ATLANTA
LUNG CANCER SYMPOSIUM

Debate

Stephen Liu, MD

Date 9/28/2023

PIM Postgraduate Institute for Medicine
Bio Ascend™

17th Annual

ATLANTA

LUNG CANCER SYMPOSIUM

Targeted therapy should *not* be used for unresectable stage III NSCLC

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Disclosures

Advisory Board / Consultant:

Abbvie, Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Catalyst, Daiichi Sankyo, Eisai, Elevation Oncology, Genentech/Roche, Gilead, Guardant Health, Janssen, Jazz Pharmaceuticals, Merck, Merus, Mirati, Novartis, Regeneron, Sanofi, Takeda, Turning Point Therapeutics

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Data Safety Monitoring Board:

Candel Therapeutics

Disclosures

IASLC MEETING

FEB 21 - FEB 24 2024

IASLC 2024 Targeted Therapies of Lung Cancer

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Unresectable Stage III NSCLC

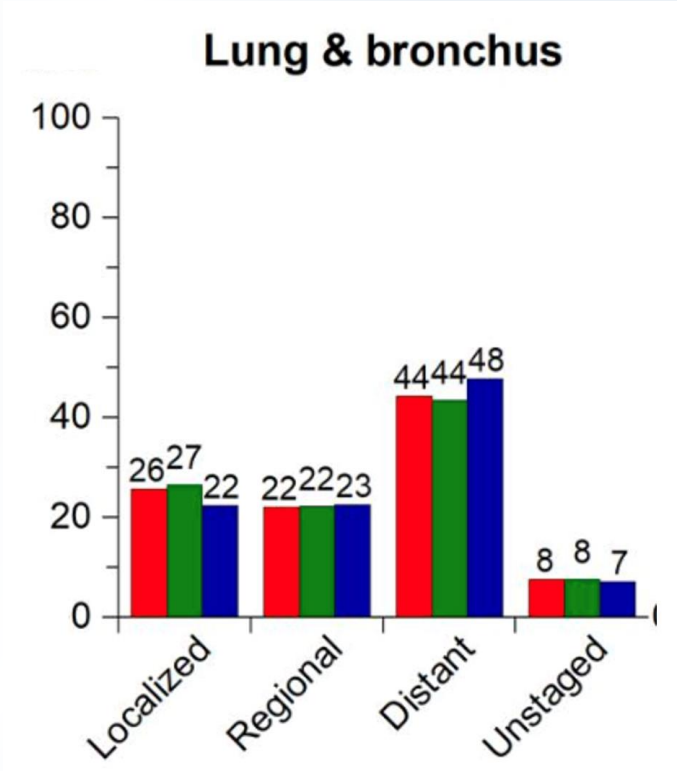
More than 1 in 5 patients present with regional disease

- *Surgery for resectable stage III (with perioperative therapy)*
- *Chemoradiation for unresectable stage III*

We pursue definitive therapy when possible

- *Surgery if resectable despite higher relapse*
- *Chemoradiation despite notable toxicity*

Why? Because we can cure stage III NSCLC.



Siegel, CA Cancer J Clin 2023

Chemoradiation for Stage III NSCLC

Long-Term Results of NRG Oncology RTOG 0617: Standard- Versus High-Dose Chemoradiotherapy With or Without Cetuximab for Unresectable Stage III Non–Small-Cell Lung Cancer

Jeffrey D. Bradley, MD[1]; Chen Hu, PhD[2,3]; Ritsuko R. Komaki, MD[4]; Gregory A. Masters, MD[5]; George R. Blumenschein, MD[4]; Steven E. Schild, MD[6]; Jeffrey A. Bogart, MD[7]; Kenneth M. Forster, PhD[8]; Anthony M. Magliocco, MD[9]; Vivek S. Kavadi, MD[10]; Samir Narayan, MD[11]; Puneeth Iyengar, MD[12]; Clifford G. Robinson, MD[13]; Raymond B. Wynn, MD[14]; Christopher D. Koprowski, MD[15]; Michael R. Olson, MD[16]; Joanne Meng, MD[17]; Rebecca Paulus, BS[2]; Walter J. Curran Jr, MD[18]; and Hak Choy, MD[12]

