Advancements in Radiation Therapy

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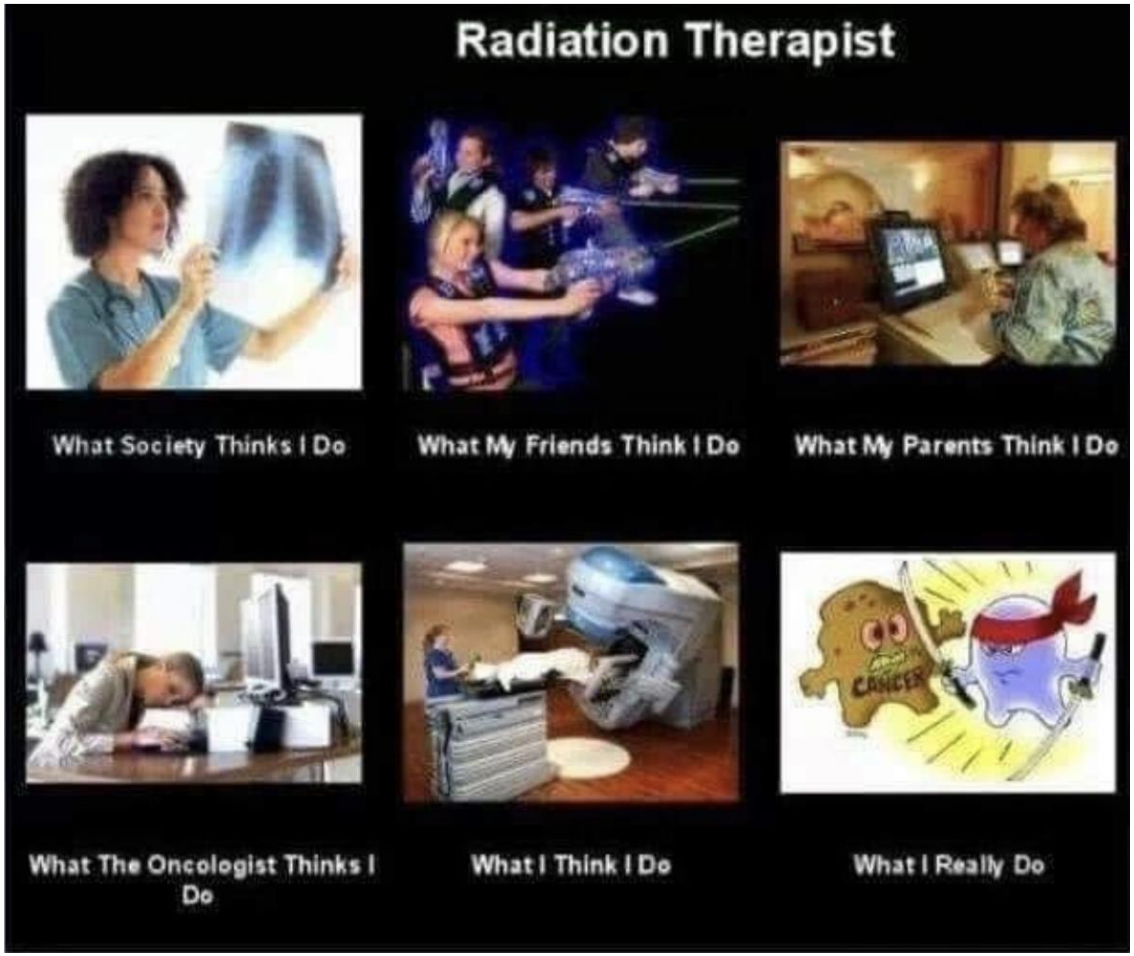
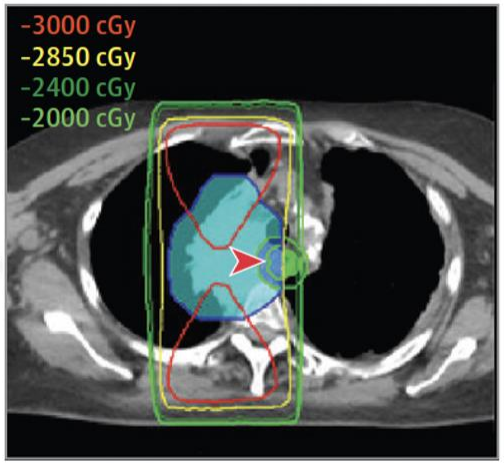
What is the role of Rad Onc?



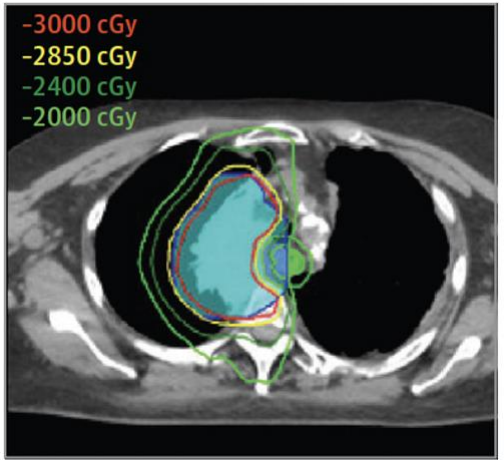
What type of RT is needed?

