Stage 3 Non-Small Cell Lung Cancer Moving Clinical Trials into Clinical Practice

James J Urbanic, MD

Professor, Clinical Radiation Medicine and Applied Sciences

Vice Chair – Academic Affairs

Co-Lead UCSD Lung Cancer Program

Vice Chair – Respiratory Committee – Alliance for Clinical Trials in Oncology

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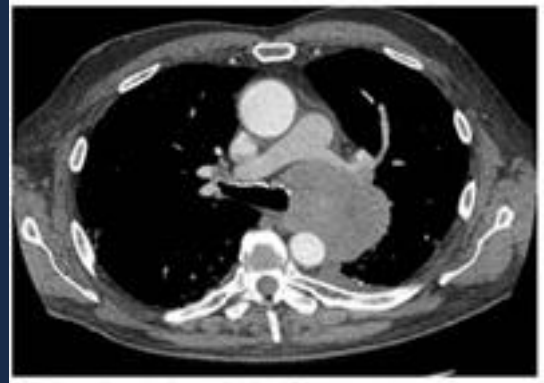
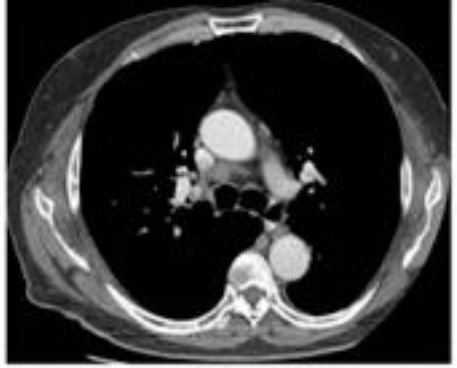
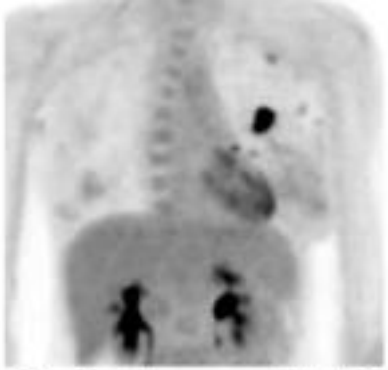


Mediastinal Infiltration

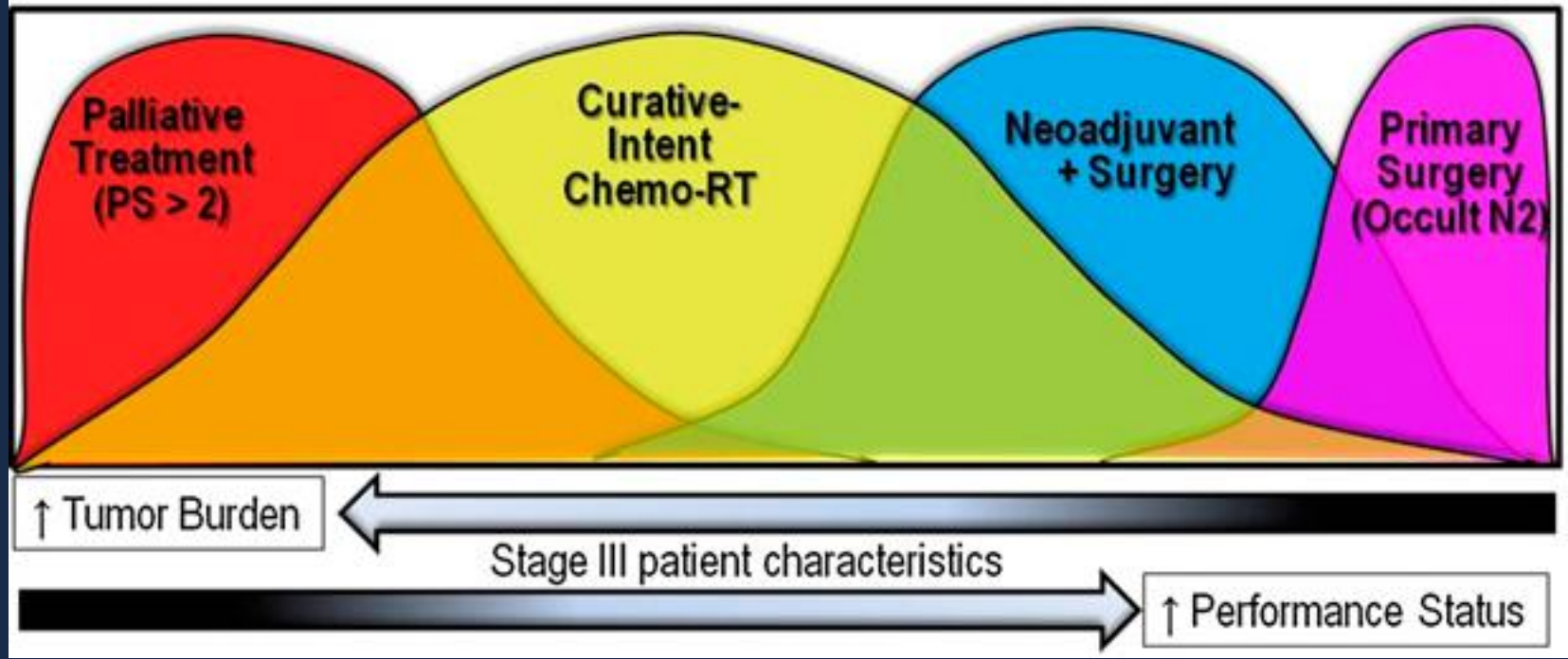


Discrete node enlargement



Clinically occult N2

chematic of types of patients included in studies using different treatment approaches



CHEST 2013; 143(5)(Suppl):e314S–e340S

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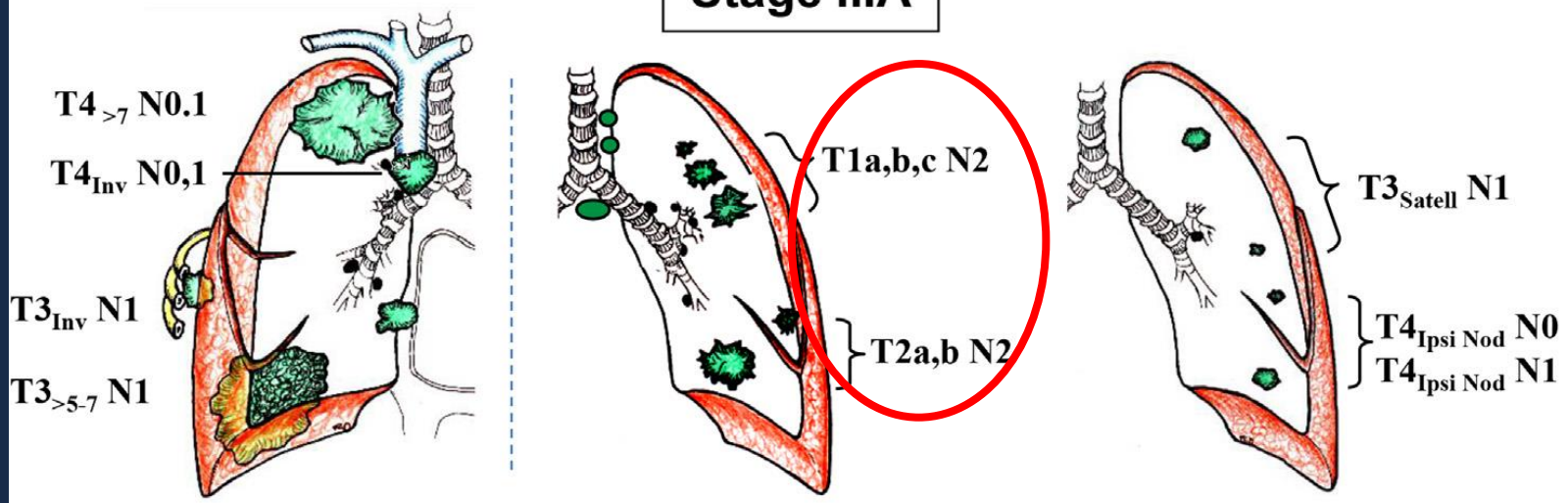
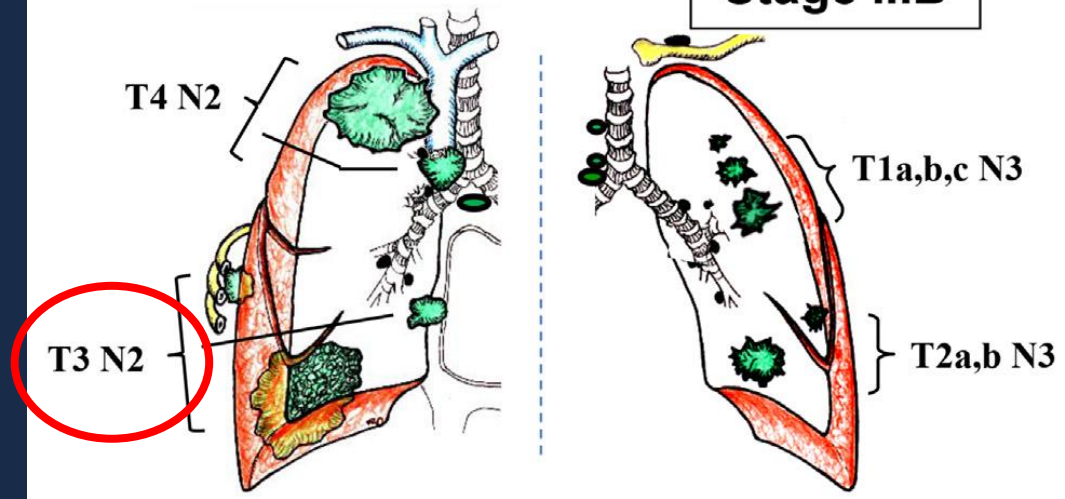
Stage IIIA



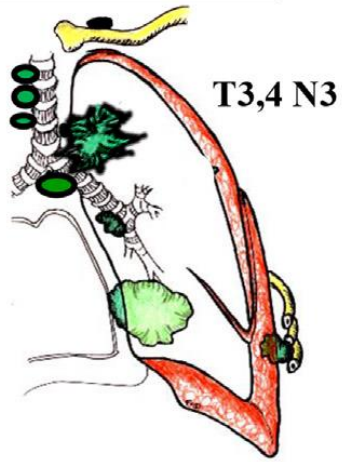
Specific Notes:

- Tumor size defined as largest dimension of the solid (imaging, c-stage) or invasive (p-stage) component
- Direct extension of the primary tumor into an adjacent node counts as nodal involvement
- Extension of a nodal metastasis into a T structure does not count for the T category
- The highest T category is used when there is a discrepancy between T by size or by other factors

Stage IIIB

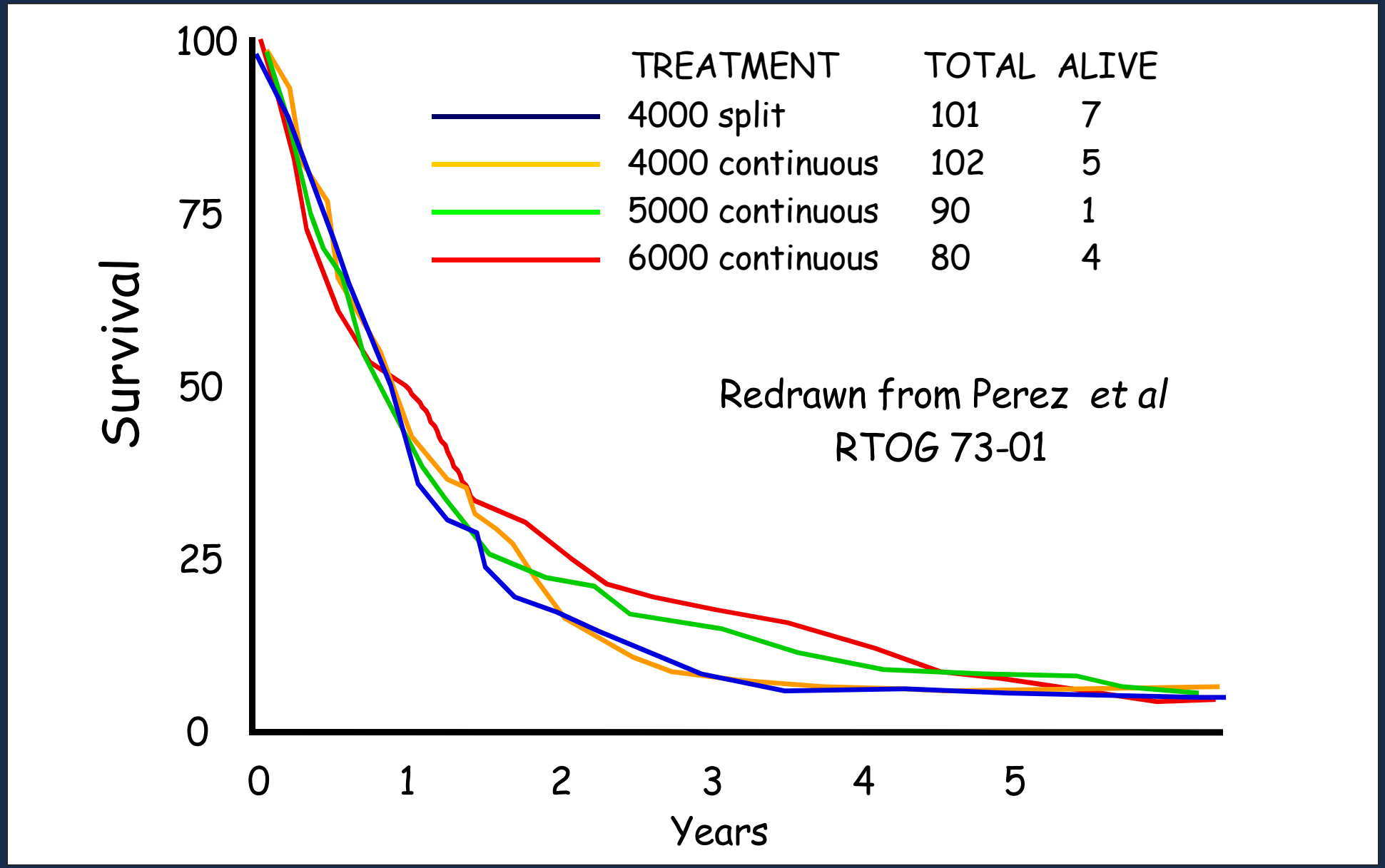


Stage IIIC



AJCC 8th edition: CHEST 2017; 151(1):193-203[3]