RTOG 0617: randomized phase III study

Standard-dose versus high-dose chemoradiotherapy with or without cetuximab

Explored intensification of therapy

60 Gy or 74 Gy given 5 days a week in 2 Gy fractions

30 treatments in 6 weeks versus 37 treatments in 7+ weeks

Chemotherapy weekly with or without cetuximab

Significant toxicities

High grade toxicity in > 70%

TABLE 2. Maximum Treatment-Related Adverse Events by Arm

	Arm, No. (%)			
Adverse Event	**A: 60 Gy (n = 152)**	**B: 74 Gy (n = 107)**	**C: 60 Gy + Cetuximab (n = 137)**	**D: 74 Gy + Cetuximab (n = 100)**
No grade ≥ 3 toxicity	42 (27.6)	32 (29.9)	20 (14.6)	10 (10.0)
Grade ≥ 3 toxicity	110 (72.4)	75 (70.1)	117 (85.4)	90 (90.0)
*P**	.0002			

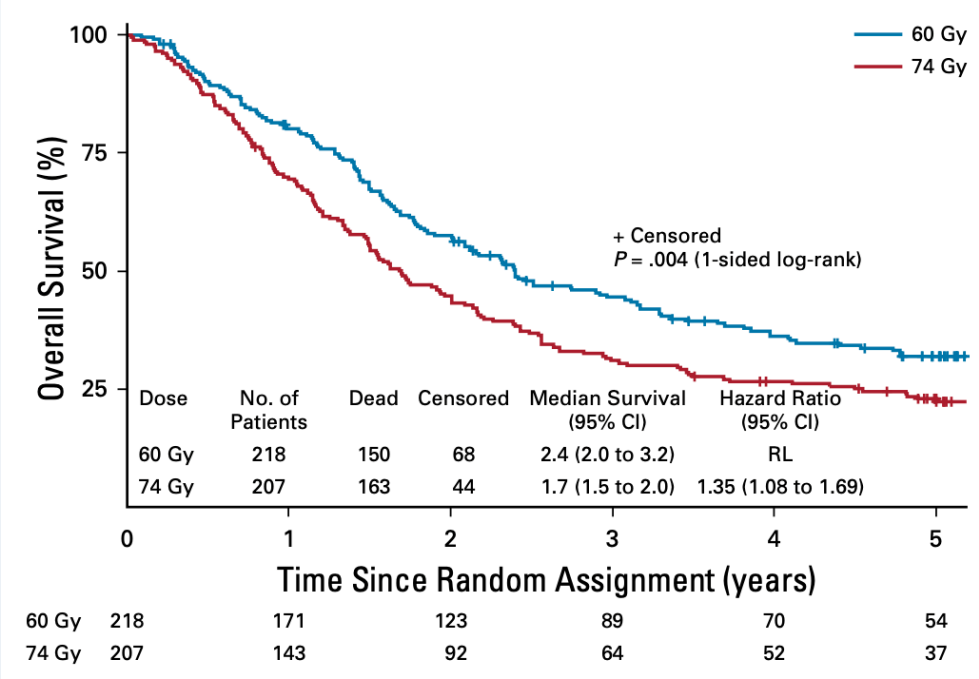
Bradley, JCO 2020

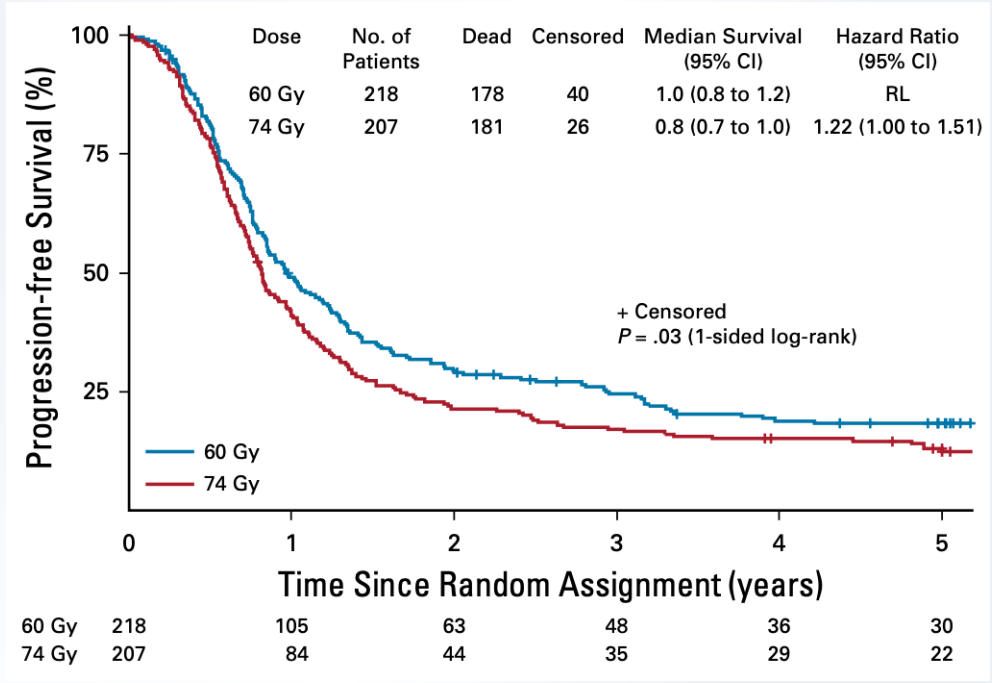
Chemoradiation for Stage III NSCLC

RTOG 0617: standard vs high-dose chemoradiation

*Toxicity balanced by efficacy and opportunity for **cure***

In the standard arm, 5y survival rate 32.1%, 5y progression free rate 18.3%





Bradley, JCO 2020

Chemoradiation for Stage III NSCLC

Some patients with unresectable stage III NSCLC are cured with chemoradiation.