A POP



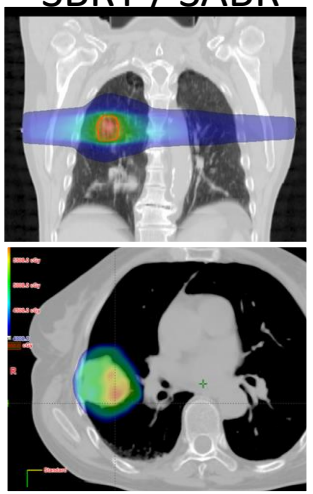
LOW TECH PALLIATIVE
HOURS TO DAYS

B ES-IMRT



HIGH TECH PALLIATIVE
1 - 2 WEEKS

SBRT / SABR



HIGH TECH ABLATIVE
1 - 2 WEEKS

Louie et al. JAMA Oncol 2022

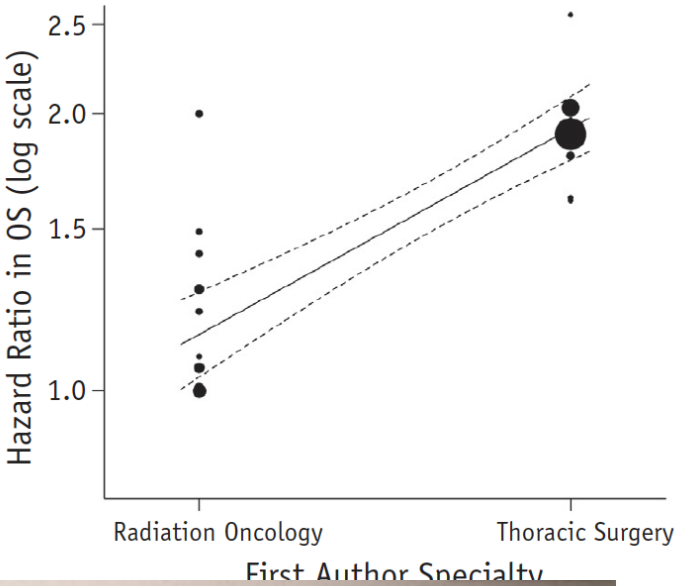
Early Stage NSCLC

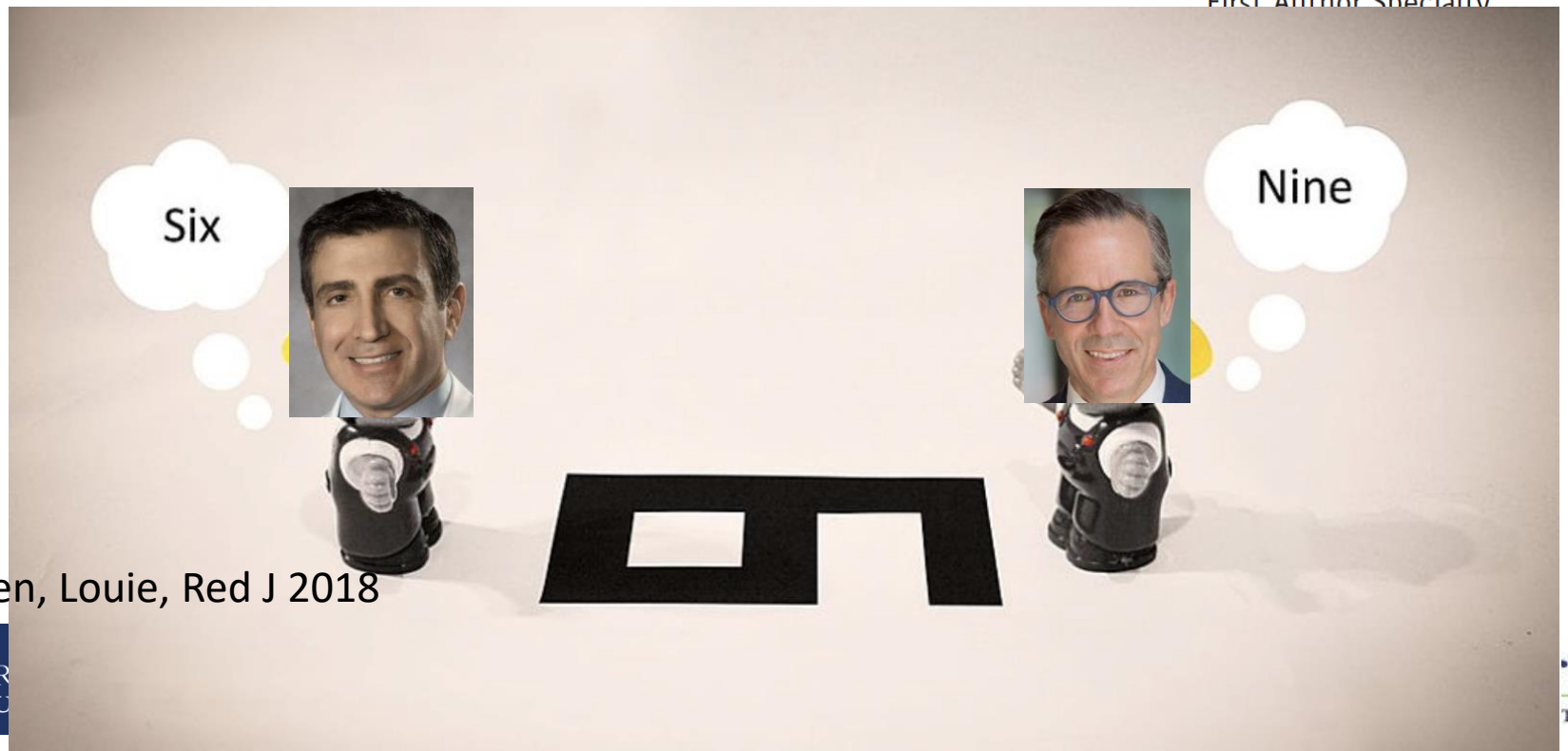
International Journal of Radiation Oncology biology • physics
www.redjournal.org

Clinical Investigation

Stereotactic Ablative Radiation Therapy Versus Surgery in Early Lung Cancer: A Meta-analysis of Propensity Score Studies

Hanbo Chen, MD,* Joanna M. Laba, MD,* R. Gabriel Boldt, MLIS,*
Christopher D. Goodman, MD,* David A. Palma, MD, PhD,*
Suresh Senan, MRCP, PhD,† and Alexander V. Louie, MD, PhD*





Chen, Louie, Red J 2018

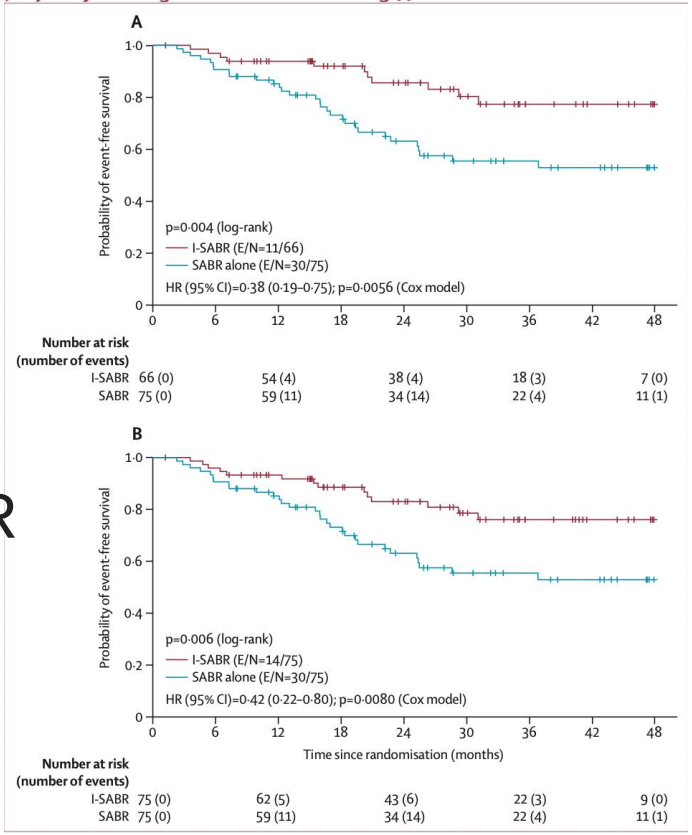
Stereotactic ablative radiotherapy with or without immunotherapy for early-stage or isolated lung parenchymal recurrent node-negative non-small-cell lung cancer: an open-label, randomised, phase 2 trial

