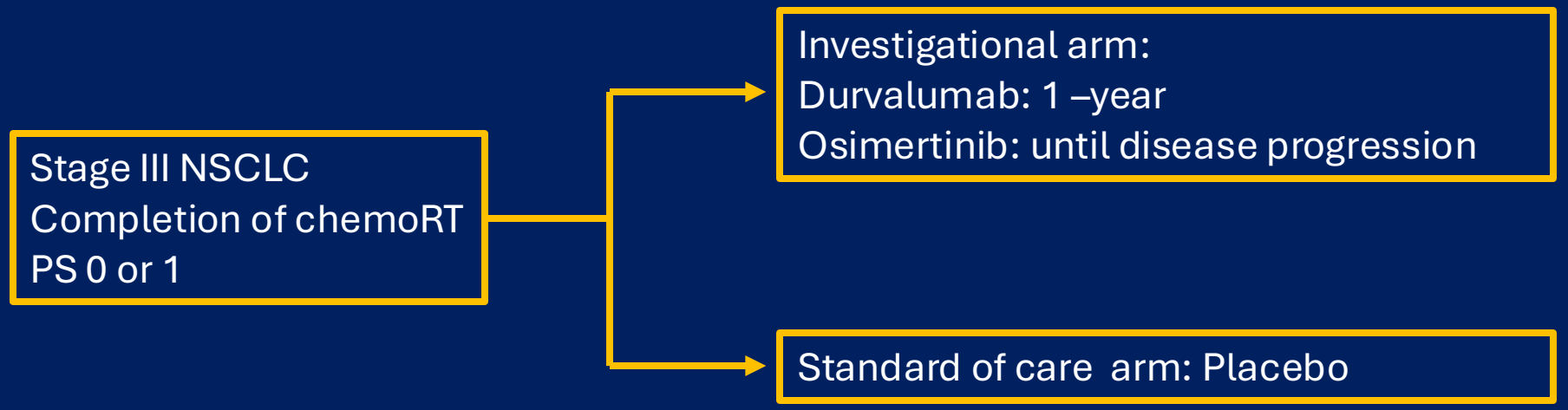
Consolidation therapy for patients with non-actionable and actionable molecular alterations