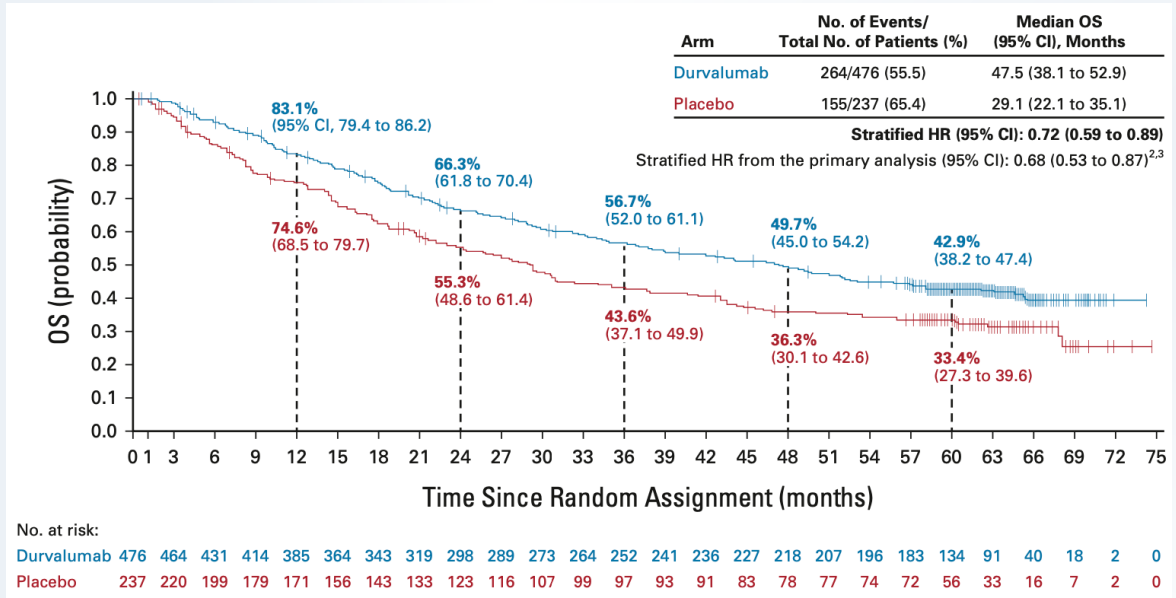
Bradley, JCO 2020

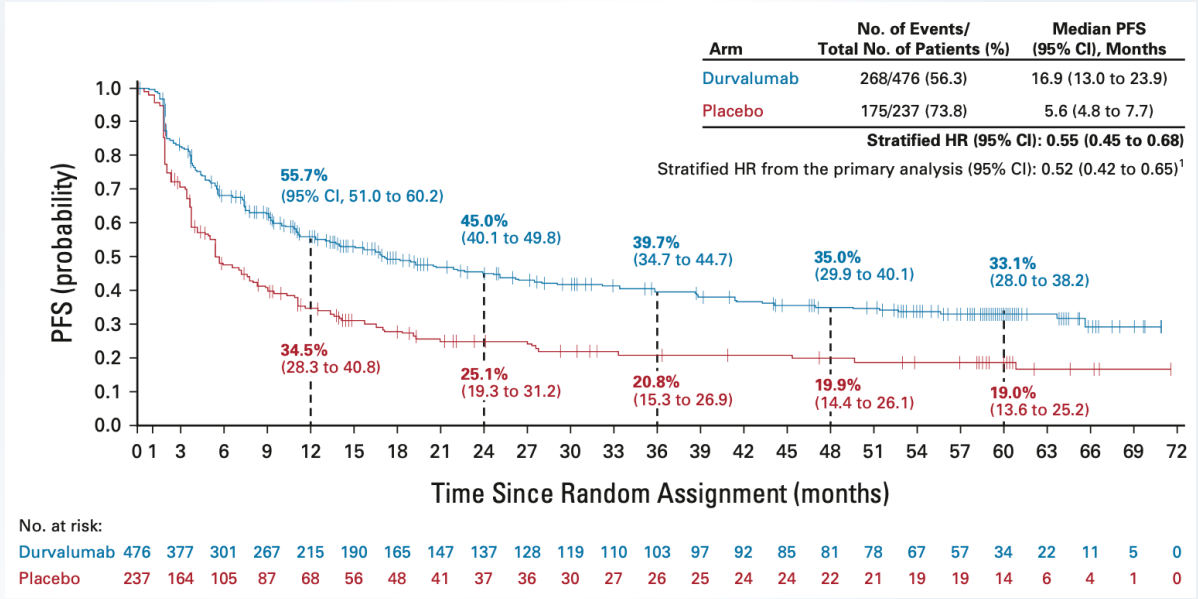
PACIFIC: Immunotherapy Consolidation after Chemoradiation

Durvalumab after chemoradiation improves survival

With durvalumab, 43% alive, 33% progression free at 5 years

Even in the standard arm: 33% alive, 19% progression free at 5 years





Spigel, JCO 2022

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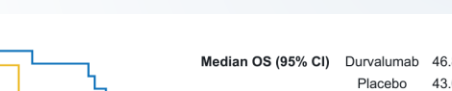
PACIFIC: Immunotherapy Consolidation after Chemoradiation

Durvalumab after chemoradiation improves survival

But not all subsets derive the same benefit from consolidation immunotherapy

EGFR / ALK positive with a wide confidence interval, not a clear benefit

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)
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)



There seems to be less benefit from consolidation immunotherapy in EGFR/ALK NSCLC

