The Future of Combined Modality Therapy

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Considerations for **Adjuvant** Therapy

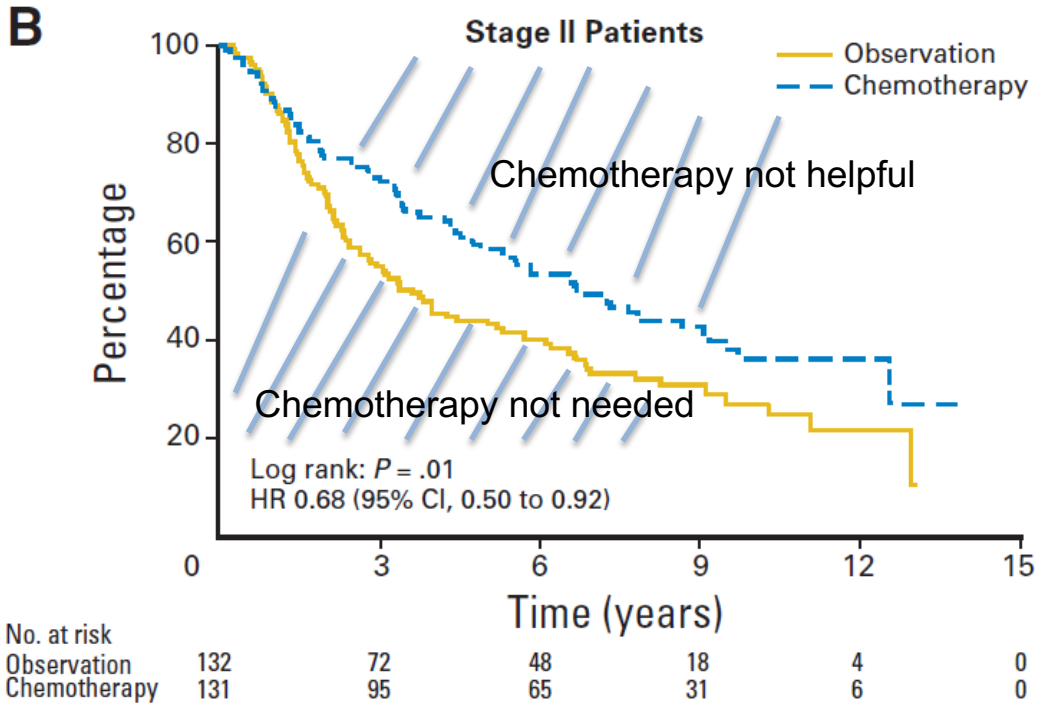
PRO

- Adjuvant is evidence-based standard of care for resected stage IB and II disease
- Tumor biomarkers can guide therapeutic decisions
- No delay of surgery
- No hilar or mediastinal fibrosis
- No risk of disease progression resulting in missed opportunity for curative surgery

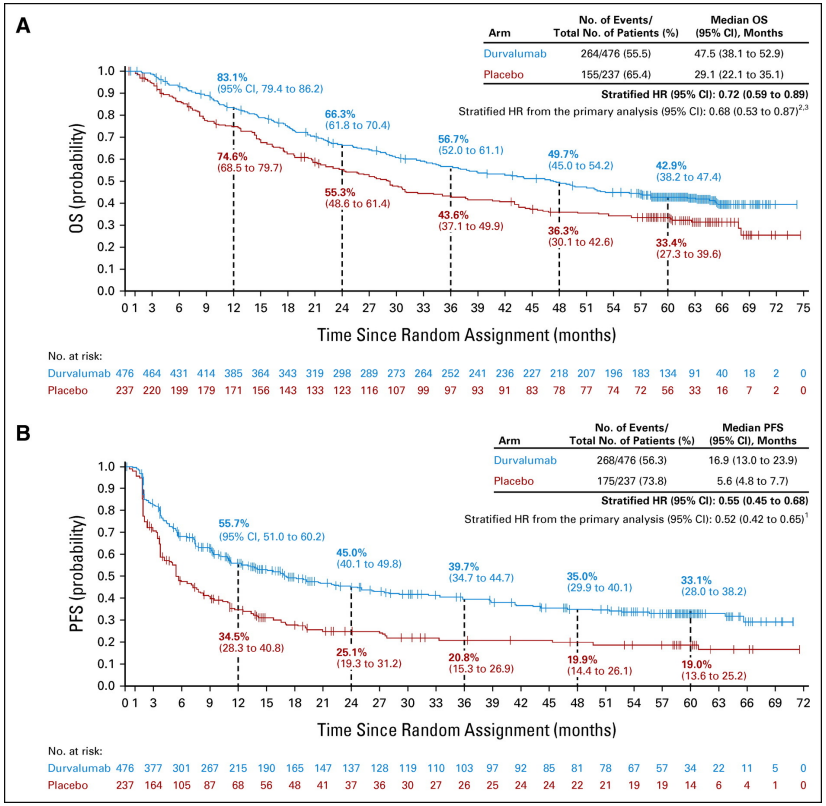
CON

- Poor tolerance and compliance with adjuvant protocols
- Longer treatment (4 cycles or much longer if TKI/IO)
- No intermediate endpoints
- Long follow up required for DFS or OS

JBR.10 – Overall Survival



Updated OS and PFS in the intent-to-treat population



Spigel DR et al, J Clin Oncol, 40(12); 1301-1311, 2022

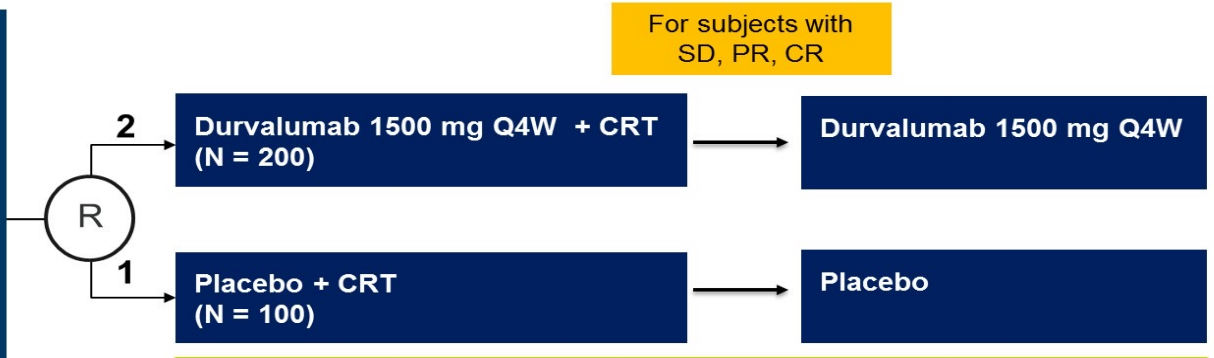
PACIFIC-2: Study Design

AZ IO TRIALS PACIFIC-2

Study Population

- Patients with unresectable, Stage III NSCLC
- All-comers (PD-L1 expression-agnostic)
- ECOG PS 0-1

Randomised N = 300 patients



- Early IDMC safety assessment in first 15 and 60 TOTAL subjects (CRT+28 days)
- In Japan, assessment after first 9 TOTAL subjects (CRT+28 days)

Stratification
- Age (≤65, >65)
- Stage (IIIA vs IIIB/C)

- **Primary Endpoints: ORR, PFS**
- **Key Secondary Endpoints:** OS, OS24
- **Treat to progression**

Study Chair: Bradley

Central Challenge to Curative Therapies

- Does current staging provide accurate enough information
- How do we know when enough is enough
- Can we achieve cure with less toxicity (duration, intensity, cost of treatment)
- Can biomarkers provide information in real time
- Can we design De-escalation Trials

Curative Therapies need to be personalized

Surrogate Endpoints:

- DFS (CTs, PET)
- PRO's
- (mPR), pCR
- Systemic Markers of Minimal Residual Disease

Biomarkers in (Neo)adjuvant Setting

Specific Tumor Biomarker (mutation):

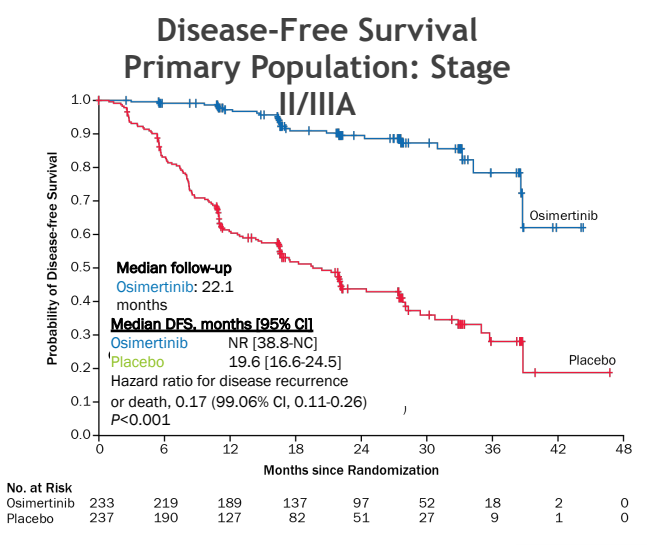
- Validates choice of drug
- Can be used to measure efficacy and relapse (Guardant)
- Refines optimal patient population
- Limits cost and toxicity

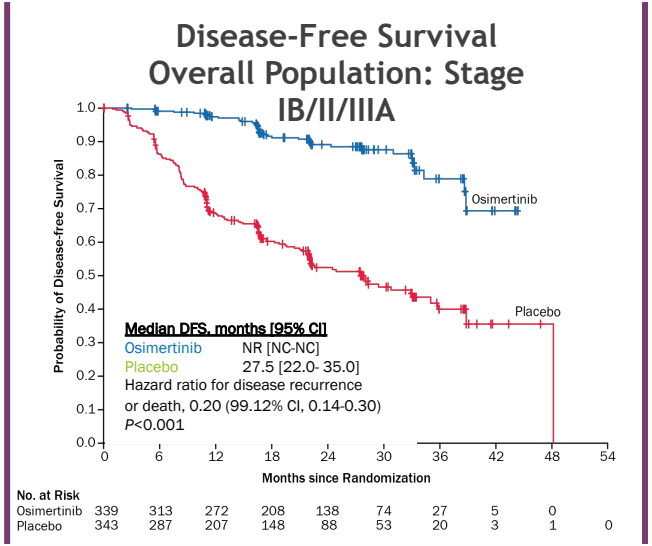
Role of Biomarkers

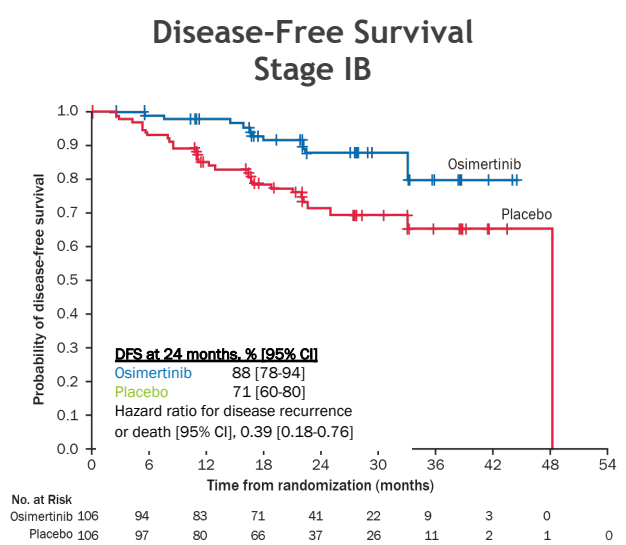
Related to Disease:

- Allow to measure treatment efficacy
- ctDNA
- Imaging technologies

ADAURA: Efficacy



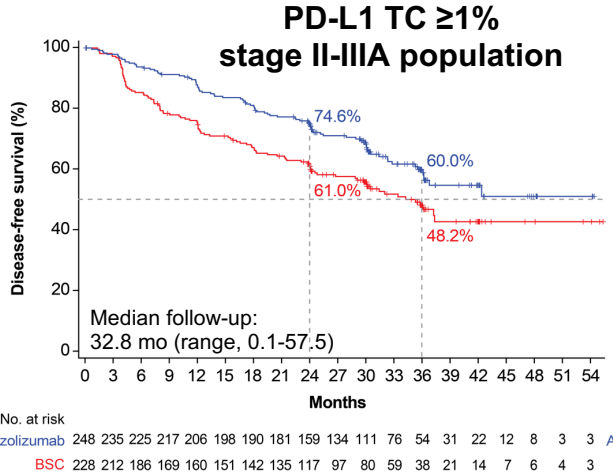


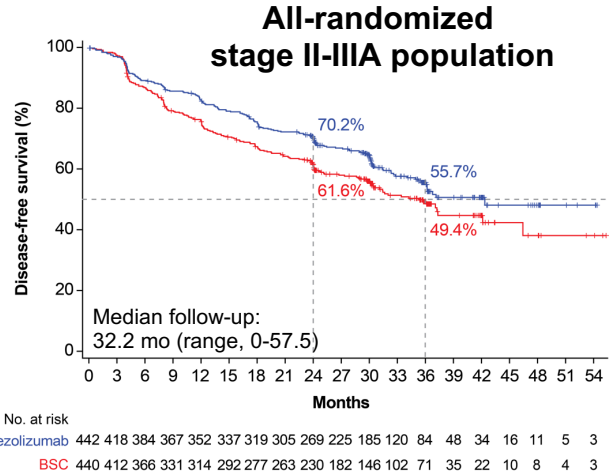


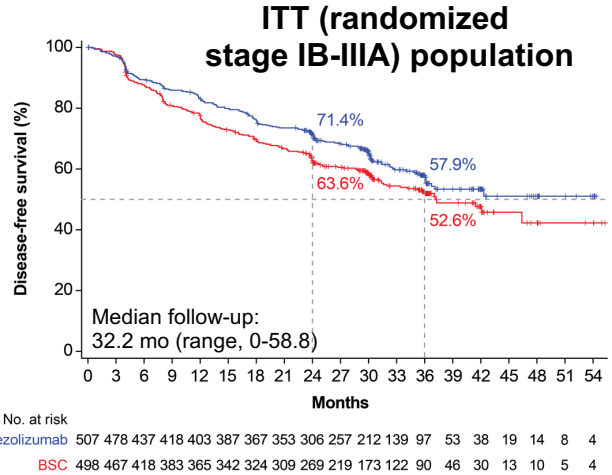
	Stage IB	Stage II	Stage IIIA
2 year DFS rate, % (95% CI)			
– Osimertinib	87 (77, 93)	91 (82, 95)	88 (79, 94)
– Placebo	73 (62, 81)	56 (45, 65)	32 (23, 42)
Overall HR (95% CI)	**0.39 (0.18, 0.76)**	**0.17 (0.08, 0.31)**	**0.12 (0.07, 0.20)**

Wu YL et al. *N Engl J Med.* 2020;383(18):1711-1723

DFS in the PD-L1 TC ≥1% Stage II-IIIA, All-Randomized Stage II-IIIA and ITT Populations (primary endpoint)







	Atezolizumab (n=248)	BSC (n=228)
Median DFS (95% CI), mo	NE (36.1, NE)	35.3 (29.0, NE)
Stratified HR (95% CI)	0.66 (0.50, 0.88)	
P value[b]	0.004[c]	

	Atezolizumab (n=442)	BSC (n=440)
Median DFS (95% CI), mo	42.3 (36.0, NE)	35.3 (30.4, 46.4)
Stratified HR (95% CI)	0.79 (0.64, 0.96)	
P value[b]	0.02[c]	

	Atezolizumab (n=507)	BSC (n=498)
Median DFS (95% CI), mo	NE (36.1, NE)	37.2 (31.6, NE)
Stratified HR (95% CI)	0.81 (0.67, 0.99)	
P value[b]	0.04[d]	

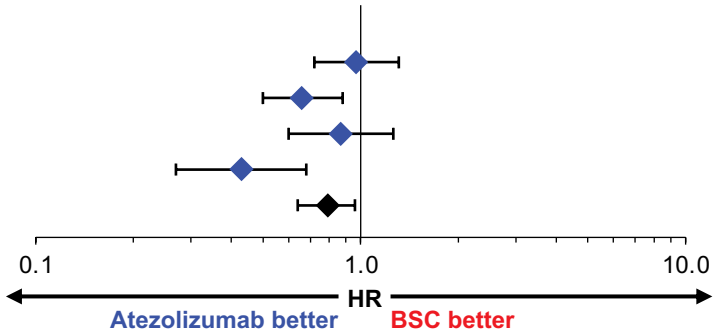
Clinical cutoff: 21 January 2021. [a] Per SP263 assay. [b] Stratified log-rank. [c] Crossed the significance boundary for DFS.
[d] The statistical significance boundary for DFS was not crossed. 1. Wakelee H, et al. J Clin Oncol. 2021;39(suppl 15):8500.