Chemoradiotherapy


100
75
50
25
0
Survival
0
1
2
3
4
5
Years
TREATMENT
TOTAL
ALIVE
4000 split
101
7
4000 continuous
102
5
5000 continuous
90
1
6000 continuous
80
4
Redrawn from Perez et al
RTOG 73-01

RTOG 88-08: RT alone vs seq chemo RT

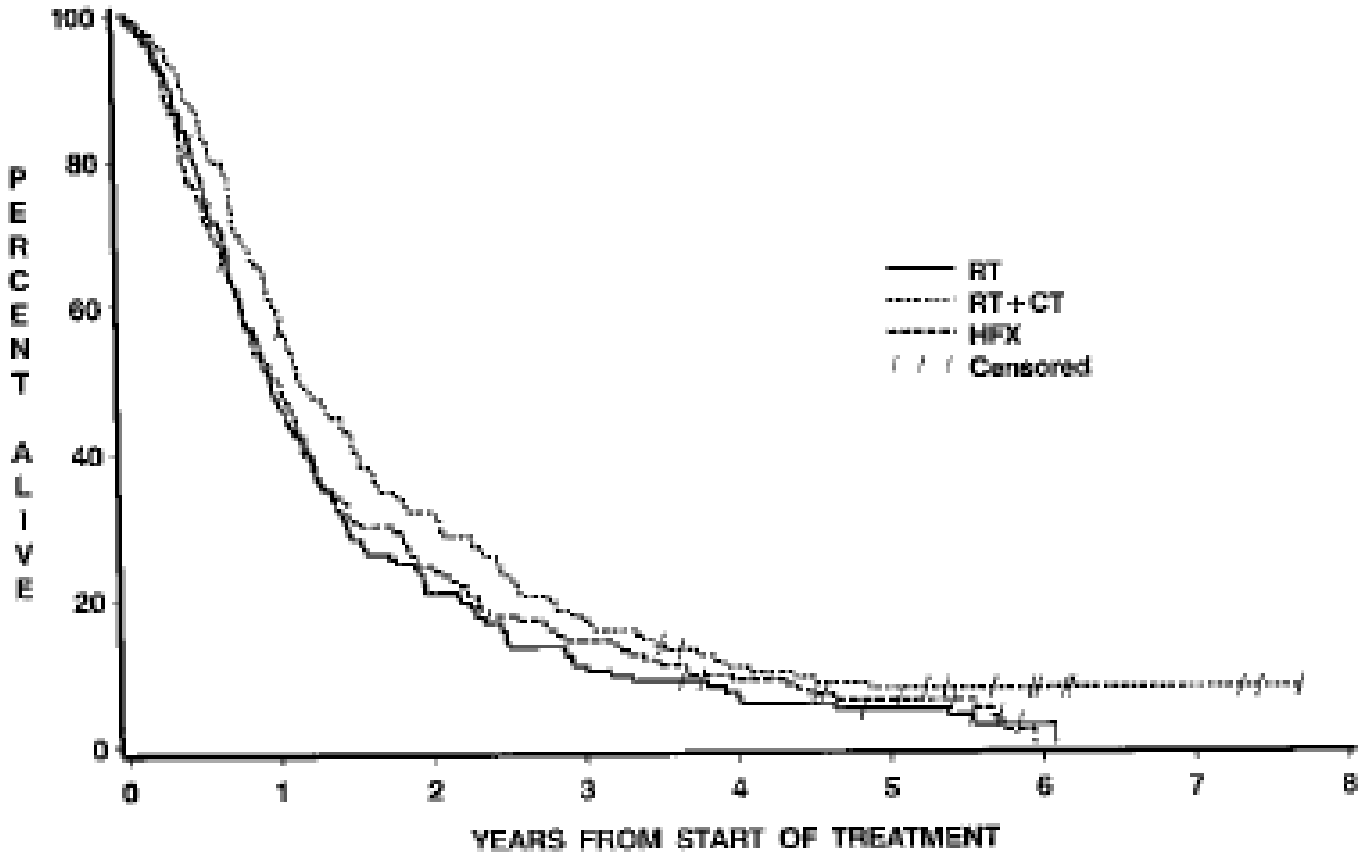


FIGURE 1. RTOG 8808 survival by treatment, all patients. RT = radiation therapy; RT + CT = radiation therapy plus chemotherapy; HFX = hyperfractionated irradiation therapy.

Sause Chest 2000

458 patients

3 arms

60 Gy RT +/- cis vinblast

69.6 1.2 Gy BID

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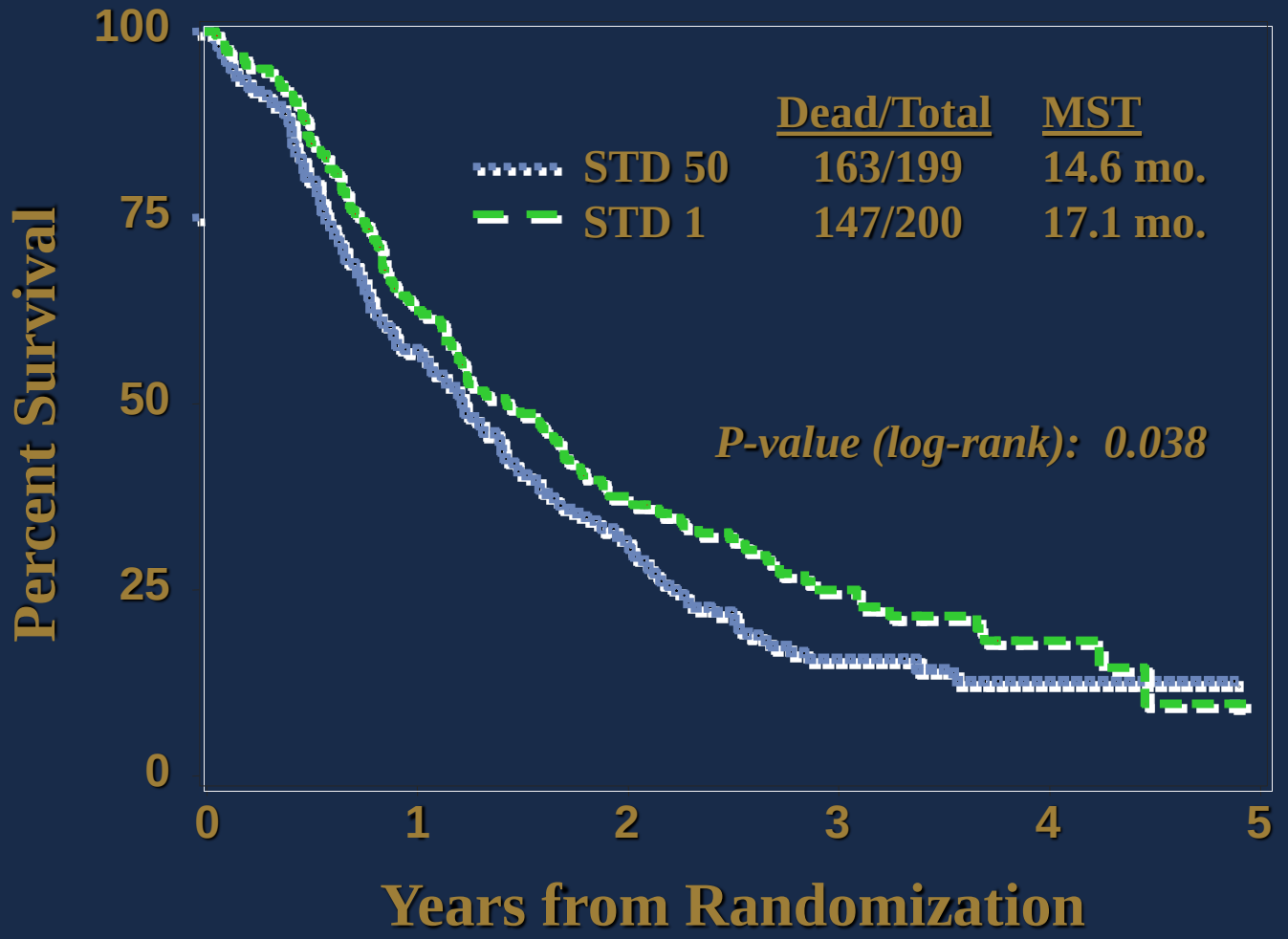
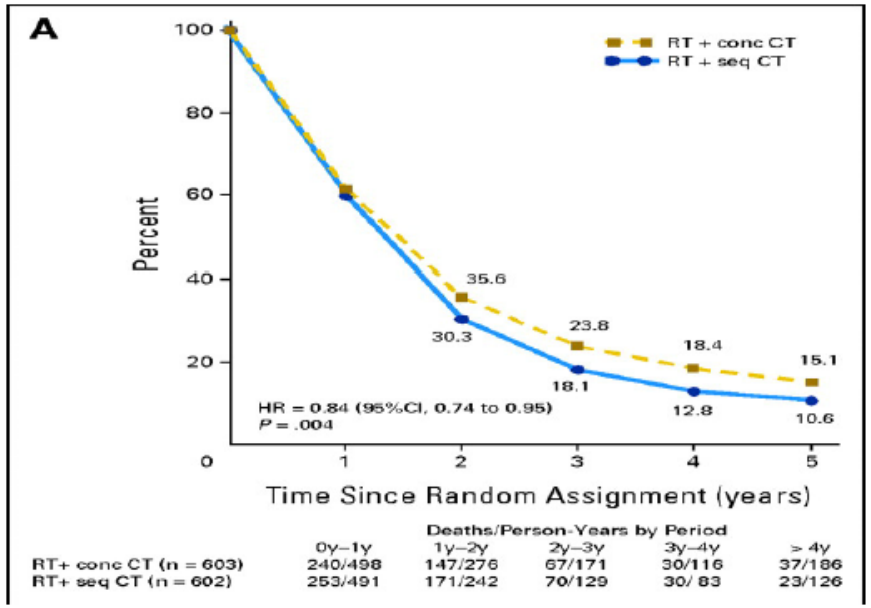
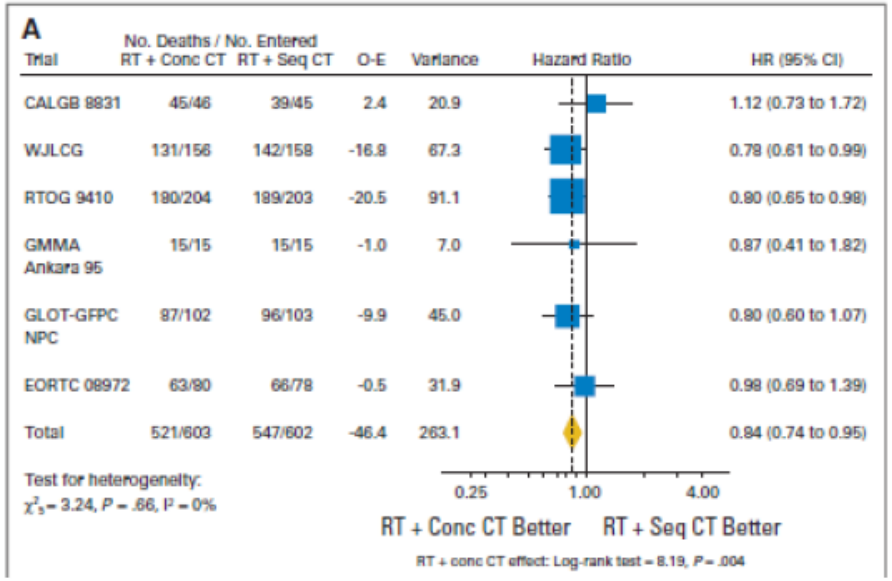
Survival Results for Stage III NSCLC (9410)

Concurrent vs. Sequential Chemo-RT



Concurrent vs Sequential – Meta-analysis

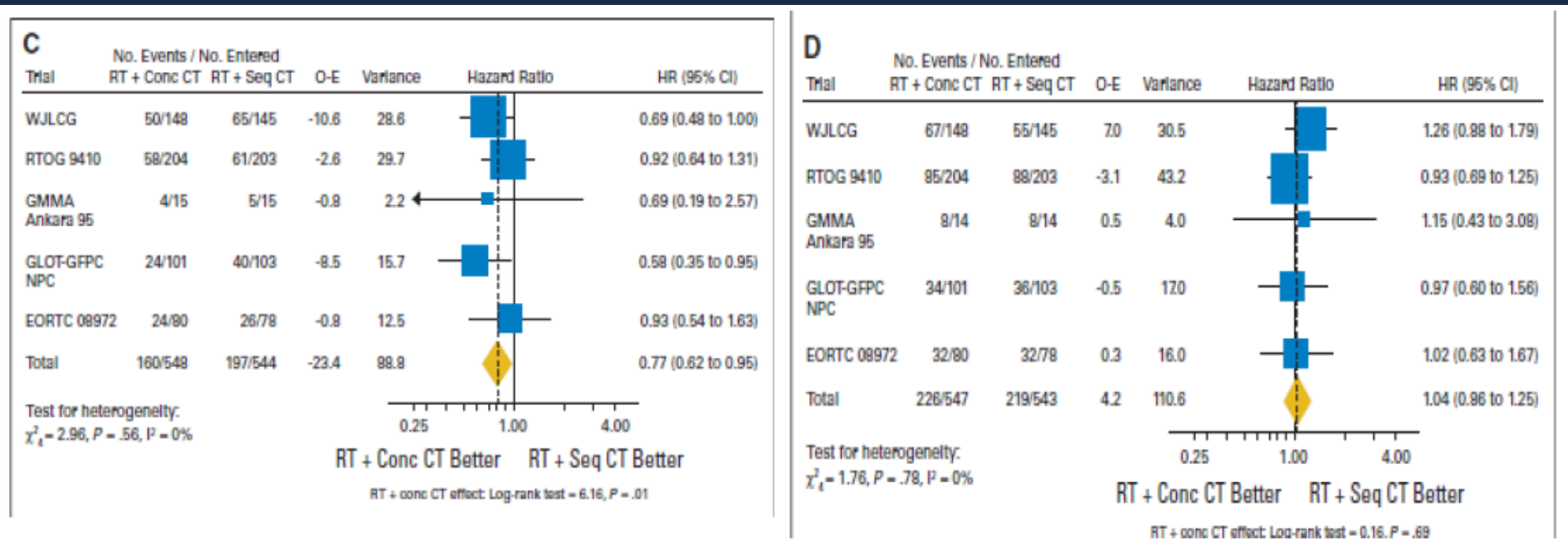




- 1205 patients pooled
- Median f/u 6 years
- OS benefit with concurrent chemo RT (HR 0.84, SS); 3-years absolute benefit 5.7% (18% to 24%), 5-years 4.5% (11% to 15%)