Moving the bar beyond PACIFIC and LAURA

Tom Stinchcombe
Medical Oncology at Duke Cancer Institute

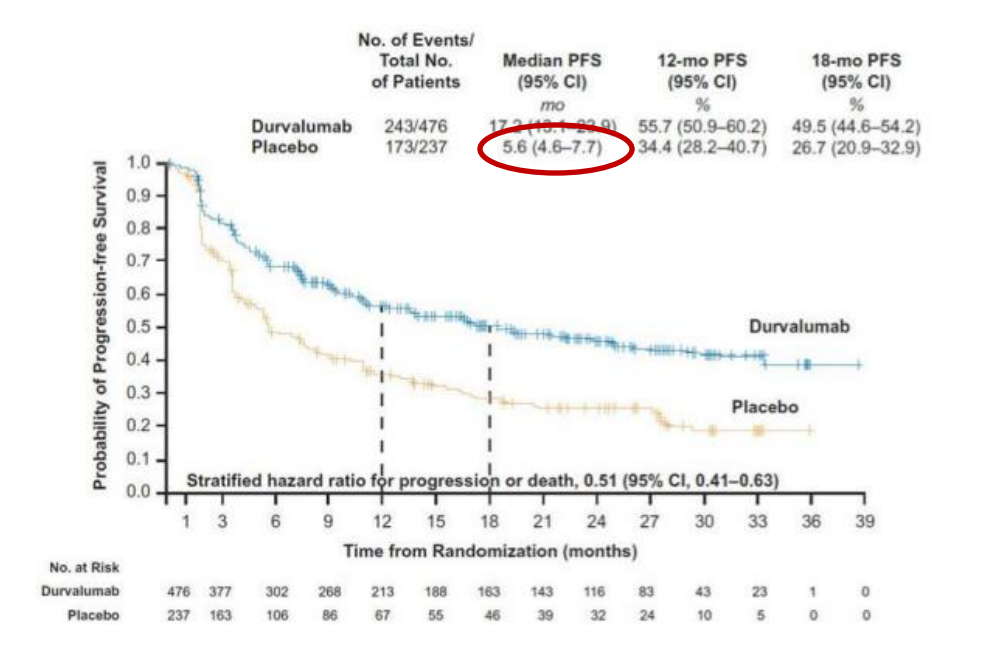
PACIFIC and LAURA trials



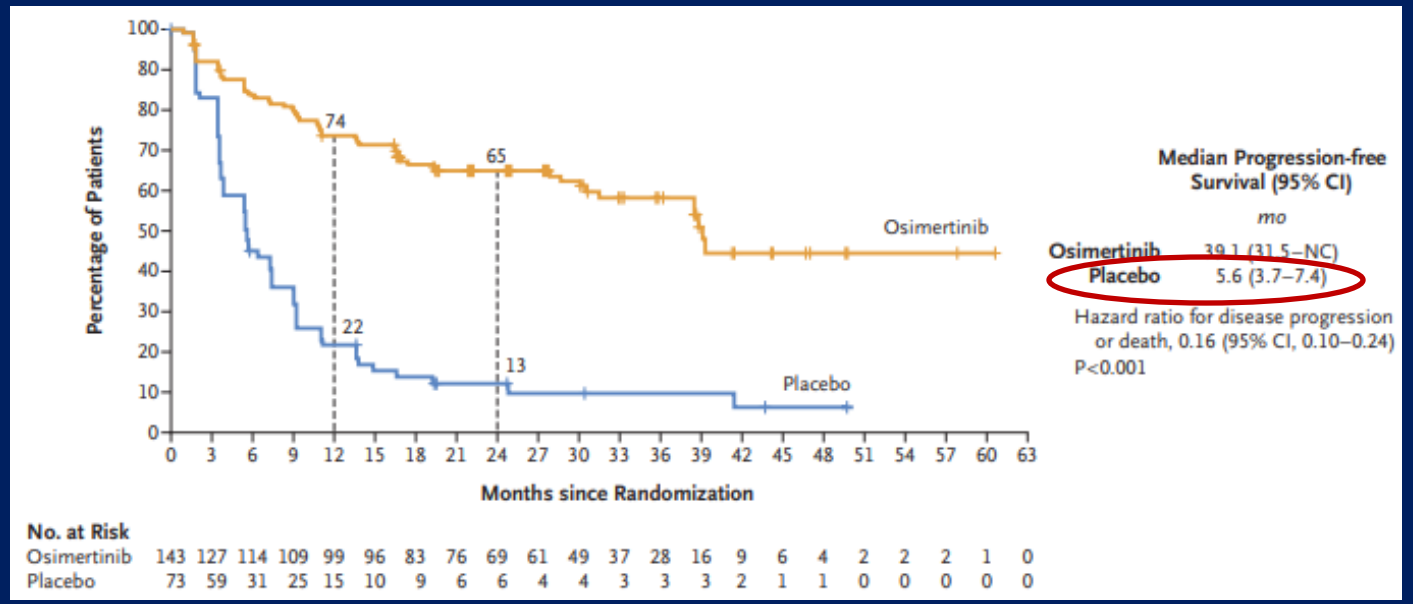
Lu et al NEJM 2024, Antonia et al NEJM 2018

