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Unresectable Locally Advanced NSCLC:
The Case for Targeted Therapy

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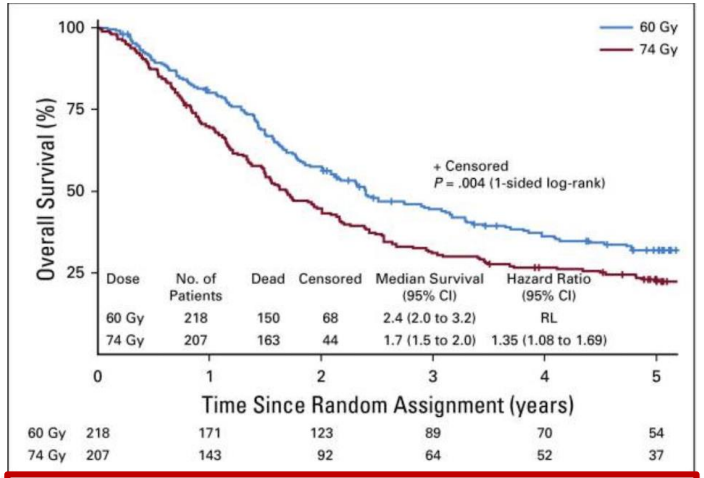
Disclosures

- Advisor: AbbVie, AnHeart, Astra Zeneca, Blueprint, Daiichi Sankyo, Genentech, Gileal, Janssen, Sanofi, Takeda
- Travel reimbursement: Daiichi Sankyo, Tempus

Locoregional Lung Cancer

- Stage III accounts for 20% of NSCLC at diagnosis
- Prior to immunotherapy era, RTOG 0617 confirmed weekly carbo/pac with 60Gy as a SOC



5-year OS 32.1% and PFS 18.3%

EORTC Lung Cancer Group Initiative 2023
Resectability for clinical trials

	N0	N1	N2 SINGLE (non-bulky, non-invasive)	N2 MULTI (non-bulky, non-invasive)	N2 BULKY[¶]	N2 INVASIVE	N3
T1-2	NOT STAGE III DISEASE	NOT STAGE III DISEASE	RESECTABLE	POTENTIALLY RESECTABLE*	UNCLEAR	UNRESECTABLE	UNRESECTABLE
T3 size / satellite / invasion	NOT STAGE III DISEASE	RESECTABLE	RESECTABLE	POTENTIALLY RESECTABLE*	UNRESECTABLE	UNRESECTABLE	UNRESECTABLE
T4 size / satellite	RESECTABLE	RESECTABLE	RESECTABLE	POTENTIALLY RESECTABLE*	UNRESECTABLE	UNRESECTABLE	UNRESECTABLE
T4 invasion	POTENTIALLY RESECTABLE[§]	POTENTIALLY RESECTABLE[§]	POTENTIALLY RESECTABLE[§]	POTENTIALLY RESECTABLE*[§]	UNRESECTABLE	UNRESECTABLE	UNRESECTABLE

Bradley, JCO 2020; Dingemans, WCLC 2023

The Supremacy of PACIFIC?

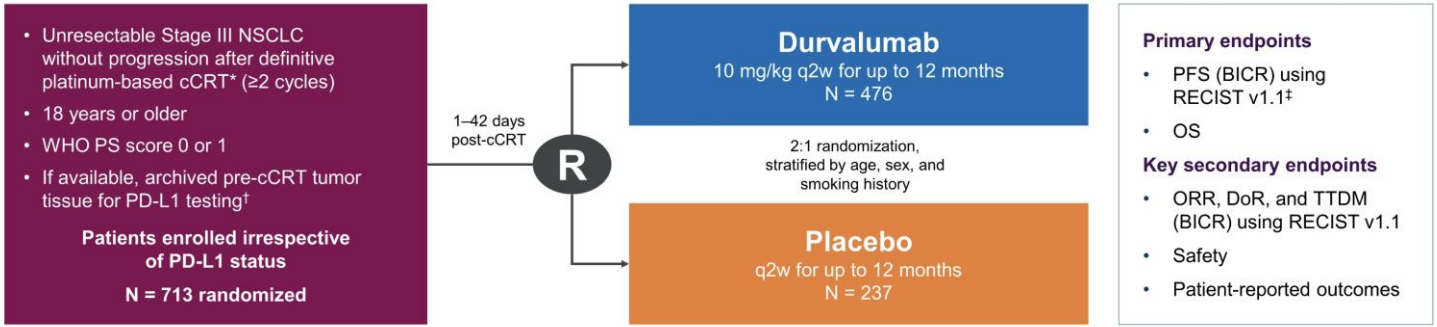
Is first ALWAYS best?

- Randomized Phase 3 Trial
- Beware of subsets
- Don’t fall for cross trial comparisons
- Be pragmatic

PACIFIC: Standard of Care

Spigel, JCO 2022

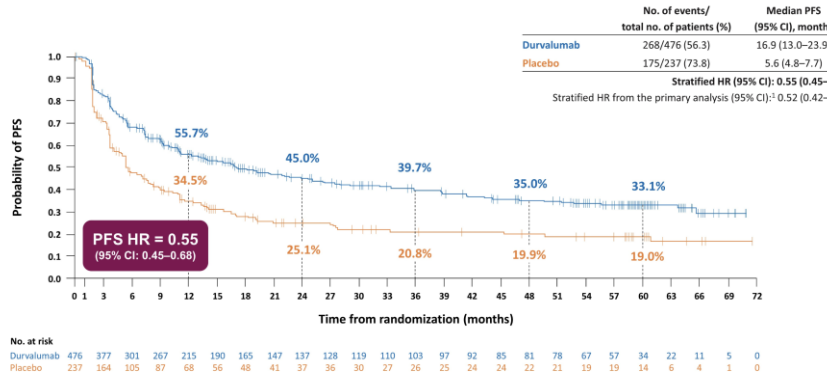
PACIFIC: Phase 3, Randomized, Double-blind, Placebo-controlled, Multicenter, International Trial