Felip et al. IMpower010 Relapse Patterns. https://bit.ly/3mNMSAi

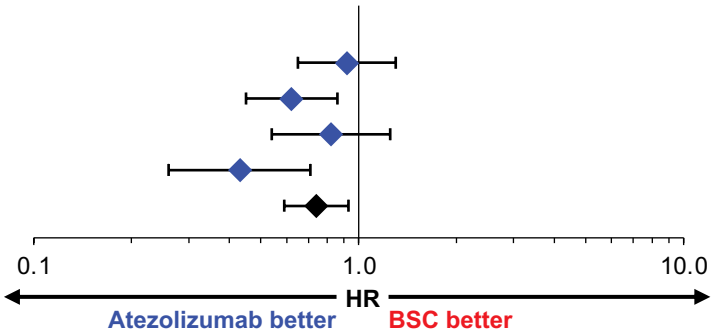
DFS by PD-L1 Status[a]

All-randomized stage II-IIIA population (+/-EGFR/ALK+ disease)

Subgroup *(including EGFR/ALK+)*	**n**	**HR (95% CI)[b,c]**
PD-L1 status by SP263		
TC <1%	383	0.97 (0.72, 1.31)
TC ≥1%	476	0.66 (0.50, 0.88)
TC 1-49%	247	0.87 (0.60, 1.26)
TC ≥50%	229	0.43 (0.27, 0.68)
All patients[d]	882	0.79 (0.64, 0.96)



Subgroup *(excluding EGFR/ALK+)*[e]	**n**	**HR (95% CI)[f,g]**
PD-L1 status by SP263		
TC <1%	312	0.92 (0.65, 1.30)
TC ≥1%	410	0.62 (0.45, 0.86)
TC 1-49%	201	0.82 (0.54, 1.25)
TC ≥50%	209	0.43 (0.26, 0.71)
All patients[h]	743	0.74 (0.59, 0.93)



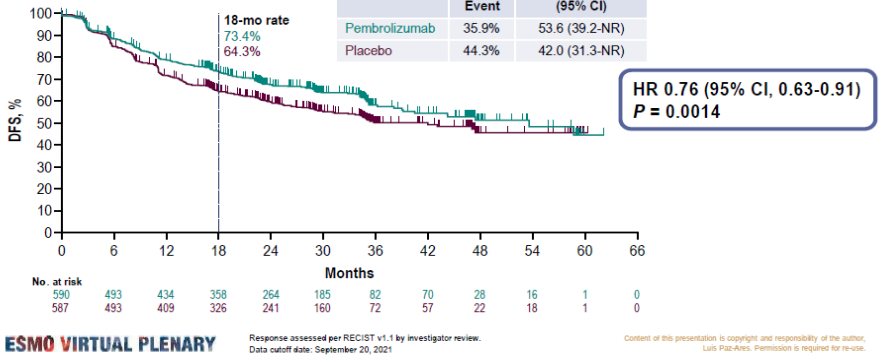
Clinical cutoff: 21 January 2021. [a] Per SP263 assay.
[b] Stratified for all patients and PD-L1 TC ≥1%; unstratified for all other subgroups. [c] DFS analyses in the PD-L1 TC <1% and TC 1-49% subgroups were exploratory. [d] 23 patients had unknown PD-L1 status as assessed by SP263. [e] Excluding patients with known *EGFR/ALK*+ NSCLC. [f] Unstratified for all subgroups. [g] EGFR/ALK+ exclusion analyses were post hoc. [h] 21 patients had unknown PD-L1 status as assessed by SP263.

Felip et al. IMpower010 Relapse Patterns. https://bit.ly/3mNMSAi

PEARLS/KEYNOTE-091

Randomized, Triple-Blind, Phase 3 Trial

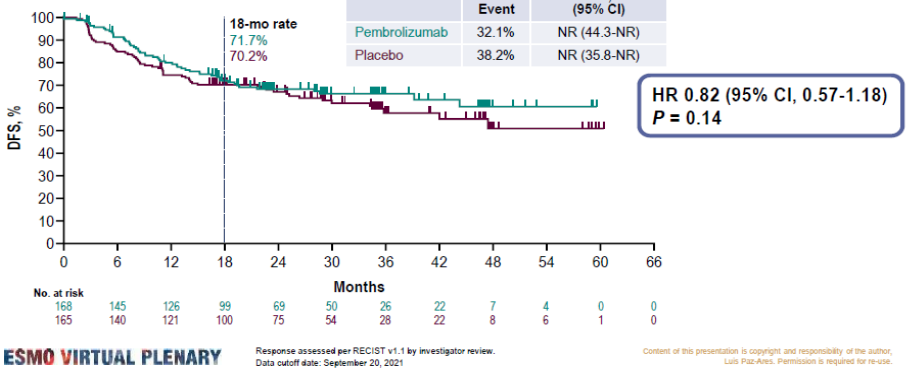
DFS, Overall Population



ESMO VIRTUAL PLENARY

Response assessed per RECIST v1.1 by investigator review.
Data cutoff date: September 20, 2021

DFS, PD-L1 TPS ≥50% Population

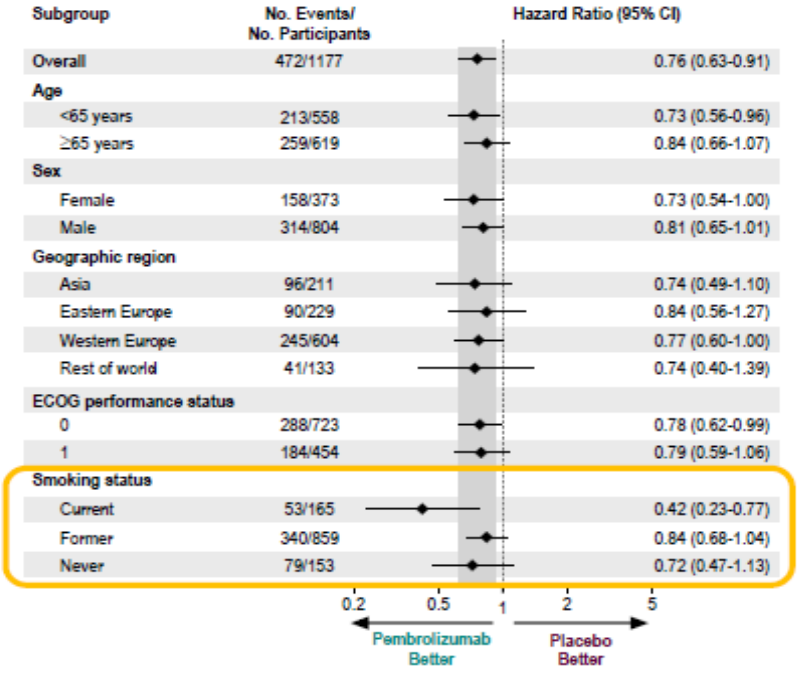


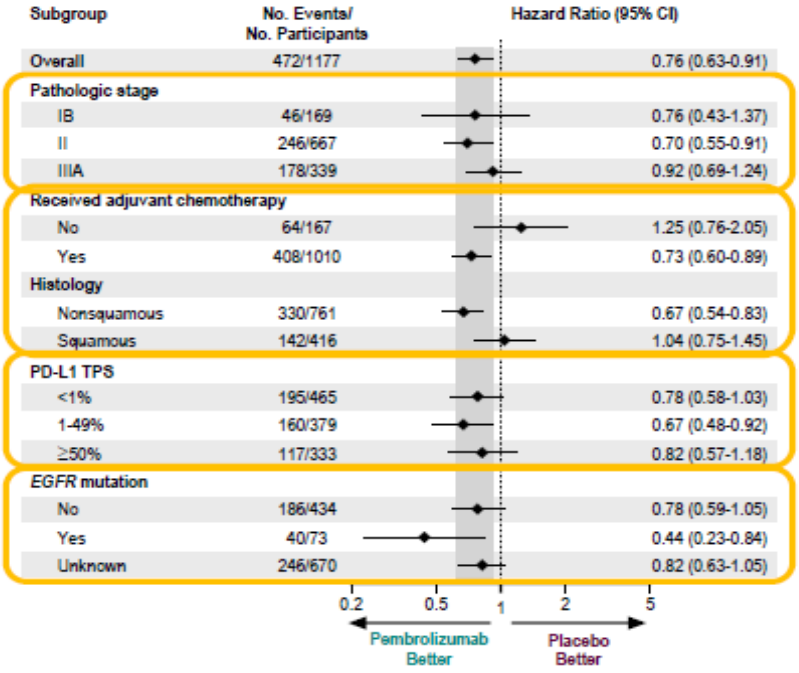
ESMO VIRTUAL PLENARY

Response assessed per RECIST v1.1 by investigator review.
Data cutoff date: September 20, 2021

Paz-Ares, L, et al, ESMO Virtual Plenary, 2022

DFS in Key Subgroups, Overall Population



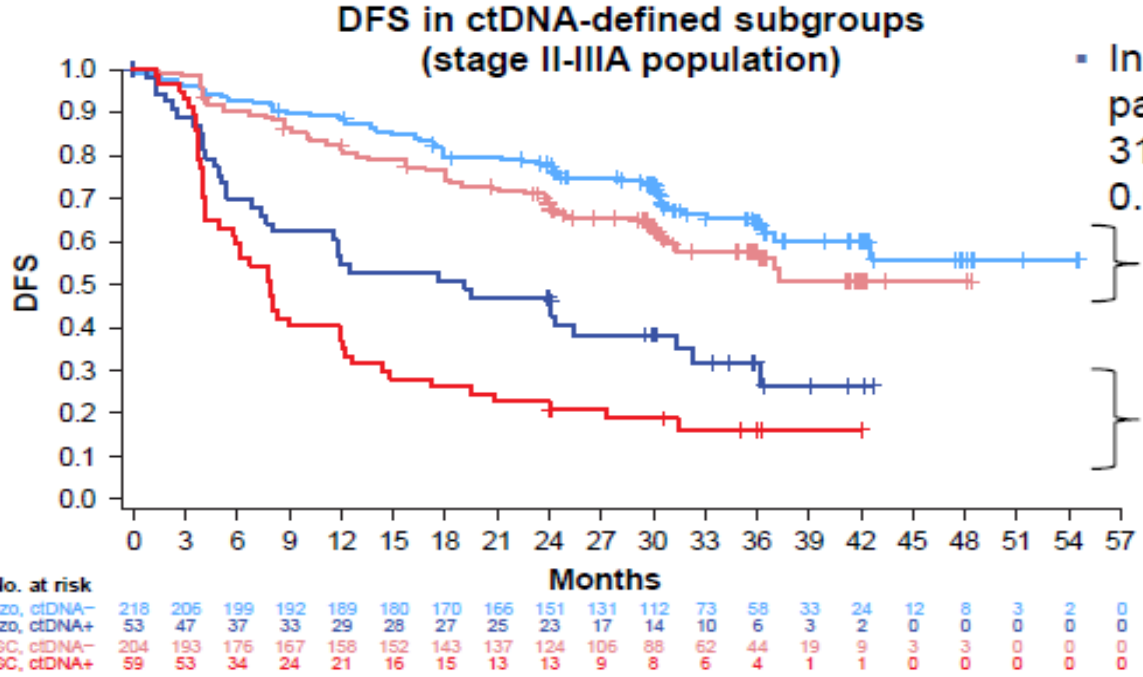


ESMO VIRTUAL PLENARY

Response assessed per RECIST v1.1 by investigator review.
Data cutoff date: September 20, 2021

Zhou C et al, ESMO IO 2021

Impower 010 – Exploratory results for ctDNA



- In all ctDNA-evaluable stage II-IIIA patients, mDFS was NR (atezo) vs 31.4 months (BSC), with an HR of 0.69 (95% CI: 0.53, 0.89)

ctDNA–	Atezo (n=218)	BSC (n=204)
mDFS, mo	NR	NR
HR (95% CI)	0.72 (0.52, 1.00)	

ctDNA+	Atezo (n=53)	BSC (n=59)
mDFS, mo	19.1	7.9
HR (95% CI)	0.61 (0.39, 0.94)	

Clinical cutoff: 21 January 2021. Unstratified HRs are shown.