PACIFIC and LAURA trials: PFS outcome

PACIFIC



LAURA



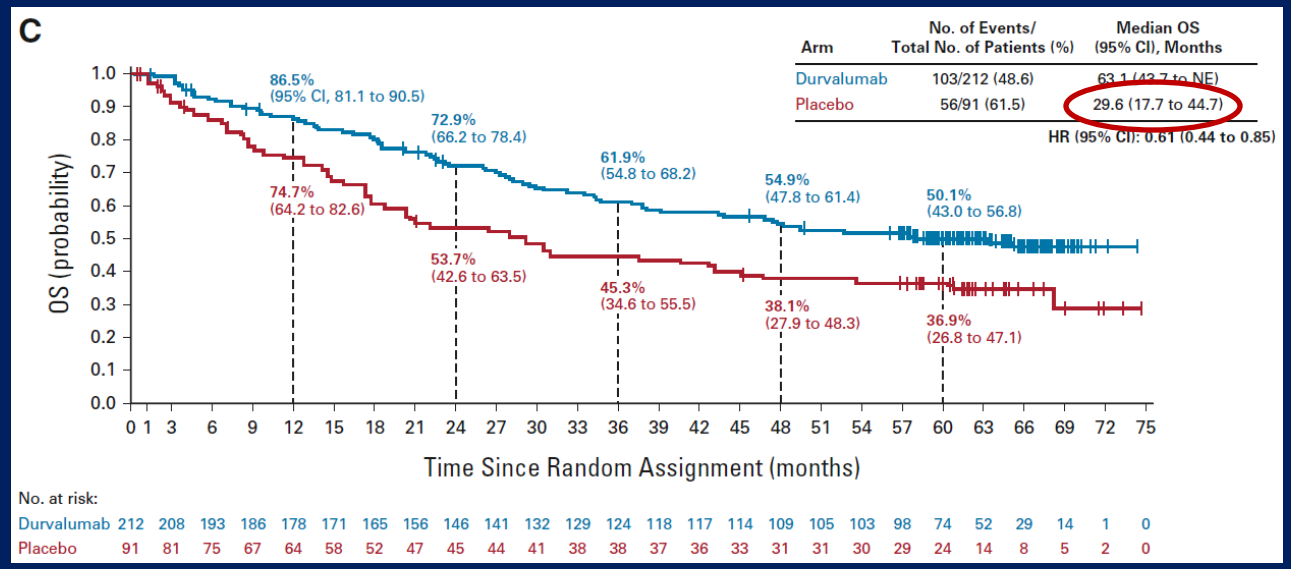
Lu et al NEJM 2024, Spigel et al JCO 2022

What follows PACIFIC?

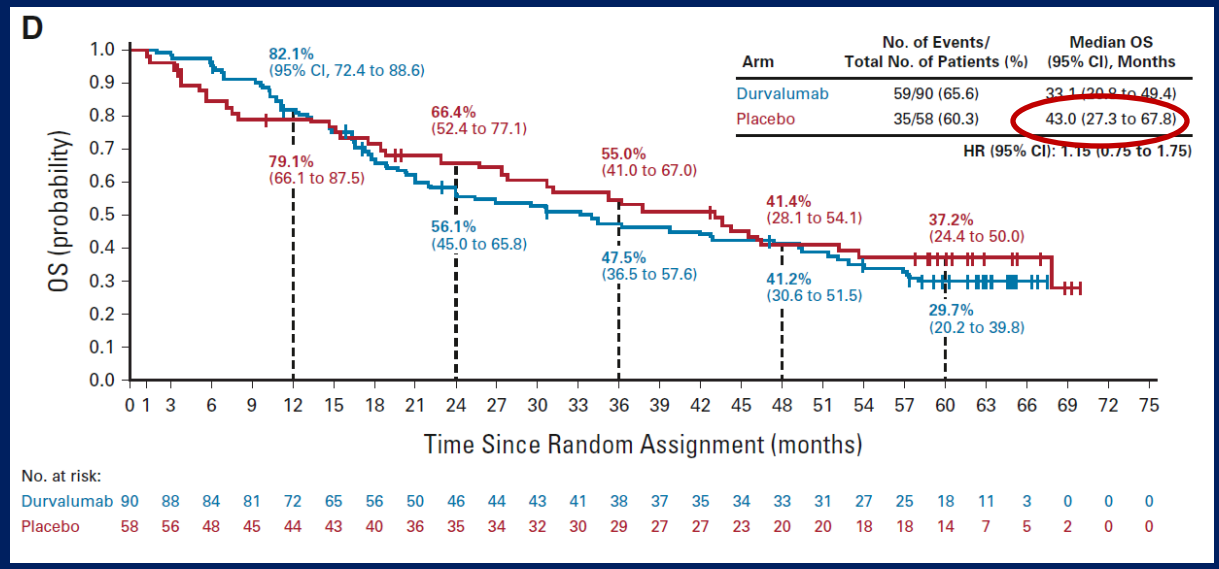
- Sub-segmentation of the patient population by biomarker:
  - By PD-L1 status
  - Mutation status: STK11 and/or KEAP1
- Induction chemotherapy and immunotherapy
- Immunotherapy combinations