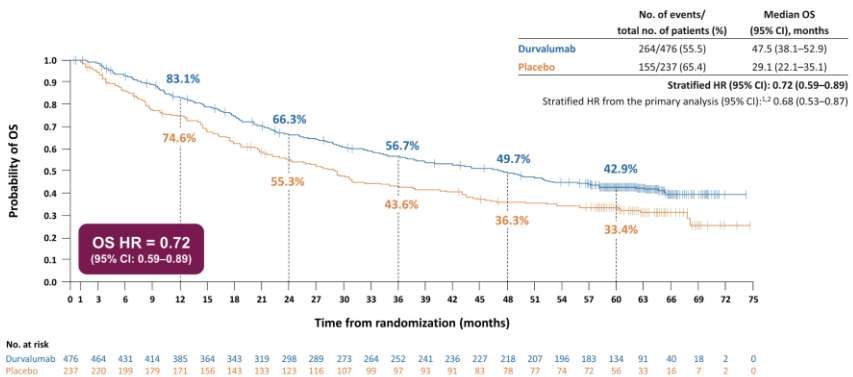
PACIFIC: 5 year Outcomes

Spigel, JCO 2022

Updated PFS (ITT; BICR)



Updated OS (ITT)



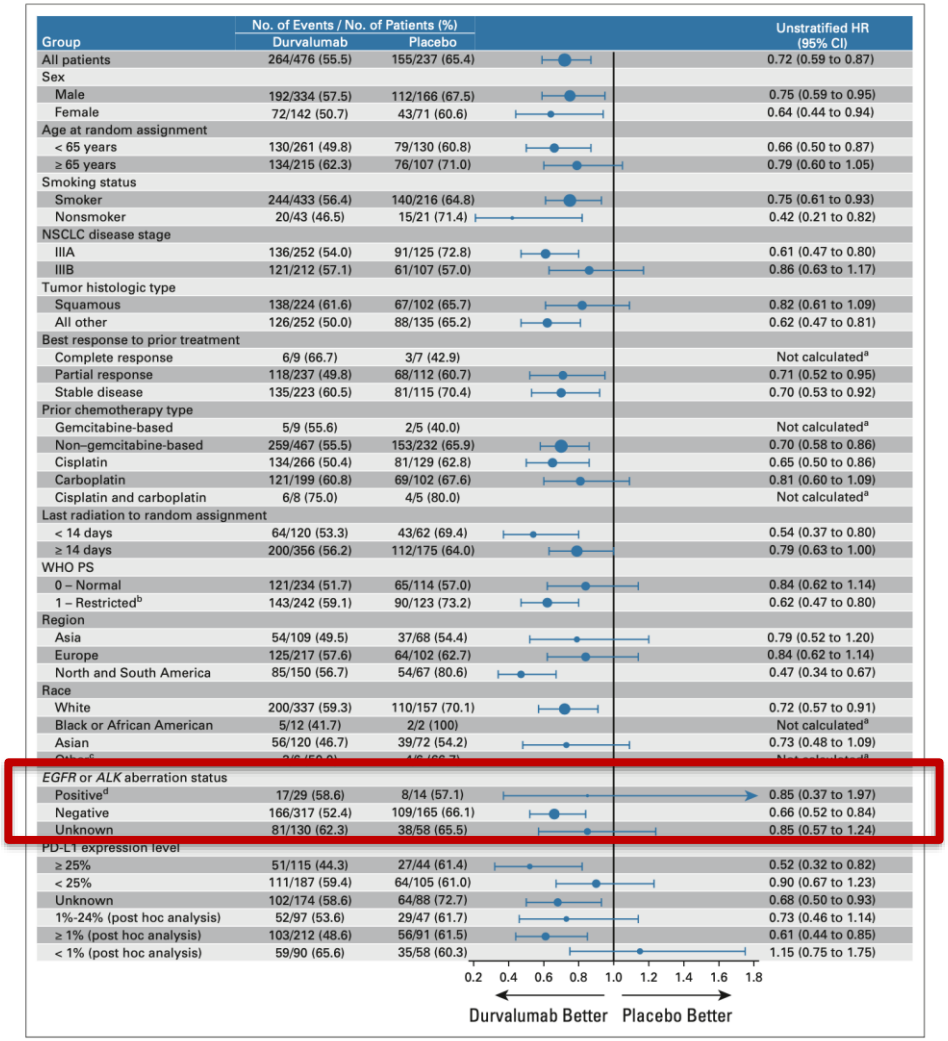
60.3% relapse by 3 years

PACIFIC

Spigel, JCO 2022

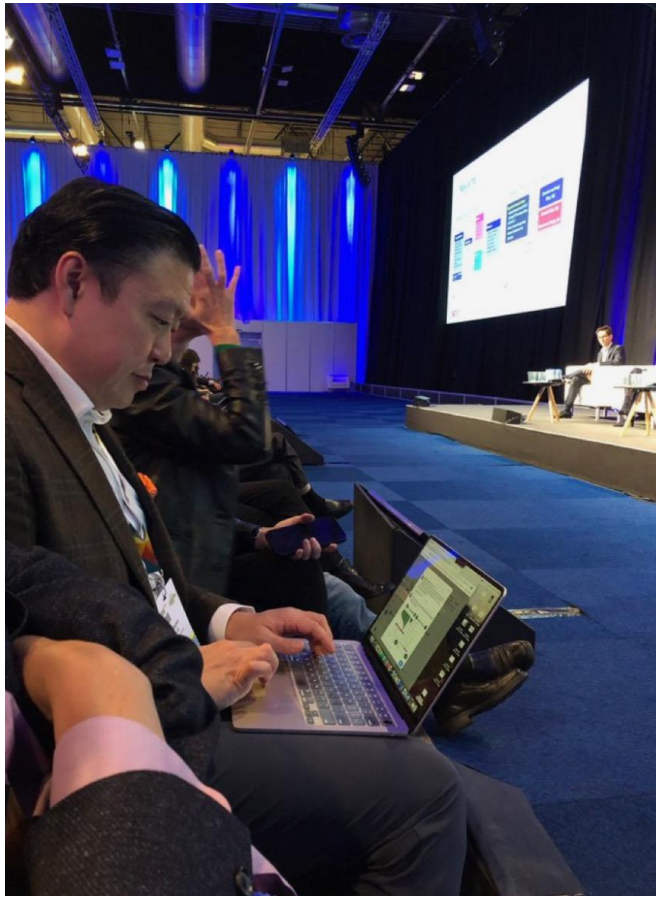
NOT SPECIFIC: Good

Beware of subsets!