Immune Checkpoint Inhibitors for Resectable NSCLC

Neoadjuvant setting

Considerations for **Neoadjuvant** I/O or Targeted Therapy

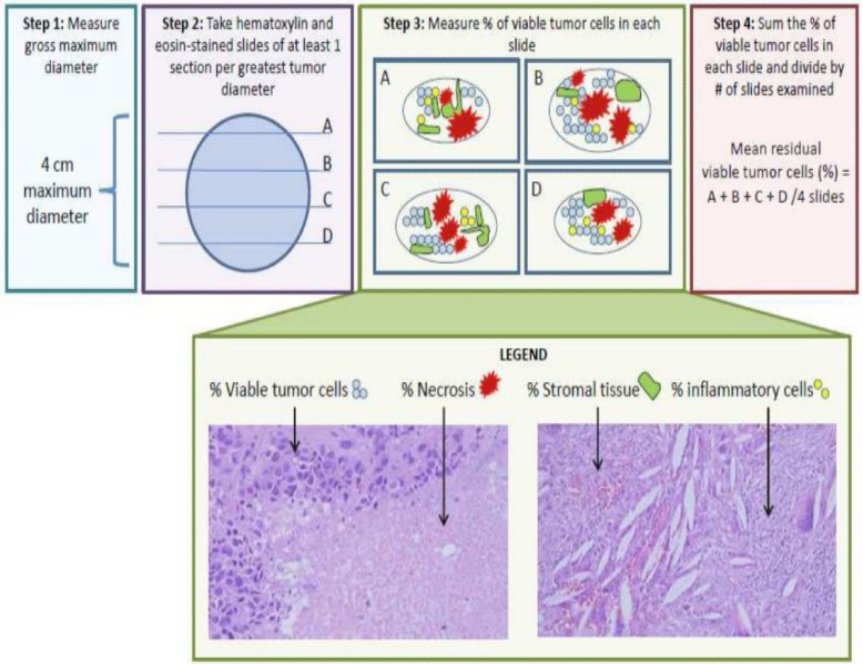
PRO

- Early eradication of micrometastatic disease
- Improved tolerance of toxicities
- Improved compliance and higher drug exposure
- Pre- and post-treatment tissue to assess biomarkers or adjust treatment
- Guide for need of adjuvant therapy
- Early trial endpoints and shorter trial duration
- Presence of whole tumour allows activation of broader & more diverse immune response

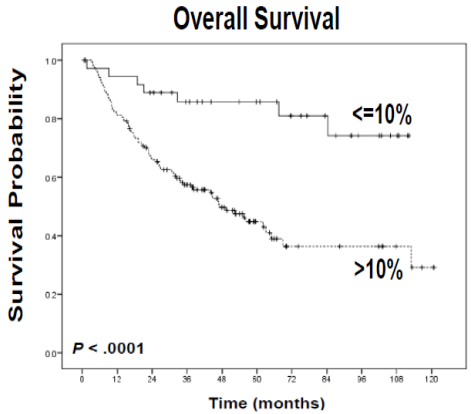
CON

- Delays of surgery (treatment-related toxicity)
- Increased surgical complications or fewer minimally invasive resection
- Risk of disease progression resulting in missed opportunity for curative surgery
- However, phase 2 neoadjuvant immunotherapy data show approximately **90% of patients underwent surgery**, similar to studies with adjuvant chemotherapy

Major Pathological Response (<10% viable tumor cells) after Neoadjuvant Chemotherapy as Surrogate Endpoint

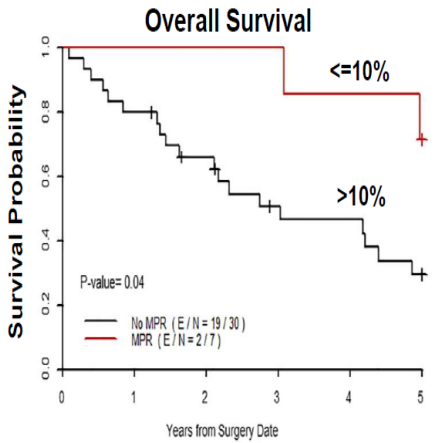


Histopathologic Response Criteria Predict Survival of NSCLC Patients Treated with Neoadjuvant Chemotherapy



Pataer A *et al.*, *J Thorac Oncol*, 2012

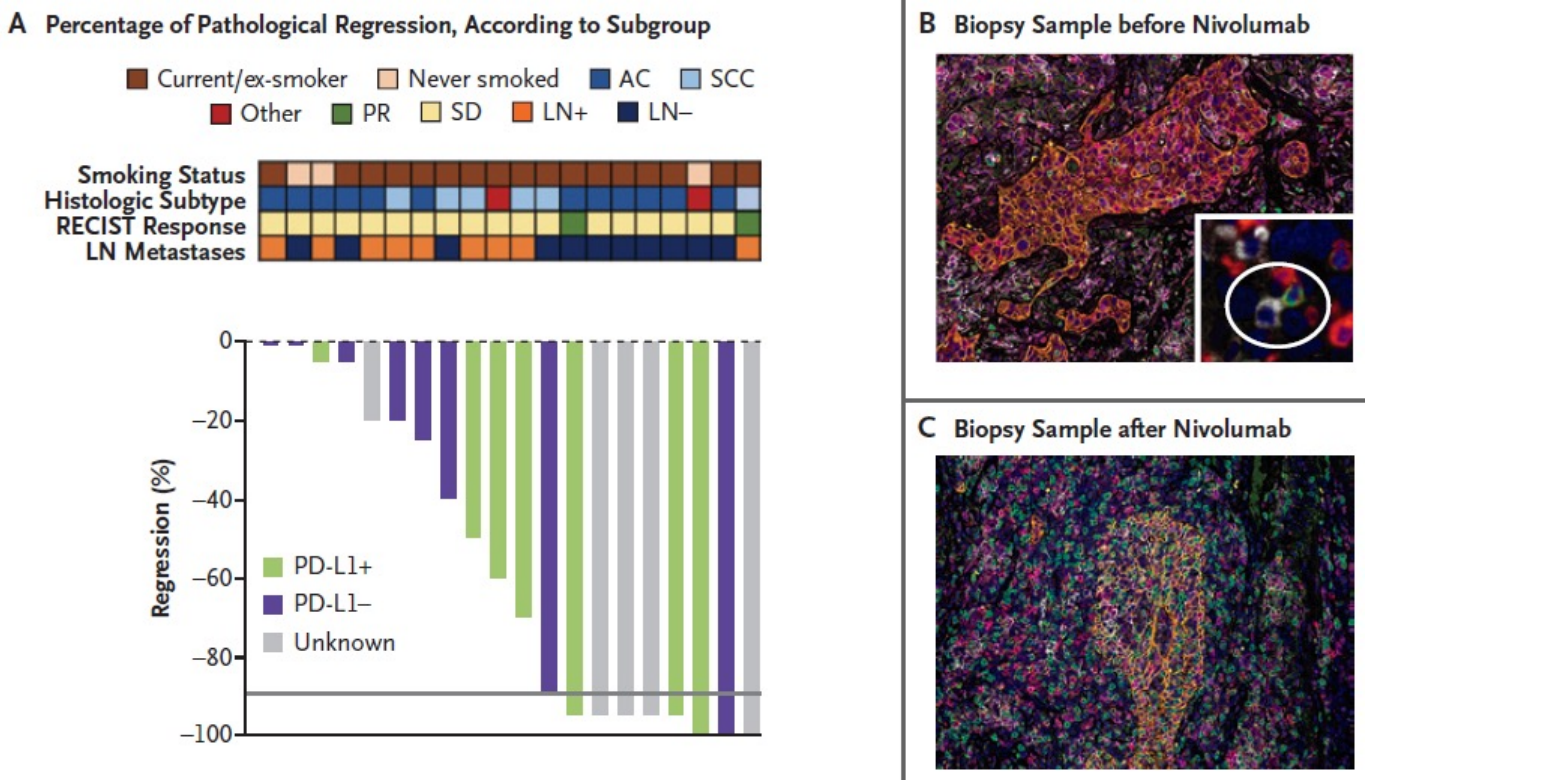
Neoadjuvant Cisplatin Docetaxel Followed by Surgery and Erlotinib in NSCLC Patients



Cascone T *et al. Ann Thorac Surg*, 2017

Hellmann MD et al. *Lancet Oncol*. 2014;15(1):e42-e50

Pathological Assessment of Response to Neoadjuvant Blockade of Programmed Death 1



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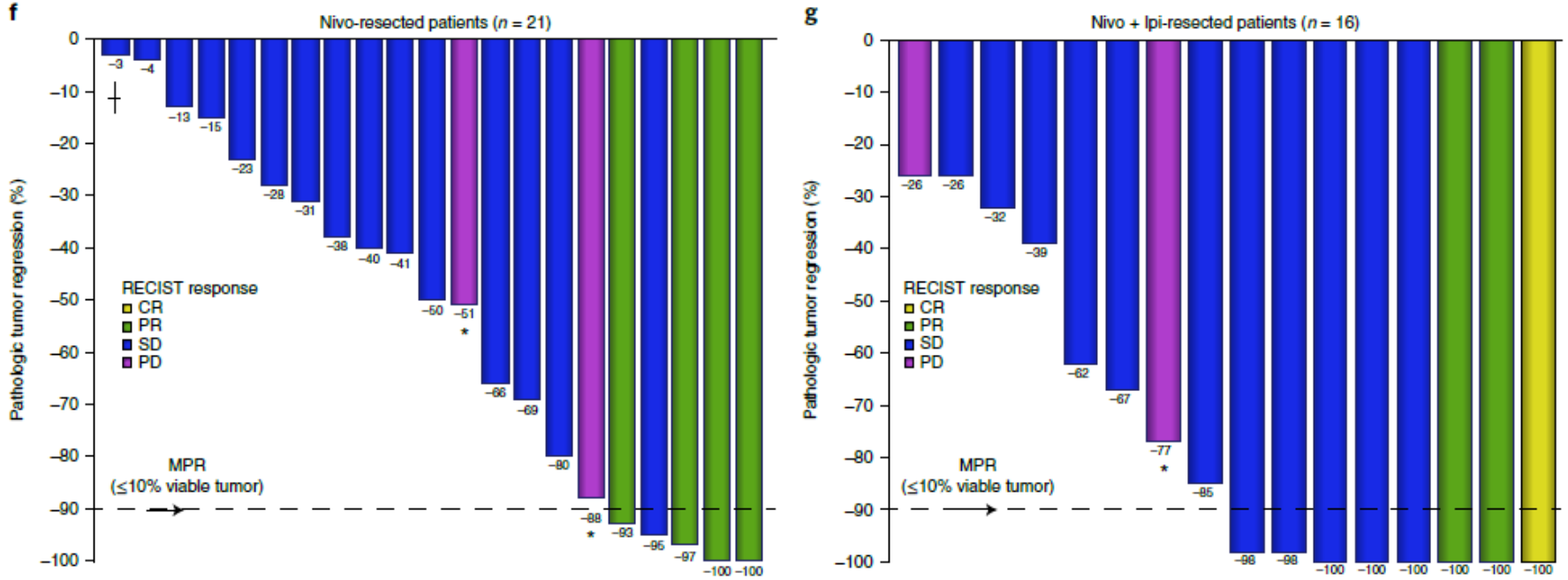
Forde PM et al. *N Engl J Med*. 2018;378(21):1976-1986

Neoadjuvant Nivolumab or Nivolumab Plus Ipilimumab in Operable NSCLC: The Phase 2 Randomized NEOSTAR Trial

Endpoints: MPR (vs historical control with chemotherapy)
Goal of 28% (6/21) vs 15%

Cascone T et al. *Nat Med*. 2021;27(3):504-514

Pathologic Responses to Neoadjuvant Nivolumab and Nivolumab + Ipilimumab in Resected Patients



Cascone T et al. *Nat Med*. 2021;27(3):504-514

CheckMate 816 Study Design[a]

Key Eligibility Criteria

- Newly diagnosed, resectable, stage IB (≥ 4 cm)–IIIA NSCLC (per TNM 7th edition)
- ECOG performance status 0–1
- No known sensitizing *EGFR* mutations or *ALK* alterations

Stratified by
Stage (IB–II vs IIA), PD-L1[b] (≥ 1% vs < 1%[c]), and sex

Primary analysis population

N = 358
R 1:1

- NIVO 360 mg Q3W + chemo[d] Q3W (3 cycles)
- Chemo[e] Q3W (3 cycles)
- NIVO 3 mg/kg Q2W (3 cycles) + IPI 1 mg/kg (cycle 1 only)[f]

Radiologic restaging → Surgery (within 6 weeks post-treatment) → Optional adjuvant chemo ± RT[g] → Follow-up

Primary endpoints
- pCR by BIPR
- EFS by BICR

Secondary endpoints
- MPR by BIPR
- OS
- Time to death or distant metastases

Exploratory endpoints
- ORR by BICR
- Predictive biomarkers (PD-L1, TMB, ctDNA[h])

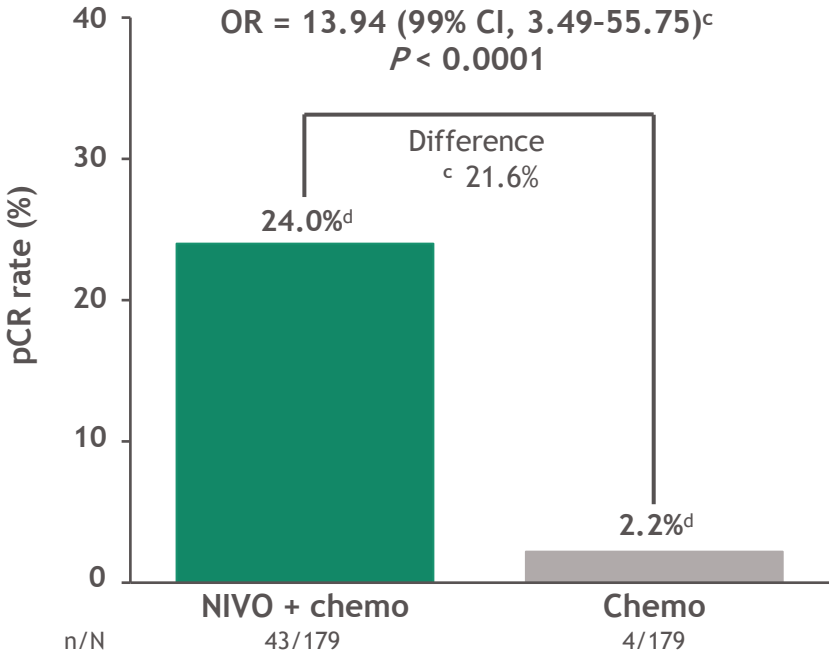
Database lock: September 16, 2020; minimum follow-up: 7.6 months for NIVO + chemo and chemo arms.

[a]NCT02998528; [b]Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako); [c]Included patients with PD-L1 expression status not evaluable and indeterminate; [d]NSQ: pemetrexed + cisplatin or paclitaxel + carboplatin; SQ: gemcitabine + cisplatin or paclitaxel + carboplatin; [e]Vinorelbine + cisplatin, docetaxel + cisplatin, gemcitabine + cisplatin (SQ only), pemetrexed + cisplatin (NSQ only), or paclitaxel + carboplatin; [f]Randomized exploratory arm (enrollment closed early); [g]Per healthcare professional choice; [h]Performed using tumor-guided personalized ctDNA panel (ArcherDX Personalized Cancer Monitoring).