Auperin A, J Clin Oncol 2010 May 1;28(13):2181-2190

Concurrent vs Sequential – Meta-analysis



- Decrease in locoregional progression (HR 0.777, SS); absolute decrease of 6% at 5 years (35% to 29%)
- No difference in PFS (HR 0.9, p=0.07). No difference on distant progression (HR 1.04, NS), with 5-year rate of ~40%
- Toxicity: Acute Grade 3-4 esophageal toxicity worse (RR 4.9, SS), increase from 4% to 18%; no significant difference in acute pulmonary toxicity

Immunotherapy

Checkmate 227 - Ipi/Nivo vs Chemo - High Mutational Burden

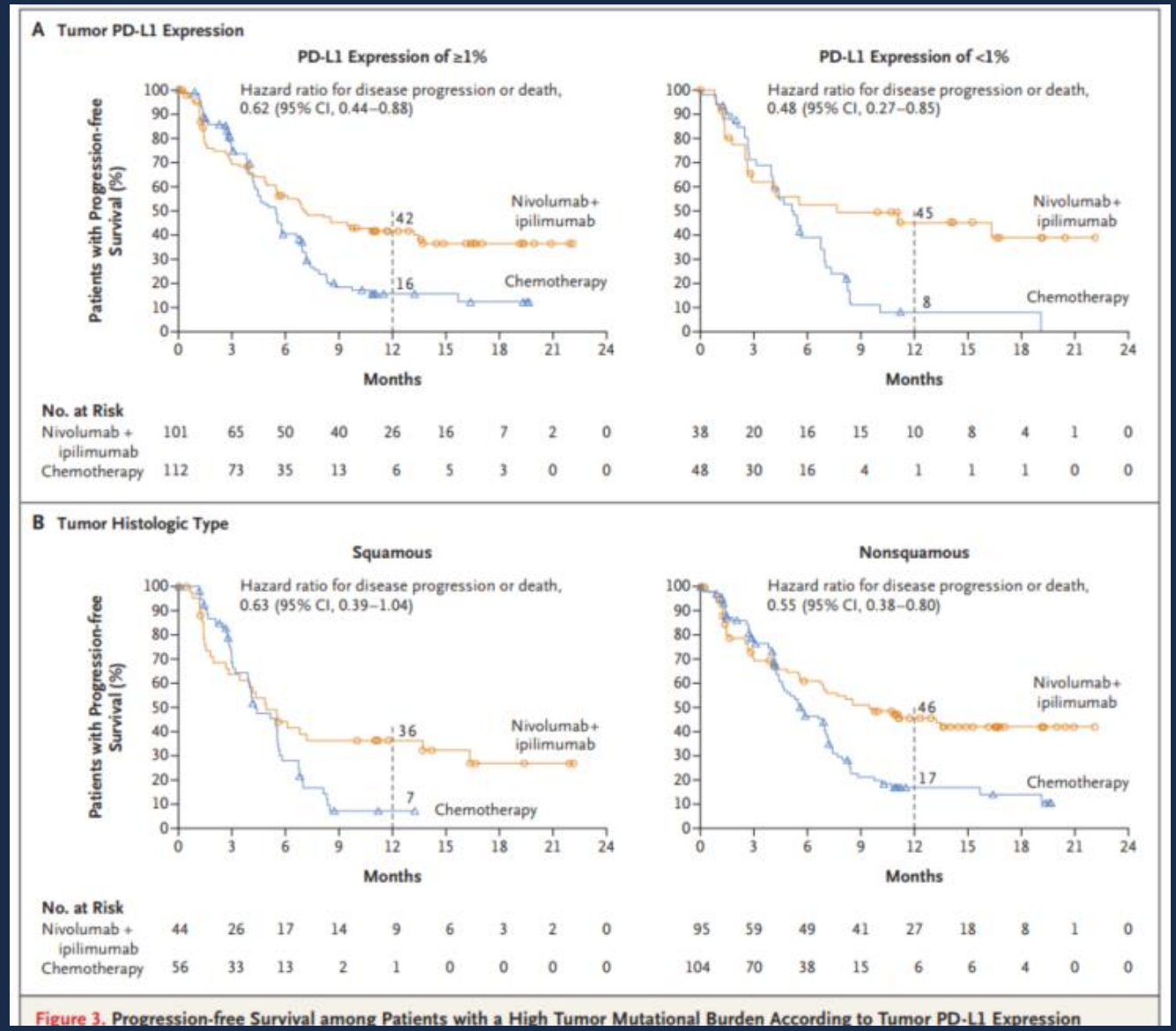


Figure 3. Progression-free Survival among Patients with a High Tumor Mutational Burden According to Tumor PD-L1 Expression

Hellman NEJM 2018

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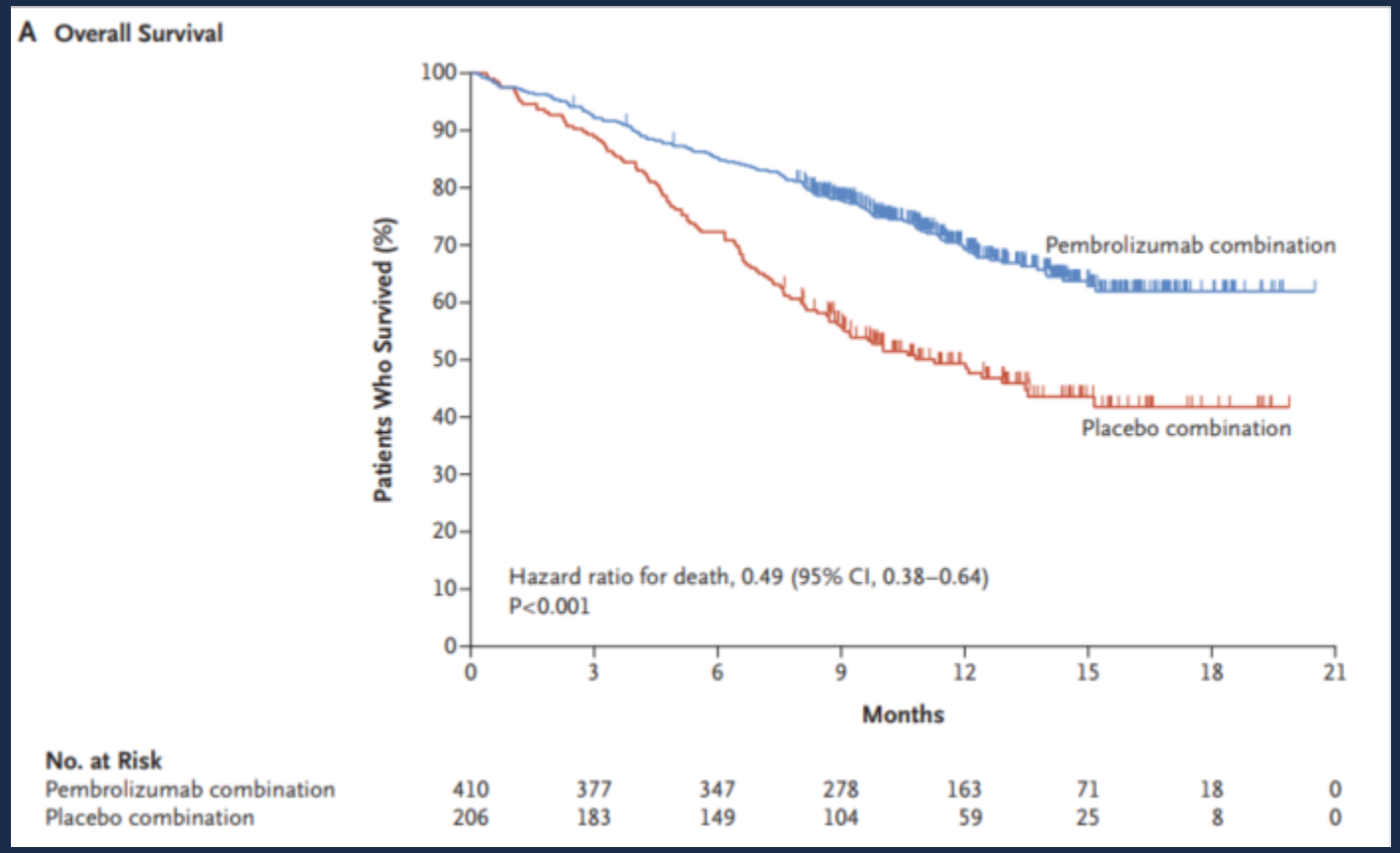
Keynote 189 – chemo pembro vs chemo



Gandhi NEJM 2018

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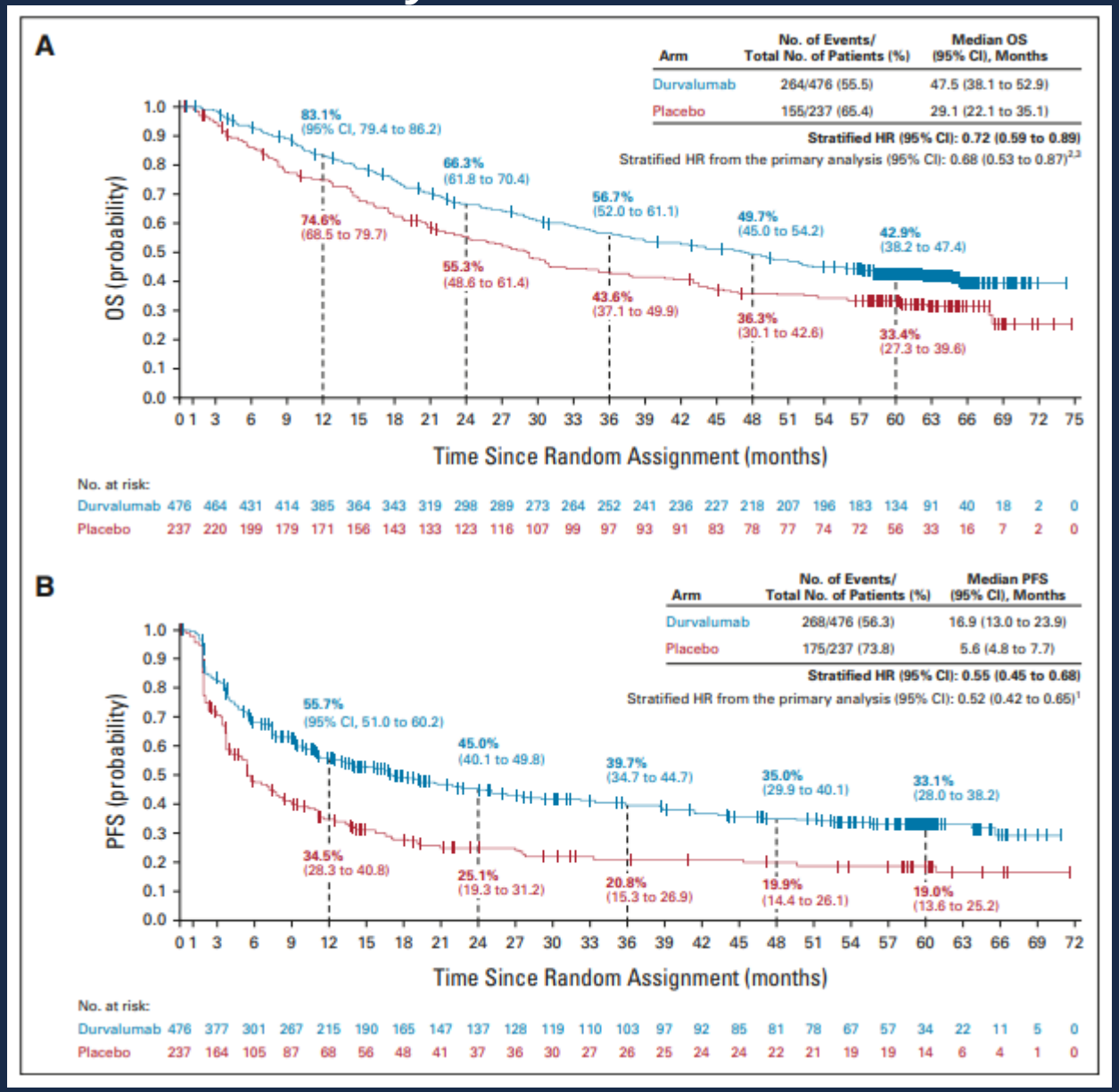
PACIFIC Trial - 5 year data