KM for PD-L1 <1% and ≥ 1%

PD-L1 ≥ 1%



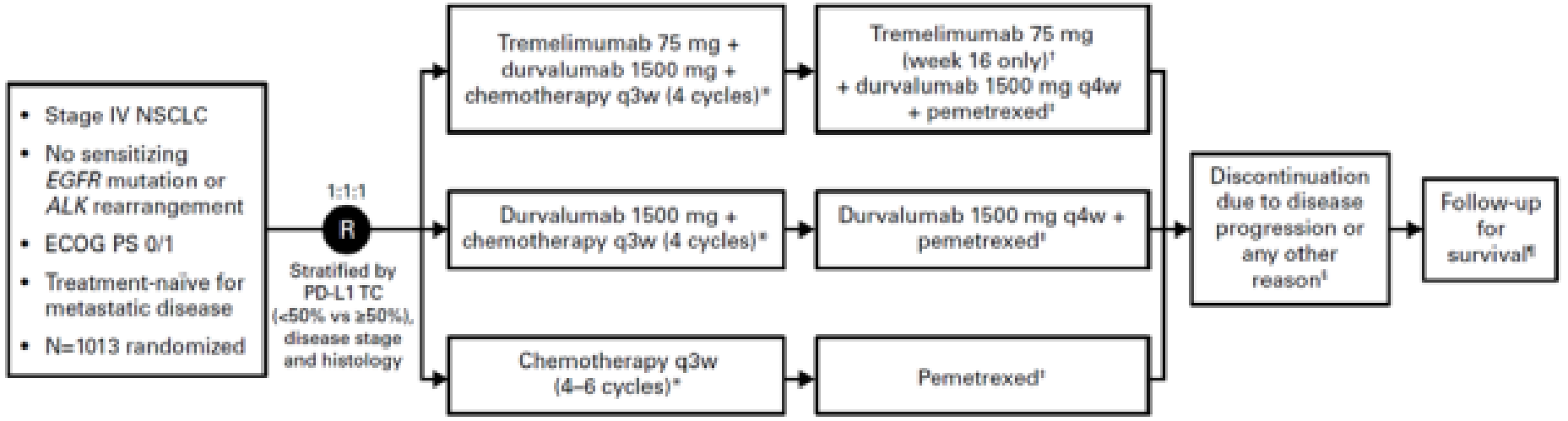
PD-L1 < 1%



Samples unavailable on 37% of patients

Spigel et al JCO 2022

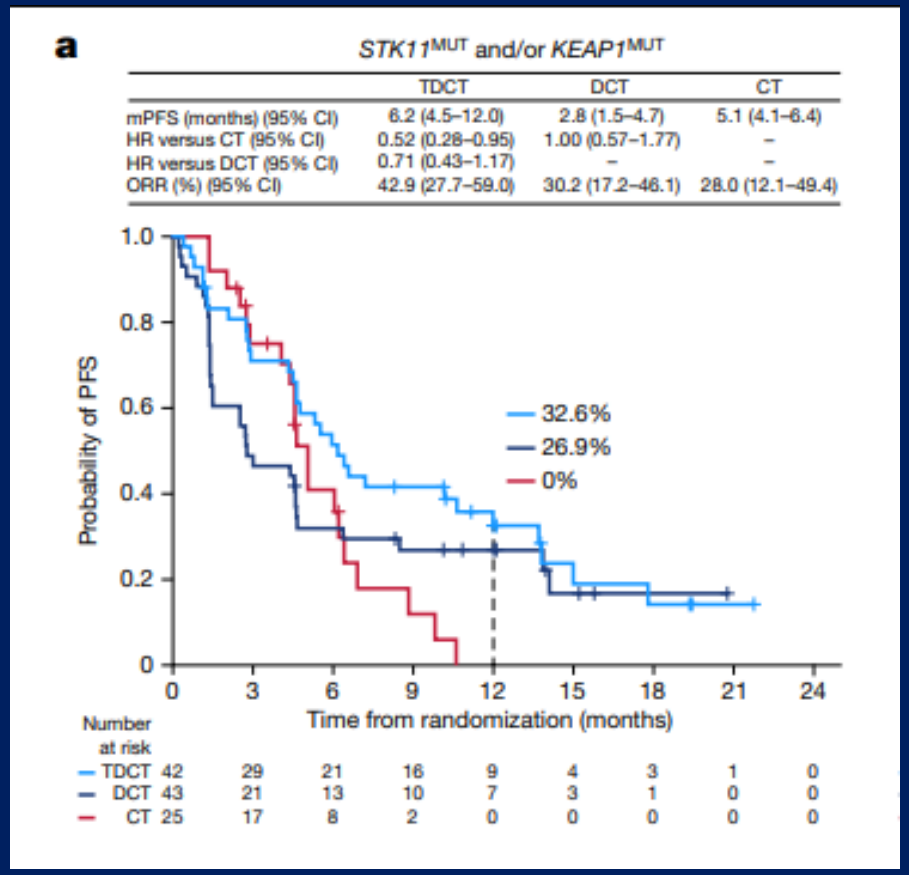
Chemotherapy alone, with durvalumab or durvalumab and tremelimumab for stage IV NSCLC