Joe Y Chang, Steven H Lin, Wenli Dong, Zhongxing Liao, Saumil J Gandhi, Carl M Gay, Jianjun Zhang, Stephen G Chun, Yasir Y Elamin, Frank V Fossella, George Blumenschein, Tina Cascone, Xiuning Le, Jenny V Pozadzides, Anne Tsao, Vivek Verma, James W Welsh, Aileen B Chen, Mehmet Altan, Reza J Mehran, Ara A Vaporciyan, Stephen G Swisher, Peter A Balter, Junya Fujimoto, Ignacio I Wistuba, Lei Feng, J Jack Lee, John V Heymach

Primary endpoint 4-year EFS (LR, RR, DR, SPLC, death)

iSABR 53% vs. 77%

15% vs. 0% gr 3 toxicity in iSABR arm



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RCTs of SBRT +/- IO

Table 1 Select randomized active trials combining immunotherapy and radiation therapy in NSCLC

Trial name/NCT number	Phase	Stage/inclusion	ICB agent	Trial design	RT technique/dose	RT and ICB timing
Early stage						
SWOG/ NRG S1914 NCT04214262	3	Stage I–II	Atezolizumab	SBRT +/– ICB up to 5 months	SBRT	ICB first, then SBRT and ICB concurrent, then ICB adjuvant
PACIFIC 4 NCT03833154	3	Stage I–II	Durvalumab	SBRT +/– ICB up to 24 months	SBRT	SBRT first, ICB adjuvant
I-SABR NCT03110978	2R	Stage I–IIA	Nivolumab	SBRT +/– ICB up to 3 months	SBRT to 50 Gy/4 fx, or (if constraints cannot be met) 70 Gy/10 fx	SBRT and IO concurrent
ASTEROID NCT03446547	2R	Stage I	Durvalumab	SBRT +/– ICB up to 12 months	SBRT in 3 or 4 fractions	SBRT first, ICB adjuvant

Beware ILD!

Patients with fibrotic (ILD) are at a higher risk of pneumonitis!

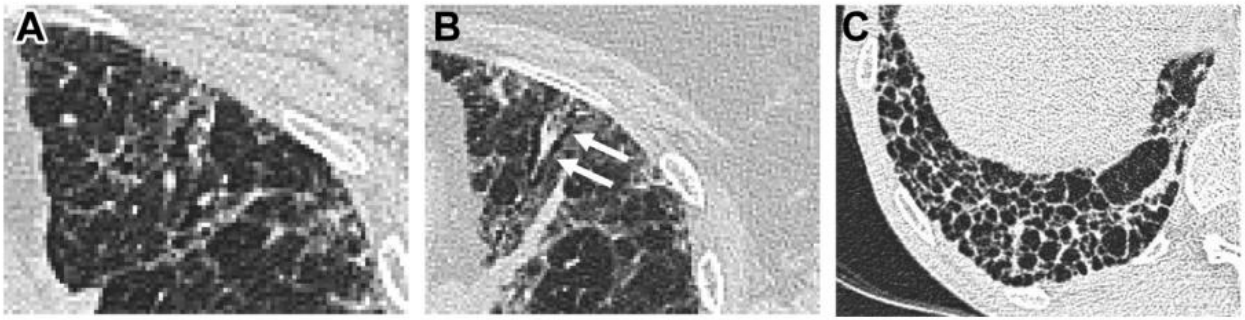
Critical Review

Treatment-Related Toxicity in Patients With Early-Stage Non-Small Cell Lung Cancer and Coexisting Interstitial Lung Disease: A Systematic Review

Hanbo Chen, MD,* Suresh Senan, MRCP, FRCR, PhD,†
Esther J. Nossent, MD,‡ R. Gabriel Boldt, RLIS,* Andrew Warner, MSc,*
David A. Palma, MD, PhD, FRCPC,* and
Alexander V. Louie, MD, PhD, FRCPC*

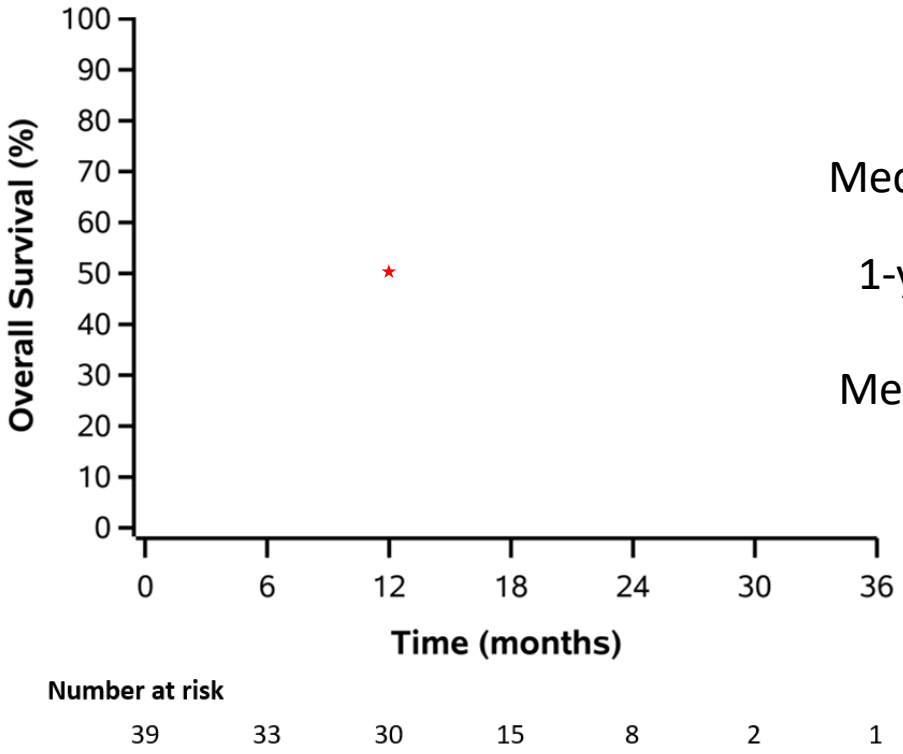
Department of Radiation Oncology, London Health Sciences Centre, London, Ontario, Canada, and Departments of †Radiation Oncology and ‡Pulmonology, VU University Medical Center, Amsterdam, The Netherlands