Antonia NEJM 2016
Spigel JCO 2022

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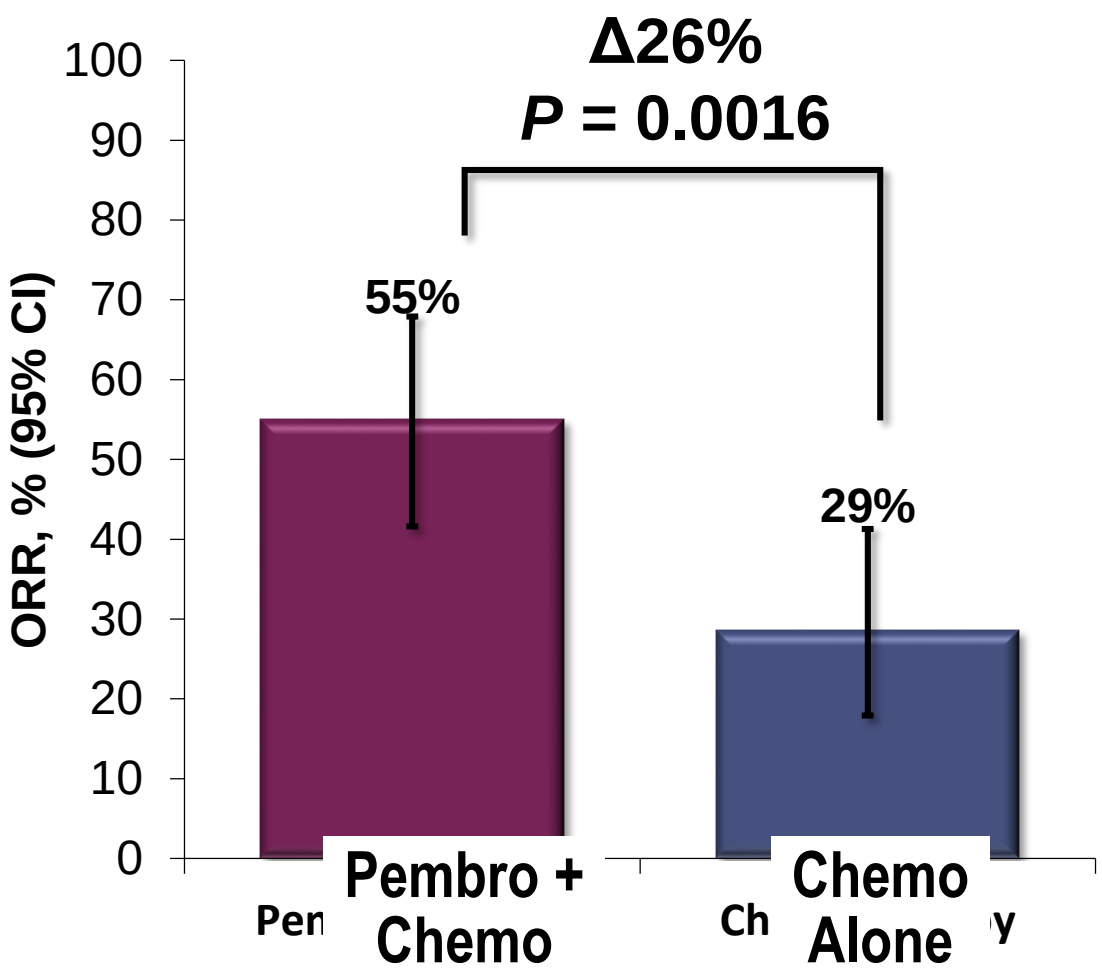
Keynote 21: Confirmed Objective Response Rate

(RECIST v1.1 by Blinded, Independent Central Review)



	Pembro + Chemo Responders n = 33	Chemo Alone Responders n = 18
TTR, mo median (range)	1.5 (1.2-12.3)	2.7 (1.1-4.7)
DOR, mo median (range)	NR (1.4+-13.0+)	NR (1.4+-15.2+)
Ongoing response,[a] n (%)	29 (88)	14 (78)

DOR = duration of response; TTR = time to response.

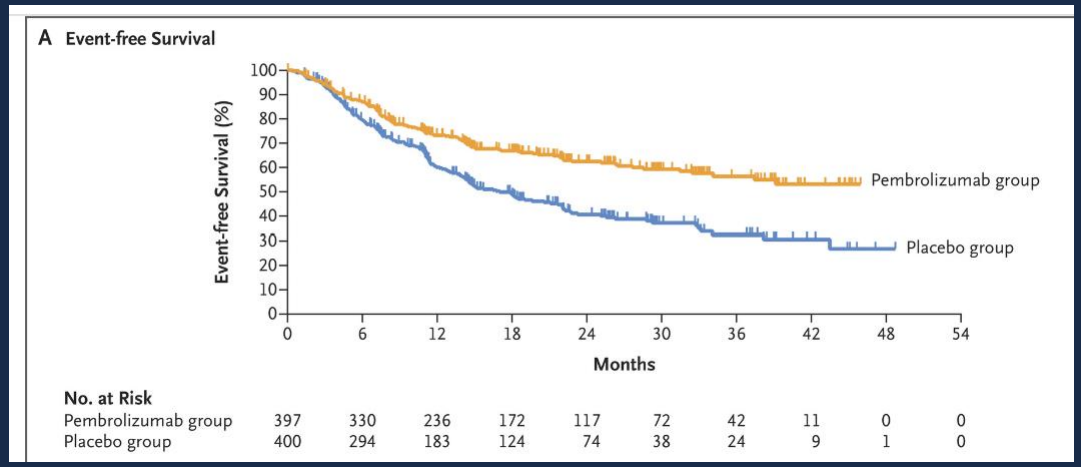
[a]Alive without subsequent disease progression.

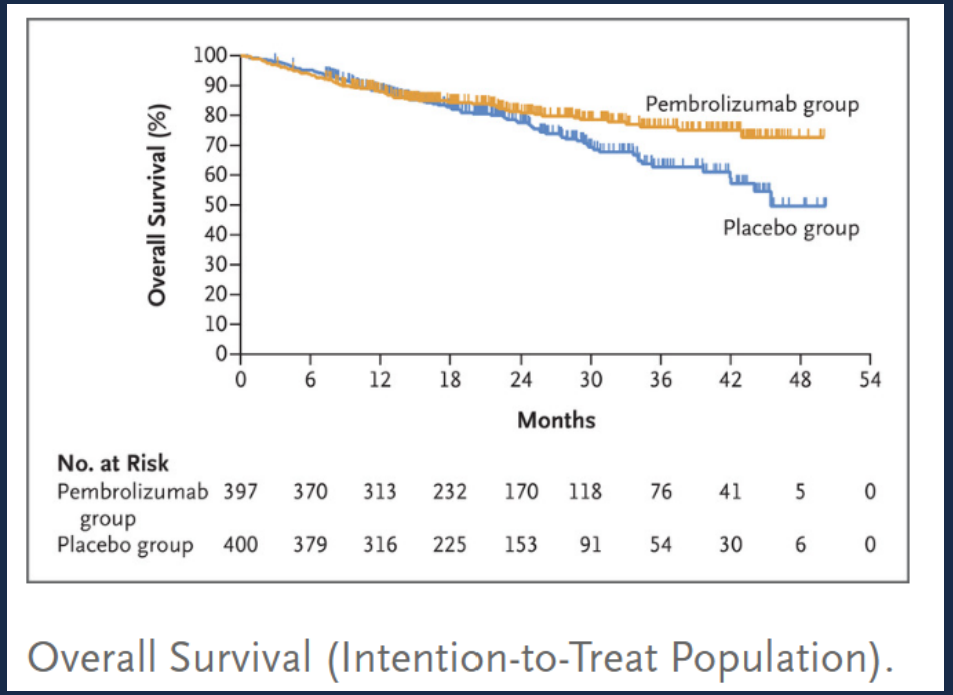
Data cut-off: August 8, 2016.

Keychain 671 – neoadj ChemoPembro

Table 1. Demographic and Disease Characteristics of the Participants at Baseline (Intention-to-Treat Population).*

Characteristic	Pembrolizumab Group (N=397)	Placebo Group (N=400)
III	279 (70.3)	279 (69.8)
IIIA	217 (54.7)	225 (56.2)
IIIB	62 (15.6)	54 (13.5)
Tumor stage — no. (%)		
T1	55 (13.9)	61 (15.2)
T2	106 (26.7)	126 (31.5)
T3	121 (30.5)	109 (27.2)
T4	115 (29.0)	104 (26.0)
Node stage — no. (%)		
N0	148 (37.3)	142 (35.5)
N1	81 (20.4)	71 (17.8)
N2	168 (42.3)	187 (46.8)
Histologic features — no. (%)		
Nonsquamous	226 (56.9)	227 (56.8)
Squamous	171 (43.1)	173 (43.2)
PD-L1 tumor proportion score — no. (%)		
≥50%	132 (33.2)	134 (33.5)
<50%	265 (66.8)	266 (66.5)





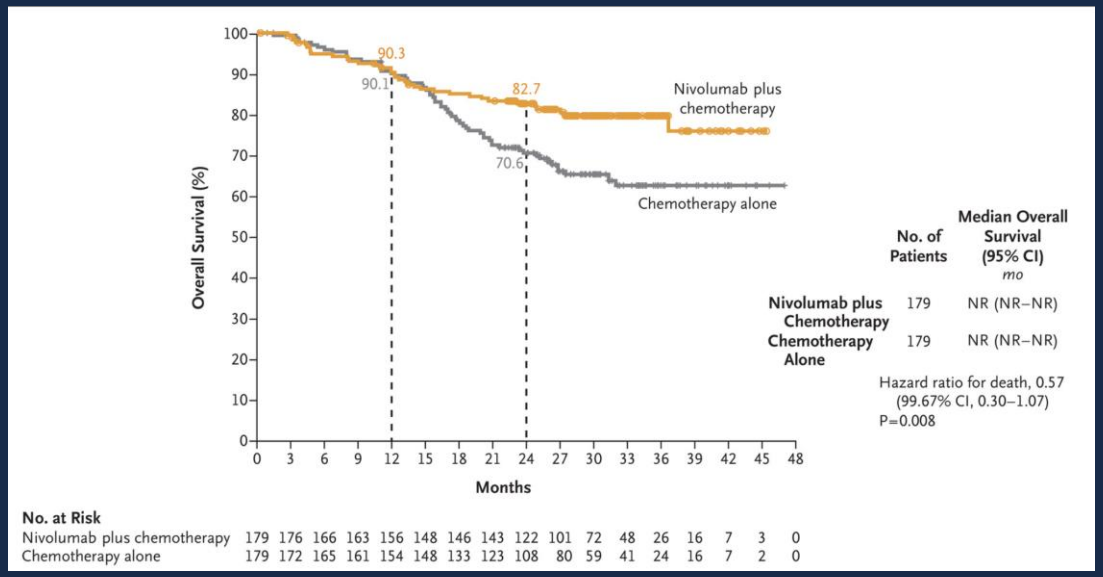
Overall Survival (Intention-to-Treat Population).

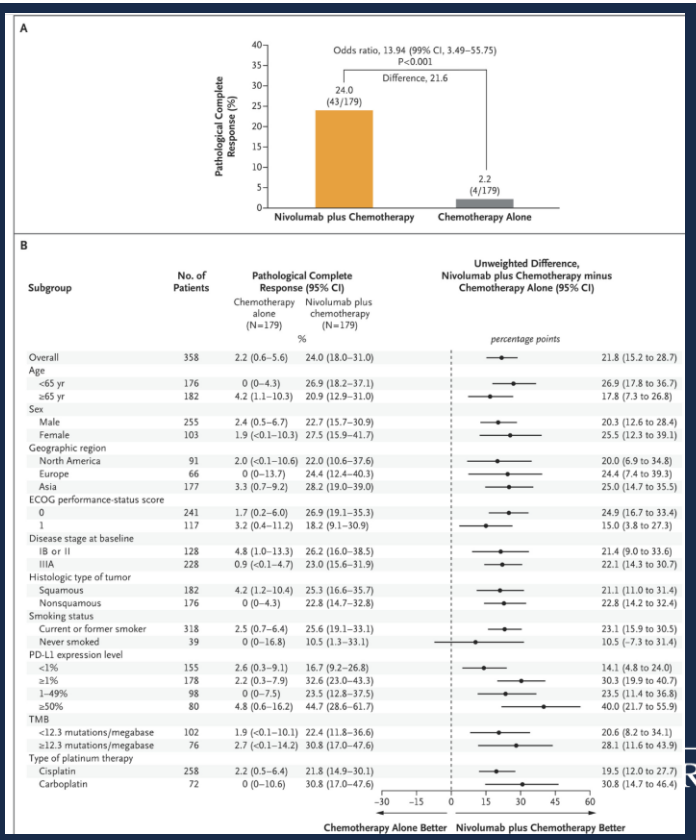
Wakelee NEJM 2023

Checkmate 816 – Neoadj ChemoNivo

Table 1. Characteristics of the Patients at Baseline.

Characteristic	Nivolumab plus Chemotherapy (N=179)	Chemotherapy Alone (N=179)
IB or II	65 (36.3)	62 (34.6)
IIIA	113 (63.1)	115 (64.2)
Histologic type of tumor — no. (%)		
Squamous	87 (48.6)	95 (53.1)
Nonsquamous	92 (51.4)	84 (46.9)
Smoking status — no. (%)§		
Never smoked	19 (10.6)	20 (11.2)
Current or former smoker	160 (89.4)	158 (88.3)
PD-L1 expression level — no. (%)¶		
Could not be evaluated	12 (6.7)	13 (7.3)
<1%	78 (43.6)	77 (43.0)
≥1%	89 (49.7)	89 (49.7)
1–49%	51 (28.5)	47 (26.3)
≥50%	38 (21.2)	42 (23.5)
Tumor mutational burden — no. (%)‖		
Could not be evaluated or was not reported	91 (50.8)	89 (49.7)
<12.3 mutations per megabase	49 (27.4)	53 (29.6)