Spigel, JCO 2022; Naidoo, JTO 2023

PACIFIC: Immunotherapy Consolidation after Chemoradiation

Unclear benefit with immunotherapy in EGFR mutant NSCLC

Safety concern of giving immunotherapy followed by a need for targeted therapy

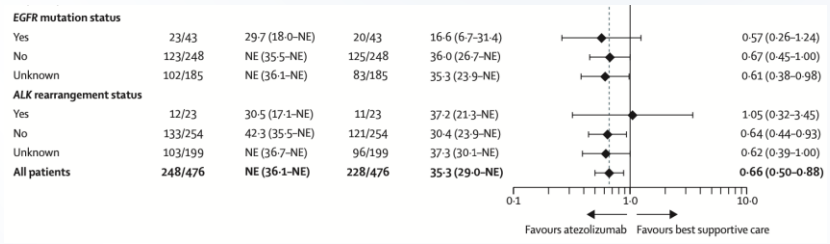
Understudied subset

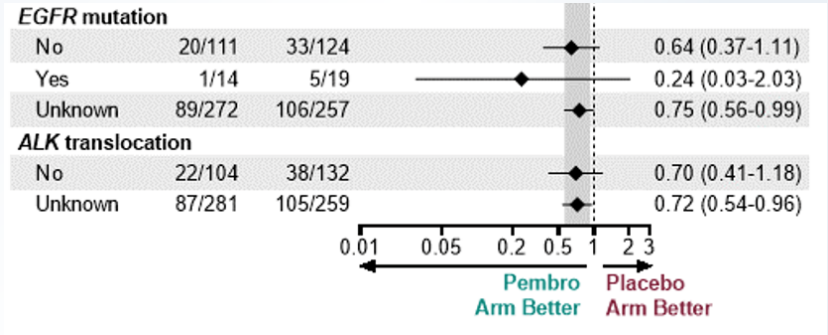
EGFR mutations uncommon in PACIFIC (of 713 randomized patients, 35 EGFR)

Need to understand the impact of EGFR in early stage

EGFR subset in IMpower 010 (adjuvant atezolizumab) did well

EGFR subset in KEYNOTE 671 (perioperative pembrolizumab) did well





Naidoo, JTO 2023; Spicer, ESMO 2023; Felip, Lancet 2021

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Chemoradiation for Unresectable Stage III NSCLC