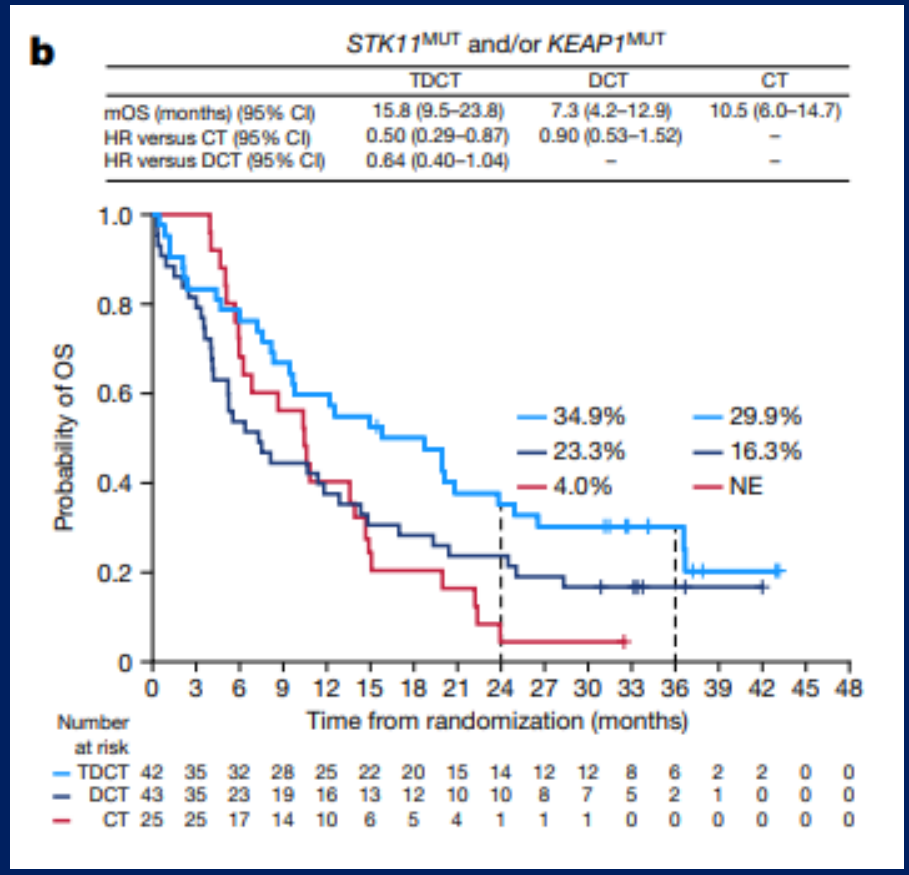
Johnson et al JCO 2023

Stage IV disease: Chemo vs. Chemo+Durva or Druva/Treme: *STK11* and/or *KEAP1* mutation subset