Forde NEJM 2022

Adaura – EGFR mutant - osimirtinib

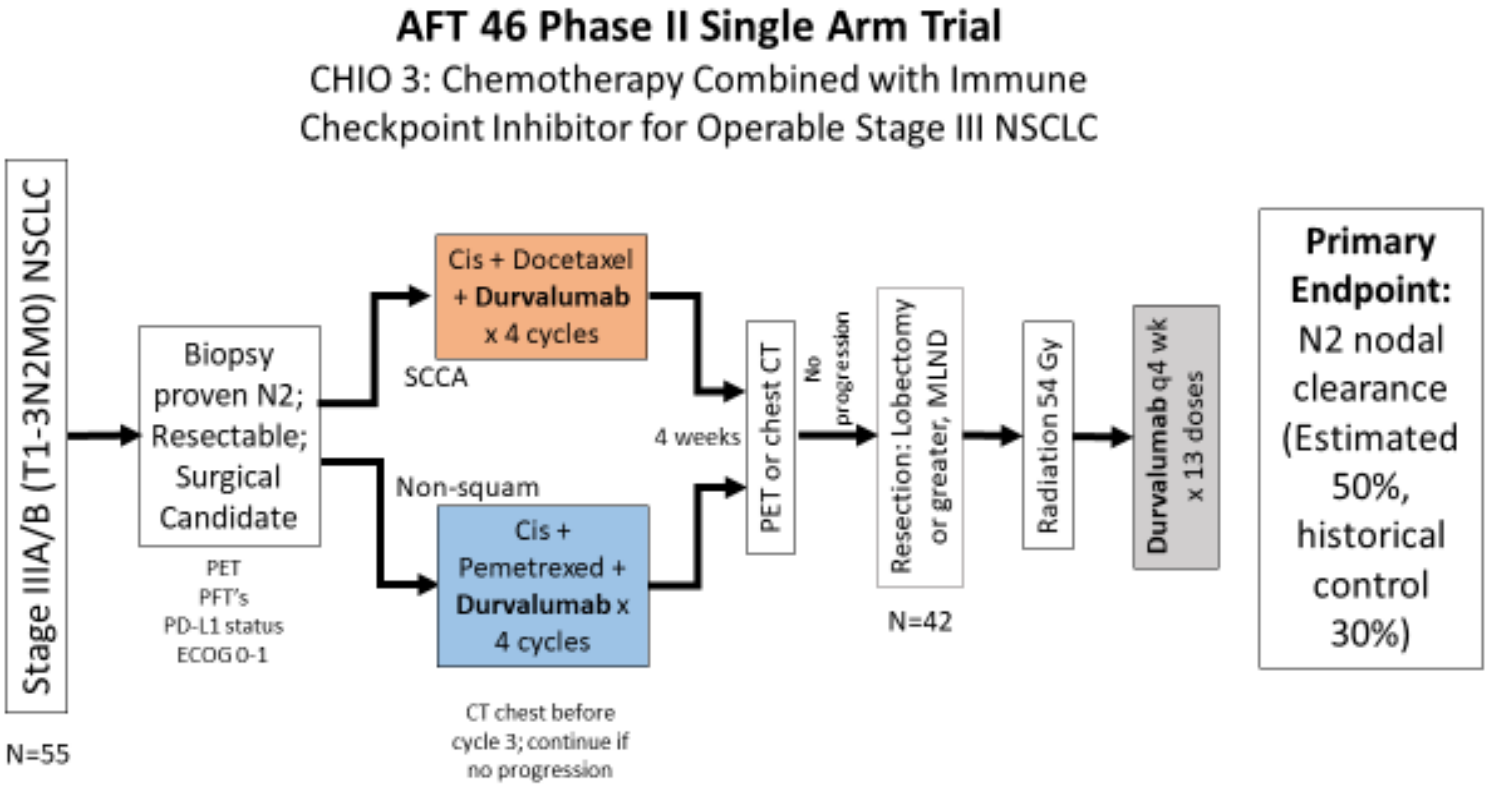
Summary of OS results: ADAURA[i]

	Tagrisso	Placebo
Stages II-IIIA (primary population)	**(n=233)**	**(n=237)**
Median OS (in months)	Not reached	Not reached
Hazard ratio (95.03% CI)	0.49 (0.33-0.73)	
p-value	0.0004	
OS rate (%) (five years) (95% CI)	85 (79-89)	73 (66-78)
Stage IB-IIIA (overall population)	**(n=339)**	**(n=343)**
Median OS (in months)	Not reached	Not reached
Hazard ratio (95.03% CI)	0.49 (0.34-0.70)	
p-value	<0.0001	
OS rate (%) (five years) (95% CI)	88 (83-91)	78 (73-82)

i The data cut-off date was 27 January, 2023.

Tsuboi NEJM 2023

Study Schema



L Martin, J Patel, J Urbanic

How is this different from CM816?

- Stage 3 patients only
- Endpoint is N2 nodal clearance
- 4 cycles instead of 3 for induction
- Will look at roll of adjuvant IO (Durva) for a year post resection in this higher risk population
  - Patients can’t get this regimen outside of this trial

If Immunotherapy is So Good – How Good does the RT need to be???

- The Holy Grail (other than prevention)
  - Curative non-toxic treatment.

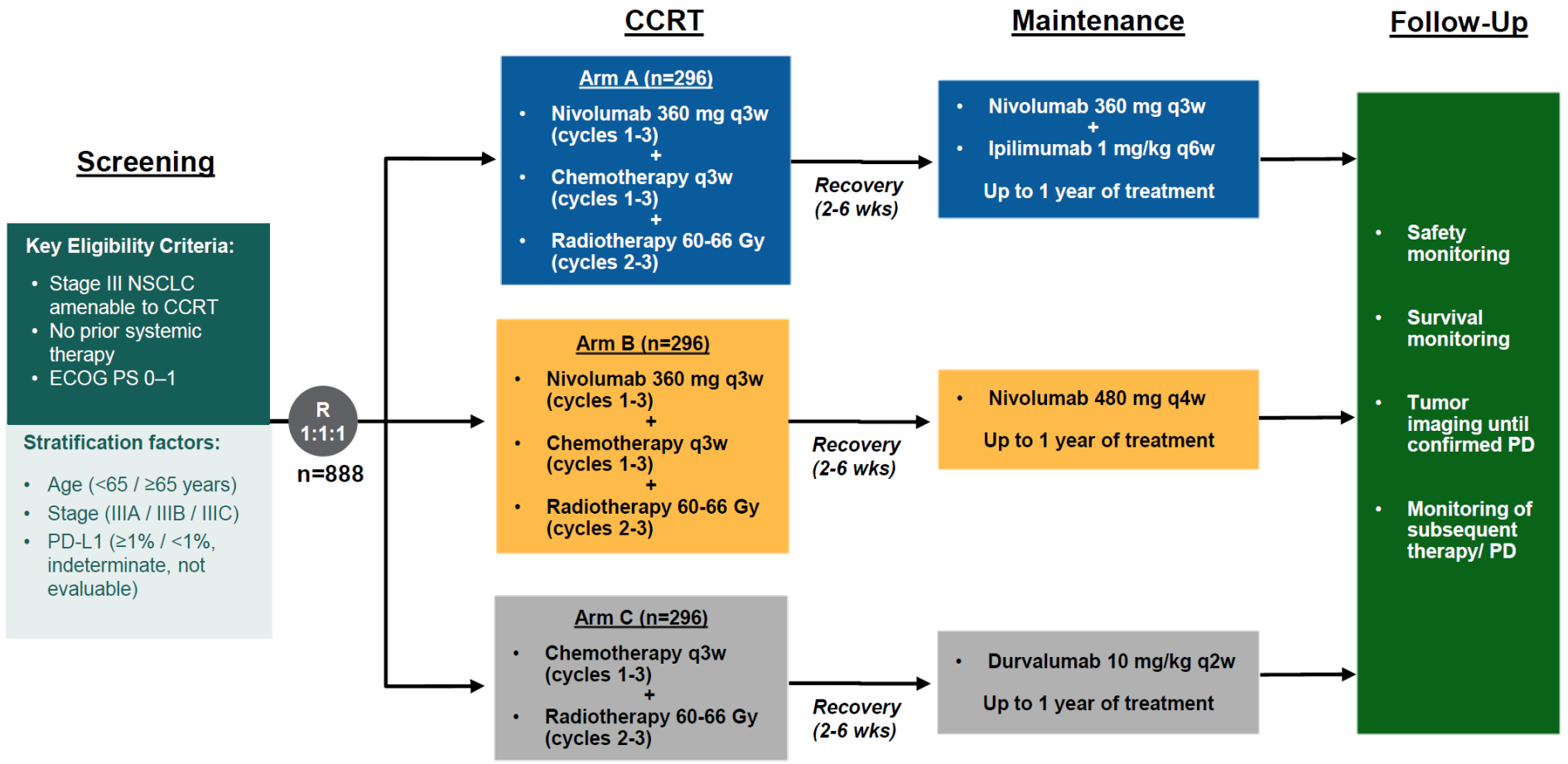
- If we can salvage with immunotherapy OR if we can augment RT –
  - Perhaps we can dial back the RT??????

  - Food for thought.

NSCLC
CheckMate 73L
CHECKpoint pathway and nivoluMAb clinical Trial Evaluation

Study Design

CA209-73L

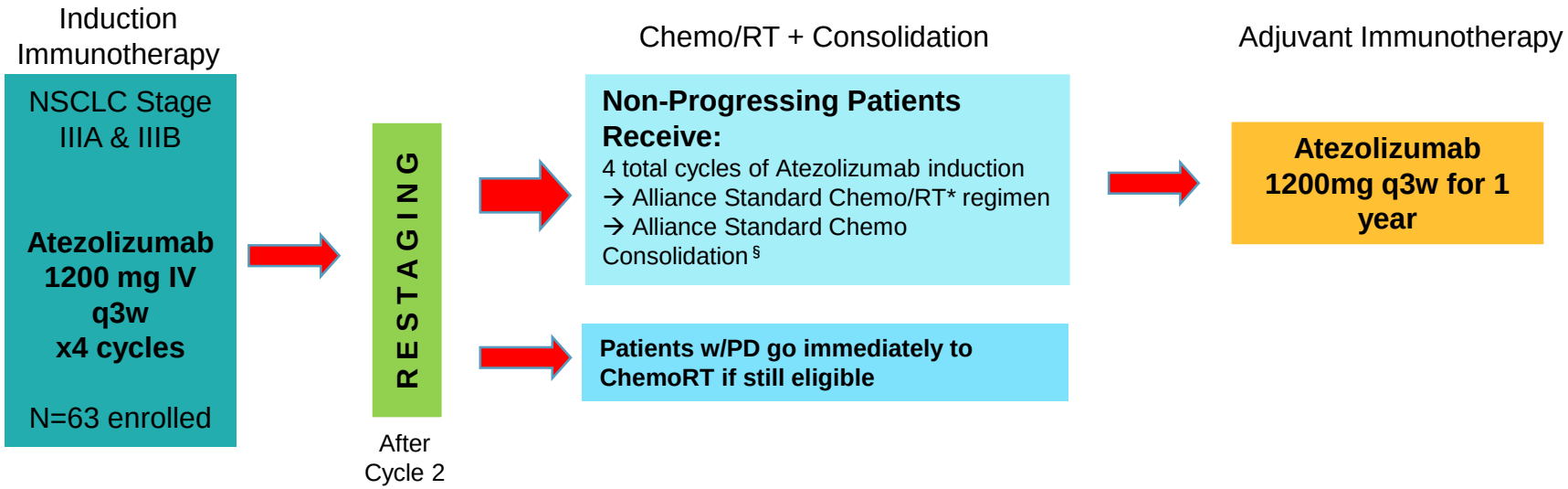


Primary Analysis:

- **PFS** per RECIST 1.1 (blinded central review) for **Arm A vs. Arm C**
- **OS** for **Arm A vs. Arm C**

Estimated Start Date: August, 2019

Alliance Foundation Trial (AFT-16) Chemoradiation in Stage III Unresectable NSCLC



*Chemo/RT= carboplatin (AUC2) + paclitaxel 50 mg/m2 IV weekly x6 cycles +60 Gy qd x 30fxn

§ Consolidation chemotherapy = carboplatin AUC6 + paclitaxel 200 mg/m2 IV q21 days x 2 cycels

ORR=objective response rate; PD=progressive disease; RT=radiotherapy; QoL=quality of life

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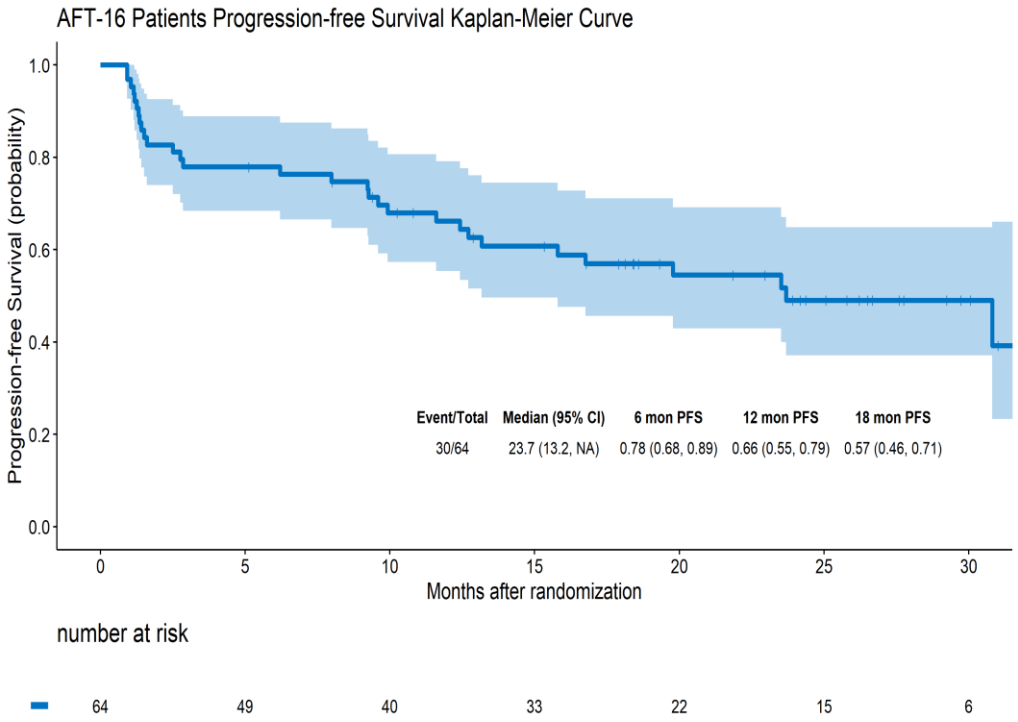
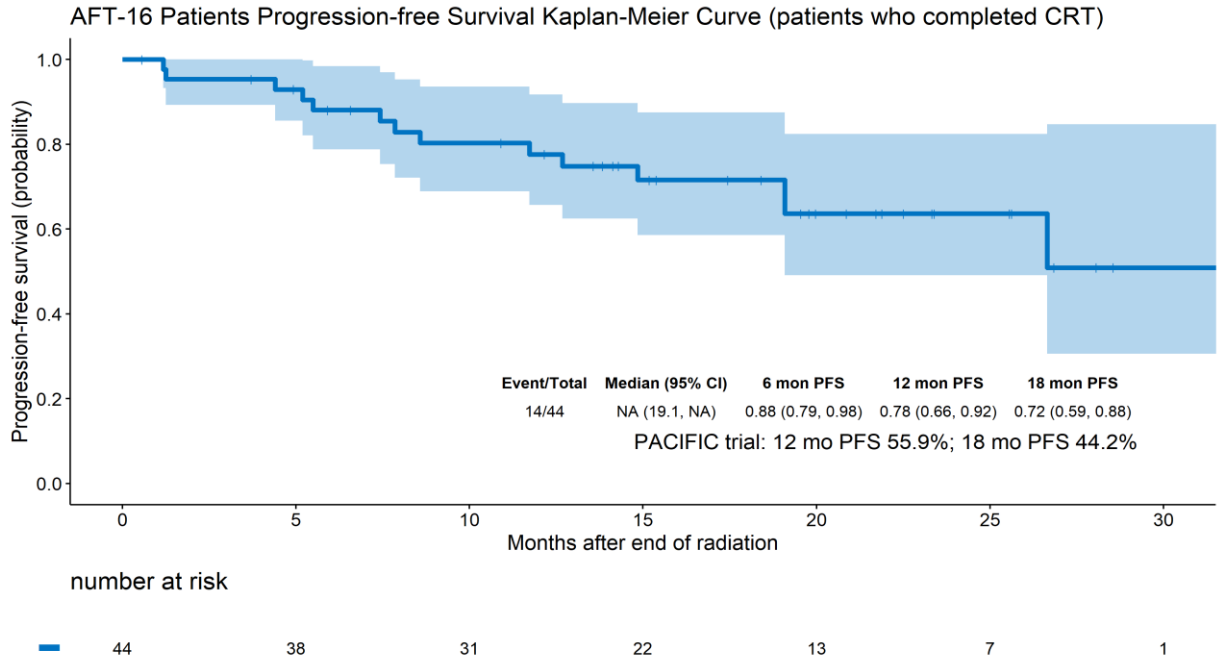
AFT-16 Outcomes