Chemoradiation is potentially curative for stage III NSCLC

Consolidation immunotherapy needs further study in EGFR

Targeted therapy now plays a role after surgery

- *3 years of adjuvant osimertinib (ADAURA) improves DFS and OS*
- *2 years of adjuvant alectinib (ALINA) improves DFS*

Should we use targeted therapy here?

- *Post-surgery, osimertinib (ADAURA) and alectinib (ALINA) improve DFS*
- *Why not use targeted therapy post chemoradiation?*

Targeted Therapy for Unresectable Stage III NSCLC? No!

Current data showing targeted therapy improves survival after chemoradiation for stage III NSCLC

Targeted Therapy for Unresectable Stage III NSCLC? No!

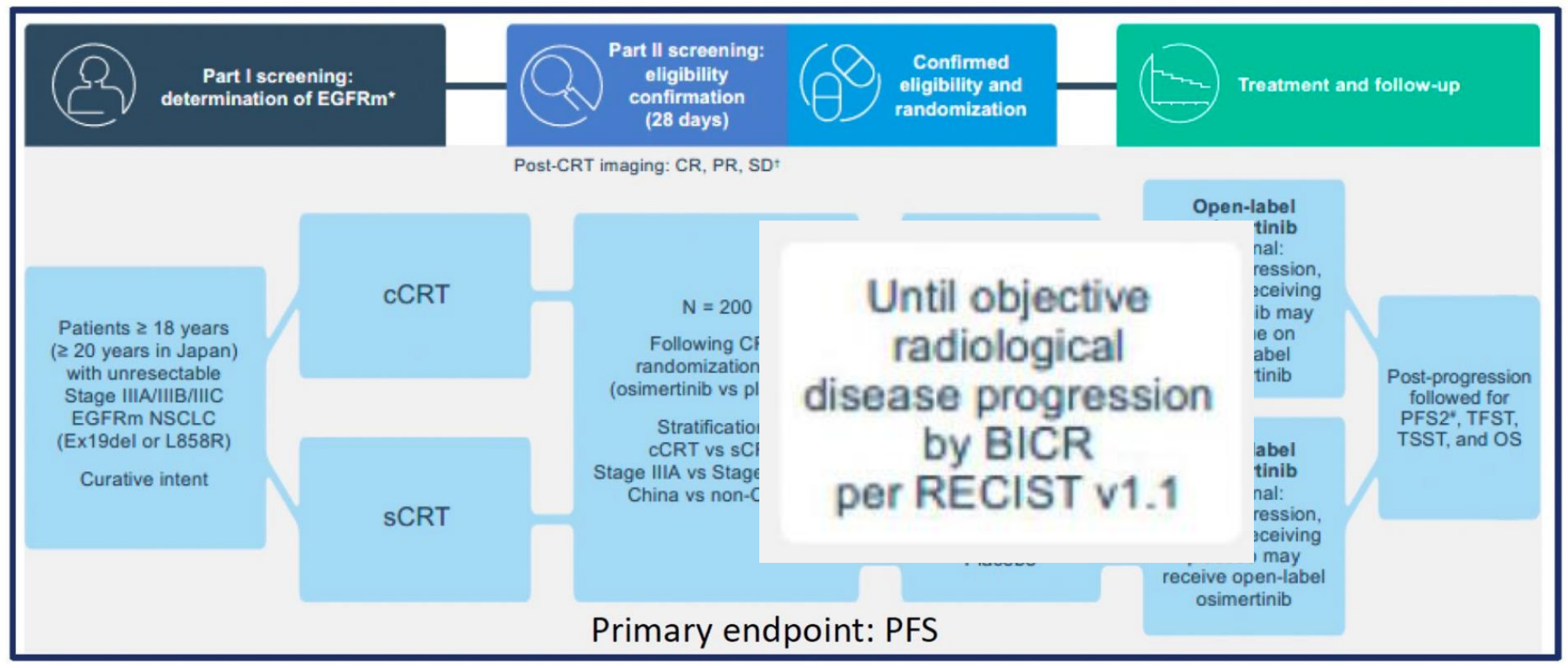
Follow the Data.