Group	Mortality	Toxicity
All ILD subtypes	15.6%	25%
IPF only studies	33%	71%



Subpleural reticulation Traction bronchiectasis Honeycombing

ASPIRE ILD – (n=39)



Median follow-up: 19 months (IQR: 14-25 months)

1-year OS: 79% (95% CI 62-89%, p<0.001)

Median OS 25 months (95% CI 14 months – not reached)

Toxicity

Adverse Event (includes all events per patient)	G1	G2	G3	G4	G5
Back pain	1	-	-	-	-
Bronchopulmonary hemorrhage	-	-	1	-	-
Cough	1	-	-	-	-
Dyspnea	1	3	2	-	2
Esophagitis	-	1	-	-	-
Fatigue	4	1	-	-	-
Lung infection	-	-	1	-	-
Nausea	-	1	-	-	-
Non-cardiac chest pain	-	1	-	-	-
Pleural effusion	-	1	-	-	-
Pneumonitis	-	1	2	-	-
Pulmonary fibrosis	2	-	-	-	-
Respiratory failure	-	-	-	-	1

Three grade 5 events (7.7%), all due to respiratory deterioration

- 3.7, 4.2, and 13 months post-SABR
- 2 in patients with CTD-ILD and 1 with IPF

- Four patients (10%) gr 3 events

Locally Advanced NSCLC

Locally advanced NSCLC is a heterogenous group

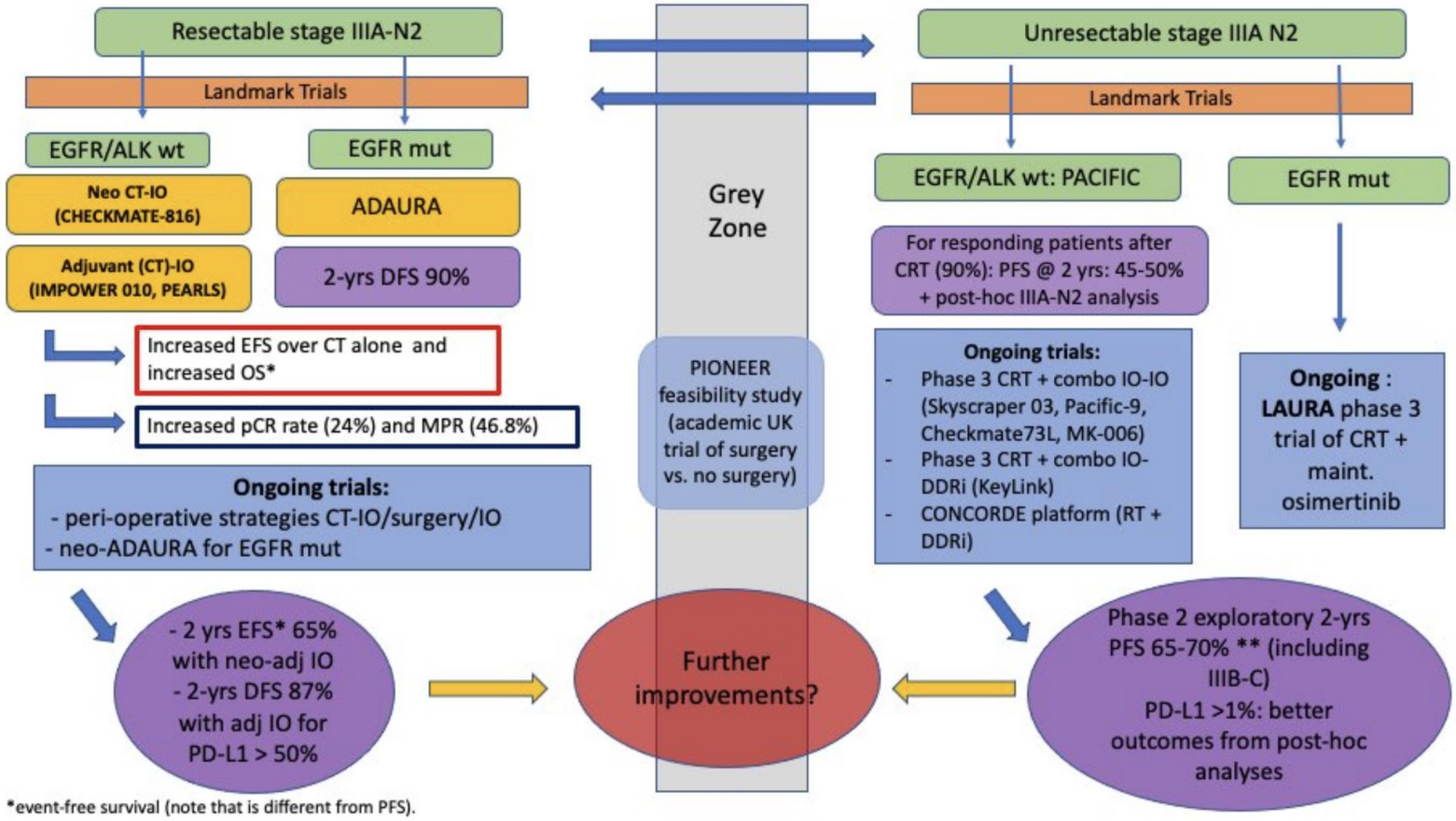


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Figure – @AndreaisDr

Dr Alex Xouie

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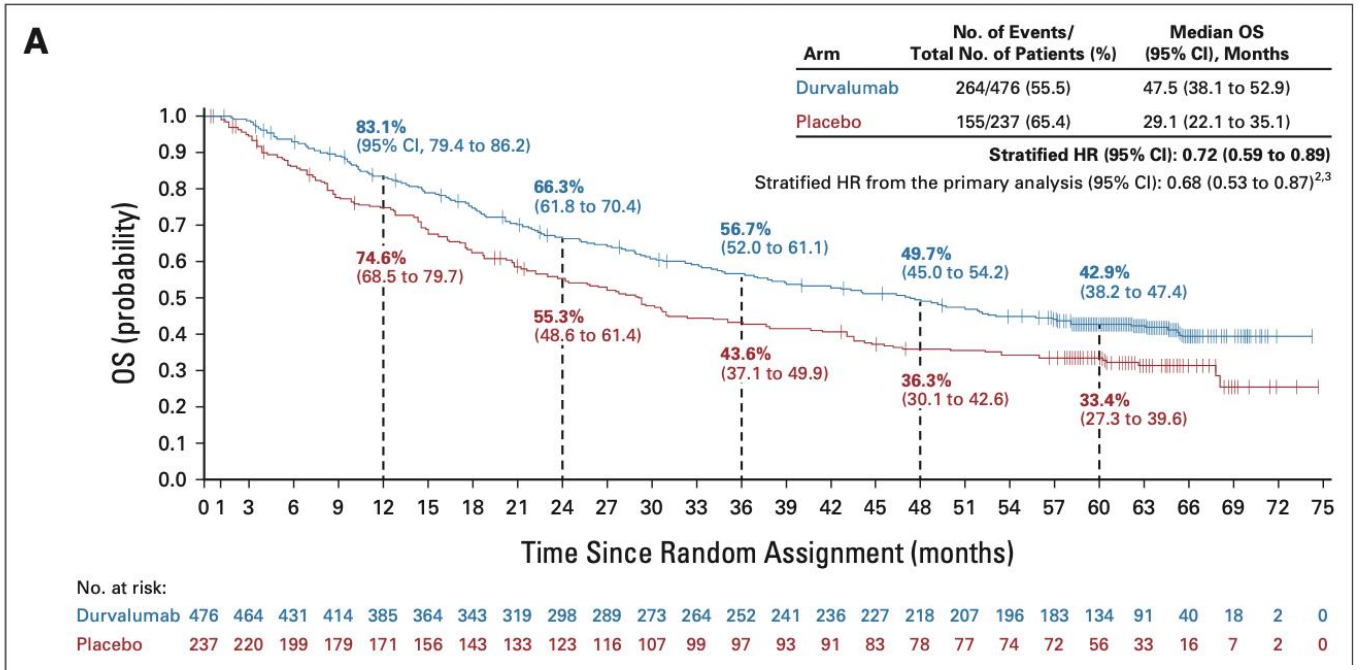
	N0	N1	N2 SINGLE (non-bulky, non-invasive)	N2 MULTI (non-bulky, non-invasive)	N2 BULKY[¶]	N2 INVASIVE	N3
T1-2	NOT STAGE III DISEASE	NOT STAGE III DISEASE	RESECTABLE	POTENTIALLY RESECTABLE*	UNCLEAR	UNRESECTABLE	UNRESECTABLE
T3 size / satellite / invasion	NOT STAGE III DISEASE	RESECTABLE	RESECTABLE	POTENTIALLY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