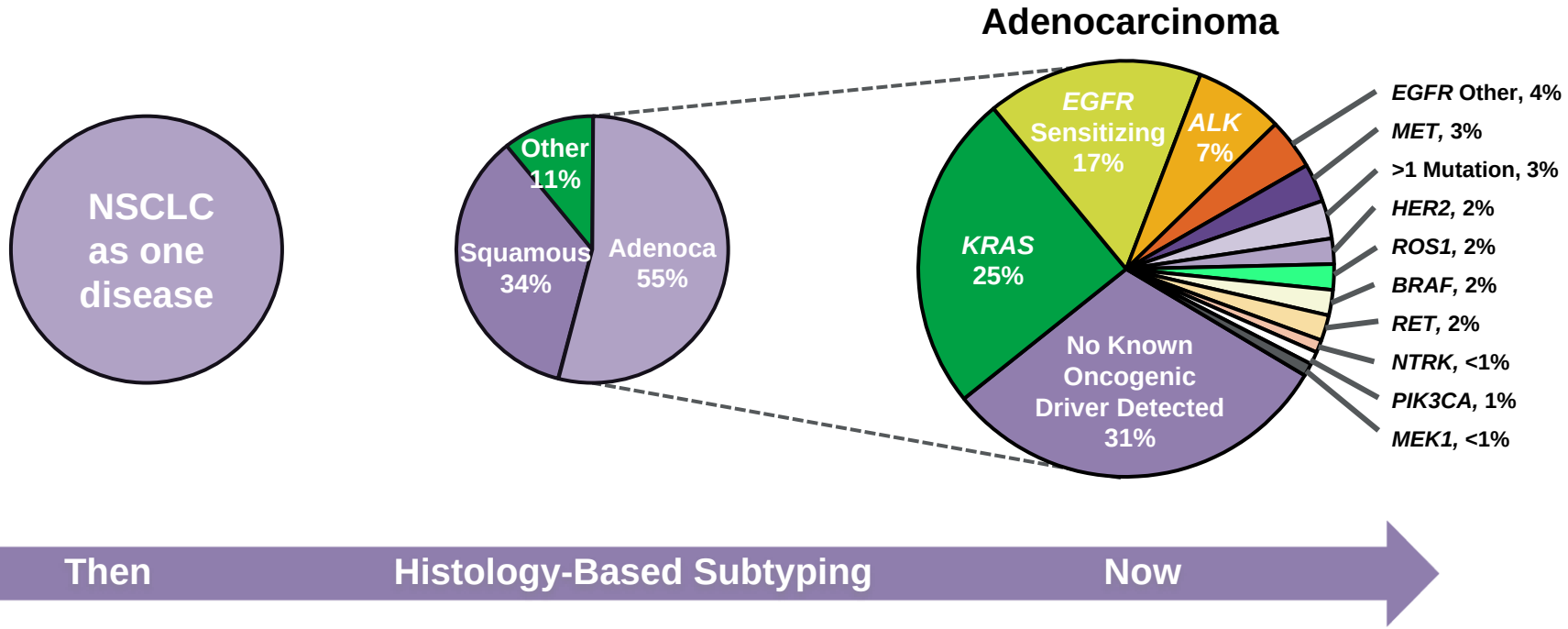


Group	No. of Events / No. of Patients (%) Durvalumab	Placebo	Unstratified HR (95% CI)
All patients	264/476 (55.5)	155/237 (65.4)	0.72 (0.59 to 0.87)
Sex			
Male	192/334 (57.5)	112/166 (67.5)	0.75 (0.59 to 0.95)
Female	72/142 (50.7)	43/71 (60.6)	0.64 (0.44 to 0.94)
Age at random assignment			
< 65 years	130/261 (49.8)	79/130 (60.8)	0.66 (0.50 to 0.87)
≥ 65 years	134/215 (62.3)	76/107 (71.0)	0.79 (0.60 to 1.05)
Smoking status			
Smoker	244/433 (56.4)	140/216 (64.8)	0.75 (0.61 to 0.93)
Nonsmoker	20/43 (46.5)	15/21 (71.4)	0.42 (0.21 to 0.82)
NSCLC disease stage			
IIIA	136/252 (54.0)	91/125 (72.8)	0.61 (0.47 to 0.80)
IIIB	121/212 (57.1)	61/107 (57.0)	0.86 (0.63 to 1.17)
Tumor histologic type			
Squamous	138/224 (61.6)	67/102 (65.7)	0.82 (0.61 to 1.09)
All other	126/252 (50.0)	88/135 (65.2)	0.62 (0.47 to 0.81)
Best response to prior treatment			
Complete response	6/9 (66.7)	3/7 (42.9)	Not calculated[a]
Partial response	118/237 (49.8)	68/112 (60.7)	0.71 (0.52 to 0.95)
Stable disease	135/223 (60.5)	81/115 (70.4)	0.70 (0.53 to 0.92)
Prior chemotherapy type			
Gemcitabine-based	5/9 (55.6)	2/5 (40.0)	Not calculated[a]
Non–gemcitabine-based	259/467 (55.5)	153/232 (65.9)	0.70 (0.58 to 0.86)
Cisplatin	134/266 (50.4)	81/129 (62.8)	0.65 (0.50 to 0.86)
Carboplatin	121/199 (60.8)	69/102 (67.6)	0.81 (0.60 to 1.09)
Cisplatin and carboplatin	6/8 (75.0)	4/5 (80.0)	Not calculated[a]
Last radiation to random assignment			