Bradley, JCO 2020

LAURA: Consolidation Osimertinib

Post-chemoradiation for EGFR-mt NSCLC, role for osimertinib?

Phase III registration trial, expecting results 2024



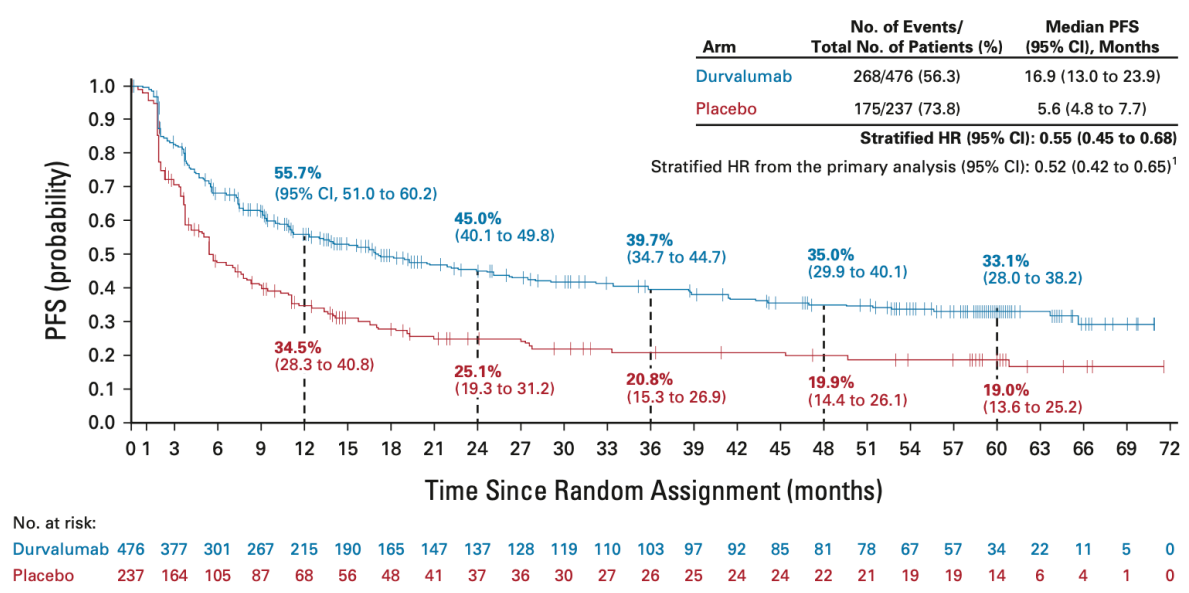
Lu, ESMO Asia 2020

Targeted Therapy for Unresectable Stage III NSCLC? No!

LAURA – osimertinib until progression

Lifelong therapy *for patients, some already cured with chemoradiation*

5y progression free survival rate 19% with standard chemoradiation



Spigel, JCO 2022

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Targeted Therapy for Unresectable Stage III NSCLC? No!

There are costs to overtreating our patients.