Median f/u 25.1 mo

PFS 23.7 mo

- PACIFIC Durva Arm PFS at 18 mo = 44.2%
- AFT-16 PFS at 18 mo from CRT = 72%





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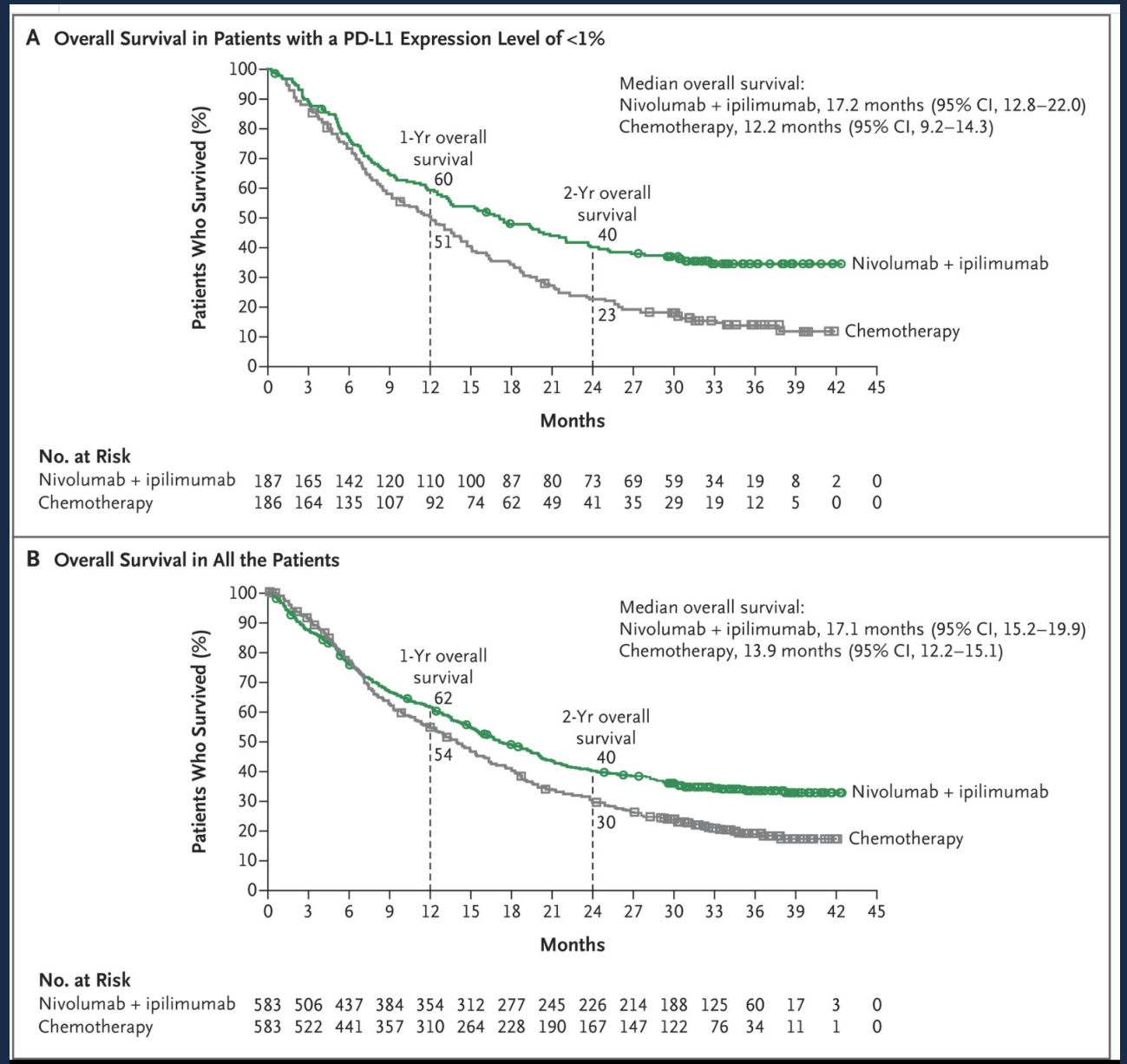
Ipi/Nivo vs Chemo – Stage 4



Hellmann NEJM 2019

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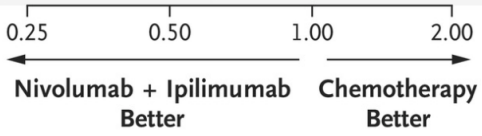
Ipi / Nivo Checkmate 227

Subgroup	No. of Patients	Median Overall Survival		Unstratified Hazard Ratio for Death (95% CI)
		Nivolumab + ipilimumab (N=583)	Chemotherapy (N=583)	
		months		
Randomized Groups				
PD-L1				
All randomized	1166	17.1	13.9	0.73 (0.64–0.84)
<1%	373	17.2	12.2	0.62 (0.49–0.79)
≥1%	793	17.1	14.9	0.79 (0.65–0.96)
Additional Exploratory Subgroup Analyses				
PD-L1				
1–49%	396	15.1	15.1	0.94 (0.75–1.18)
≥50%	397	21.2	14.0	0.70 (0.55–0.90)
Tumor mutational burden				
Low, <10 mut/Mb	380	16.2	12.6	0.75 (0.59–0.94)
High, ≥10 mut/Mb	299	23.0	16.4	0.68 (0.51–0.91)
PD-L1 and tumor mutational burden (mut/Mb) combined				
PD-L1 <1%				
Tumor mutational burden <10	111	15.5	13.0	0.69 (0.46–1.05)
Tumor mutational burden ≥10	86	20.4	11.2	0.51 (0.30–0.87)
PD-L1 ≥1%				
Tumor mutational burden <10	269	16.2	12.1	0.78 (0.59–1.02)
Tumor mutational burden ≥10	213	24.4	18.1	0.77 (0.54–1.09)
PD-L1 ≥50%				
Tumor mutational burden <10	125	18.1	8.1	0.67 (0.44–1.03)
Tumor mutational burden ≥10	111	NR	17.2	0.63 (0.37–1.07)



Hellmann NEJM 2019

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Cityscape trial – Atezo + tiragolumab; stage 4 NSCLC

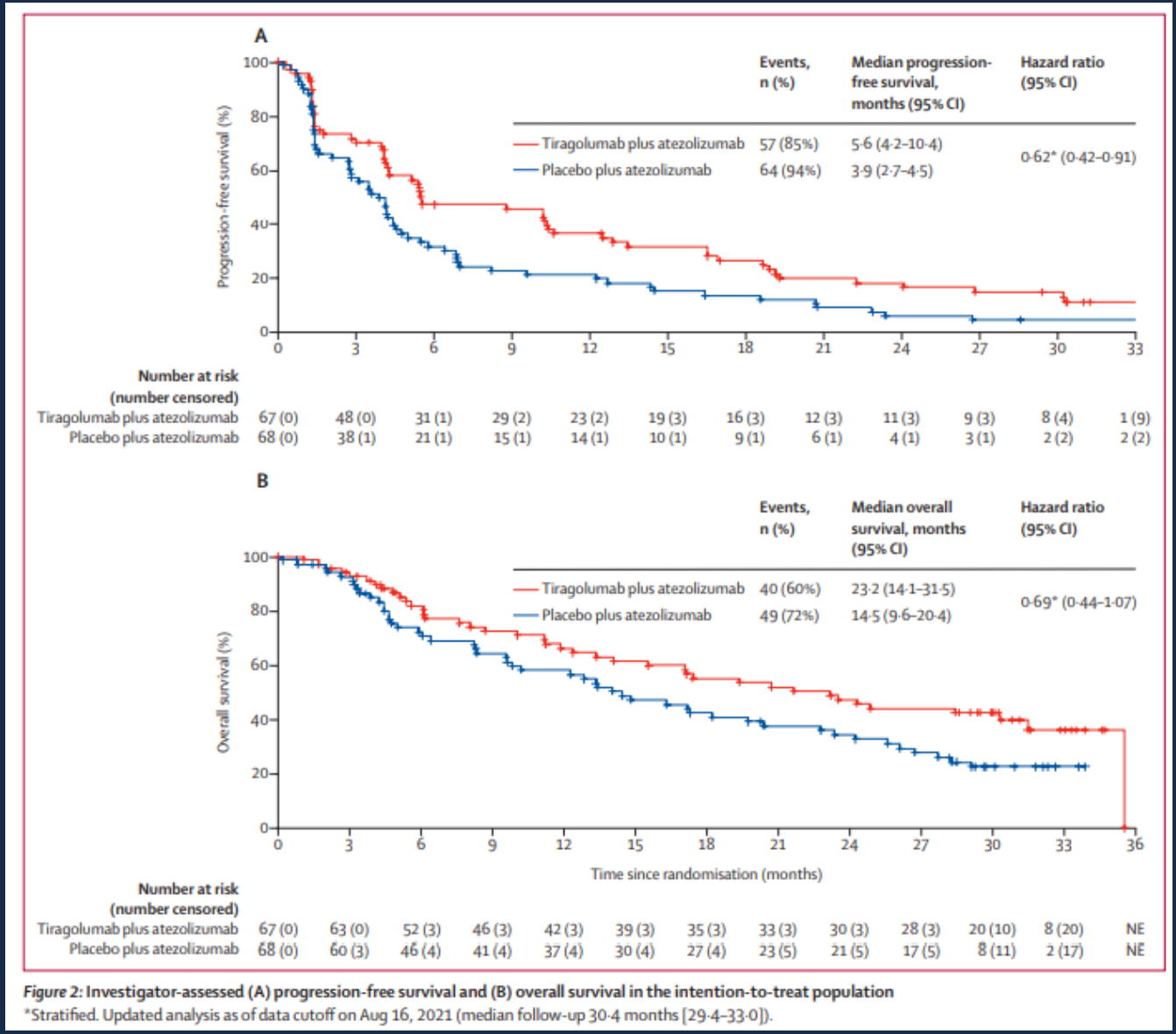

Figure 2: **Investigator-assessed (A) progression-free survival and (B) overall survival in the intention-to-treat population**
*Stratified. Updated analysis as of data cutoff on Aug 16, 2021 (median follow-up 30·4 months [29·4–33·0]).

Chul Cho Lanc Onc 2022

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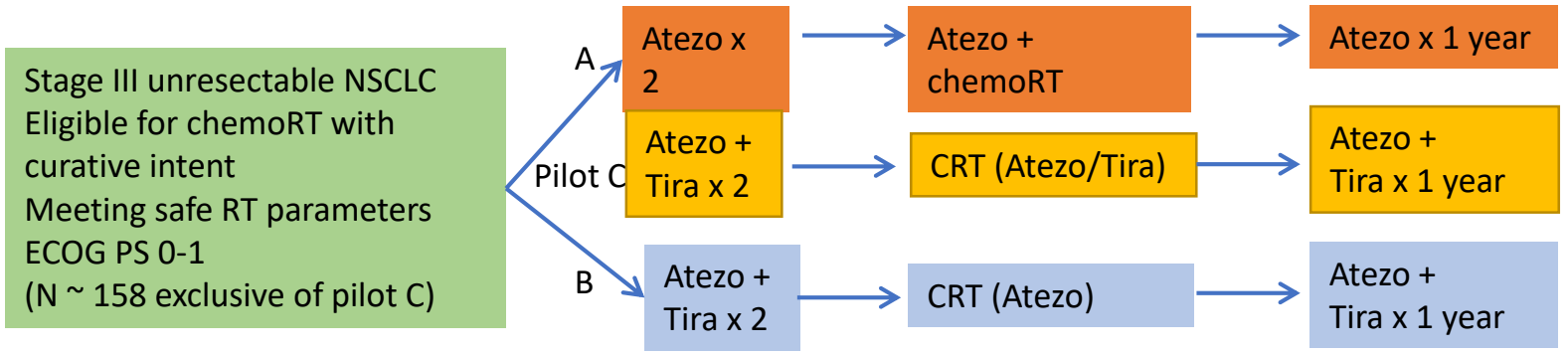
AFT-57 Randomized phase II trial of induction and adjuvant atezolizumab with or without tiragolumab concurrent with CRT in stage III NSCLC



- Open label randomized phase II
- 1:1 randomization stratifying for sex, histology, PD-L1
- Primary endpoint: PFS
- Secondary endpoints: OS, ORR, safety
- Correlative endpoints: PD-L1 correlation with clinical and immunologic benefit, tissue and blood based immune-related biomarkers

Metastatic Lung Cancer

Is the Current Treatment Paradigm Flawed?