Forde PM et al. AACR 2021. Abstract CT003

CM 816: Primary Endpoint: pCR rate

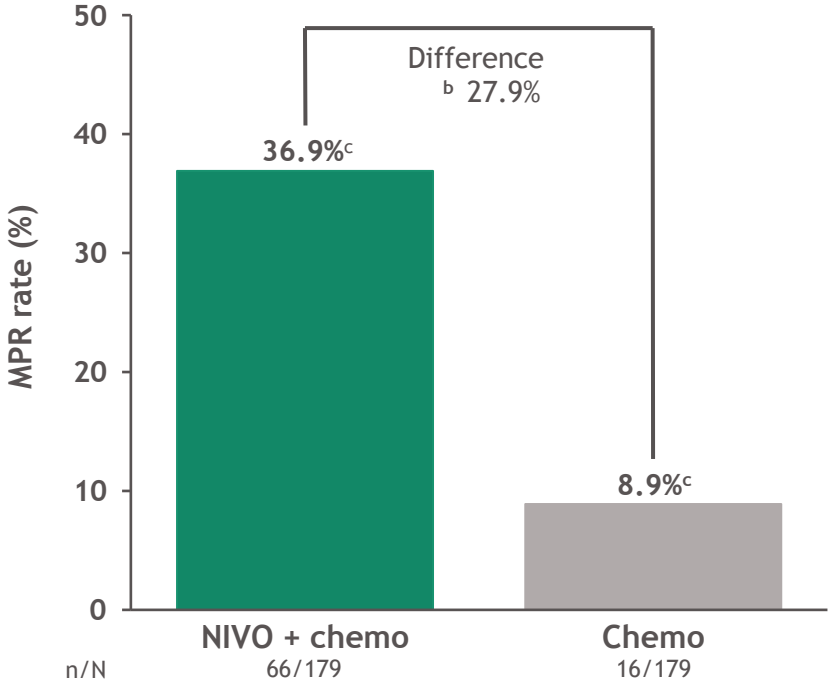
Primary endpoint: ITT (ypT0N0)[b]



mPR rate

ITT

OR = 5.70 (95% CI, 3.16-10.26)[b]

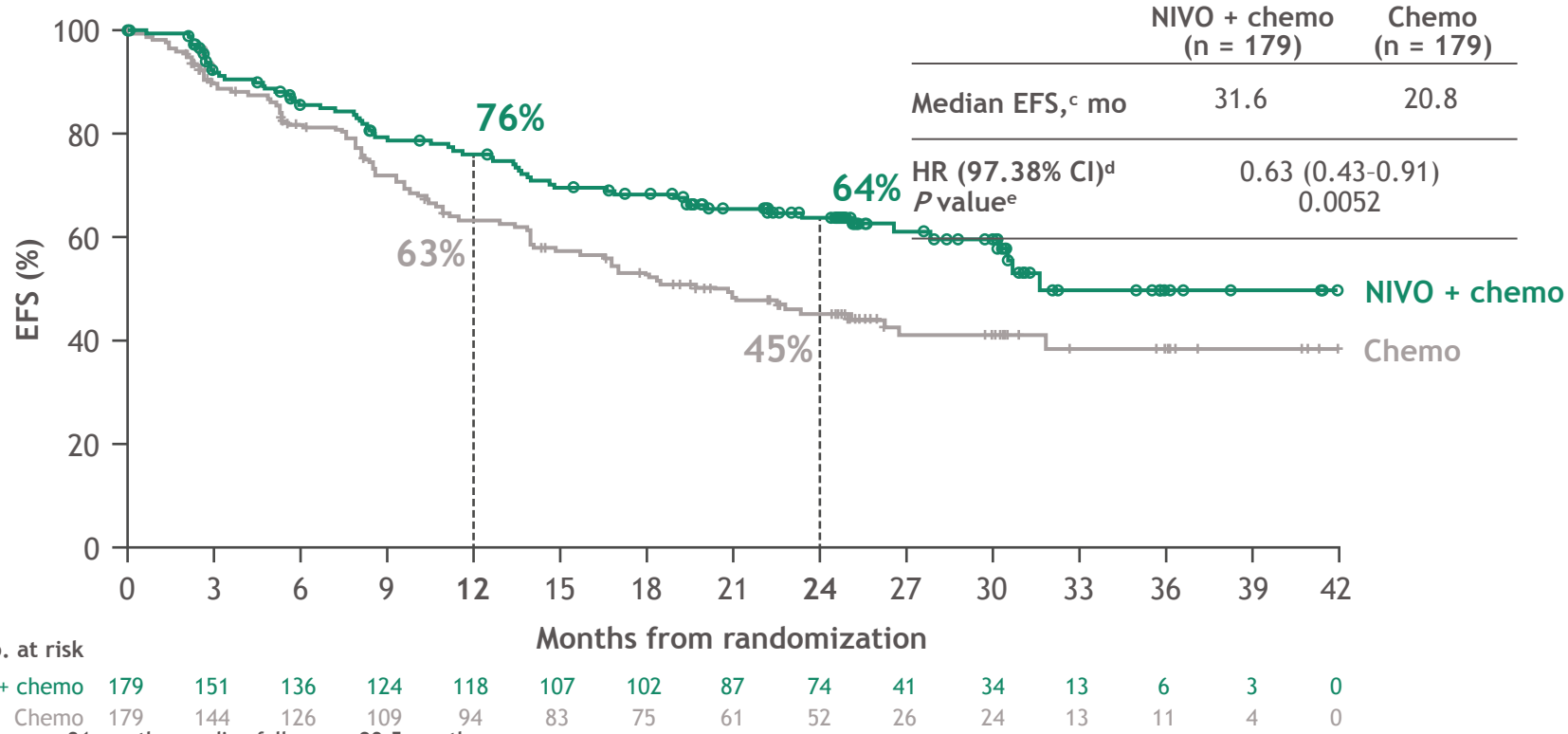


- pCR rate in the exploratory NIVO + IPI arm (ITT) was 20.4% (95% CI, 13.4-29.0)

[a]Per BIPR; pCR: 0% residual viable tumor cells in both primary tumor (lung) and sampled lymph nodes; [b]ITT principle: patients who did not undergo surgery counted as non-responders for primary analysis; [c]Calculated by stratified Cochran-Mantel-Haenszel method; [d]pCR rates 95% CI: NIVO + chemo, 18.0-31.0; chemo, 0.6-5.6; [e]Patients who underwent definitive surgery with an evaluable pathology sample for BIPR.

Forde PM et al. AACR 2021. Abstract CT003

Primary endpoint: EFS[a,b] with neoadjuvant NIVO + chemo vs chemo



	NIVO + chemo (n = 179)	Chemo (n = 179)
Median EFS,[c] mo	31.6	20.8
HR (97.38% CI)[d]	0.63 (0.43-0.91)	
P value[e]	0.0052	

Minimum follow-up: 21 months; median follow-up, 29.5 months.

[a]Per BICR; [b]EFS defined as the time from randomization to any progression of disease precluding surgery, progression or recurrence of disease after surgery, progression for patients without surgery, or death due to any cause; patients with subsequent therapy were censored at the last evaluable tumor assessment on or prior to the date of subsequent therapy; [c]95% CI = 30.2-NR (NIVO + chemo) and 14.0-26.7 (chemo);
[d]95% CI = 0.45-0.87; [e]The significance boundary at this interim analysis was 0.0262.

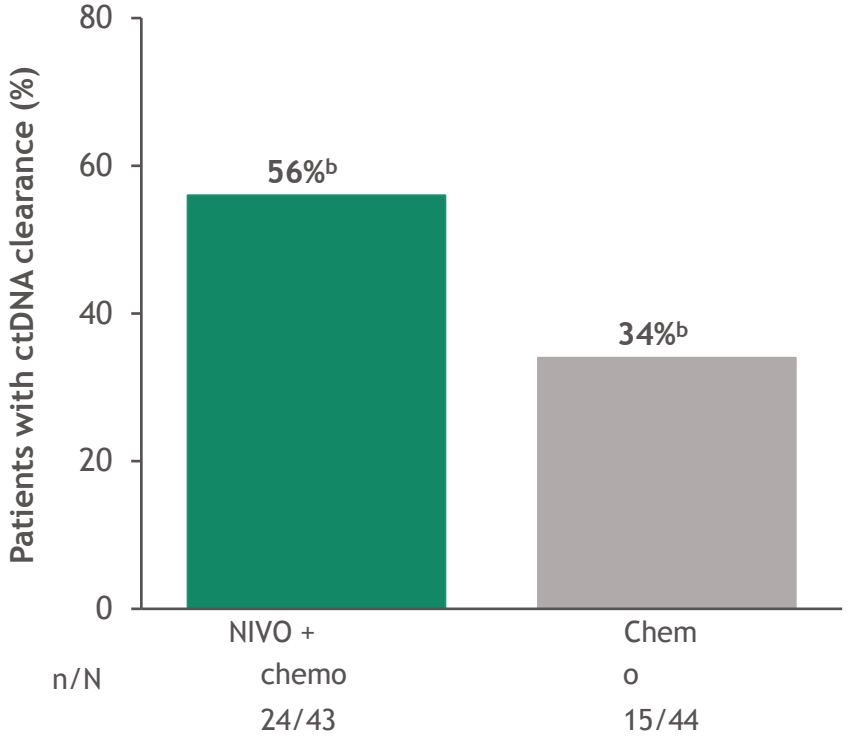
EFS subgroup analysis

	Median EFS[a], mo		Unstratified HR (95% CI)	Unstratified HR
	NIVO + chemo (n = 179)	Chemo (n = 179)		
Overall (N = 358)	32	21		0.63
< 65 years (n = 176)	NR	21		0.57
≥ 65 years (n = 182)	30	18		0.70
Male (n = 255)	31	17		0.68
Female (n = 103)	NR	32		0.46
North America (n = 91)	NR	NR		0.78
Europe (n = 66)	32	21		0.80
Asia (n = 177)	NR	16		0.45
ECOG PS 0 (n = 241)	NR	23		0.61
ECOG PS 1 (n = 117)	30	14		0.71
Stage IB-II (n = 127)	NR	NR		0.87
Stage IIIA (n = 228)	32	16		0.54
Squamous (n = 182)	31	23		0.77
Non-squamous (n = 176)	NR	20		0.50
Current/former smoker (n = 318)	32	22		0.68
Never smoker (n = 39)	NR	10		0.33
PD-L1 < 1% (n = 155)	25	18		0.85
PD-L1 ≥ 1% (n = 178)	NR	21		0.41
PD-L1 1-49% (n = 98)	NR	27		0.58
PD-L1 ≥ 50% (n = 80)	NR	20		0.24
TMB < 12.3 mut/Mb (n = 102)	30	27		0.86
TMB ≥ 12.3 mut/Mb (n = 76)	NR	22		0.69
Cisplatin (n = 258)	NR	21		0.71
Carboplatin (n = 72)	NR	11		0.31

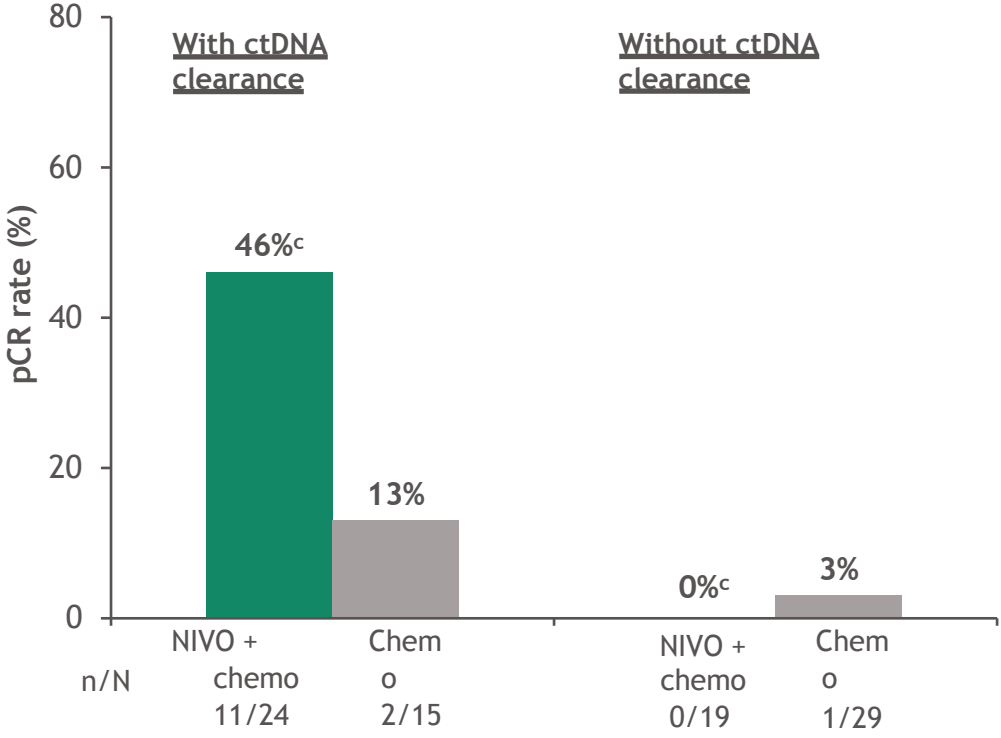
[a]Per BICR.

ctDNA Clearance and Association With Pathological Response

ctDNA clearance and mPR rates



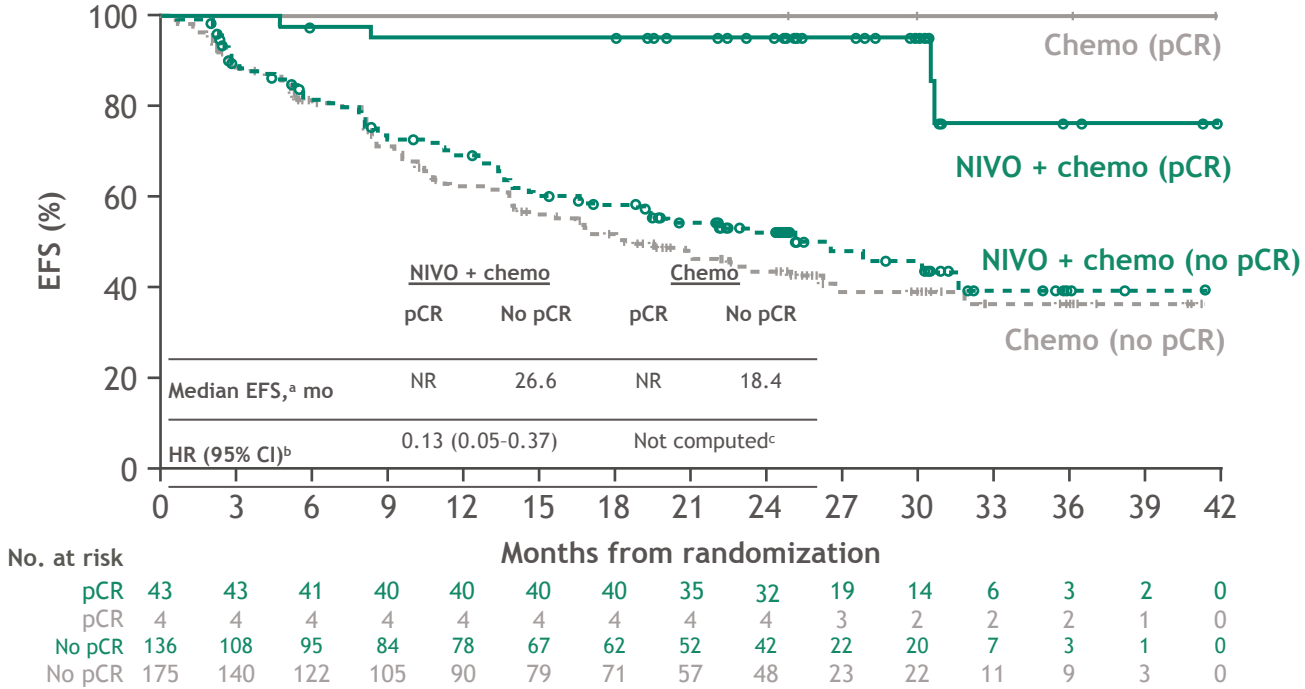
ctDNA clearance and pCR rates



aPerformed using tumor-guided personalized ctDNA panel (ArcherDX Personalized Cancer Monitoring); 90 patients were ctDNA evaluable and 87 had detectable ctDNA at C1D1; main reason for sample attrition were lack of tissue for WES and lack of quality control pass for tissue and plasma; bctDNA clearance 95% CI: NIVO + chemo, 40-71; chemo, 20-50; cpCR rates 95% CI for NIVO + chemo: with ctDNA clearance, 26-67; without ctDNA clearance, 0-18.