Bradley, JCO 2020

Targeted Therapy for Unresectable Stage III NSCLC? No!

LAURA – osimertinib until progression

Lifelong therapy *for patients, some already cured with chemoradiation*

$16,080.12 for 1 month of osimertinib

x 60 months ~ $1 million for 5y per patient

238,340 new diagnoses in the US per year

~20% sensitizing EGFR ~ 50K

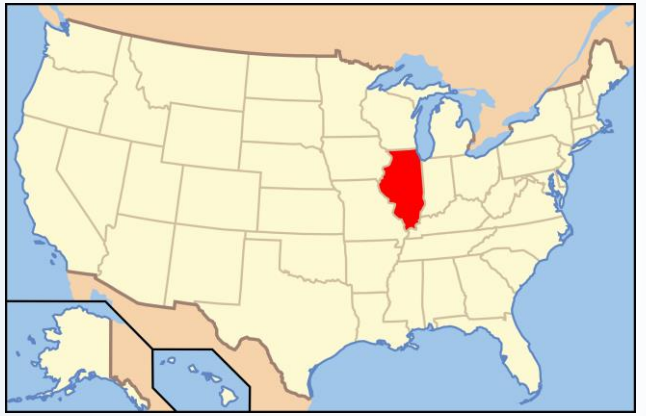
~22% locally advanced ~ 10K

Acceptable cost each year to treat patients already cured?

Siegel, CA Cancer.J Clin 2023

Targeted Therapy for Unresectable Stage III NSCLC? No!

Exorbitant financial cost to protect patients already cured



Spigel, JCO 2022

Targeted Therapy for Unresectable Stage III NSCLC? No!

LAURA trial recommends indefinite “adjuvant” osimertinib

Is this what “cure” looks like?

Some patients are already cured with chemoradiation

Massive healthcare system costs

Even a fraction of that as an out-of-pocket co-pay is significant

Additional cost in the form of chronic toxicity

Lu, ESMO Asia 2020

Targeted Therapy for Unresectable Stage III NSCLC? No!

Chronic toxicity in ADAURA

Adverse Event	Osimertinib (N=337)			
	Any Grade	Grade 1	Grade 2	Grade 3
Diarrhea	156 (46)	116 (34)	32 (9)	8 (2)
Paronychia	85 (25)	31 (9)	50 (15)	3 (1)
Dry skin	79 (23)	75 (22)	3 (1)	1 (<1)
Pruritus	65 (19)	49 (15)	16 (5)	0
Cough	62 (18)	43 (13)	19 (6)	0
Stomatitis	59 (18)	35 (10)	18 (5)	6 (2)
Nasopharyngitis	47 (14)	30 (9)	17 (5)	0
Upper respiratory tract infection	45 (13)	24 (7)	19 (6)	2 (1)
Decreased appetite	44 (13)	29 (9)	13 (4)	2 (1)
Mouth ulceration	39 (12)	32 (9)	7 (2)	0
Dermatitis acneiform	37 (11)	29 (9)	8 (2)	0

Wu, NEJM 2020

CTCAE Term	Grade 1	Grade 2	Grade 3
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL	Increase of >=7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL
Definition: A disorder characterized by an increase in frequency and/or loose or watery bowel movements.			
Paronychia	Nail fold edema or erythema; disruption of the cuticle	Local intervention indicated; oral intervention indicated (e.g., antibiotic, antifungal, antiviral); nail fold edema or erythema with pain; associated with discharge or nail plate separation; limiting instrumental ADL	Operative intervention indicated; IV antibiotics indicated; limiting self care ADL
Definition: A disorder characterized by an infectious process involving the soft tissues around the nail.			

Targeted Therapy for Unresectable Stage III NSCLC? No!

Another cost of lifelong targeted therapy?

Being a lifelong patient.

If you are taking a cancer medicine every day – are you ever cancer free?

Atlanta traffic among worst in the world, study finds

The Atlanta Journal-Constitution

Gridlock Guy: Breaking down Atlanta's top bottlenecks

Is there a fix for I-85 traffic?

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Targeted Therapy for Unresectable Stage III NSCLC? No!

Are patients who require lifelong targeted therapy cured?