***Multiple station N2**: case-by-case discussion; the exact number of nodes/stations cannot be defined
[¶]**Bulky N2**: lymph nodes with a short-axis diameter >2.5-3 cm; in specific situations of *highly selected patients*, including those patients in multidisciplinary trials with surgery as local therapy can be discussed
[§]Some **T4 tumours by infiltration of major structures** are potentially resectable – see Table 1

Figure – Brandao WCLC 2023

Five-Year Survival With Durvalumab After CRT in Stage III NSCLC

Spigel JCO 2022



Summary of neoadjuvant/perioperative trials

	CM-816 (n=358)	KN-671 (n-786)	AEGEAN (n=802)
Squamous	48.6%	43.1%	46.2%
AJC 8th ed Stage II **Stage IIIA** **Stage IIIB**	AJCC 7th) IB/II 36% IIIA 63%	29.7% 54.7% 15.6%	28.4% 47.3% 24.0%
Pneumonectomy allowed	Yes	Yes	No
EGFR/ALK allowed	No	Yes, included in analysis	Yes, not included in mITT analysis
Chemo regimen	Investigator discretion	Cis/Pem, Cis/Gem only	Investigation discretion
Primary endpoint	EFS & pCR	EFS & OS	EFS (mITT) & pCR
EFS 24 months	63.8% (HR 0.63)	62.4 % (HR 0.58)	63.3% (HR 0.68)
pCR rate	24%	18%	17.2%
Surgical resection rate	83.2%	82.1%	80.6%
Started adjuvant therapy	N/A	73.2%	65.8%

* Subgroups: squamous didn't do as well with CM-816, ~ Aegean; PD-L1 increasing levels = greater benefit

- Up to 20% of patients pot neo-IO do not undergo surgery. Data from CM816 below

	Nivolumab plus Chemotherapy (N = 179)	Chemotherapy (N = 179)
Patients with definitive surgery* — no. (%)	149 (83.2)	135 (75.4)
Time from last neoadjuvant dose to definitive surgery — wk		
Median (IQR)	5.3 (4.6–6.0)	5.0 (4.6–5.9)
Patients with cancelled definitive surgery — no. (%)	28 (15.6)	37 (20.7)
Disease progression	12 (6.7)	17 (9.5)
Adverse event	2 (1.1)	1 (0.6)
Other†	14 (7.8)	19 (10.6)