Forde PM et al. AACR 2021. Abstract CT003

Exploratory analysis: EFS by pCR status



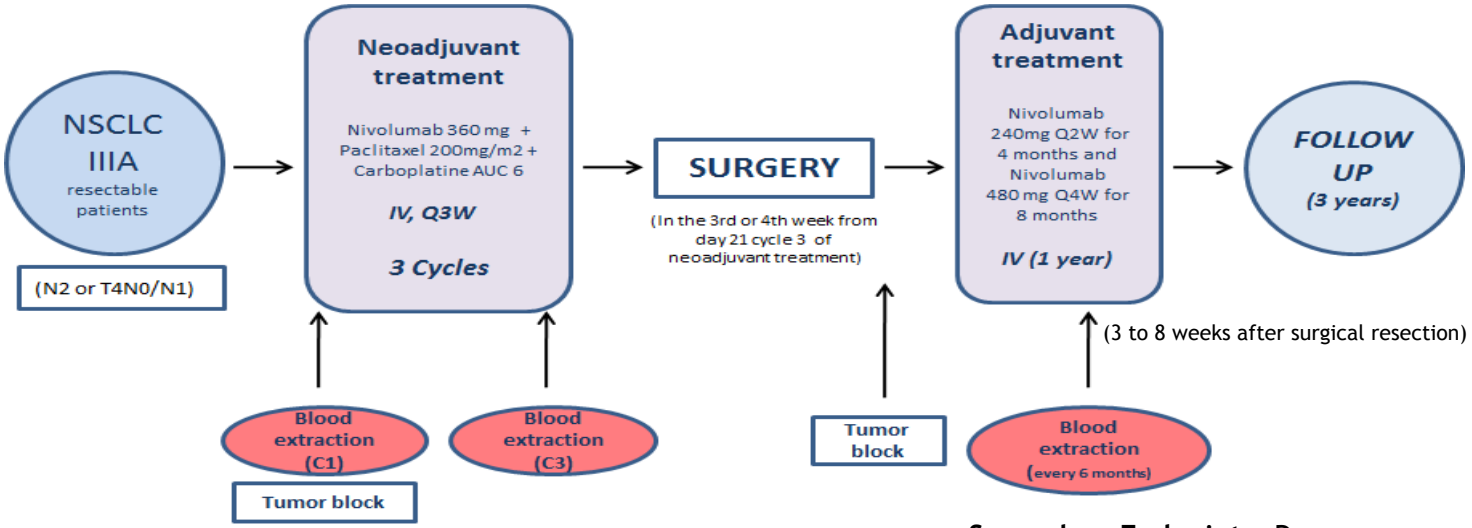
- pCR rates were significantly improved with NIVO + chemo vs chemo (24.0% vs 2.2%)
- In patients without pCR, HR (95% CI) for NIVO + chemo vs chemo was 0.84 (0.61–1.17)

Minimum follow-up: 21 months; median follow-up, 29.5 months.

[a]95% CI = 30.6-NR (NIVO + chemo, pCR), 16.6-NR (NIVO + chemo, no pCR) and NR-NR (chemo, pCR), 13.9-26.2 (chemo, no pCR); [b]In the pooled patient population (NIVO + chemo and chemo arms combined), EFS HR (95% CI) was 0.11 (0.04-0.29) for patients with pCR vs those without pCR; [c]HR was not computed for the chemo arm due to only 4 patients having a pCR.

Overall Survival and Biomarker Analysis of Neoadjuvant Nivolumab Plus Chemotherapy in Operable Stage IIIA NSCLC (NADIM phase II trial)

Open-label, multicenter (18), single-arm phase 2



Sample size: 46
Study start: April 2017
Enrollment completion: August 2018

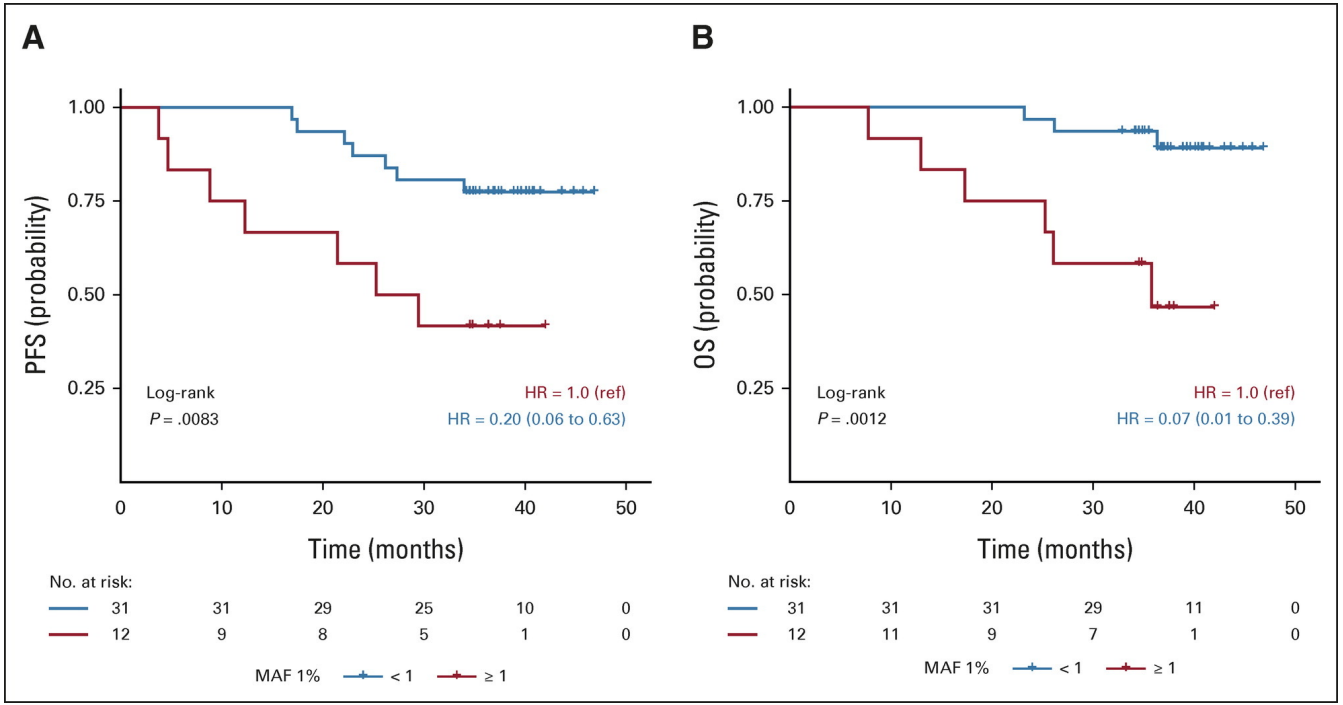
Primary Endpoint:
PFS at 24 months

Secondary Endpoints: Down-staging rate, complete resection rate, ORR, safety, TTP, OS at 3 years

THE UNIVERSITY OF CHICAGO
UChicago Medicine
Department of Medicine

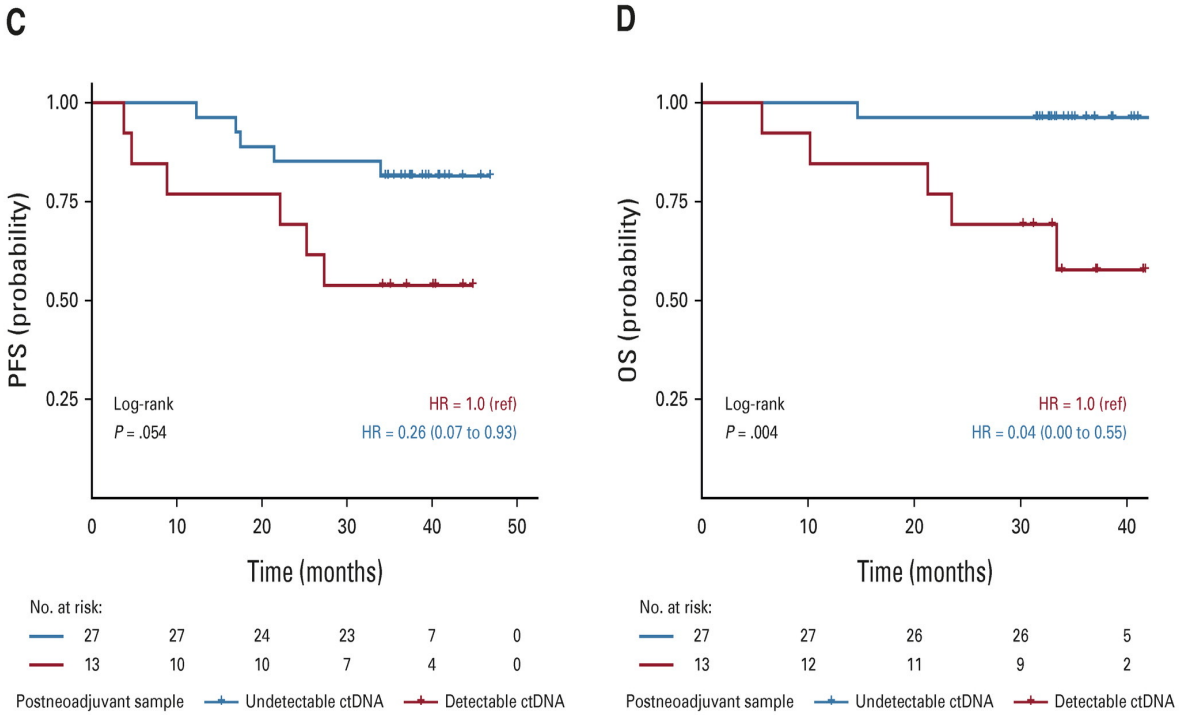
Provencio M et al. *Lancet Oncol*. 2020;21(11):1413-1422

PFS and OS by ctDNA levels at baseline, using a cutoff of <1% MAF



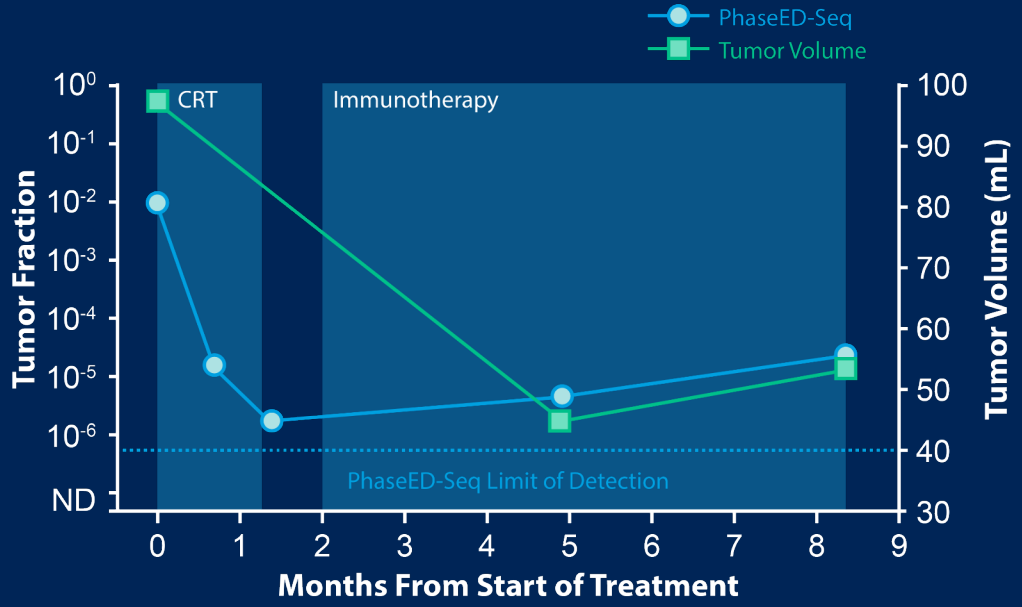
Provencio et al, JCO, epub ahead of print, 2022

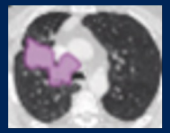
PFS and OS according to ctDNA detection after neoadjuvant treatment



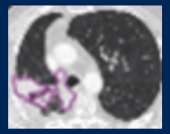
Provencio et al, JCO, epub ahead of print, 2022

“Liquid Biopsy” — an Innovation in Diagnostic Testing

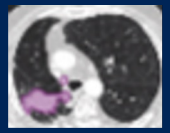




Pretreatment Mass



Treatment Response with Residual Fibrosis, Tumor DNA Detected in Plasma



Biopsy confirmed recurrent disease

D Kurtz, M Diehn, et al. *Nature Biotechnol* 2021

Impact of Neoadjuvant IO in Early-Stage NSCLC

- **Ideal primary endpoint: a surrogate for EFS, PFS, or OS**
- **Potential surrogate endpoints and predictors of IO response**
  - mPR (based on neoadjuvant chemotherapy)
  - pCR (supported by CM-816)
  - ctDNA (also to monitor recurrence)

  - TMB
  - Tumor microenvironment (ex. Immune cellular infiltrates, cytokines, PD-L1)
  - Microbiome

Biomarker-Based De-escalated curative-intent Therapy

Examples:

- Dynamic Trial in Colorectal Cancer
- Dostarlimab De-escalation Trial in Rectal Cancer as example for HPV-related Head and Neck Cancer

DYNAMIC Study Design

ACTRN12615000381583

Stage II Colon Cancer

- R0 resection
- ECOG 0 – 2
- Staging CT within 8 weeks
- Provision of adequate tumor tissue within 4 weeks post-op
- No synchronous colorectal cancer