< 14 days	64/120 (53.3)	43/62 (69.4)	0.54 (0.37 to 0.80)
≥ 14 days	200/356 (56.2)	112/175 (64.0)	0.79 (0.63 to 1.00)
WHO PS			
0 – Normal	121/234 (51.7)	65/114 (57.0)	0.84 (0.62 to 1.14)
1 – Restricted[b]	143/242 (59.1)	90/123 (73.2)	0.62 (0.47 to 0.80)
Region			
Asia	54/109 (49.5)	37/68 (54.4)	0.79 (0.52 to 1.20)
Europe	125/217 (57.6)	64/102 (62.7)	0.84 (0.62 to 1.14)
North and South America	85/150 (56.7)	54/67 (80.6)	0.47 (0.34 to 0.67)
Race			
White	200/337 (59.3)	110/157 (70.1)	0.72 (0.57 to 0.91)
Black or African American	5/12 (41.7)	2/2 (100)	Not calculated[a]
Asian	56/120 (46.7)	39/72 (54.2)	0.73 (0.48 to 1.09)
[illegible]	[illegible]	[illegible]	[illegible]
EGFR or *ALK* aberration status			
Positive[d]	17/29 (58.6)	8/14 (57.1)	0.85 (0.37 to 1.97)
Negative	166/317 (52.4)	109/165 (66.1)	0.66 (0.52 to 0.84)
Unknown	81/130 (62.3)	38/58 (65.5)	0.85 (0.57 to 1.24)
PD-L1 expression level			
≥ 25%	51/115 (44.3)	27/44 (61.4)	0.52 (0.32 to 0.82)
< 25%	111/187 (59.4)	64/105 (61.0)	0.90 (0.67 to 1.23)
Unknown	102/174 (58.6)	64/88 (72.7)	0.68 (0.50 to 0.93)
1%-24% (post hoc analysis)	52/97 (53.6)	29/47 (61.7)	0.73 (0.46 to 1.14)
≥ 1% (post hoc analysis)	103/212 (48.6)	56/91 (61.5)	0.61 (0.44 to 0.85)
< 1% (post hoc analysis)	59/90 (65.6)	35/58 (60.3)	1.15 (0.75 to 1.75)

Beware of subsets?



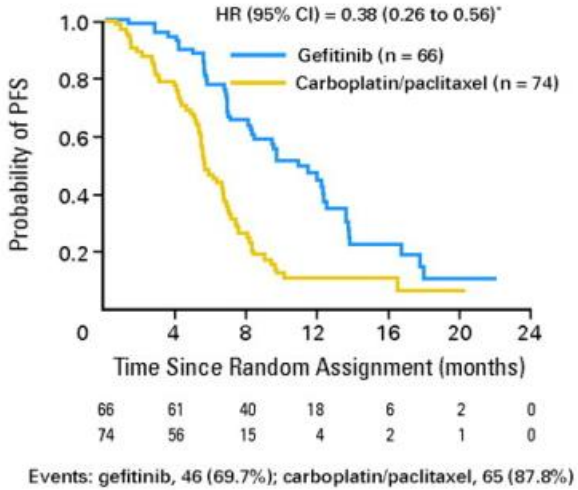
NSCLC: Lung Cancer is Heterogenous



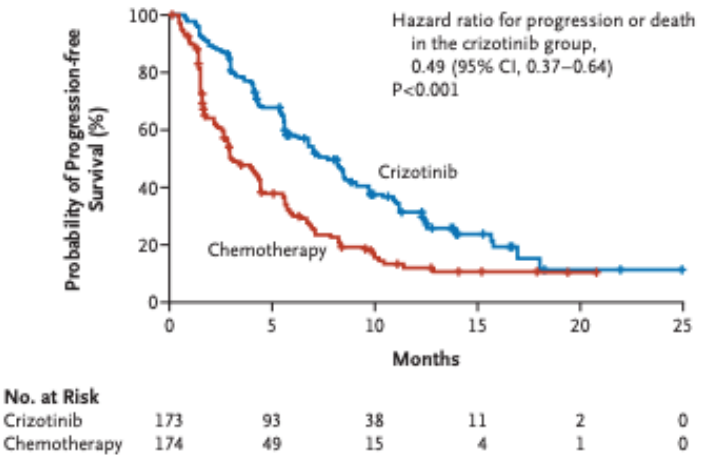
Adenoca, adenocarcinoma; NSCLC, non-small-cell lung cancer.

