = 111		
EVAN [13]	erlotinib	N = 51	59	IIIA	0	0	2 year DFS	N = 51	2.75(IQR1.48-3.59)	23.9(IQR20.7–24
	Vinorelbine plus cisplatin	N = 51	57	IIIA	51	0	2 year DFS	N = 51		

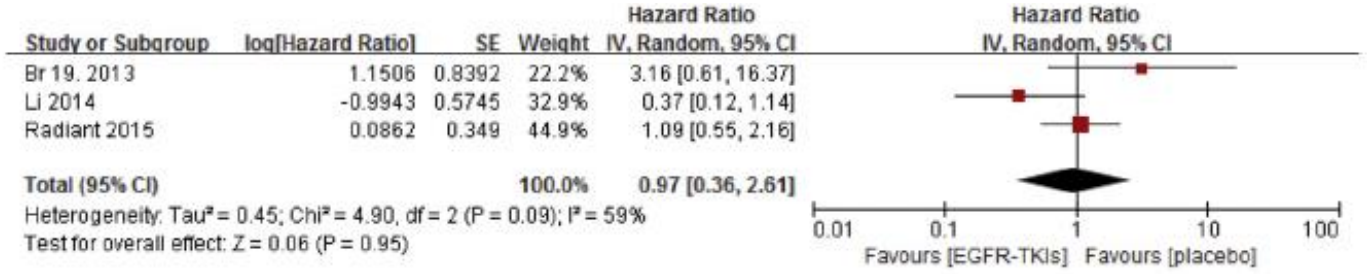
Lung Cancer 2019;137:7-13

Disease-free survival (DFS)





Overall survival (OS)



Lung Cancer 2019;137:7-13

Guidelines Do Not Universally Advocate for Molecular Testing to Guide Treatment or Recommend Treatment With Targeted Agents in the Adjuvant Setting

NCCN (2020)[1]	ESMO (2017)[2]	ASCO / Cancer Care Ontario Clinical Practice Guideline Update (2017)[3]	Society for Translational Medicine (2019)[4] (Consensus reached among Chinese experts)	Chinese Guidelines for Diagnosis and Treatment of Primary Lung Cancer 2018[5]
⊗	⊗	⊗	✓	✓
	Stage I / II disease: • Choice of adjuvant therapy should not be guided by molecular analyses • Targeted agents should not be used in the adjuvant setting for Stage I/II disease **Stage III disease:** • There is currently no role for targeted agents in Stage III NSCLC outside clinical trials	• Data insufficient to justify routine use of EGFR-TKIs in patients with sensitizing EGFR mutations	• Routine testing for EGFR mutations in surgically resected specimens of non-squamous NSCLC is recommended • Other driver mutations may also be detected if the conditions of hospital and patient allow • Adjuvant EGFR-TKI is an option for patients with Stage II–IIIA or high-risk Stage IB EGFRm NSCLC • Adjuvant therapies in patients with EGFRm NSCLC may include: chemotherapy, EGFR-TKI, and chemotherapy plus EGFR-TKI	• Postoperative targeted therapy is not recommended for completely resected Stage IA or IB NSCLC patients • EGFR mutation should be examined for Stage II−IIIA non-squamous-cell lung cancer with positive N1/N2 • For Stage III N2 EGFRm NSCLC, surgery + adjuvant EGFR-TKI treatment +/– postoperative radiotherapy is recommended

⊗ EGFRm testing and/or EGFR-TKI treatment not recommended/no comment. ✓ EGFRm testing and/or EGFR-TKI treatment recommended.

EGFRm = epidermal growth factor receptor mutation positive; EGFR-TKI = epidermal growth factor receptor tyrosine kinase inhibitor; NSCLC = non-small cell lung cancer.

1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer. V.4.2020. ©National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed May 18, 2020. To view the most recent and complete version of the guideline, go to NCCN.org. 2. Postmus PE et al. *Ann Oncol*. 2017;28:iv1-iv21. 3. Kris MG et al. *J Clin Oncol*. 2017;35:2960-2974. 4. Liang W et al. *Transl Lung Cancer Res*. 2019;8:1163-1173. 5. National Health Commission of the People's Republic of China. *Chin J Cancer Res*. 2019;31:1-28.

ADAURA Phase III double-blind study design

Patients with completely resected stage* IB, II, IIIA NSCLC, with or without adjuvant chemotherapy†

Key inclusion criteria:
≥18 years (Japan / Taiwan: ≥20)
WHO performance status 0 / 1
Confirmed primary non-squamous NSCLC Ex19del / L858R‡
Brain imaging, if not completed pre-operatively
Complete resection with negative margins§
Max. interval between surgery and randomization:
- 10 weeks without adjuvant chemotherapy
- 26 weeks with adjuvant chemotherapy

Stratification by:
stage (IB vs II vs IIIA)
EGFRm (Ex19del vs L858R)
race (Asian vs non-Asian)

Randomization 1:1 (N=682)

Osimertinib 80 mg, once daily

Placebo, once daily

Planned treatment duration: 3 years

Treatment continues until:
- Disease recurrence
- Treatment completed
- Discontinuation criterion met

Follow up:
- Until recurrence: Week 12 and 24, then every 24 weeks to 5 years, then yearly
- After recurrence: every 24 weeks for 5 years, then yearly

Endpoints

- **Primary**: DFS, by investigator assessment, in stage II/IIIA patients; designed for superiority under the assumed DFS HR of 0.70
- **Secondary**: DFS in the overall population¶, DFS at 2, 3, 4, and 5 years, OS, safety, health-related quality of life

- **Following IDMC recommendation, the study was unblinded early due to efficacy; here we report an unplanned interim analysis**
- **At the time of unblinding the study had completed enrollment and all patients were followed up for at least 1 year**