Plasma Collections

Week 4 + 7 post-op

R
2:1

ctDNA-Guided Management

- **ctDNA-Positive → Adjuvant Chemo** (oxaliplatin-based or single agent FP)
- **ctDNA-Negative → Observation**

ctDNA-Positive = Positive result at week 4 and/or 7

Standard Management

Adjuvant treatment decisions based on conventional clinico-pathologic criteria

Endpoints

Primary
- RFS rate at 2 years

Key Secondary
- Proportion receiving adjuvant chemo

Secondary
- RFS by ctDNA status for ctDNA-guided arm
- TTR
- OS

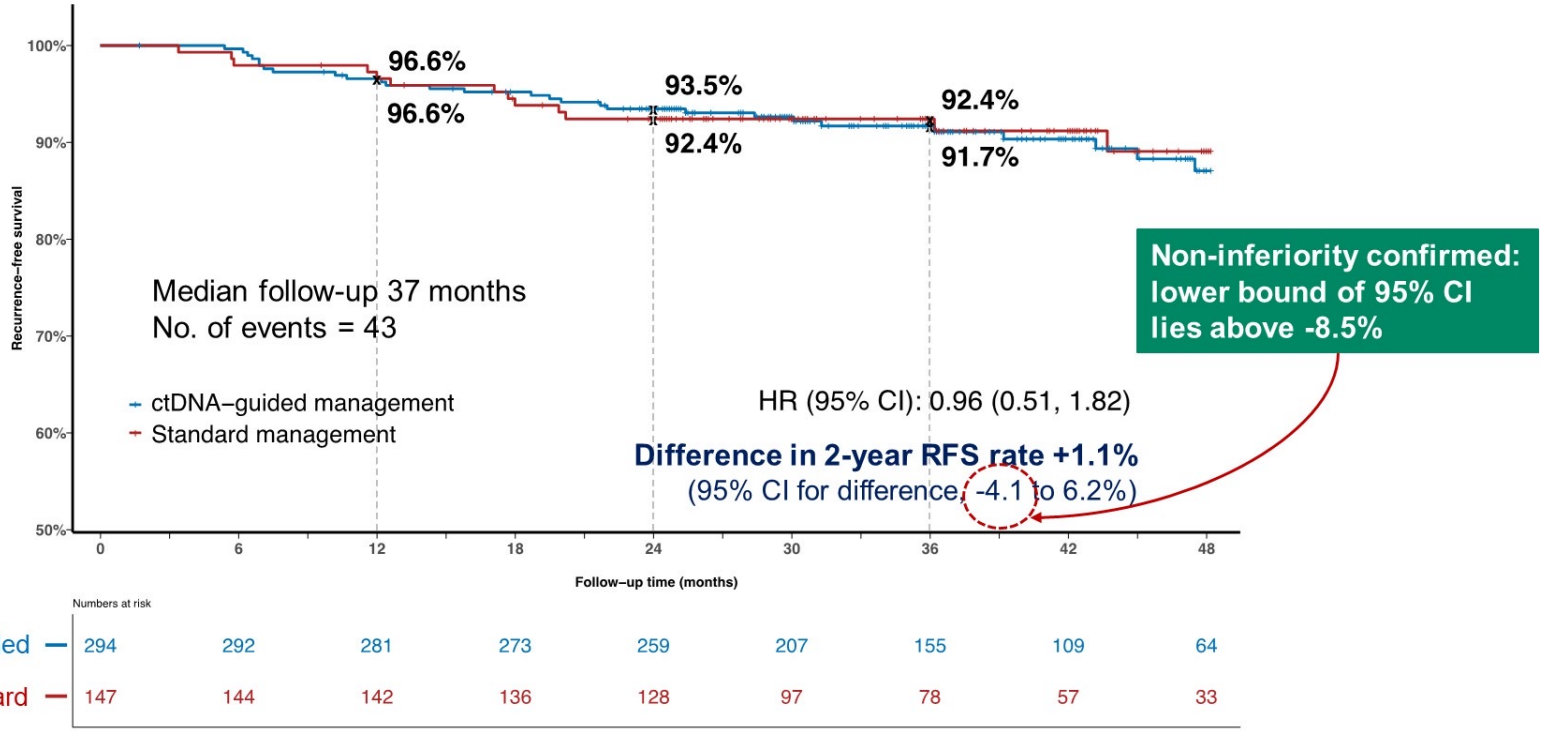
Stratification Factors
- T stage (T3 vs T4)
- Type of participating center (metropolitan vs regional)

Surveillance:
- CEA → 3-monthly for 24M, then 6-monthly for 36M
- CT C/A/P → 6-monthly for 24M, then at 36M

Adjuvant Treatment Delivery

Treatment Information	ctDNA-Guided N = 294	Standard Management N = 147	P-value
Adjuvant Chemotherapy received, n	45 **(15%)**	41 **(28%)**	0.0017
Chemotherapy regimen received, n			
Oxaliplatin-based doublet	28/45 **(62%)**	4/41 **(10%)**	
Single agent fluoropyrimidine	17/45 **(38%)**	37/41 **(90%)**	<.0001
Time from surgery to commencing chemotherapy, median (IQR), days	83 (76, 89)	53 (49, 61)	<.0001
Treatment duration, median (IQR), weeks	24 (19, 24)	24 (21, 24)	0.9318
Completed planned treatment, n	38 (85%)	32 (78%)	0.7036
Percentage of full dose delivered, median (IQR)	78 (56, 100)	84 (64, 100)	0.6194

Recurrence-Free Survival



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Summary

- **For patients with stage II colon cancer, a ctDNA-guided approach (treating only patients with a positive ctDNA after surgery) compared to standard-of-care**
  - Substantially reduced the proportion receiving adjuvant chemotherapy (28% → 15%)
  - Did not compromise recurrence-free survival (2-year RFS: 93.5% vs 92.4%)
- **Patients with a positive ctDNA after surgery may derive RFS benefit from adjuvant chemotherapy**
  - Favorable 3-year RFS in patients treated with adjuvant chemotherapy (86.4%) versus low RFS in historical series (< 20%) if untreated
  - Ongoing trials (e.g., COBRA, CIRCULATE, CIRCULATE-PRODIGE) will provide further guidance regarding the optimal use of ctDNA-informed management
- **ctDNA-negative patients have a low recurrence risk without adjuvant chemotherapy**
  - 3-year RFS 92.5% (clinical low risk: 96.7%; T3: 94.2%)

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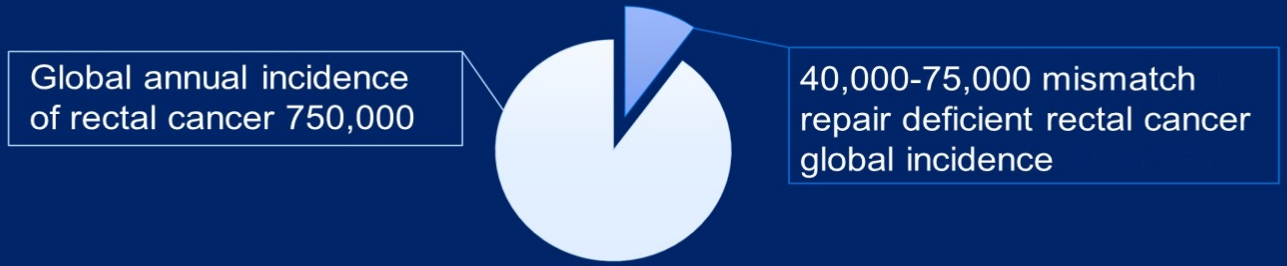
Dynamic Trial as Example for NSCLC

- Continue to use stage to determine need for neoadjuvant therapy at diagnosis but obtain ctDNA
- pCR as optimal goal and primary endpoint
- Use ctDNA to determine number of neoadjuvant chemo-IO cycles and
- To determine the need to give additional adjuvant therapy (NADIM II)

Mismatch repair deficient rectal cancer



- Approximately 5-10% of rectal cancers are mismatch repair deficient
- Relatively resistant to chemotherapy
- Checkpoint blockade is highly effective in metastatic mismatch repair deficient cancers with a complete response rate ~10%

Cercek A, Clin Cancer Res 2020
Andre T, N Engl J Med 2020
Le DT, N Engl J Med 2015

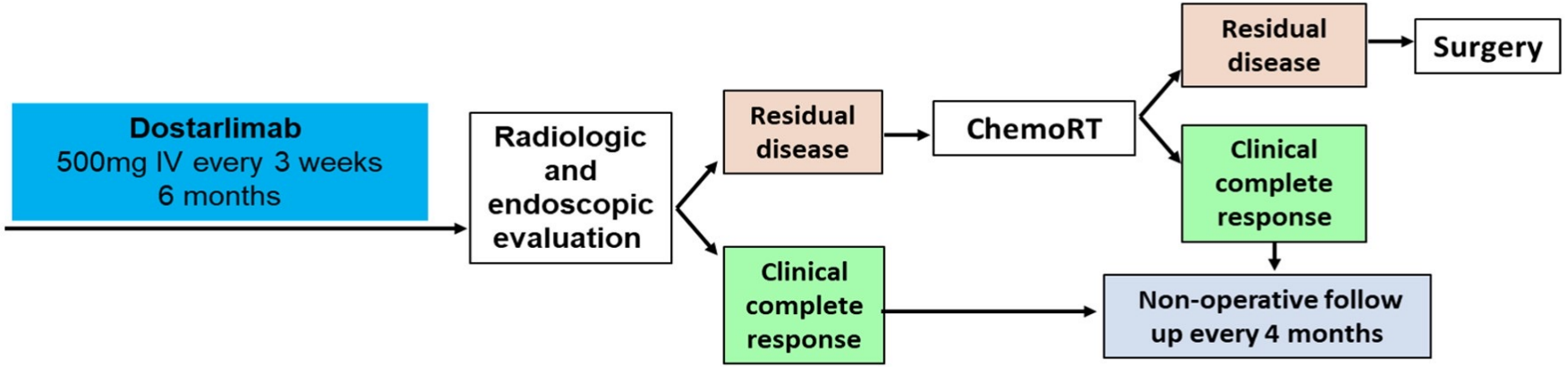
Hypothesis:

In mismatch repair deficient rectal cancer, PD-1 blockade may be able to either:

a) replace chemotherapy

b) replace chemo *and* radiation therapy

c) replace chemo *and* radiation, *and* surgery



Patient population: Stage II and III mismatch repair deficient rectal cancer

Target Enrollment: 30 subjects

Study Design: Simon's two stage minimax design

NCT04165772

Individual responses to PD-1 blockade with dostarlimab

Patients who completed 6-months of dostarlimab

ID	Age	Stage T	Stage N	FU (months)	Digital rectal exam response	Endoscopic best response	Rectal MRI best response	Overall response 100%
1	38	T4	N+	23.8	CR	CR	CR	cCR
2	30	T3	N+	20.5	CR	CR	CR	cCR
3	61	T1/2	N+	20.6	CR	CR	CR	cCR
4	28	T4	N+	20.5	CR	CR	CR	cCR
5	53	T1/2	N+	9.1	CR	CR	CR	cCR
6	77	T1/2	N+	11.0	CR	CR	CR	cCR
7	77	T1/2	N+	8.7	CR	CR	CR	cCR
8	55	T3	N+	5.0	CR	CR	CR	cCR
9	68	T3	N+	4.9	CR	CR	CR	cCR
10	78	T3	N-	1.7	CR	CR	CR	cCR
11	55	T3	N+	4.7	CR	CR	CR	cCR
12	27	T3	N+	4.4	CR	CR	CR	cCR
13	26	T3	N+	0.8	CR	CR	CR	cCR
14	43	T3	N+	0.7	CR	CR	CR	cCR

Potential Impact on Patients is Huge

- Unprecedented 100% clinical complete response rate
- Possibility of decreased morbidity from elimination of pelvic radiation and surgery
  - Bowel dysfunction
  - Urinary dysfunction
  - Sexual dysfunction
  - Infertility
  - Permanent ostomy
- Particularly relevant as incidence of rectal cancer is increasing steadily in young people

American Cancer Society. *Cancer Facts & Figures 2022*. Atlanta: American Cancer Society; 2022.

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Remaining Questions

- Can tumor regrowth and recurrence be successfully salvaged?
- Are there biomarkers (e.g., ctDNA, PET scans) that can better predict pCR?
- What is the optimal duration of neoadjuvant immunotherapy?
- Is there a role for combination with anti-CTLA4 antibodies, chemotherapy, and/or radiation?
- Can neoadjuvant checkpoint blockade alone prevent additional Lynch-related CRCs and other Lynch-associated cancers?

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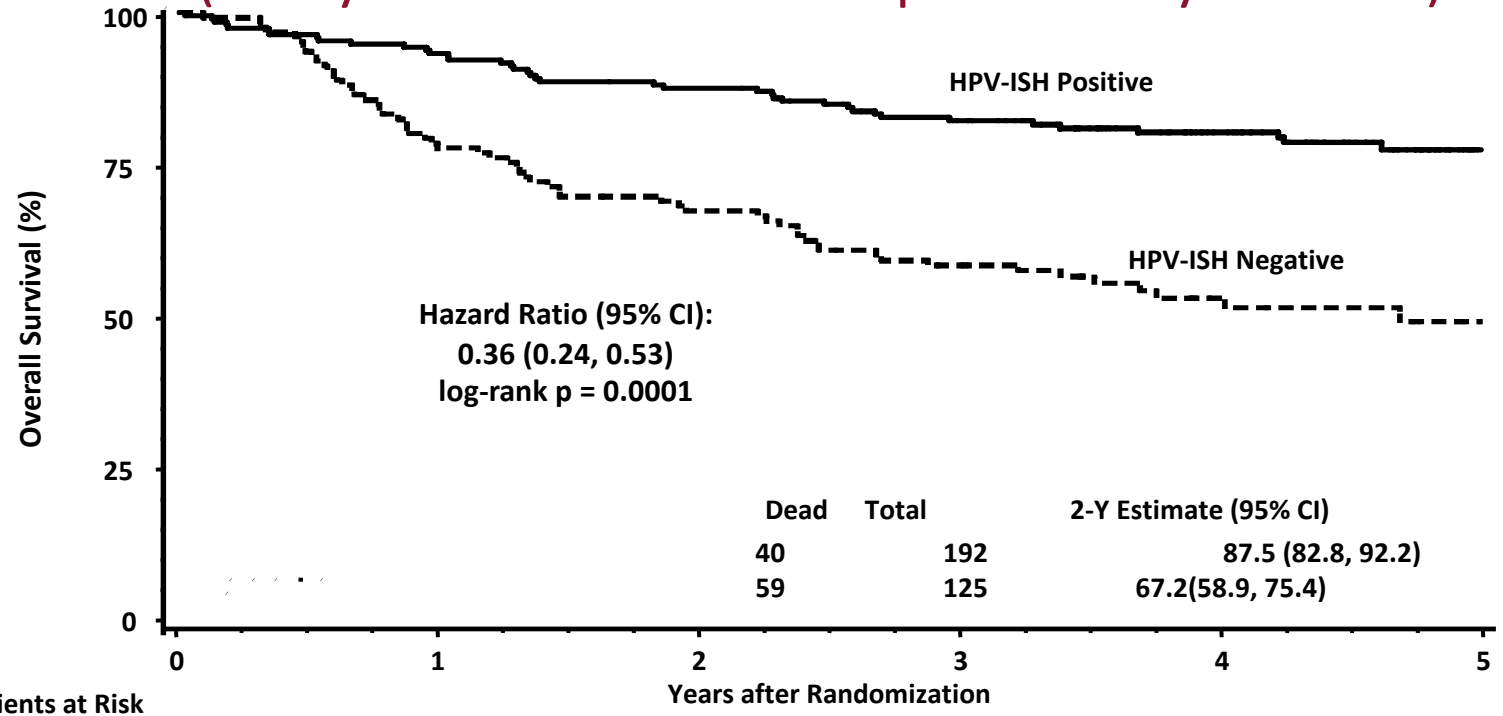
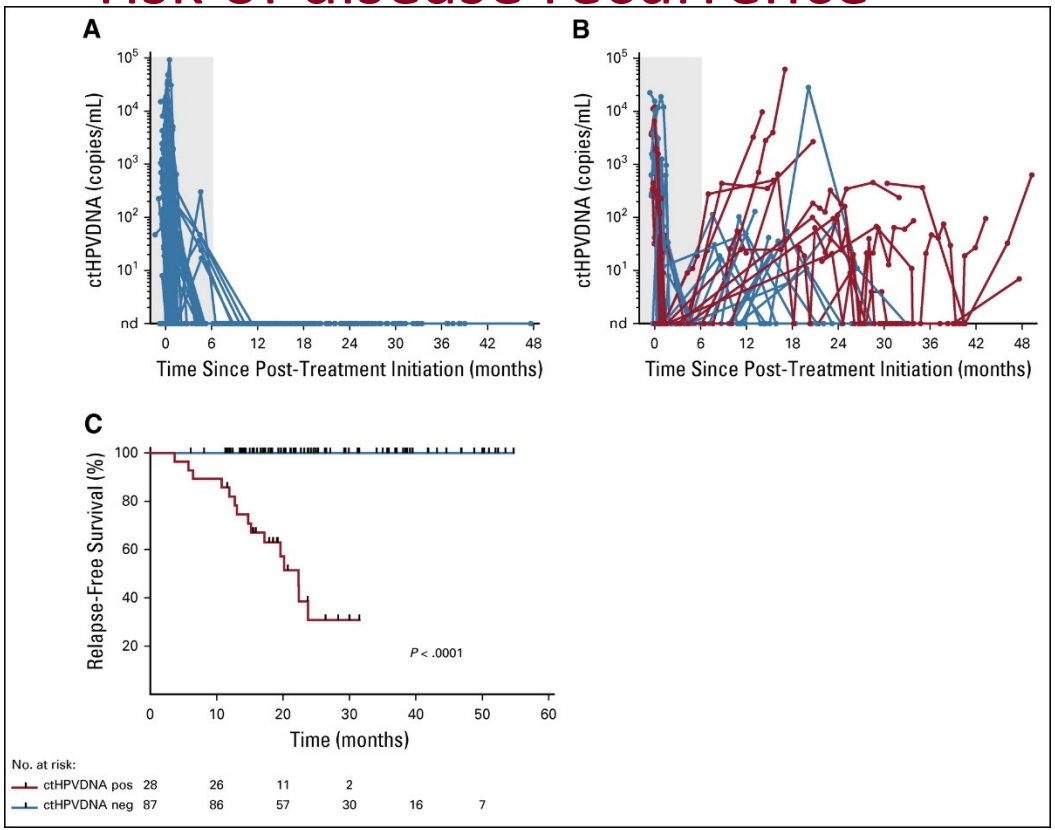
Role of HPV in Locoregionally Advanced HNC
Phase III Trial RTOG 0129 – Survival by HPV Status
(70 Gy and concomitant cisplatin every 3 weeks)