Molecular Testing Identifies Targeted Therapy Options

EGFR



ALK



Fukuoka JCO 2011, Shaw NEJM 2013

First-Line Selpercatinib or Chemotherapy and Pembrolizumab in *RET* Fusion–Positive NSCLC

Zhou, NEJM, Oct 23, 2023 & ESMO 2023

Key Eligibility Criteria

- Stage IIIB-IIIC[1], IV non-squamous NSCLC
- No prior systemic therapy for metastatic disease
- *RET* fusion identified via NGS or PCR
- ECOG PS 0-2
- Symptomatic CNS metastases excluded

Stratification factors:

- Geography (East Asian vs. non-East Asian)
- Brain metastases (present vs. absent/unknown)[2]
- Investigator's choice of treatment with pembrolizumab

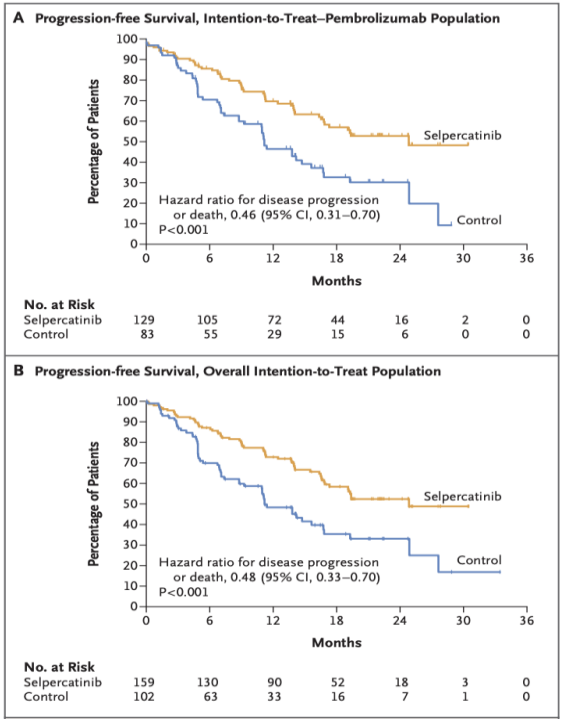
R 2:1[3]

Selpercatinib (160 mg BID)
N= 159

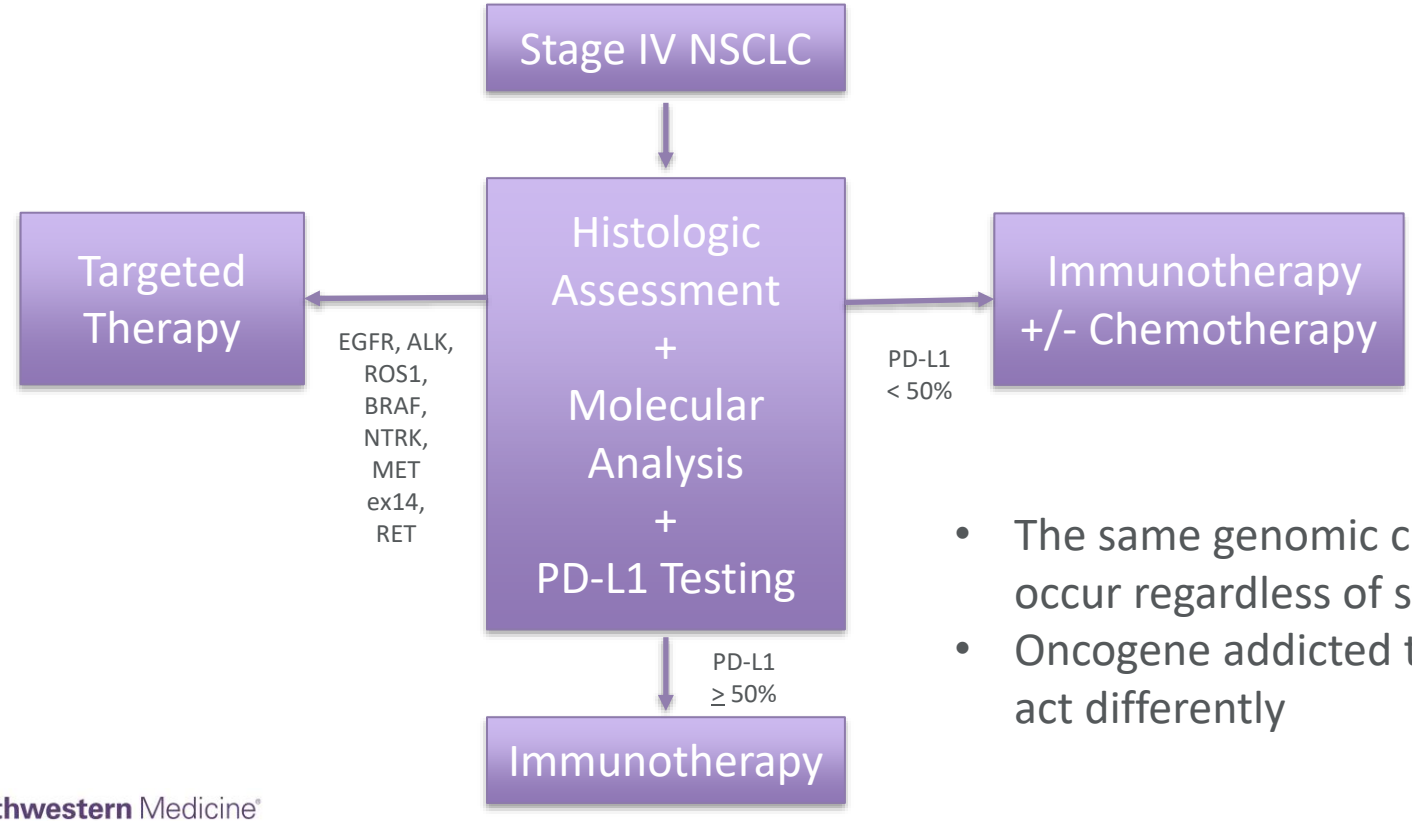
Carboplatin (AUC 5) or **Cisplatin** (75 mg/m^2)
+ **Pemetrexed** (500 mg/m^2)
+/- **Pembrolizumab** (200 mg)
N= 102

Optional Crossover

Selpercatinib
(Upon BICR confirmed PD)



Treatment Landscape for Metastatic NSCLC



- The same genomic changes occur regardless of stage
- Oncogene addicted tumors act differently

Management of locoregional oncogene driven NSCLC

- Management of locoregional oncogene driven NSCLC-*significant impact!*
  - ADAURA (resected) (OS HR 0.49)
  - ALINA (resected) (PFS HR 0.24)

- Use our tools to limit therapy that doesn't work and give therapy that is impactful!