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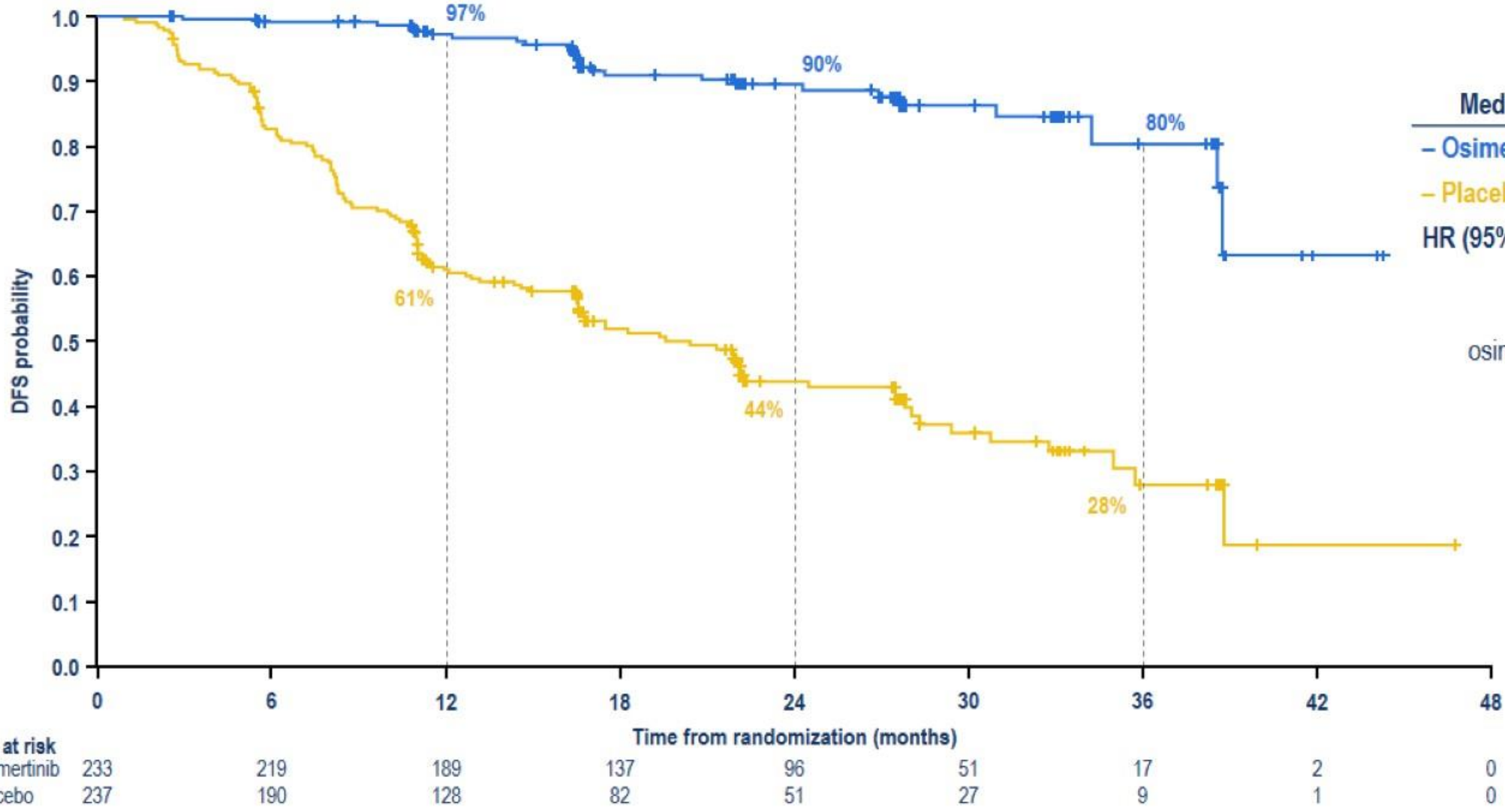
NCT02511106; ADAURA data cut-off: January 17, 2020. *AJCC 7th edition; †Prior, post, or planned radiotherapy was not allowed; ‡Centrally confirmed in tissue; §Patients received a CT scan after resection and within 28 days prior to treatment; ¶Stage IB / II / IIIA.
CT, computed tomography; Ex19del, exon 19 deletion; IDMC, Independent Data Monitoring Committee; WHO, World Health Organization.

Primary endpoint: DFS in patients with stage II/IIIA disease



Median DFS, months (95% CI)	
– Osimertinib	NR (38.8, NC)
– Placebo	20.4 (16.6, 24.5)
HR (95% CI)	0.17 (0.12, 0.23); p<0.0001

Maturity 33%:
osimertinib 11%, placebo 55%

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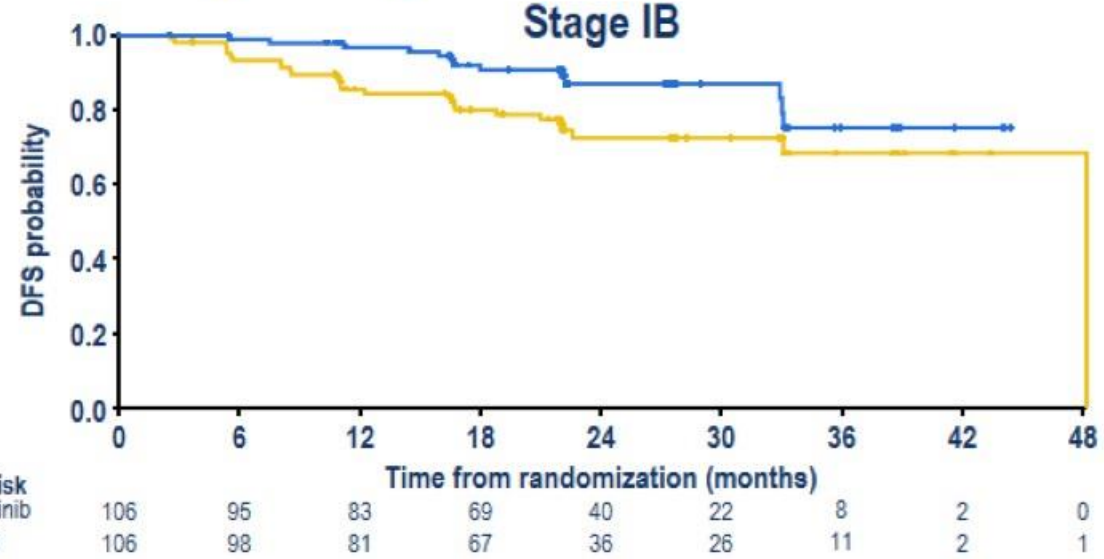
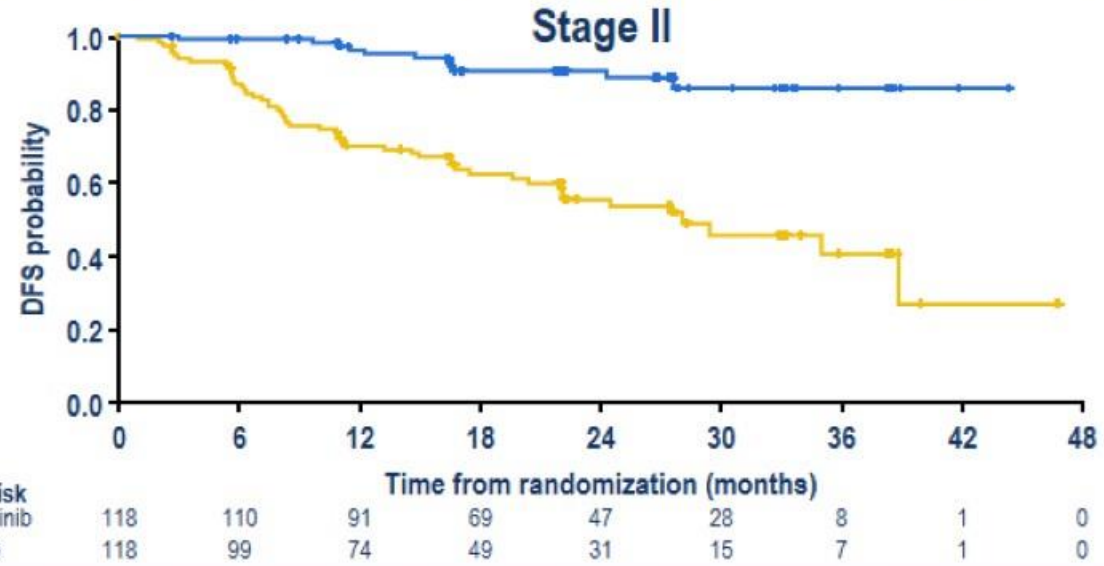
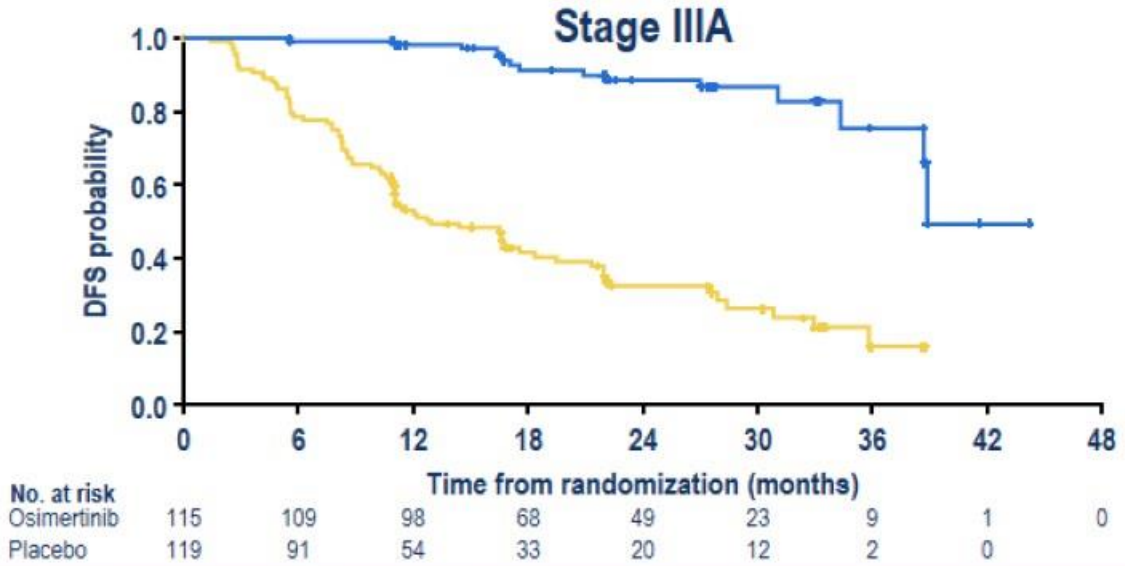
ADAURA data cut-off: January 17, 2020.
Median follow-up: osimertinib 22.1, placebo: 15.0 months;
DFS by investigator assessment; Tick marks indicate censored data.
NC, not calculable; NR, not reached.