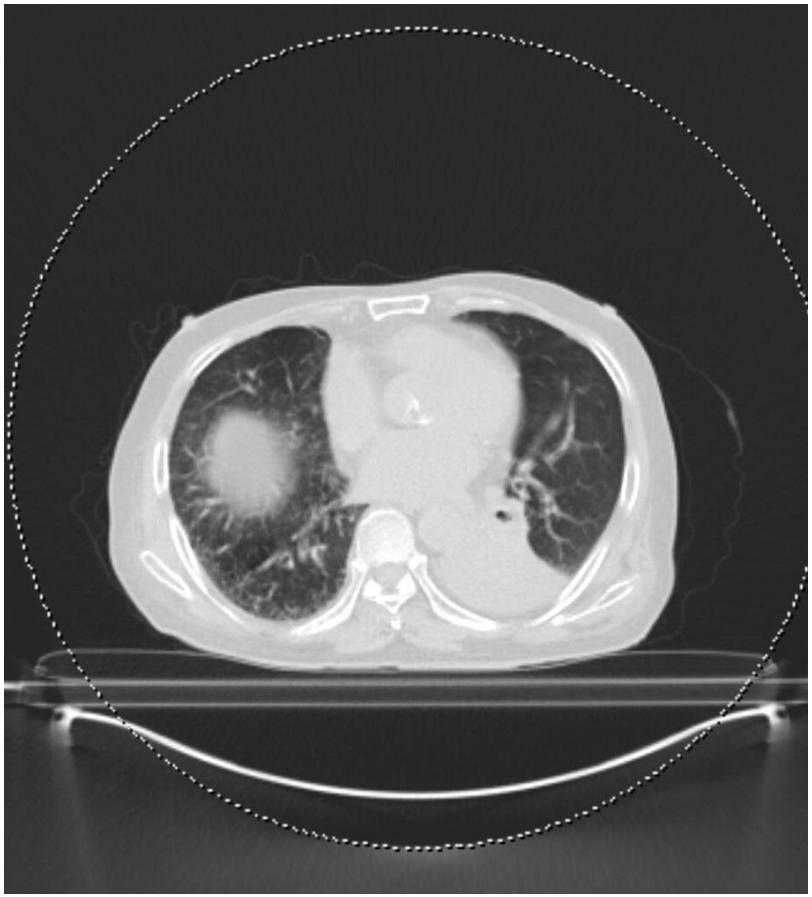
chemotherapy group.

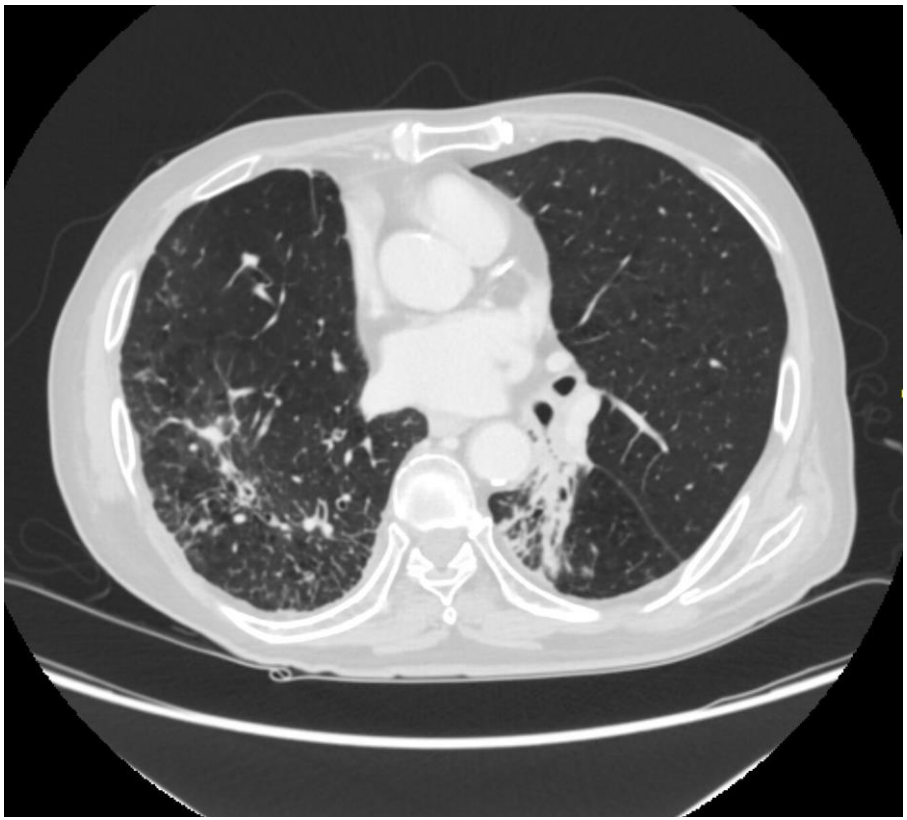
† Other reasons were patient refusal in 9 patients in the nivolumab plus chemotherapy arm and 8 patients in the chemotherapy arm; consent withdrawal in 3 patients in the chemotherapy arm; COVID-19 in 1 patient in the chemotherapy arm; unfit for surgery due to poor lung function in 2 patients in the nivolumab plus chemotherapy arm and 4 patients in the chemotherapy arm; and unresectability in 2 patients in each arm.

‡ Time from last dose to neoadjuvant surgery >6 weeks.

NEO-IO, but no surgery, what next?

Neo-IO patient, with good response but pneumonitis





EGFR+ patients

LAURA

Osimertinib Maintenance After Definitive Chemoradiation in Patients With Unresectable EGFR Mutation Positive Stage III Non–small-cell Lung Cancer: LAURA Trial in Progress

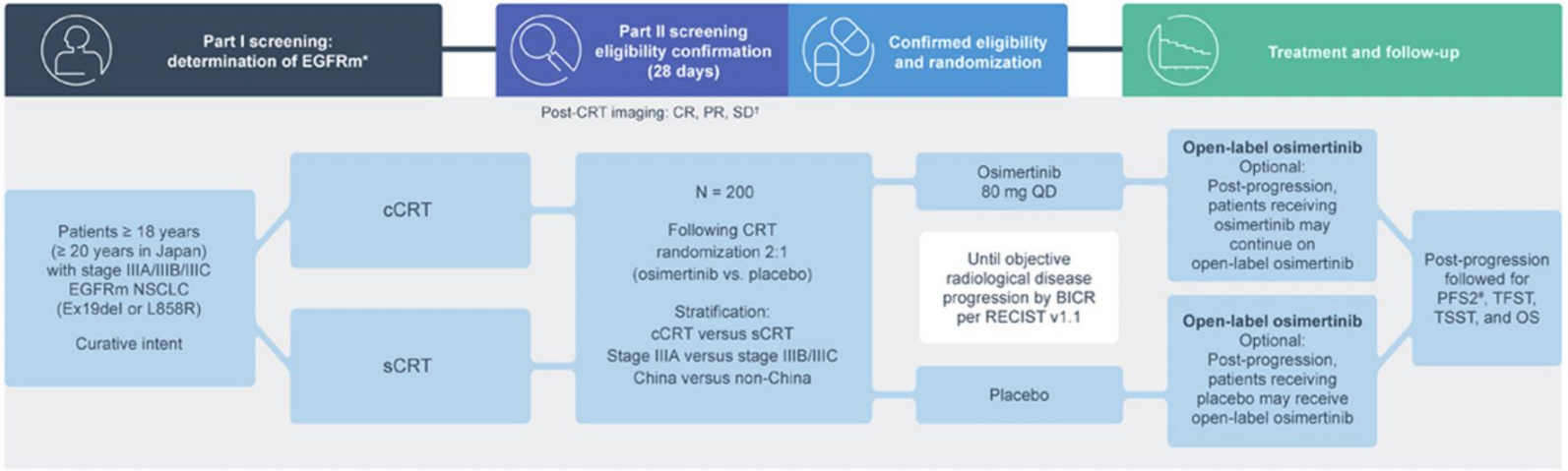
LAURA trial (NCT03521154) is recruiting
First patient enrolled **July 2018**
Primary data readout expected **late 2022**
Study completion **2026**