Do patients who will relapse without targeted therapy really have stage III NSCLC?

Can we instead work to identify who is and who is not cured?

Targeted Therapy for Unresectable Stage III NSCLC? No!

Can we let patients who are cured from lung cancer – be cured?

Bradley, JCO 2020

Targeted Therapy for Unresectable Stage III NSCLC? No!

Can we save targeted therapy for the patients who need them?

Bradley, JCO 2020

Targeted Therapy for Unresectable Stage III NSCLC? No!

Targeted Therapy for Unresectable Stage III NSCLC? No!

Management of Stage III Non–Small-Cell Lung Cancer: ASCO Guideline

Megan E. Daly, MD[1]; Navneet Singh, MD, DM[2]; Nofisat Ismaila, MD, MSc[3]; Mara B. Antonoff, MD[4]; Douglas A. Arenberg, MD[5]; Jeffrey Bradley, MD[6]; Elizabeth David, MD[7]; Frank Detterbeck, MD[8]; Martin Früh, MD[9,10]; Matthew A. Gubens, MD, MS[11]; Amy C. Moore, PhD[12]; Sukhmani K. Padda, MD[13]; Jyoti D. Patel, MD[14]; Tanyanika Phillips, MD, MPH[15]; Angel Qin, MD[5]; Clifford Robinson, MD[16]; and Charles B. Simone II, MD[17]

Unresectable disease.

Recommendation 5.1. Patients with stage III NSCLC who are medically or surgically inoperable and with good performance status should be offered concurrent instead of sequential chemotherapy and radiation therapy (Type: Evidence based; benefit outweighs harm; Evidence quality: high; Strength of recommendation: strong).

Recommendation 5.2. Concurrent chemotherapy delivered with radiation therapy for definitive treatment of stage III NSCLC should include a platinum-based doublet, preferably cisplatin plus etoposide, carboplatin plus paclitaxel, cisplatin plus pemetrexed (non-squamous only), or cisplatin plus vinorelbine (Type: Evidence based; benefit outweighs harm; Evidence quality: high; Strength of recommendation: strong).

Qualifying Statement: Carboplatin may be substituted for cisplatin in patients with contraindications to or deemed ineligible for cisplatin.

Recommendation 5.3. Patients with stage III NSCLC who are not candidates for concurrent chemoradiation but are candidates for chemotherapy should be offered sequential chemotherapy and radiation therapy over radiation alone (Type: Evidence based; benefit outweighs harm; Evidence quality: high; Strength of recommendation: strong).

Recommendation 5.4. Patients with stage III NSCLC receiving concurrent chemoradiation should be treated to 60 Gy (Type: Evidence based; benefit outweighs harm; Evidence quality: high; Strength of recommendation: strong).

Recommendation 5.5. Doses higher than 60 Gy and up to 70 Gy may be considered for selected patients, with careful attention to doses to heart, lungs, and esophagus (Type: Evidence based; benefit outweighs harm; Evidence quality: low; Strength of recommendation: strong).

Recommendation 5.6. Patients with stage III NSCLC receiving definitive radiation without chemotherapy in standard fractionation may be considered for radiation dose escalation and for modest hypofractionation from 2.15 to 4 Gy per fraction (Type: Evidence based; benefit outweighs harm; Evidence quality: low; Strength of recommendation: weak).

Recommendation 5.7. Patients with stage III NSCLC receiving concurrent chemoradiation without disease progression during the initial therapy should be offered consolidation durvalumab for up to 12 months (Type: Evidence based; benefit outweighs harm; Evidence quality: high; Strength of recommendation: strong).

Qualifying Statement: There is insufficient evidence to alter the recommendation for consolidation durvalumab following concurrent chemoradiation for molecularly defined subgroups (namely, patients with an oncogenic driver alteration or those with low or no expression of programmed death-ligand 1).

Daly, JCO 2022

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Targeted Therapy for Unresectable Stage III NSCLC? No!

No – we should *not* use targeted therapies after chemoradiation

I believe patients can be cured with this treatment

If cured, patients do not need lifelong targeted therapy

If patients need lifelong targeted therapy, they are not cured

Treat when and if needed

Avoid unnecessary toxicity and cost

Vote No!