DFS by stage



	Stage IB	Stage II	Stage IIIA
2 year DFS rate, % (95% CI)			
– Osimertinib	87 (77, 93)	91 (82, 95)	88 (79, 94)
– Placebo	73 (62, 81)	56 (45, 65)	32 (23, 42)
Overall HR (95% CI)	0.50 (0.25, 0.96)	0.17 (0.08, 0.31)	0.12 (0.07, 0.20)





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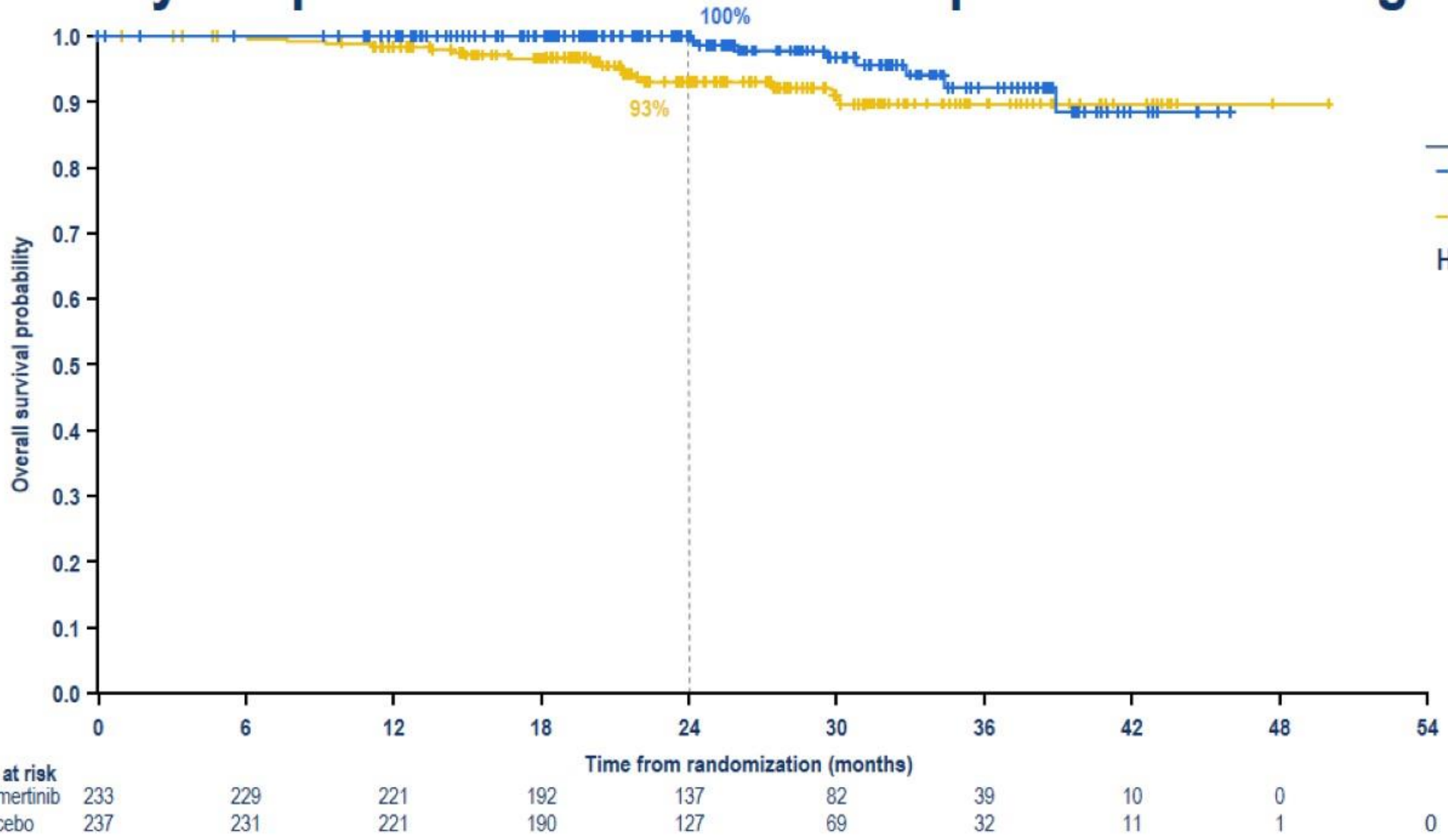
ADAURA data cut-off: January 17, 2020.
Tick marks indicate censored data.