TRIAL OVERVIEW

Study design:
Phase III
Double-blind
Randomized
Placebo-controlled

Objective:
To evaluate the efficacy and safety of osimertinib as maintenance therapy in patients with locally advanced, unresectable, EGFRm, stage III NSCLC without disease progression during/ following definitive platinum-based CRT

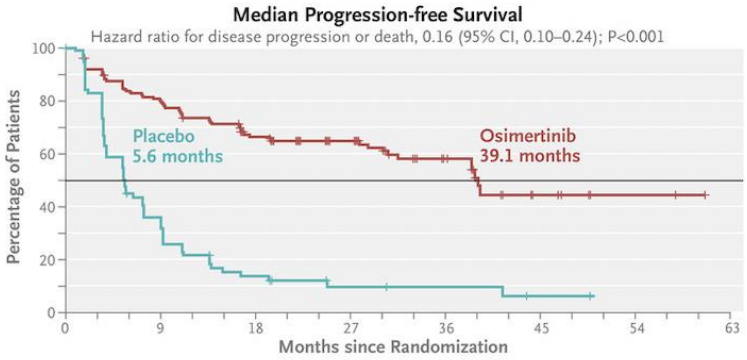
Primary endpoint: PFS by BICR per RECIST v1.1
Key secondary endpoints:
CNS PFS, OS, PFS by mutation status, and safety (adverse events by CTCAE v5)



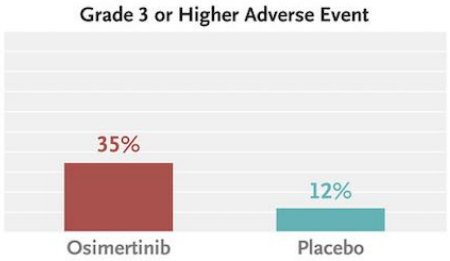
*Patients with a local cobas® EGFR Mutation Test v2 tissue positive result from a CLIA-certified or accredited laboratory do not require part I screening. †Post-CRT imaging performed to assess CR, PR and SD up to 28 days before randomization. #Assessment of PFS2 will not be collected after the primary PFS analysis.

RESULTS

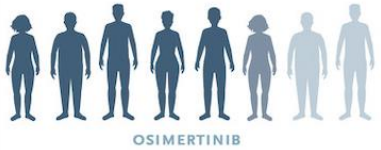
Median progression-free survival was significantly longer in the osimertinib group than in the placebo group. Interim data on overall survival showed no significant difference between the two groups.



Adverse events with osimertinib were consistent with findings in previous studies. Radiation pneumonitis of grade 1 or 2 was reported in 48% of patients receiving osimertinib and in 38% of those receiving placebo.



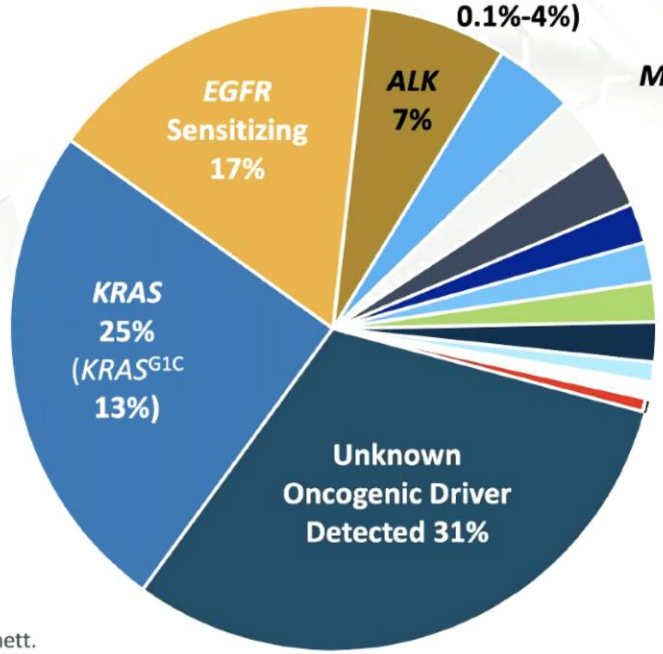
12-MONTH SURVIVAL DATA



Nearly three fourths of osimertinib recipients were alive and progression free at 12 months, as compared with nearly one fourth of placebo recipients.

Stage IV

~50% OF PATIENTS WITH ADV NONSQ NSCLC HAVE A DRIVER MUTATION TARGETABLE WITH AN FDA-APPROVED AGENT OR ON A CLINICAL TRIAL



ALK:
Crizotinib
Alectinib
Ceritinib
Lorlatinib
Brigatinib

***EGFR* Sensitizing:**
Gefitinib
Erlotinib
Afatinib
Osimertinib
Dacomitinib

***KRAS*^{G12C}:**
Sotorasib†
Adagrasib

***EGFR* Other 4%**
(*EGFR*ex20ins 0.1%-4%)

***MET* 3%**

>1 Mutation 3%

***ROS1* 2%**
***BRAF* 2%**
***RET* 2%**
***NTRK1* 1%**
***PIK3CA* 1%**
***MEK1* <1%**

EGFRex20ins:
Amivantamab*
Mobocertinib

***BRAF* V600E:**
Dabrafenib‡

***RET* fusion:**
Selpercatinib
Pralsetinib

***NTRK* fusion:**
Entrectinib
Larotrectinib

***MET*ex14:**
Capmatinib
Tepotinib

HER2
Trastuzumab deruxtecan

***ROS1*:**
Crizotinib
Entrectinib

Li. JCO. 2013;31:1039. Tsao. JTO. 2016;11:613. Burnett. PLoS One. 2021;16:e0247620. Nassar. NEJM. 2021;384:185.