Progression-free survival



Overall survival



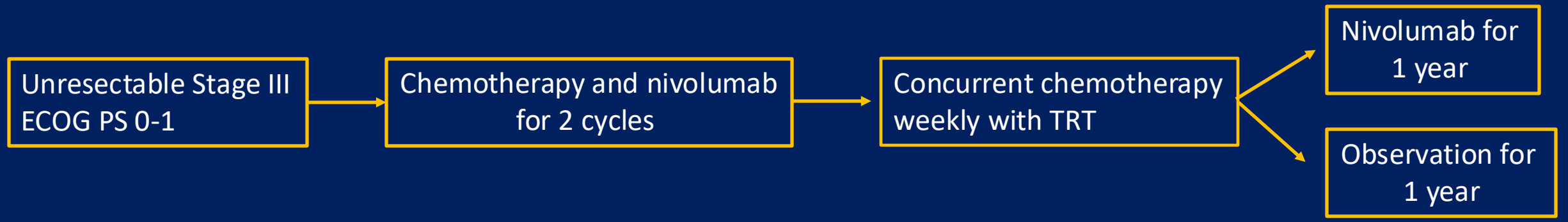
Skoulidis et al Nature 2024

Induction chemotherapy and immunotherapy

- Previous trials of induction chemotherapy did not reveal benefit
- Chemotherapy activity limited
- Induction therapy could lead to earlier treatment of micro-metastatic disease and smaller tumor volume to improve benefit from radiation therapy
- Chemotherapy and immunotherapy have demonstrated activity in surgical stage III patients

Vokes et al JCO 2007, Belani et al JCO 2005

A phase II trial of neoadjuvant chemotherapy and ICI and consolidation ICI



Primary endpoint: PFS
Secondary: OS, ORR, safety, QoL

Liu et al ASCO 2024

Efficacy results

Induction chemotherapy and immunotherapy

Parameter	Pre-treatment chemotherapy and immunotherapy (n=264)
ORR	65.5%
Relative change in tumor volume	61.1% (36.3-76.4)
Tumor volume (cc)	60.8 to 21.4

Consolidation immunotherapy

Parameter	Nivolumab consolidation (n=86)	Observation (n=86)	
PFS	NR	12.2	HR:0.49, p=0.003
OS	NR	NR	HR:0.56, p=0.050

Liu et al ASCO 2024

Sample of clinical trials of escalated consolidation therapy

Trial name	NCT #	Novel consolidation
PACIFIC 9	05221840	Durvalumab/oleclumab (CD73) or durvalumab/monalizuamb (NKG2A) vs durvalumab alone
PACIFIC 8	05211895	Domvanalimab (TIGIT) and durvalumab
Skyscraper-03	04513925	Tiragolumab (TIGIT) and atezolizumab
BTCRC 16-081[a]	03285321	Nivolumab vs nivolumab/ipilimumab
Checkmate 73L[b]	04026412	Current nivolumab with TRT and consolidation nivolumab/ipilimumab vs durvaluamb

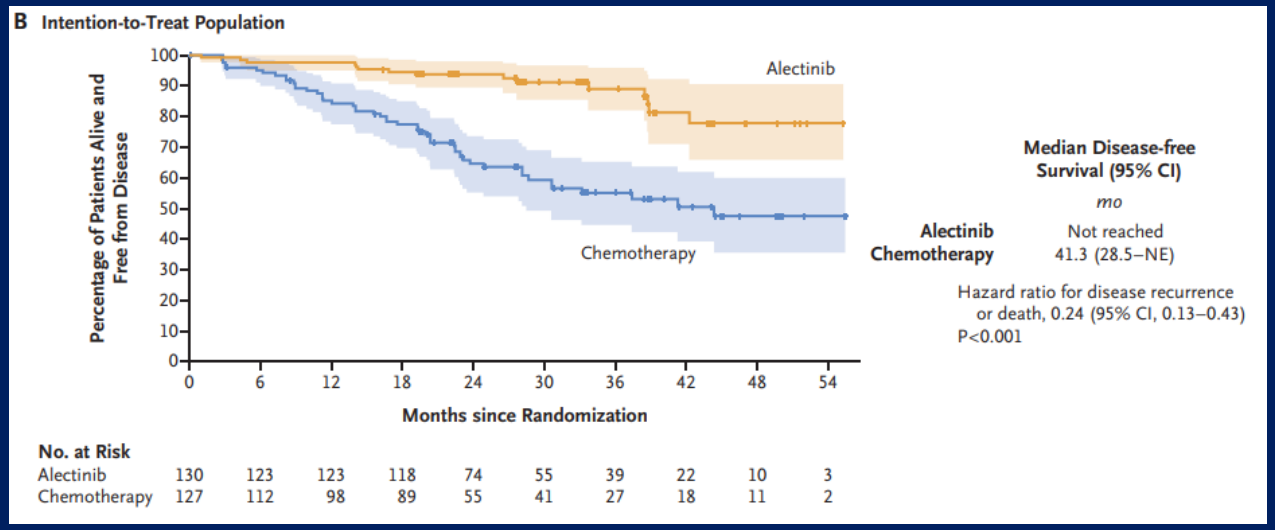
[a] Phase II trial: Drum et al ASCO 2022
[b] https://news.bms.com/news/details/2024/Bristol-Myers-Squibb-Provides-Update-on-Phase-3-CheckMate--73L-Trial/default.aspx