Early snapshot: overall survival in patients with stage II/IIIA disease



Median OS, months (95% CI)	
– Osimertinib	NR (NC, NC)
– Placebo	NR (NC, NC)
HR (95% CI)	**0.40 (0.18, 0.90)**

Maturity 5%:
osimertinib 3%, placebo 7%

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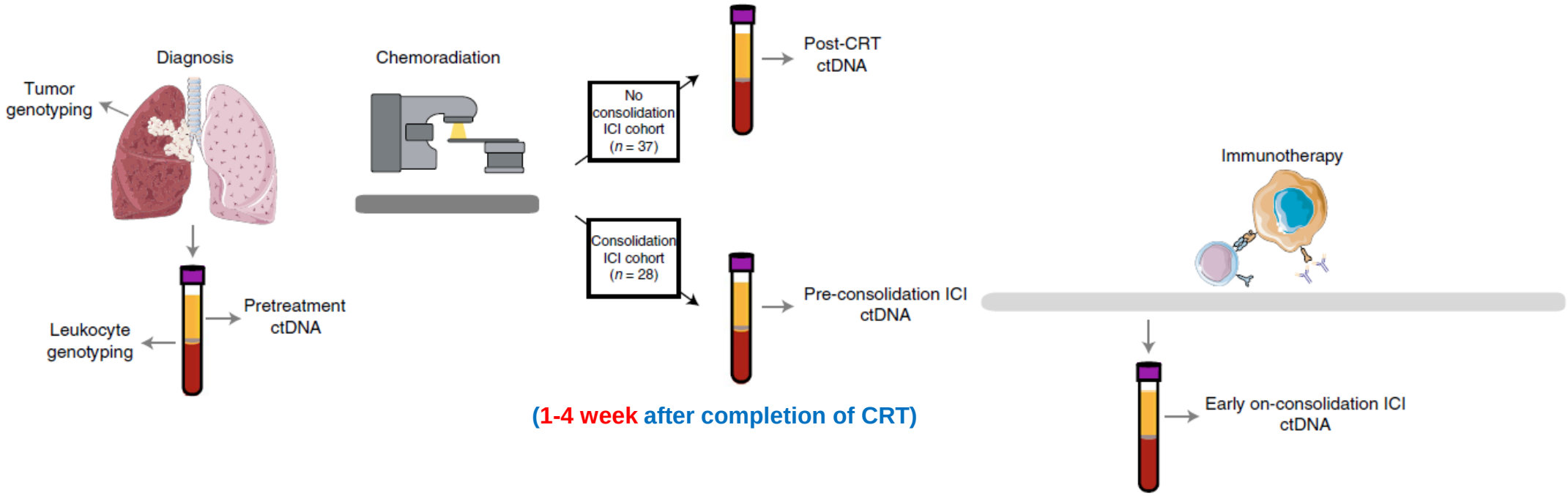
ADAURA data cut-off: January 17, 2020.
Median follow-up: osimertinib 26.1, placebo 24.7 months.
Tick marks indicate censored data.

nature cancer
ARTICLES
https://doi.org/10.1038/s43018-019-0011-0

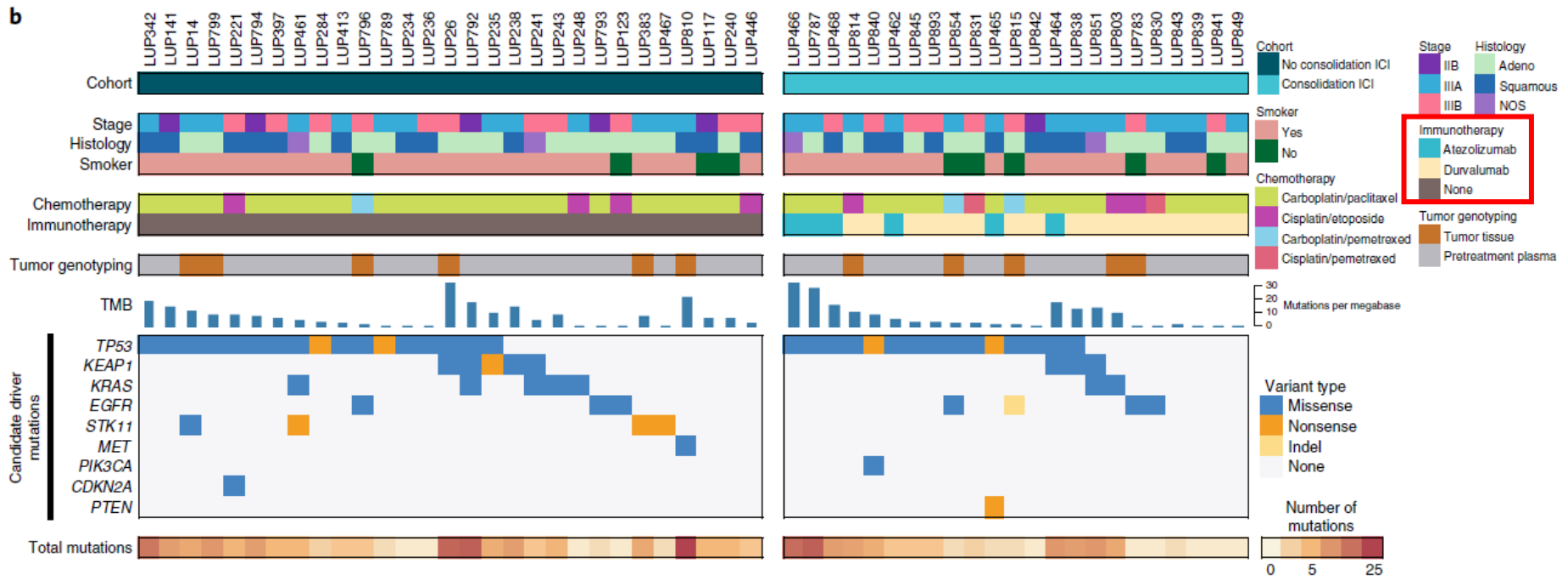
Circulating tumor DNA dynamics predict benefit from consolidation immunotherapy in locally advanced non-small-cell lung cancer