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NSCLC

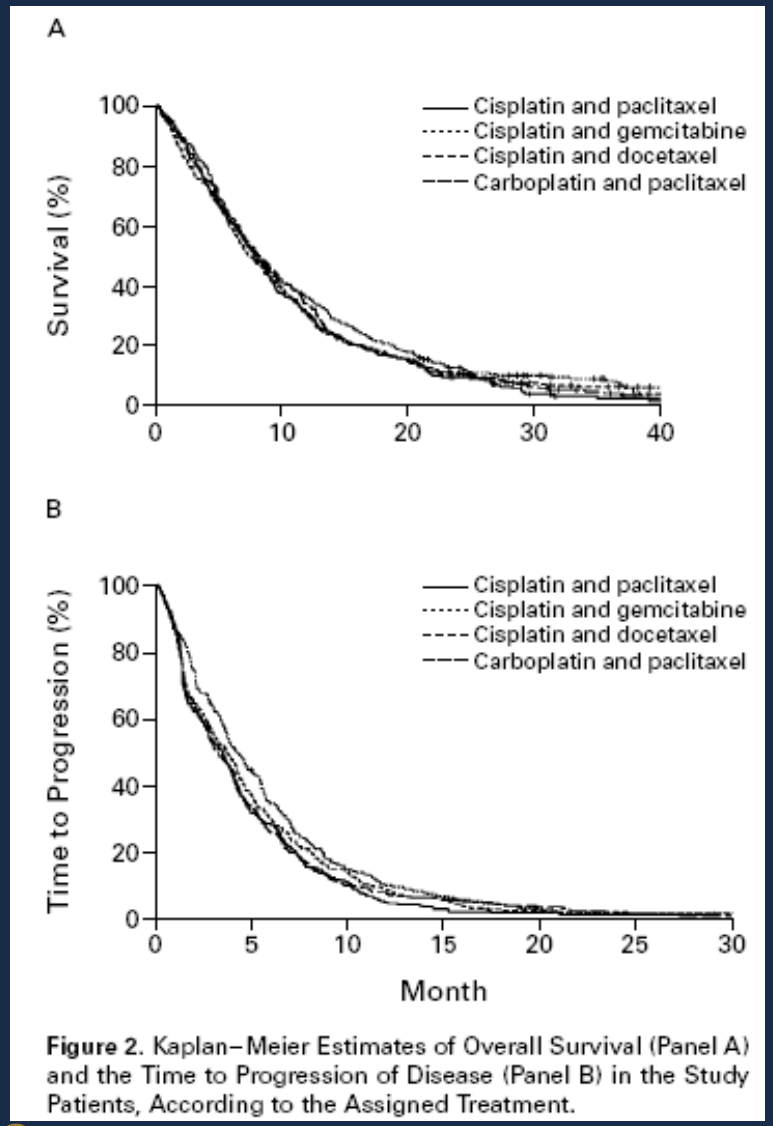

Figure 2. Kaplan–Meier Estimates of Overall Survival (Panel A) and the Time to Progression of Disease (Panel B) in the Study Patients, According to the Assigned Treatment.

Schiller NEJM 2002

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NSCLC – Solitary brain met

Study	OS influence by stage	Median OS	5 yr OS
Furak ‘05	No	19	24
Getman ‘04	No	9	19
Bonnette ’01	No	12	11
Billing ’01	Yes	24	21

NSCLC – Adrenal Met

Study	OS influence by timing	Median OS	5 yr OS
Raz ’11	No	19	34
Holy ’11	No	23	
Tanvetyanon ’08	Yes	S: 12; M 31	S 26; M 25
Porte ’01	No	24	33

NSCLC – Maintenance Chemotherapy

TABLE 2. Phase III Trials of "Switch" Maintenance Chemotherapy

First Author	No. of Patients Enrolled	Chemotherapy Comparison[a]	Median PFS	Median OS
Westeel[15]	573	Vinorelbine (N = 91)	5 mo	12.3 mo
		Observation (N = 90)	3 mo	12.3 mo
			HR = 0.77, p = 0.11	HR = 1.08, p = 0.65
Fidias[16]	566	Immediate Docetaxel (N = 153)	5.7 mo	12.3 mo
		Delayed Docetaxel (N = 156)	2.7 mo	9.7 mo
			p = 0.0001	p = 0.0853
Ciuleanu[17]	NA	Pemetrexed (N = 441)	4.0 mo[b]	13.4 mo
		Placebo (N = 222)	2.0 mo	10.6 mo
			HR = 0.60, p < 0.0001	HR = 0.79, p = 0.012
Nonsquamous (N = 481)		Pemetrexed	4.4 mo[b]	15.5 mo
		Placebo	1.8 mo	10.3 mo
			HR = 0.47, p < 0.0001	HR = 0.70, p = 0.002
Squamous (N = 182)		Pemetrexed	2.4 mo[b]	9.9 mo
		Placebo	2.5 mo	10.8 mo
			HR = 1.03, p = 0.896	HR = 1.07, p = 0.678

[a] N values represent number of patients randomized.
[b] PFS represents values from independent review.
PFS, progression-free survival; OS, overall survival; HR, hazard ratio; NA, not available.

2 month PFS and 5 month OS for adenocarcinoma

Stinchcombe JTO 2011

NSCLC – Ongoing Maintenance Trials

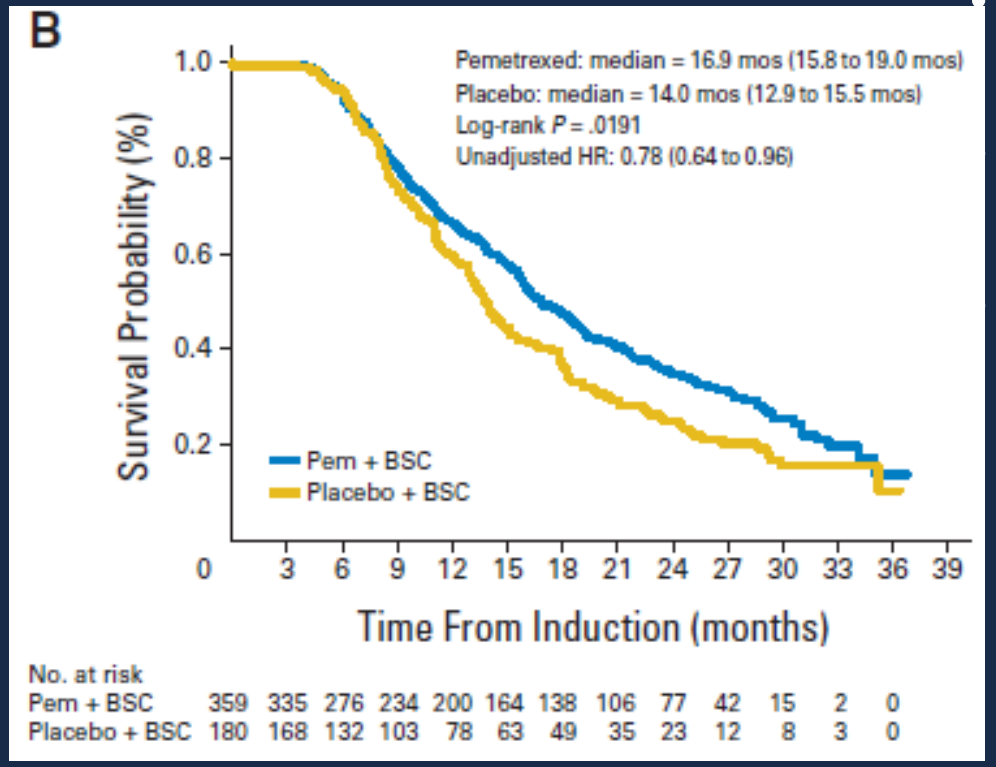
TABLE 4. Select Phase III Trials of Maintenance Therapy or Including Maintenance Therapy

NCT Trial No. (Name)	Initial Therapy		Comparison	Enrollment (No. Randomized)	Primary Endpoint
NCT00789373 (PARAMOUNT)	Cisplatin + pemetrexed × 4 cycle		Pemetrexed + BSC Placebo + BSC	900[41] (n = 558)	PFS
NCT01107626 (ECOG 5508)	Carboplatin, paclitaxel, bevacizumab × 4 cycles		Bevacizumab Pemetrexed Bevacizumab + pemetrexed	1282[42] (n = 897)	OS
NCT00961415 (AVAPERL1)	Cisplatin/pemetrexed + Bevacizumab		Bevacizumab Bevacizumab + pemetrexed	362	PFS
NCT00693992 (CALGB 30607)	Platinum based × 4 cycles		Sunitinib Placebo	244	PFS
NCT00762034[a] (Point Break)	Carboplatin, paclitaxel, and bevacizumab × 4 cycles[b]	→	Bevacizumab	900	OS
	Carboplatin, pemetrexed, and bevacizumab × 4 cycles[b]	→	Bevacizumab + pemetrexed		
NCT00946712[a] (SWOG 0819)	Carboplatin, paclitaxel + bevacizumab × 6 cycles[a]	→	Bevacizumab	1546	OS
	Carboplatin, paclitaxel, bevacizumab + cetuximab × 6 cycles	→	Bevacizumab + cetuximab		
NCT 00948675[a]	Carboplatin and pemetrexed 4 × cycles[a]	→	Pemetrexed	360	PFS[c]
	Carboplatin, paclitaxel, and bevacizumab	→	Bevacizumab		

[a] Patients randomized at the start of therapy.
[b] Patients stratified based on eligibility for bevacizumab; patients ineligible will receive carboplatin and paclitaxel with and without cetuximab.
[c] Endpoint progression-free survival without grade 4 toxicity.
ECOG, Eastern Cooperative Oncology Group; SWOG, Southwest Oncology Group; CALGB, Cancer and Leukemia Group B; OS, overall survival; PFS, progression-free survival; BSC, best supportive care.

Stinchcombe – JTO 2011

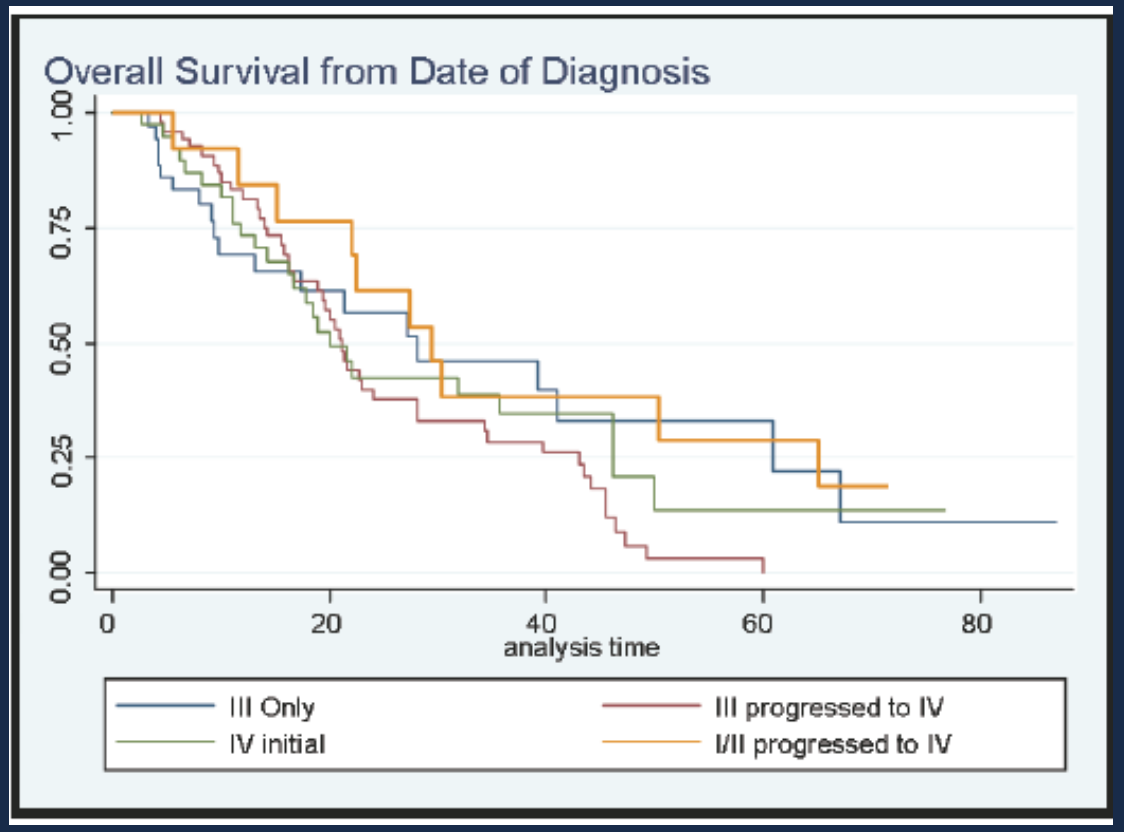
PARAMOUNT maint chemo



- 939 patients enrolled in induction phase
- 335 patient excluded due to death, progression or AE
- 539 patients randomized to maintenance pemetrexed or placebo

Paz-Ares JCO 2013

Outcome Stage 3 vs Stage 4 Lung



Cheruvu Rad Oncol 2011

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Patterns of Failure – Metastatic NSCLC

- 64 patients - metastatic NSCLC
  - 34 patient with “oligo” disease – potentially eligible for SBRT
- TTP – 4 months
- Patterns of failure:

	All	SBRT eligible
Local	**64%**	**68%**
Distant	**9%**	**14%**
L + D	**27%**	**18%**

New lung or liver lesions most common distant site

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Rusthoven Acta Oncol 2009

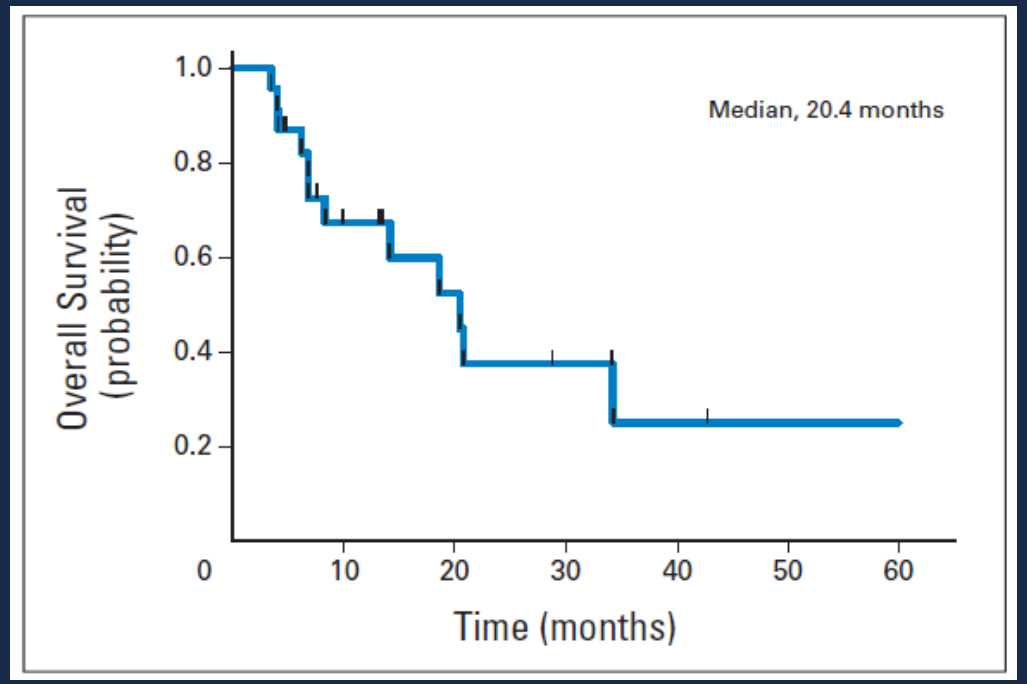
UTSW /UC Lung Consolidation

- 2007-2013 24 patient Phase II Study
  - Progression on first line chemotherapy
  - “SBRT” to residual disease with erlotinib

Table 2. SBRT Treatment Patterns

Treatment Pattern	No.	%
SBRT sites treated per patient		
1	8	33
2	8	33
3	5	21
4	2	9
5	1	4
SBRT courses to specific sites		
18	Lungs (35% of 52 sites treated)	
13	Mediastinum/hilum (25)	
7	Adrenals (13)	
6	Bone/spine/chest wall (13)	
4	Liver/paracaval (8)	
3	Nonmediastinal lymph nodes (5)	
1	Kidney (1)	
Lesions treated with specific SBRT fractionation schemas		
21	3 fx to 27-33 Gy (40)	
21	5 fx to 35-40 Gy (40)	
10	1 fx to 19-20 Gy (20)	

Abbreviations: fx, fractions; SBRT, stereotactic body radiation therapy.