Patients at Risk						
HPV-ISH Positive	192	179	167	148	104	19
HPV-ISH Negative	125	97	83	69	35	6

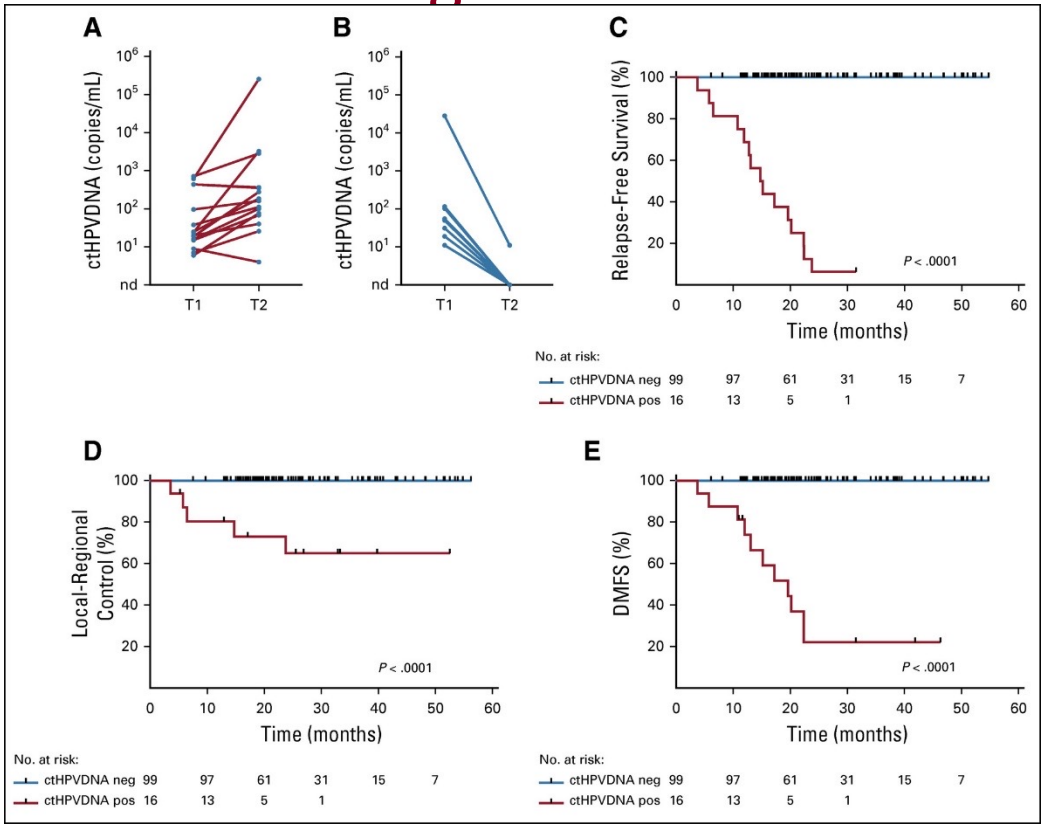
Ang KK NEJM , 2010

Longitudinal ctHPVDNA surveillance identifies patients at high risk of disease recurrence



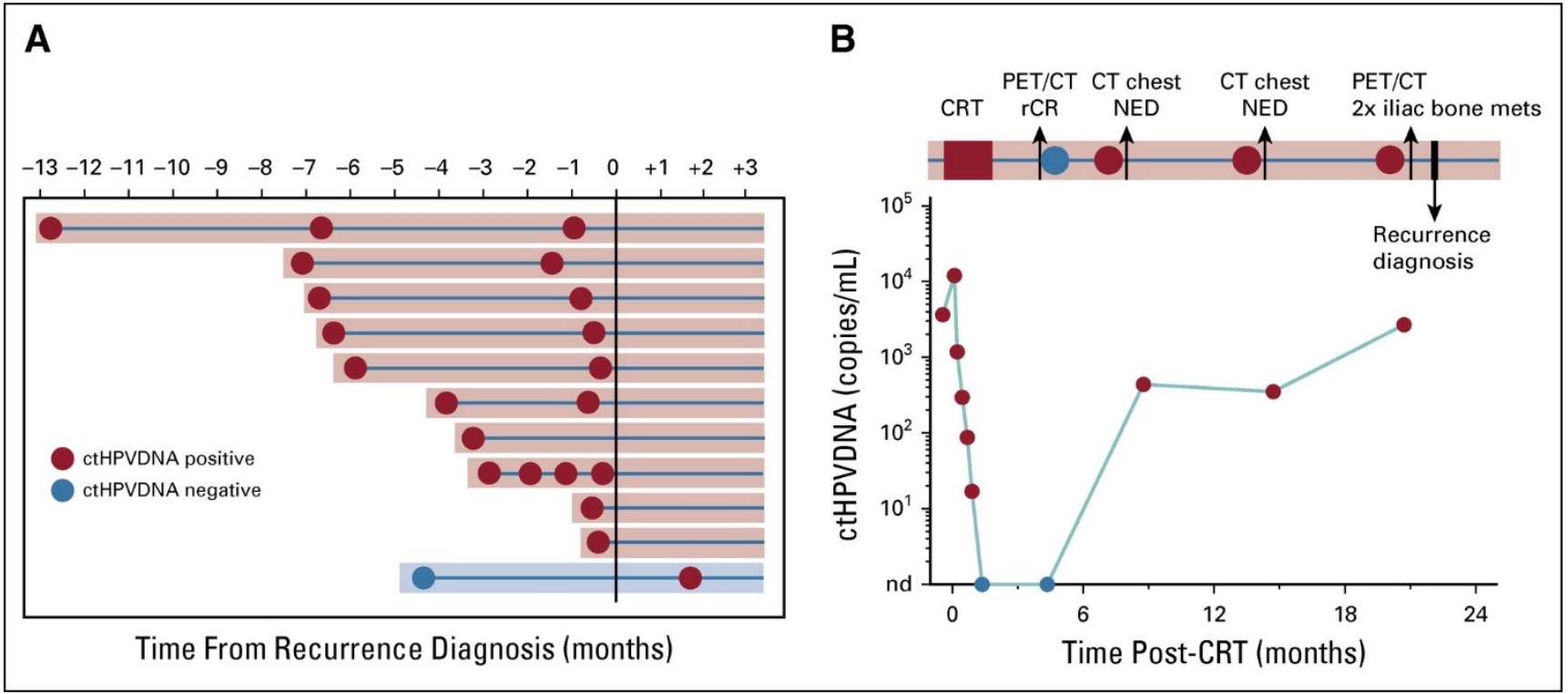
Chera BS, et al, J Clin Oncol, 38(10): 1050-1058, 2020

Patients with two consecutively abnormal ctHPVDNA surveillance tests have a higher risk for disease recurrence



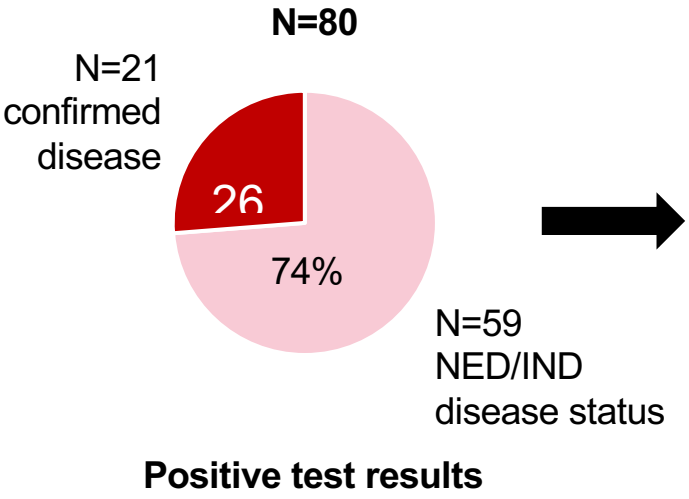
Chera BS, et al, J Clin Oncol, 38(10): 1050-1058, 2020

ctHPVDNA surveillance facilitates early detection of disease recurrence



Chera BS, et al, J Clin Oncol, 38(10): 1050-1058, 2020

Detection of Occult Recurrence

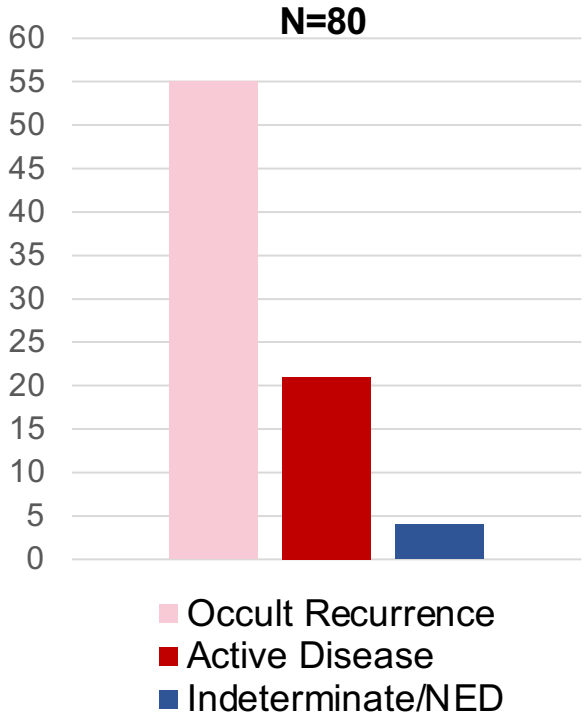


55/59 (93%) later had proven recurrent, metastatic disease on imaging and/or biopsy

Of the remaining **4**/59 (7%), **2** have clinically suspicious lesions (tongue base, pulmonary nodule), and **2** are clinically NED

All 4 have TTMV-HPV DNA values ranging from **16-79 frg/mL**

PPV of TTMV-HPV DNA to Detect Recurrence

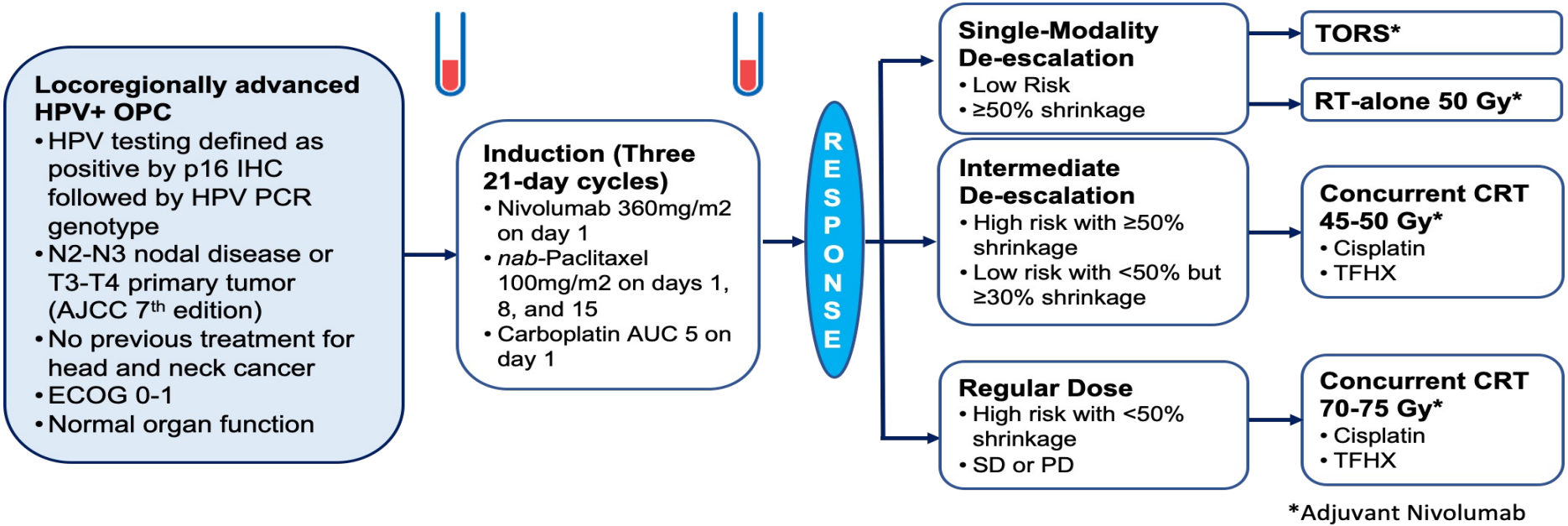


55/59 (93%) later had proven recurrent, metastatic disease on imaging and/or biopsy