Table 1 | Efficacy of anti-PD-(L)1 therapies in genomic subsets of NSCLC enriched in non-smokers

Oncogenic driver	Anti-PD-(L)1 antibody-based treatment	*n*	ORR (%)	Median PFS (months)	Ref.
EGFR mutations	Durvalumab	89	11	NR	47
	Anti-PD-(L)1 antibody monotherapy	22	4	NR	48
	Pembrolizumab	10	0	4	52
	Anti-PD-(L)1 antibody monotherapy	115	12	2	50
	Anti-PD-(L)1 antibody monotherapy	171	10	2	51
	Anti-PD-(L)1 antibody monotherapy	28 (MDACC cohort)[a] 54 (CGDB cohort)[a]	4[a] NR[a]	2[a] 2[a]	40
	Erlotinib+atezolizumab	28[b]	75[b]	15[b]	228
	Erlotinib+nivolumab	21	15	5	229
	Erlotinib+pembrolizumab	12[b]	42[b]	19[b]	230
	Gefitinib+pembrolizumab	7[b]	14[b]	1[b]	230
	Gefitinib+durvalumab	40[b]	65[b]	11[b]	231
	Osimertinib+durvalumab	23 TKI pretreated 11 TKI naive	43 82	NR 9	232
	Chemotherapy+bevacizumab+atezolizumab	34	71	10	181
	Chemotherapy+IBI305 (bevacizumab biosimilar)+sintilimab	148	44	7	184
	Chemotherapy+sintilimab	145	33	6	185
HER2 mutations	Anti-PD-(L)1 antibody monotherapy	27	8	2	50
	Anti-PD-(L)1 antibody monotherapy	23	27	2	54
	Anti-PD-(L)1 antibody monotherapy	15 (MDACC cohort) 21 (CGDB cohort)	8 NR	2 3	40
ALK fusions	Durvalumab	15	0	NR	47
	Anti-PD-(L)1 antibody monotherapy	6	0	NR	48
	Anti-PD-(L)1 antibody monotherapy	19	0	2	50
	Crizotinib+nivolumab	13[b]	38[b]	NR	233
	Ceritinib+nivolumab	20 TKI pretreated 16 TKI naive	35 69	5 NE	234
	Lorlatinib+avelumab	28	46	NR	235
	Alectinib+atezolizumab	21[b]	86[b]	NE	236
ROS1 fusions	Anti-PD-(L)1 antibody monotherapy	6	17	NR	50
RET fusions	Anti-PD-(L)1 antibody monotherapy	15	0	3	60
	Anti-PD-(L)1 antibody monotherapy	16	6	2	50
	Anti-PD-(L)1 antibody monotherapy	9	37	8	54

All studies listed were limited to patients with advanced-stage non-small-cell lung cancer (NSCLC). None of the studies was limited to the frontline setting and, unless indicated, all data derive from patients previously treated with oncogene-targeted therapies. CGDB, Clinico-Genomic Database; MDACC, MD Anderson Cancer Center; NE, not estimable; NR, not reported; ORR, objective response rate; PFS, progression-free survival; TKI, tyrosine kinase inhibitor. [a]Data from patients with tumours harbouring classic (sensitizing) *EGFR* mutations. [b]Data from patients naive to TKIs.

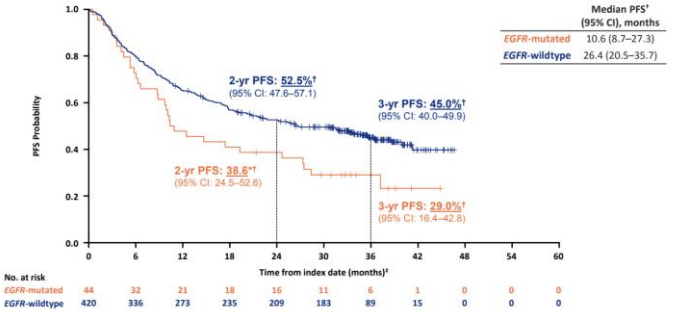
Otano, Nature Oncology Clinical Reviews, 2023

Real world outcomes with durvalumab after chemoradiotherapy in unresectable stage III *EGFR*-mutated NSCLC (PACIFIC-R)

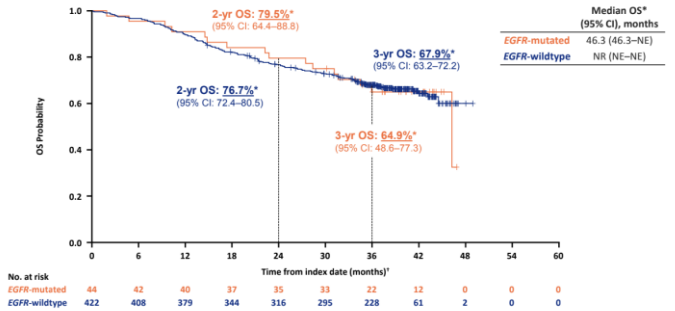
Peters et al, WCLC 2023, OA17.03

- Observational international study
- N=1154
- 3 yr OS 63.2%
- 3 yr PFS 42.2%
- 40.4% of patients with known *EGFR* status
  - 44 of 244 (9.4%) with *EGFR*mut+

Investigator-assessed PFS by *EGFR* status*



Overall survival by *EGFR* status



Consolidation EGFR-TKI vs Durvalumab vs Observation in Unresectable *EGFR*-Mutant Stage III NSCLC