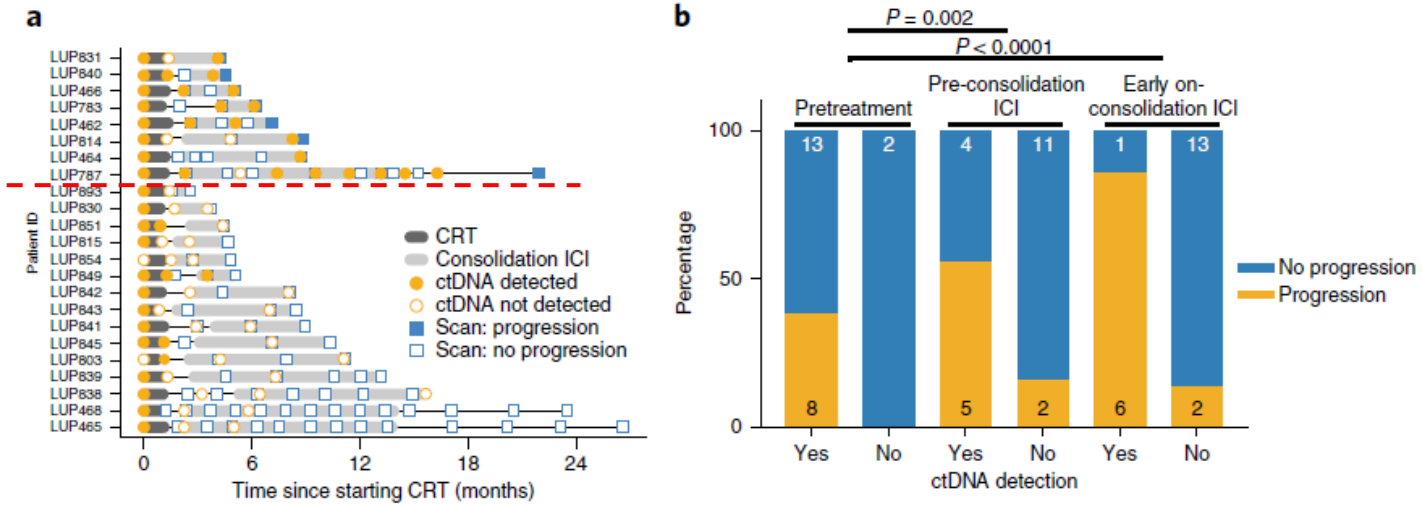


(1-4 week after completion of CRT)

(2-11 week after initiation of ICI)

Nat Cancer 2020;1(2):176-183



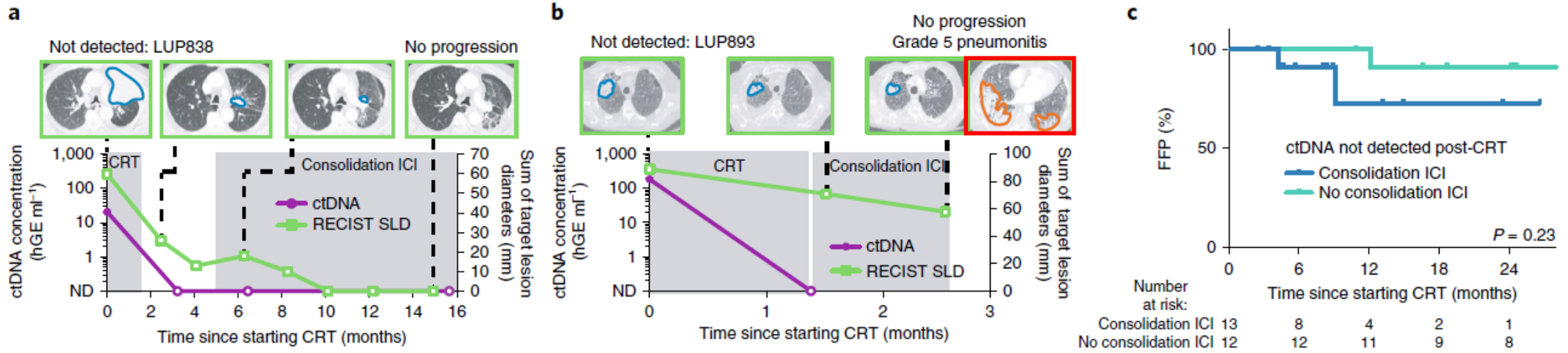


(2-11 week after initiation of ICI)