	Disease	No disease	Total
Positive	76	4	80
Negative		996	996
Total	76	1000	1076

55 + 21 = 76/80 = **95% PPV**

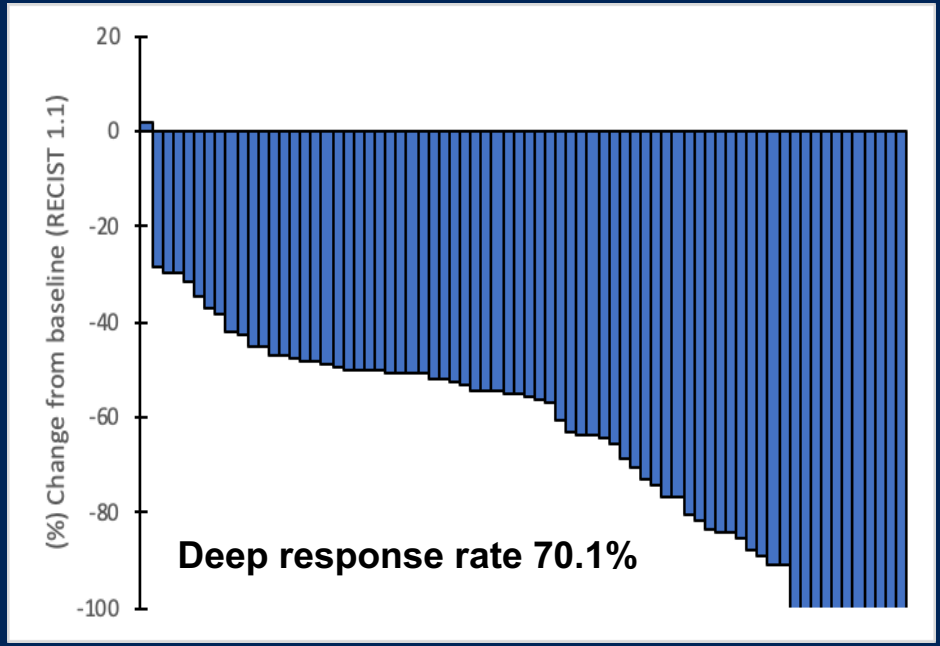
Optima 2 study design



Rosenberg AJ et al, ASCO Poster, 2021

Response Following Induction

Radiographic Response

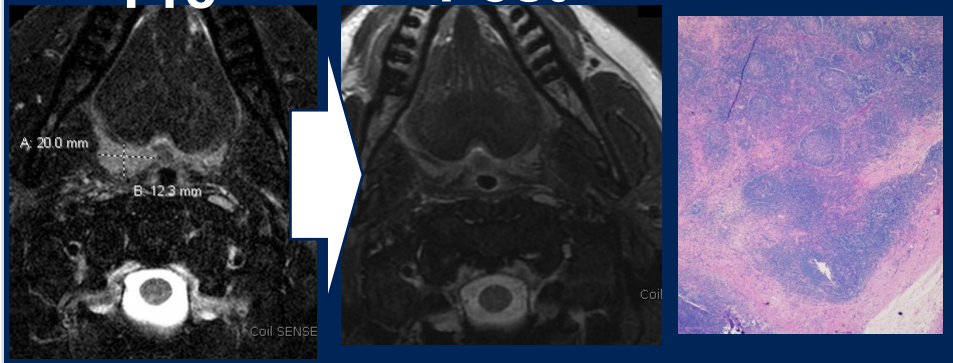


Pathologic Response

Pathologic complete response rate among TORS patients was 67% (6/9)

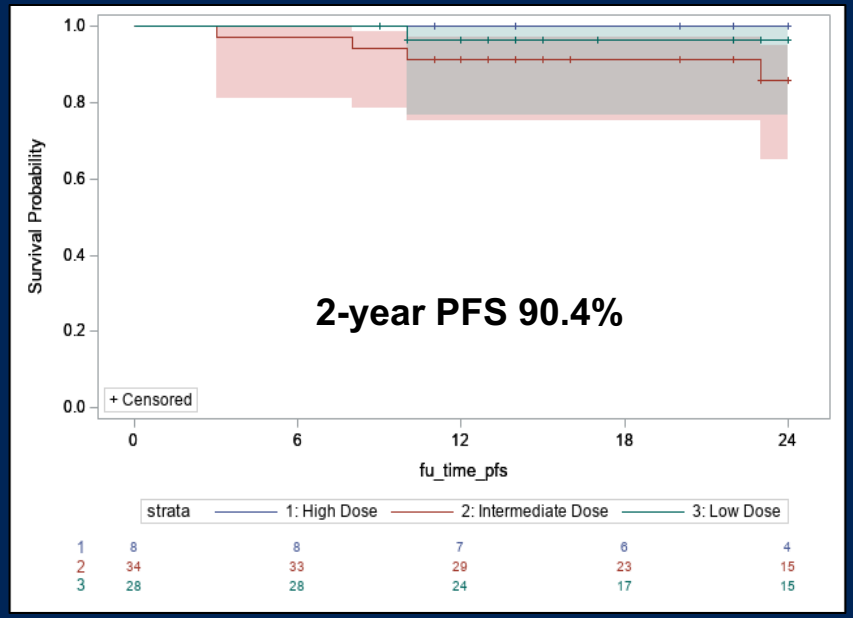
Patient #1

Pre **Post** **TORS**

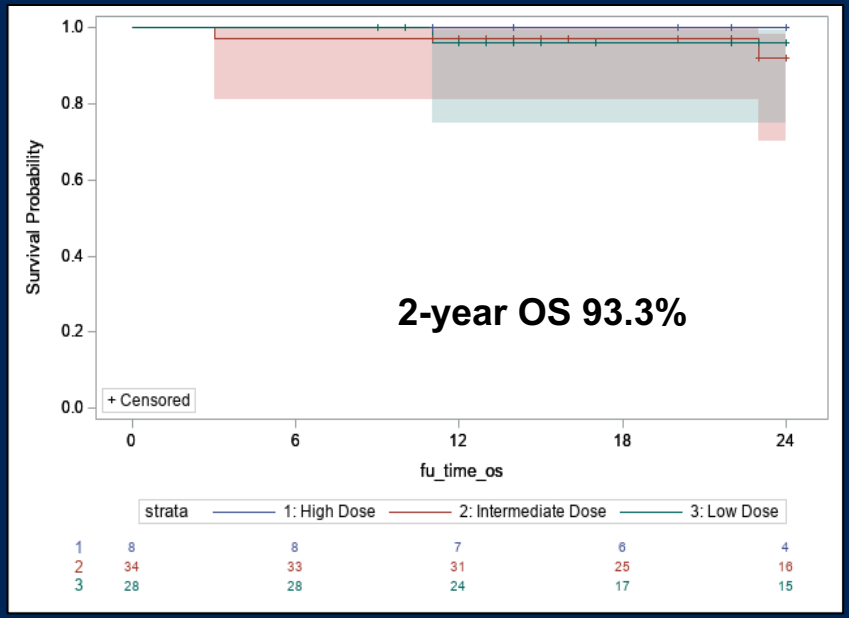


Survival Outcomes

Progression-Free Survival

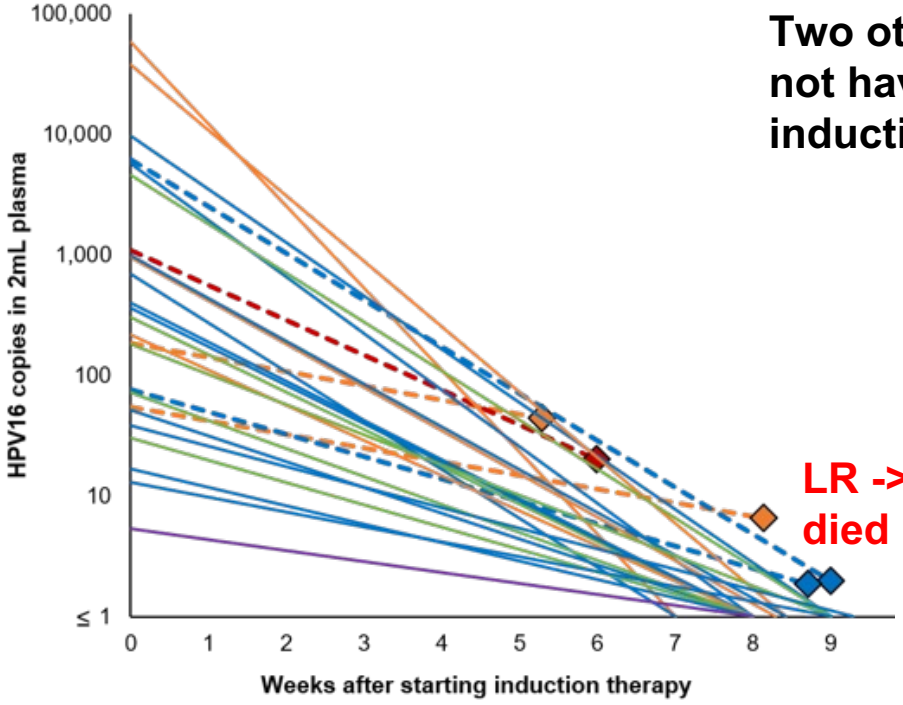


Overall Survival



Median f/u 23.1 months (IQR 13.7,31.2)

Clearance of cfDNA with induction may predict treatment failure

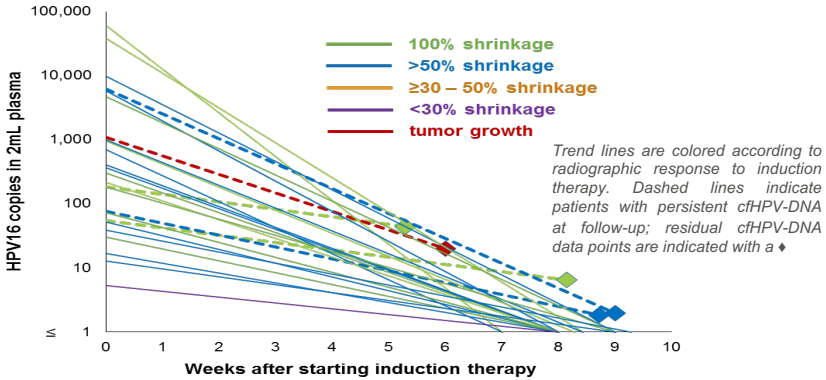


Two other recurrences did not have ctDNA post-induction collected.

LR -> RT50 -> recurred -> died

Sloan, Izumchenko…Rosenberg, Agrawal ASCO Poster, 2021

Preliminary data



- Longitudinal ctHPV-DNA analysis in patients receiving chemotherapy with immunotherapy. Trend lines are colored according to radiographic response to chemotherapy with immunotherapy. Dashed lines indicate patients with persistent ctHPV-DNA at follow-up; residual ctHPV-DNA data points are indicated with a ♦.
- All 25 patients with baseline cfHPV-DNA showed a decrease in cfHPV-DNA level at follow-up, with complete clearance observed in 21/25 of patients, consistent with tumor response (shrinkage) to induction therapy.
- Of 4 patients with persistent cfHPV-DNA: 2 patients progressed on induction therapy, 1 patient demonstrated subsequent recurrence and death, 1 patient demonstrated concern for distant metastasis followed by death.

Evaluating dynamic changes of cell-free HPV DNA in patients with locoregional HPV-associated OPSCC treated with induction chemotherapy followed by risk and response-adaptive treatment.

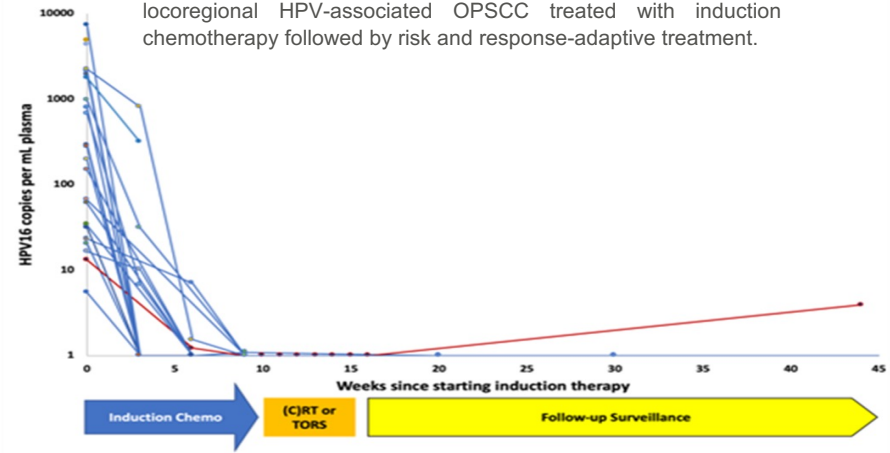
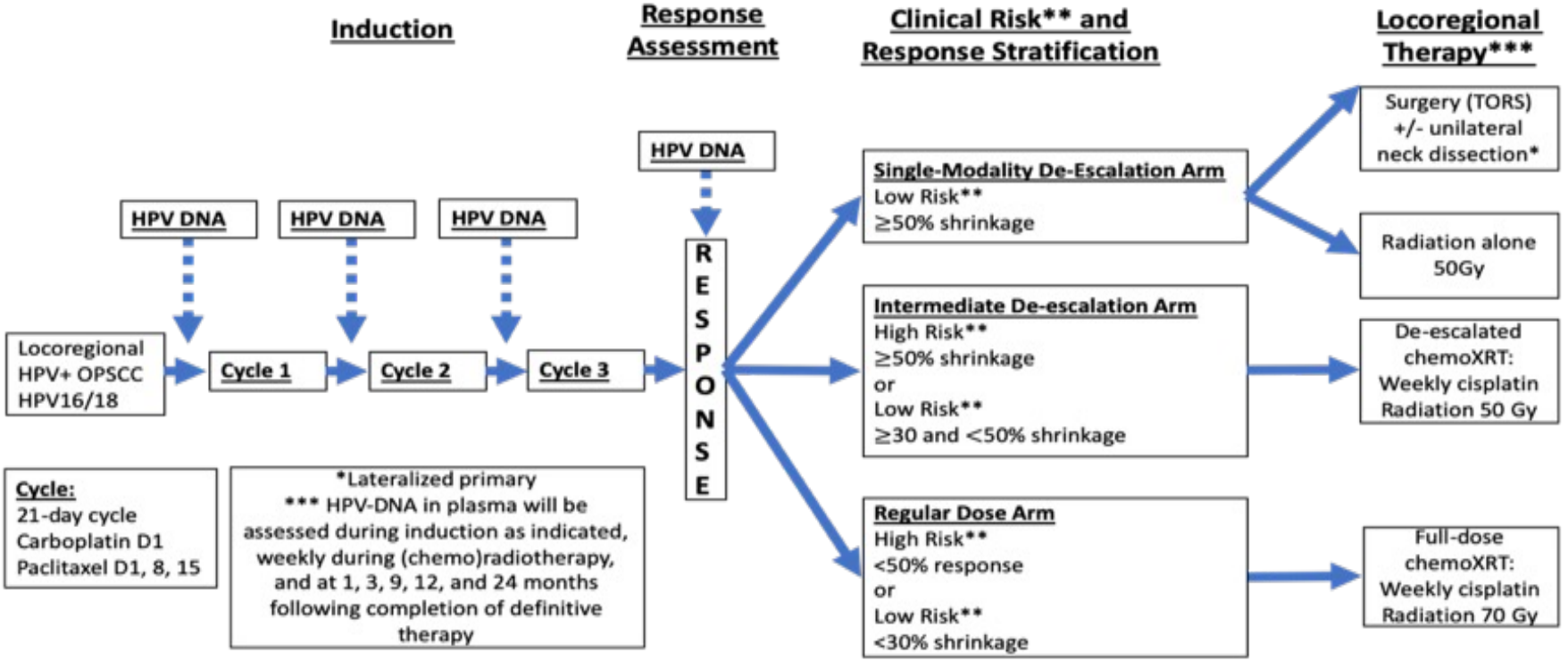


Figure 1. Serial quantitative cfHPV DNA among first 25 patients on study. *Quantitative change in ctDNA during induction chemotherapy, response-adaptive locoregional therapy including de-escalated RT +/- chemotherapy or transoral robotic surgery (TORS), and during follow-up.*

Prospective study of dynamic changes of cell-free HPV DNA in HPV+ OPC treated with risk and response-adaptive treatment



Conclusion

- Early results of low-risk de-escalated arm of OPTIMA 2 suggest that induction chemoimmunotherapy with carboplatin/nab-paclitaxel/nivolumab followed by de-escalated locoregional therapy leads to excellent oncologic outcomes with low rates of acute toxicity.
- High pCR rate to induction chemoimmunotherapy in TORS arm suggests that RT or surgery may be selectively omitted.
- cfHPV-DNA may assist in more precise selection of patients for treatment de-intensification