Nassar et al, WCLC 2023, MA16.11

Multi-institutional retrospective analysis including 24 institutions

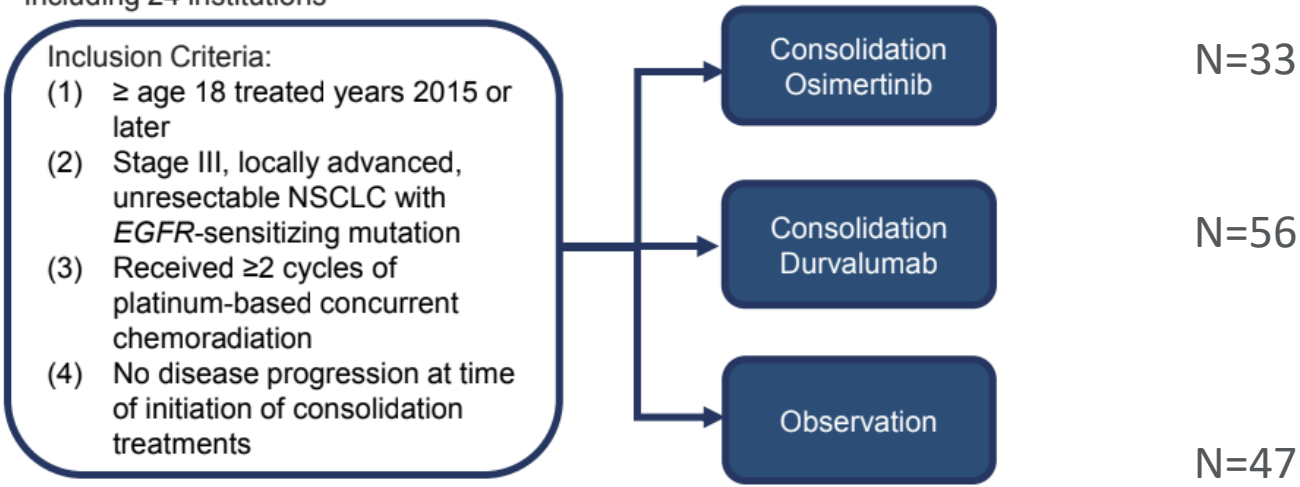
Inclusion Criteria:

(1) ≥ age 18 treated years 2015 or later

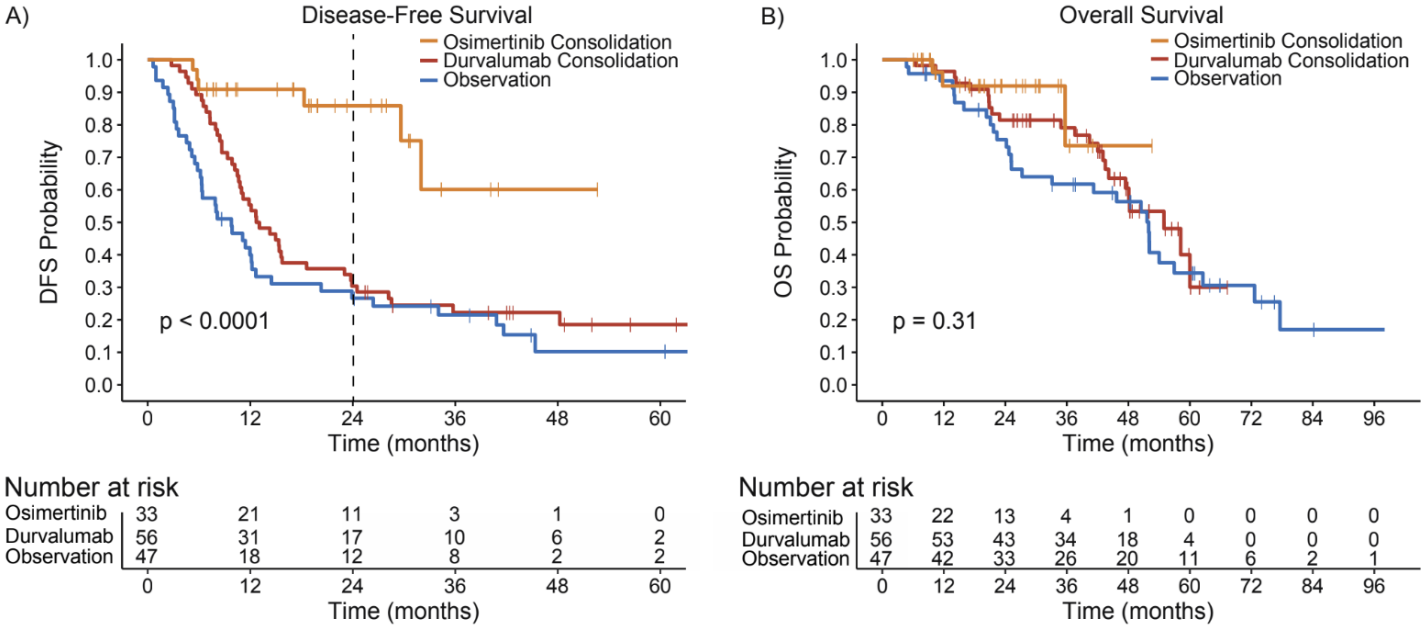
(2) Stage III, locally advanced, unresectable NSCLC with *EGFR*-sensitizing mutation