Ramalingam CLCCO 2022

Research Letter

FREE

April 4, 2019

Analysis of Toxic Effects With Antiangiogenic Agents Plus Stereotactic Body Radiation in Ultra-central Lung Tumors

Chunyu Wang, MD[1]; Andreas Rimner, MD[1]; Daphna Y. Gelblum, MD[1]; et al

» Author Affiliations

JAMA Oncol. 2019;5(5):737-739. doi:10.1001/jamaoncol.2019.0205

Table. Clinical Characteristics of Patients With SBRT-related Fatal Pulmonary Hemorrhage

Clinical Scenario	Antiangiogenic Agent (Interval Before/After SBRT, d)[a]	SBRT Dose, Gy/Fractions, No.	PTV, mL	Maximum Point Dose to PBT, Gy	Other Grade ≥3 Toxic Effects
Oligometastatic NSCLC	Bevacizumab (14/14)	45/5	100	49.4	None
Oligometastatic colorectal cancer	Bevacizumab (6/5)	50/5	95	51.4	None
Oligoprogressive NSCLC	Bevacizumab (30/230)	60/15	100	65.2	Grade 4 tracheal necrosis
					Grade 3 tracheoesophageal fistula
Oligometastatic renal cell carcinoma	Pazopanib (30/140)	60/15	335	65.9	Grade 3 pneumomediastinum
T2aN0 NSCLC	No	60/8	133	63.8	None
Metastatic NSCLC	No	50/5	63	55	None

Wang, JAMA Oncol 2019

CRITICAL REVIEW | VOLUME 92, ISSUE 3, P568-576, JULY 01, 2015

Gastrointestinal Toxicities With Combined Antiangiogenic and Stereotactic Body Radiation Therapy

Erqi L. Pollom, MD • Lei Deng, MBBS • Reetesh K. Pai, MD • J. Martin Brown, PhD • Amato Giaccia, PhD • Billy W. Loo Jr., MD, PhD • David B. Shultz, MD, PhD • Quynh Thu Le, MD • Albert C. Koong, MD, PhD • Daniel T. Chang, MD • Show less

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Radiotherapy and Oncology 152 (2020) 96–100

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journal homepage: www.thegreenjournal.com

Short Communication

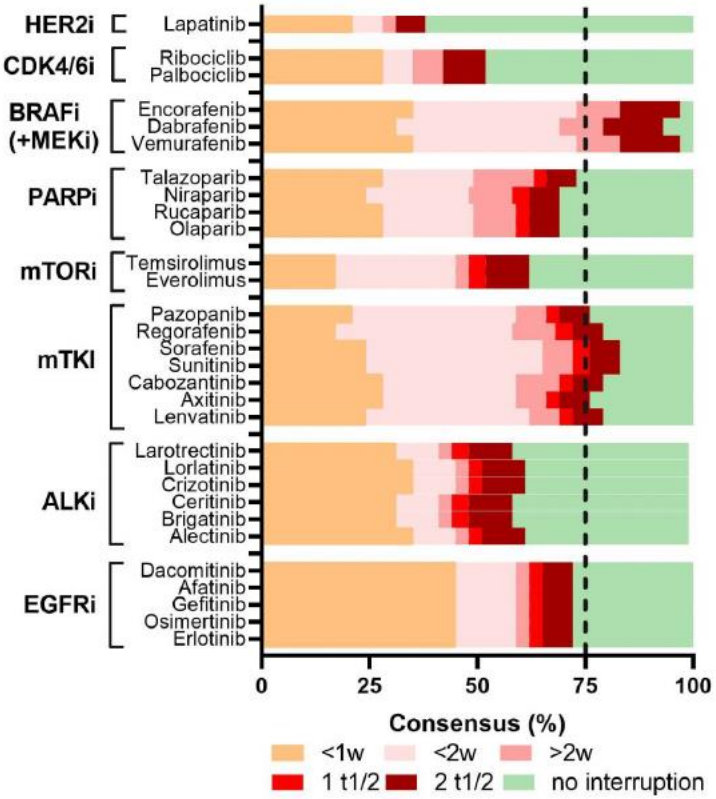
An especially high rate of radiation pneumonitis observed in patients treated with thoracic radiotherapy and simultaneous osimertinib

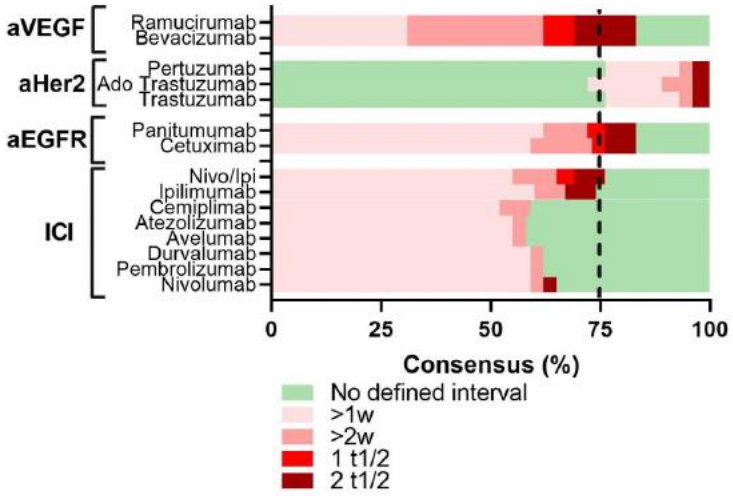
Wenxiao Jia [a], Hongbo Guo [b], Wang Jing [c], Xuquan Jing [c], Ji Li [c], Min Wang [c], Jinming Yu [c,a,*], Hui Zhu [c,a,*]

Highlights

- Risk of RP for patients simultaneous TRT and Osimertinib was first reported.
- 63.6% patients exhibited grade 2 or worse RP when simultaneous Osimertinib and TRT.
- One patient experienced a fatal RP when treated with Osimertinib and simultaneous TRT.

Jia, Radiother Oncol 2020





Kroeze, Lancet Onc 2023

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