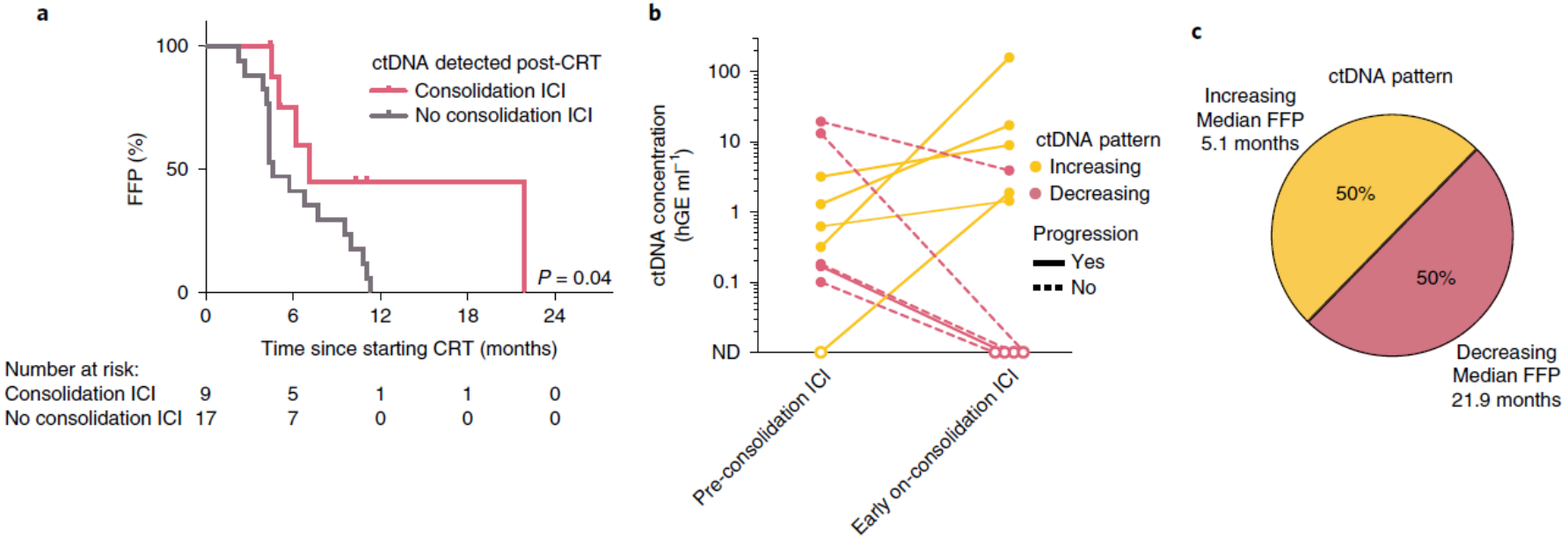
FFP : freedom from progression

Nat Cancer 2020;1(2):176-183

ctDNA(-) after CRT

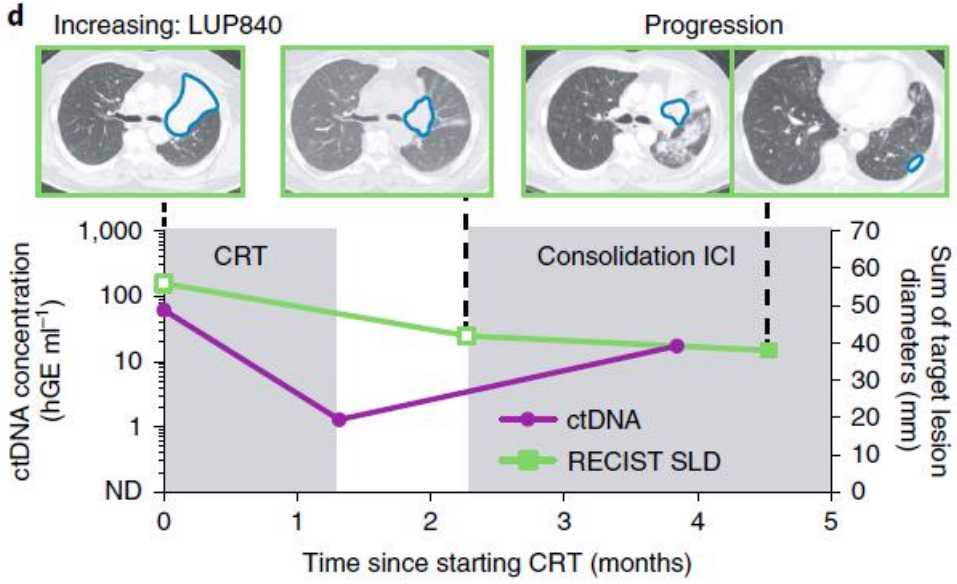


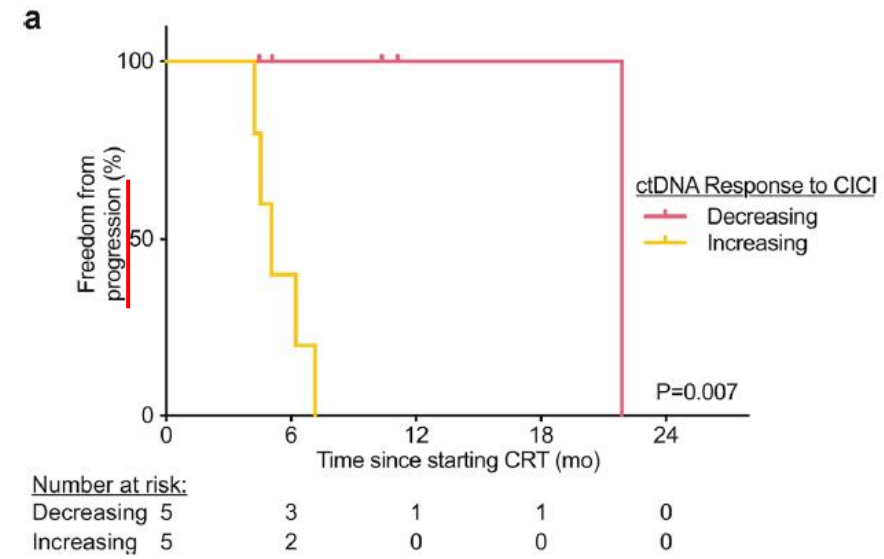
ctDNA(+) after CRT



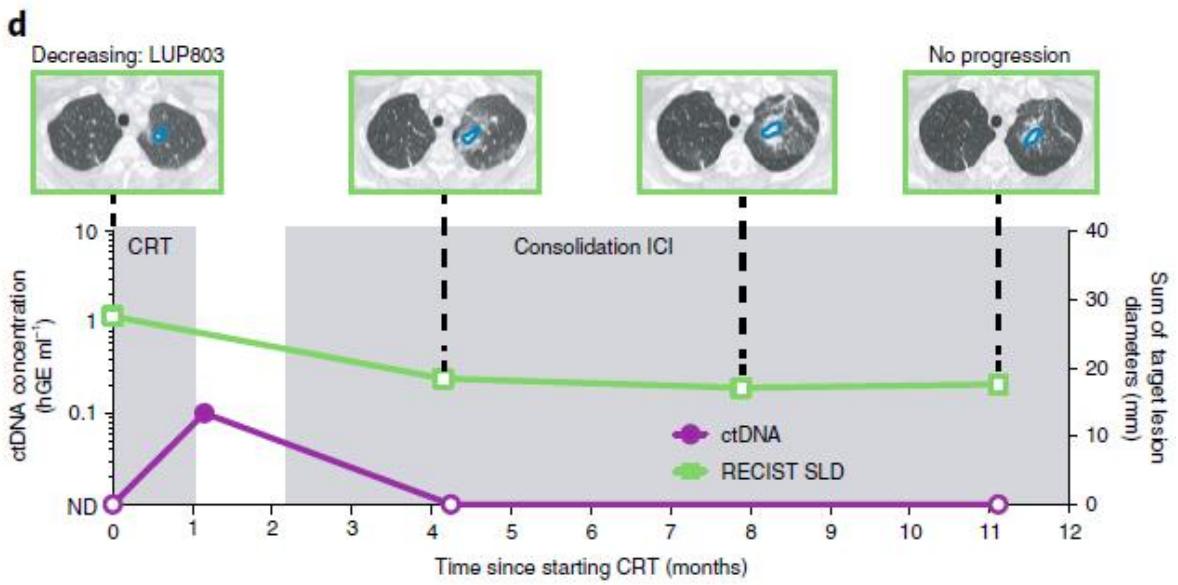
Nat Cancer 2020;1(2):176-183

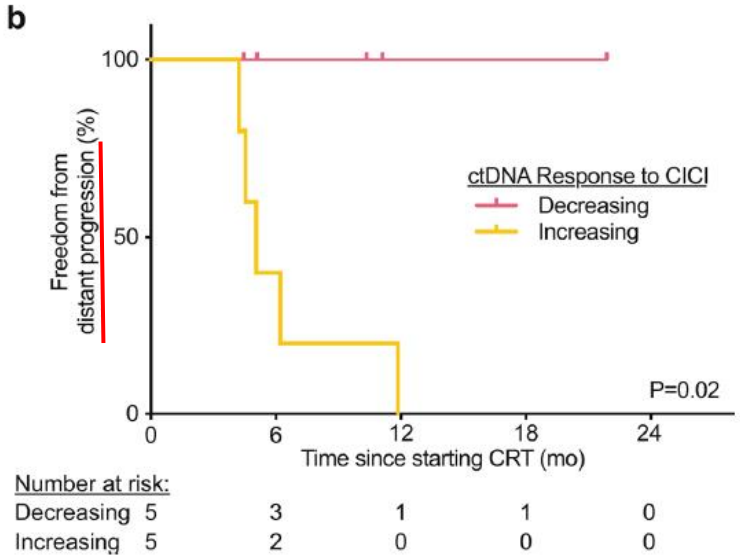
ctDNA(+) after CRT – increasing on ICI

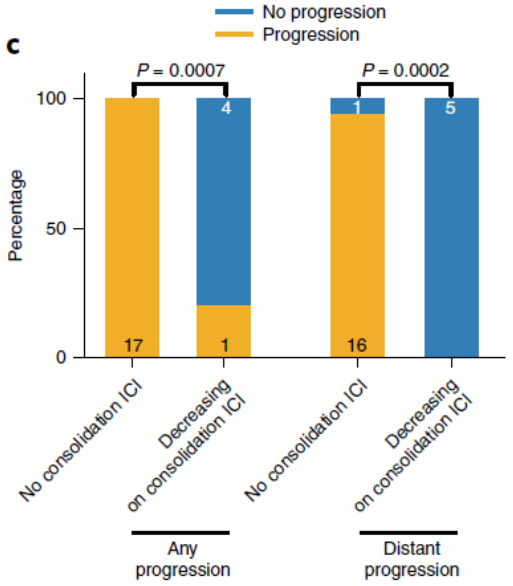