(3) Received ≥2 cycles of platinum-based concurrent chemoradiation

(4) No disease progression at time of initiation of consolidation treatments

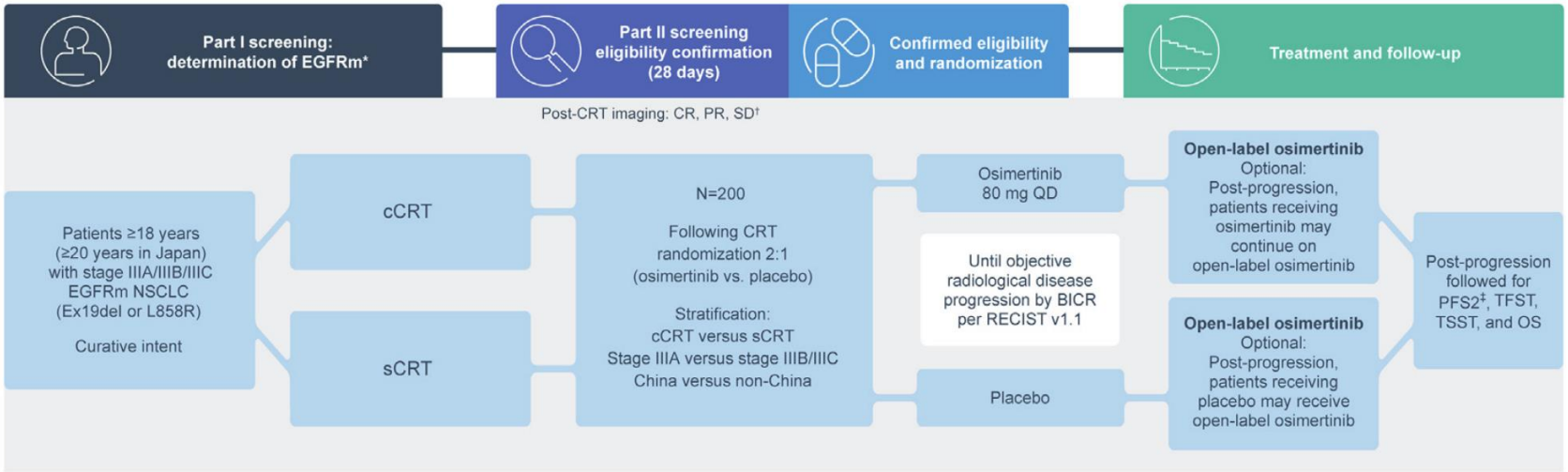


EGFR-TKI vs Obs vs Durva in *EGFR*+ LR-NSCLC



24-month CNS-DFS: Osimertinib: 6.7% (95% CI, 1.7-32); Durvalumab: 17% (95% CI, 8.1-30); Observation: 11% (95% CI, 3.8-25)

LAURA: Osimertinib after ChemoRT in Unresectable EGFR+ Stage III NSCLC



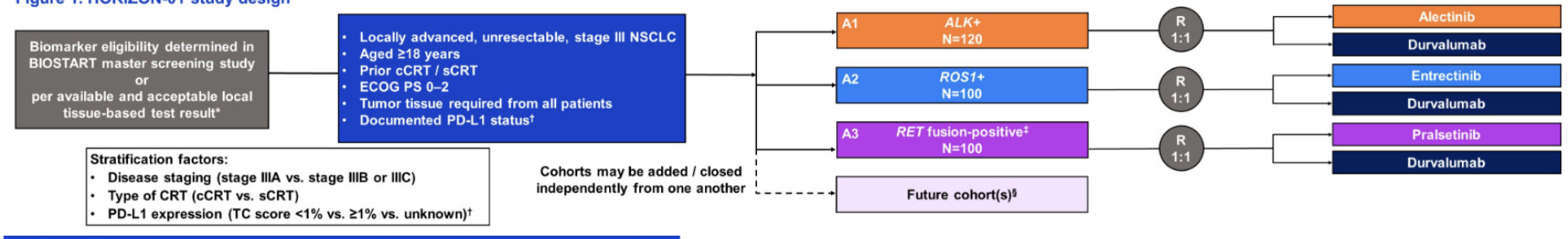
1st patient enrolled 2018, primary results 2023/2024

Lu S, Clin Lung Cancer, 2022

Phase I-III platform study in biomarker selected unresectable Stage III NSCLC

Paz-Ares, Proc ASCO 2023, TPS8605

Figure 1. HORIZON-01 study design



Therapeutic	Administration	Dose*
Alectinib	Oral†	600 mg BID in 28-day cycles for ≤3 years
Entrectinib	Oral	600 mg QD in 28-day cycles for ≤3 years
Pralsetinib	Oral	400 mg QD in 28-day cycles for ≤3 years
Durvalumab	IV infusion	1500 mg Q4W in 28-day cycles for ≤1 year

Endpoints

- The primary endpoint is progression-free survival (PFS), defined as the time from randomization to the first documented disease progression, as determined by blinded independent central review (BICR) per RECIST v1.1, or death from any cause, whichever occurs first.
- Secondary endpoints include time to CNS progression, objective response rate, duration of response, and distant metastasis-free survival (all by BICR and investigator assessment per RECIST v1.1), investigator-assessed PFS, overall survival, time to confirmed deterioration, maintenance or meaningful improvement in patient-reported outcomes (PROs), and safety
  - Safety will be assessed in all patients receiving ≥1 dose of study treatment and includes the incidence, type, and severity of adverse events as graded by the investigator as per the NCI CTCAE v5.0.
- Exploratory objectives include additional assessments of PROs and safety endpoints, as well as biomarker, pharmacokinetic, and health status utility analyses.

Unresectable Stage III NSCLC

YES to Targeted Therapy!

- Does durvalumab improve outcomes in patients with EGFR+ NSCLC?
- Do we have highly potent therapies for some targetable mutations?
- Can we harm patients who need TKIs when they relapse on ICIs?
- With 2/3 of patients relapsing from disease within 3 years, it's clear we have to do better
- The time for targeted therapies is now!
  - Shared decision making-some patients are cured with chemoRT alone
  - Ongoing toxicity (including financial)
  - Can we really do phase 3 trials in small patient populations when we see such a profound effect on outcome?