Median PFS 14.7m

Iynegar JCO 2015

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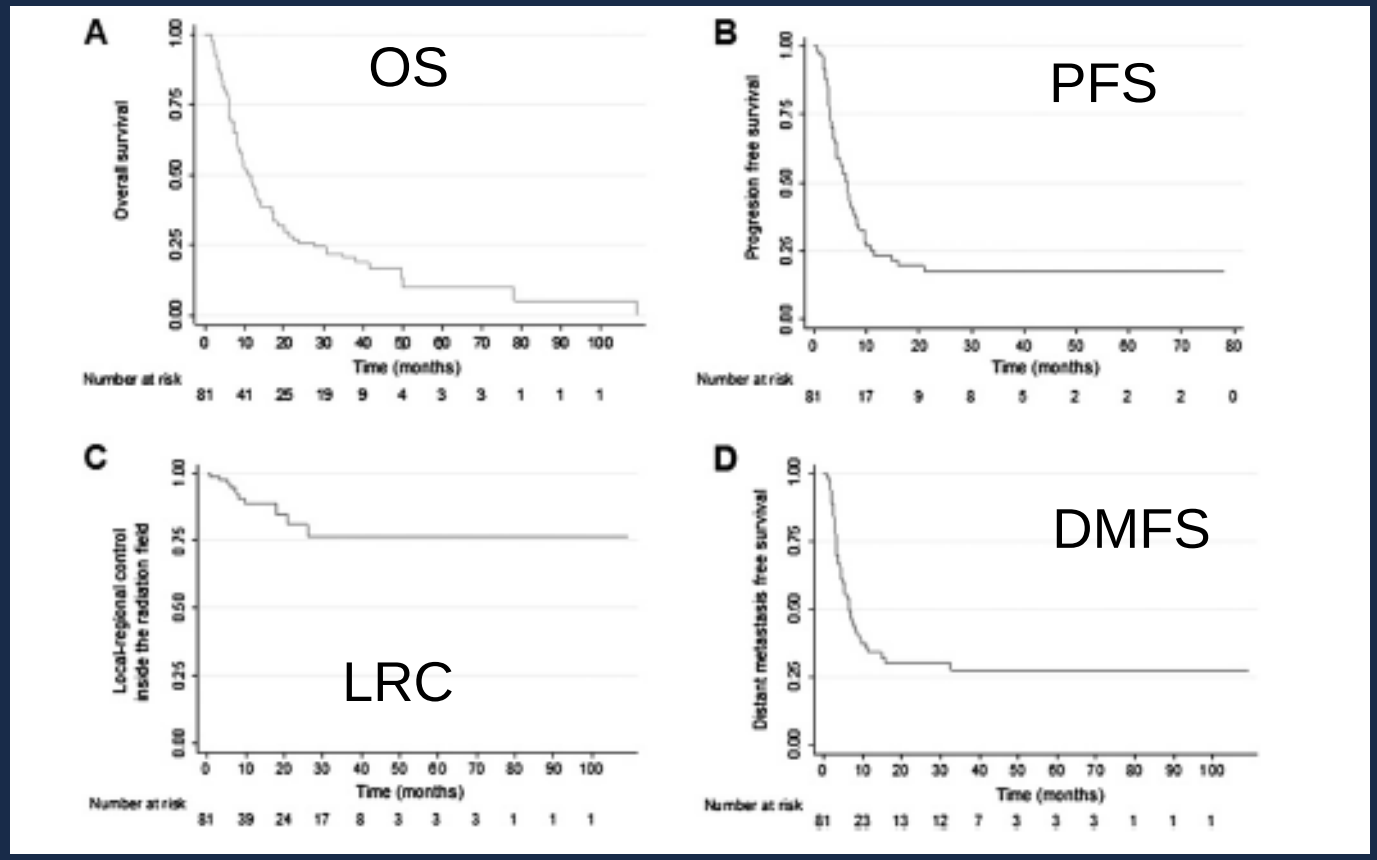
MDACC Oligomet

- 78 patients
- < 5 mets
- CRT to primary
- 44 patients tx to mets

- OS better >63 Gy



Lopez Guerra IJROBP 2012

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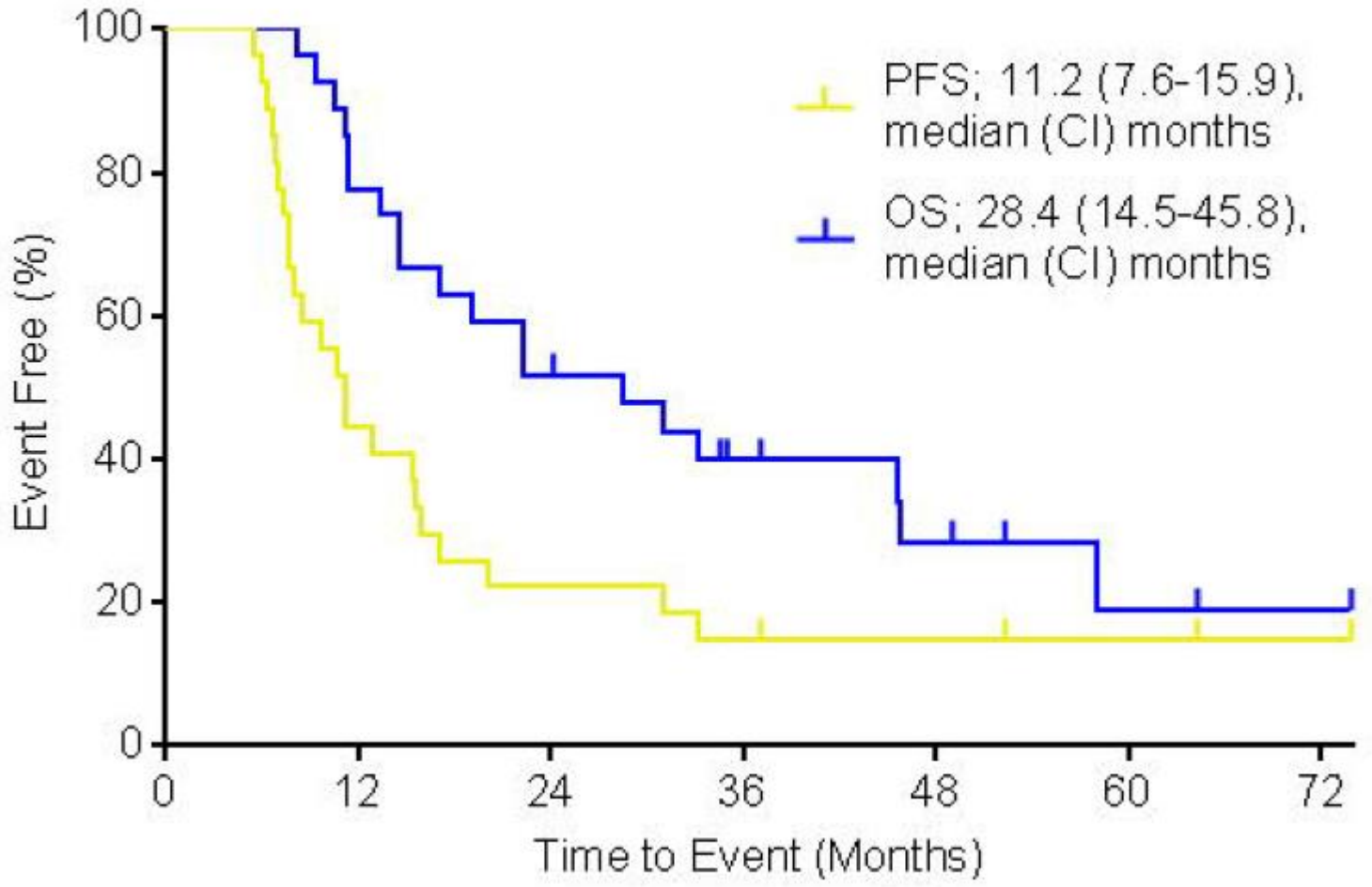
Wake 62110 – Phase 2 Lung Cancer Oligomet



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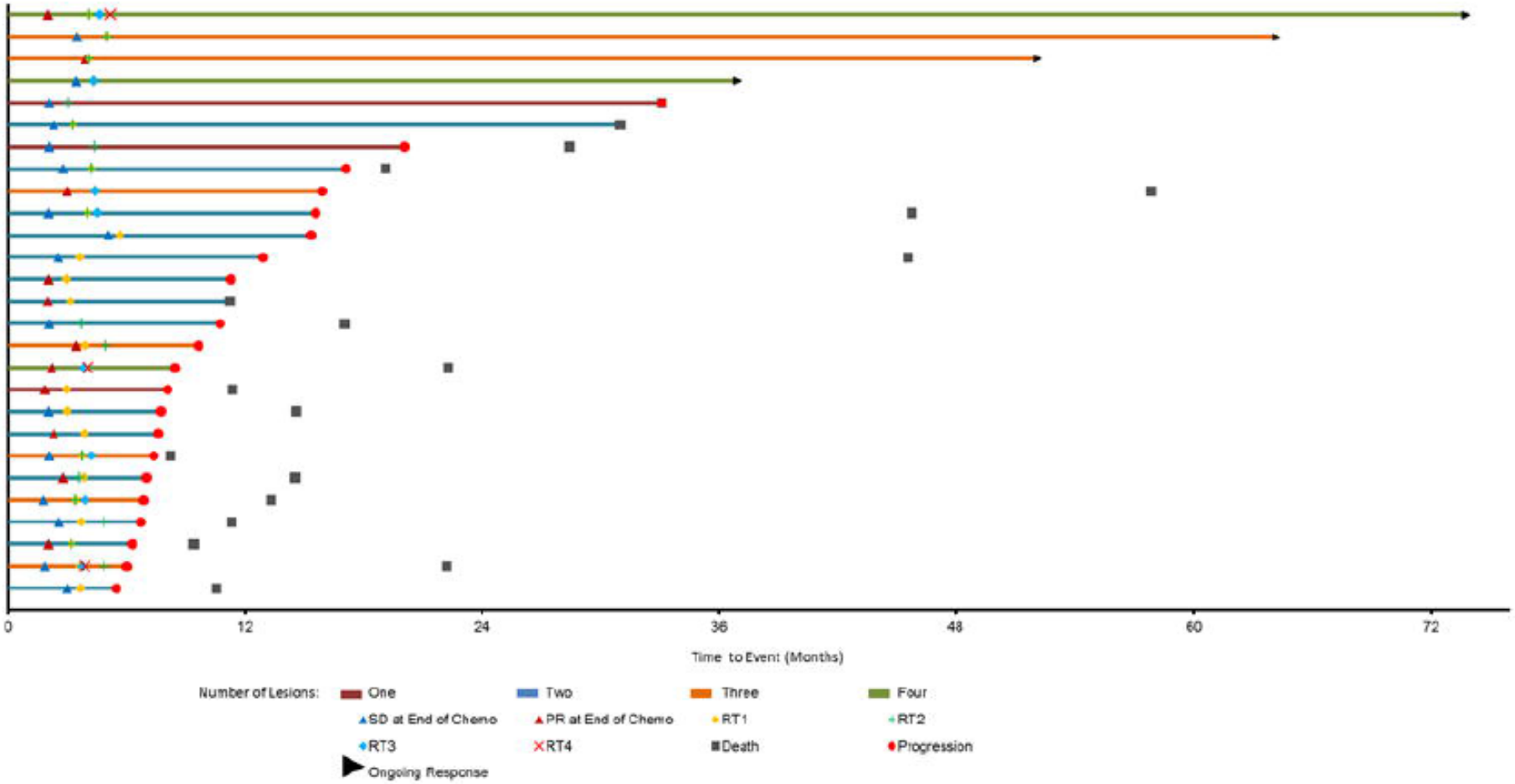
Wake 62110 – Phase 2 Lung Cancer Oligomet



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Schema of Phase II/III Study

Patients with metastatic NSCLC having completed 4 cycles of first-line/induction systemic therapy Restaging studies reveal no evidence of progression and limited (≤ 3 discrete sites) metastatic disease, all of which must be amenable to SBRT	STRATIFY	Histology: Squamous vs. Non-squamous	RANDOMIZE	Arm 1: Maintenance systemic therapy alone Arm 2: SBRT to all sites of metastases (≤ 3 discrete sites) plus irradiation of the primary site (SBRT or hypofractionated RT) followed by maintenance systemic therapy

Thank You

Time for Questions?

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