Oncogenic drivers beyond *EGFR* mutation

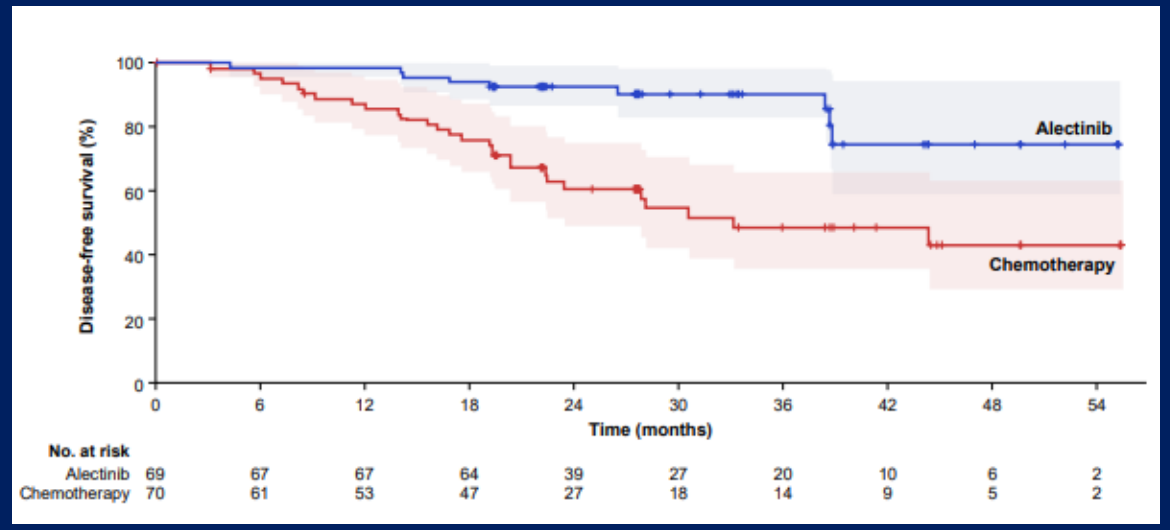
Do we need a separate trial for each molecular subgroup?

Adjuvant alectinib: Disease-free survival

Intent-to-treat



Stage IIIA



DFS HR 0.25 (95 CI: 0.12-0.53)

Wu et al NEJM 2024

What level of data are needed?

- High level activity defined ORR > 50% and PFS > 12 months
- Favorable adverse event profile
- Prevalence of molecular alteration
- Demonstrated ability to perform phase III trials

Phase III trial: Active agent and phase III trial feasible	Phase III trial: doubts about the activity and/or tolerability over years	Phase II trial: highly active agents and phase III trial not feasible	Individual judgement (i.e. we will never have prospective data)
ALK+NSCLC	MET exon 14	ROS1	*NTRK* rearrangement
	HER2 agents	RET	
	KRAS G12C	BRAF V600E	
	EGFR exon 20 agents		

Moving beyond PACIFIC and LAURA

- For oncogenic driver negative NSCLC
  - Limited value in assessing outcomes by PD-L1 alone
  - Interest in KEAP1/STK11 subtype
  - Induction chemotherapy and immunotherapy
  - Will await the results of “double immunotherapy” consolidation trials
- For actionable oncogenic driver
  - Phase III trial in ALK+ NSCLC justified and feasible
  - For other agents as a field need to define the the level of evidence needed (phase II or phase III)