ctDNA(+) after CRT – decreasing on ICI







Nat Cancer 2020;1(2):176-183

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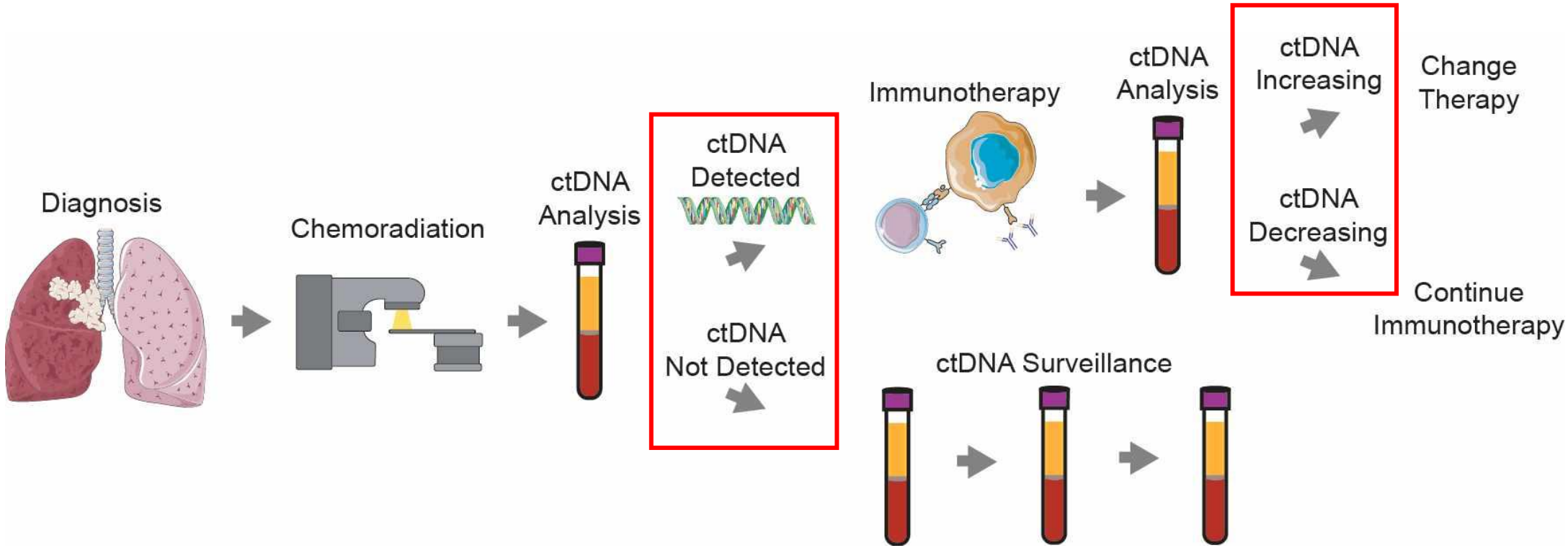
ARTICLES
https://doi.org/10.1038/s43018-019-0011-0

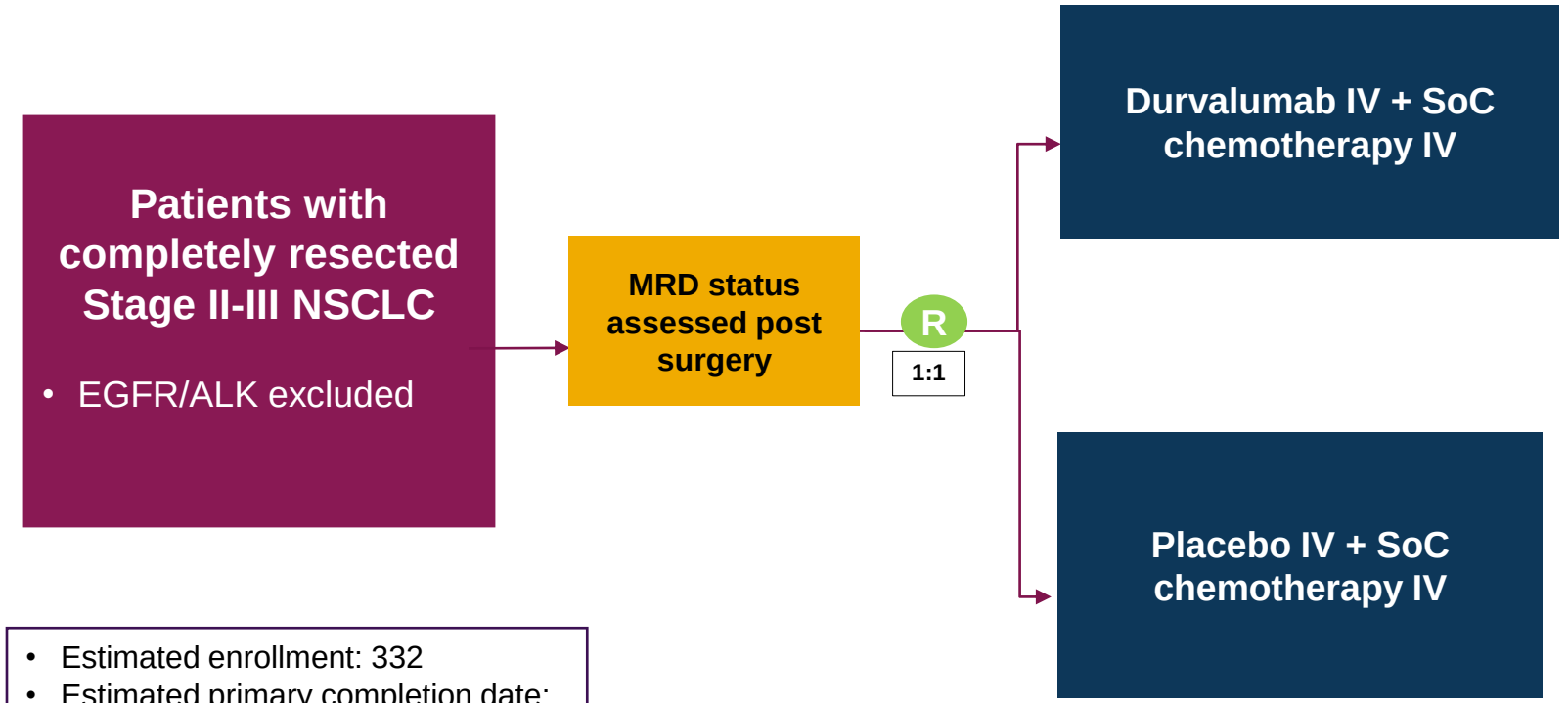
Circulating tumor DNA dynamics predict benefit from consolidation immunotherapy in locally advanced non-small-cell lung cancer



Nat Cancer 2020;1(2):176-183

MERMAID-1: Study Design

Phase 3, randomized, parallel-arm, placebo controlled, double blind, multicenter study



- Estimated enrollment: 332
- Estimated primary completion date: December 2024

Primary endpoint

DFS in MRD+ analysis set[a]

Key secondary endpoints

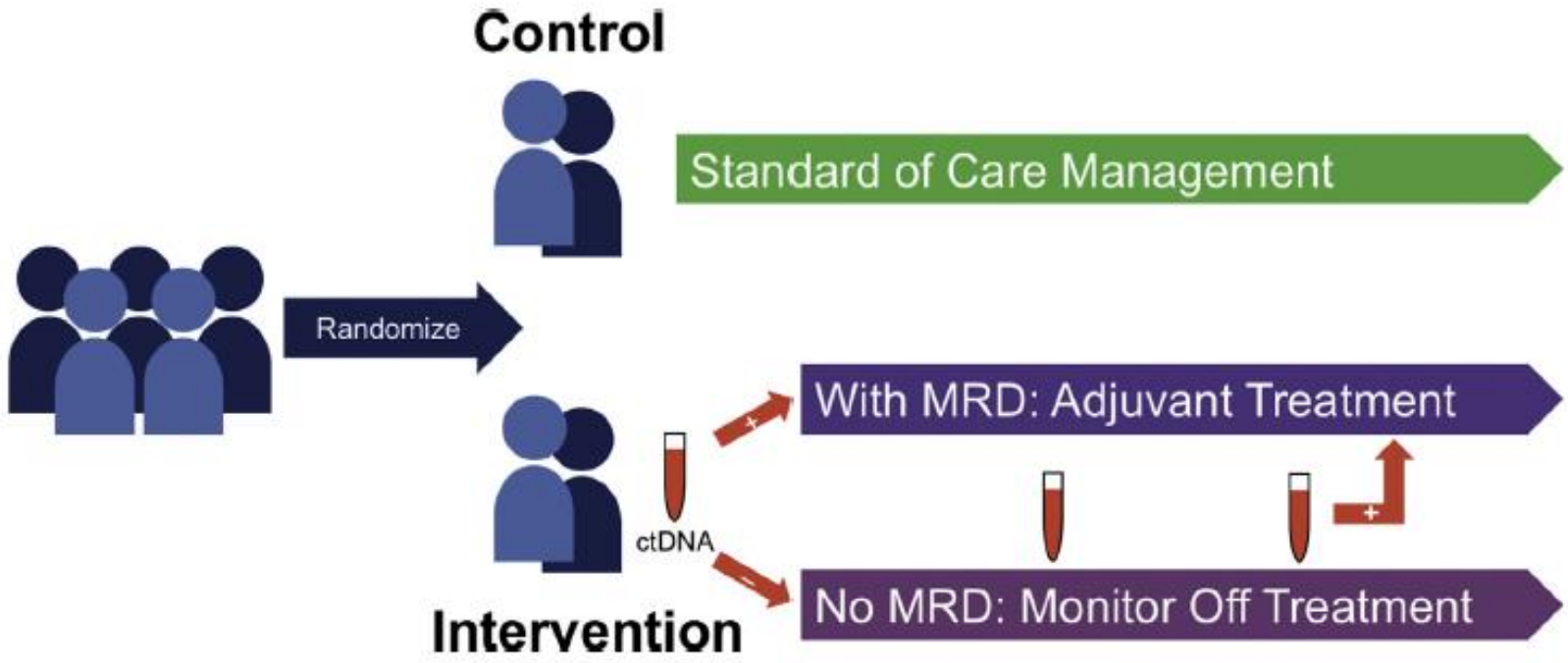
- DFS in FAS[a]
- DFS in MRD+ analysis set and in FAS[b]
- OS in MRD+ analysis set and in FAS
- Safety
- Immunogenicity
- PROs
- Pharmacokinetics

[a]Using investigator assessments according to RECIST 1.1; [b]Using BICR assessments according to RECIST 1.1.

ALK = anaplastic lymphoma kinase; BICR = Blinded Independent Central Review; DFS = disease-free survival; EGFR = epidermal growth factor receptor; FAS = full analysis set; MRD = minimal residual disease; NSCLC = non-small cell lung cancer; OS = overall survival; PROs = patient-reported outcomes; RECIST = Response Evaluation Criteria in Solid Tumors; SoC = standard of care.

Study NCT04385368. ClinicalTrials.gov website.

Future Directions: Tailored Treatment Based on ctDNA+MRD



J Thorac Oncol 2019;14(1):16-24

Potential Issues with ctDNA in Detecting MRD

- **Genomic correlation between Tissue and Liquid biopsies**
  - Tumor heterogeneity
  - Limitations in sensitivity of ctDNA detection technologies
  - Needs for advanced NGS methods & bioinformatics analytical approach

- **Modest sensitivity after Definitive treatment**
  - ctDNA << total cfDNA
  - ctDNA correlate strongly with tumor volumes

- **False positives**
  - Germline mutations : high allele fraction (>30%)
  - Driver mutations present in benign conditions (etc, BRAF V600E, TP53)
  - Clonal hematopoiesis of indeterminate potential : increased with advancing age

J Thorac Oncol 2019;14(1):16-24
J Clin Oncol 2018;36(35):3437-40

Potential Issues with CTC in Detecting MRD

- **Isolation/Enrichment**
  - No standardization
  - Laborious, less suited for translation into routine

- **Genotyping**
  - Less sensitive compared with ctDNA genotyping
  - Chr rearrangement or CNVs → Yield/Cost/TAT are inferior to plasma NGS
  - Single cell analysis → limited clinical impact, technically highly challenging

- **PD-L1 expression**
  - Predictive power for ICIs has been not confirmed to date
  - Relationship between CTCs and immune cells is extremely complex

Eur Respir Rev 2020;29(155):190052

Summary

- **Post-op adjuvant chemotherapy**
  - Based on stage or resection margin, No biomarker-driven treatment
  - Potential toxicity & Questionable durability of positive effect

- **IO (Durvalumab) consolidation therapy**
  - Standard of Care in Unresectable locally advanced NSCLC after CCRT
  - No biomarker : PD-L1?

- **Molecular residual disease (MRD) in NSCLC**
  - Resected early stage or Unresectable locally advanced stage after CCRT
  - Good or Bad prognosis, Need intervention or Unnecessary

- **ctDNA/CTC**
  - Candidate biomarkers for MRD in NSCLC
  - Issues : Sampling & Storage, Long F/U duration, Advanced technology → Cost !!