# Important Trials Recently Reported

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Ginsberg Day
March 12, 2021



# Disclosures

Commercial Interest	Relationship(s)	
Astra Zeneca	Advisory Board for Aduara Trial dissemination	
Pacira Pharmaceuticals	Advisory Board	
On Target Laboratories	Steering Committee for ELUCIDATE trial	



### Overview

- Nelson Trial
- Violet Trial
- Adaura
- LCMC3
- Nadim
- Lung ART
- Mature results of PACIFIC
- RTOG 1010
- Checkmate 577



# Nelson Trial - Lung Cancer Screening



### Nelson Trial – 2/6/20 NEJM

- Age 50-74, current and former smokers, 13195 men, 2594 women
- CT screen vs nothing
- 10 year follow up
- 24% reduction in lung cancer mortality overall
- 33% for women
- Further substantiates NLST results!

#### Reduced Lung-Cancer Mortality with Volume CT Screening in a Randomized Trial

H.J. de Koning, C.M. van der Aalst, P.A. de Jong, E.T. Scholten, K. Nackaerts, M.A. Heuvelmans, J.-W.J. Lammers, C. Weenink, U. Yousaf-Khan, N. Horeweg, S. van 't Westeinde, M. Prokop, W.P. Mali, F.A.A. Mohamed Hoesein, P.M.A. van Ooijen, J.G.J.V. Aerts, M.A. den Bakker, E. Thunnissen, J. Verschakelen, R. Vliegenthart, J.E. Walter, K. ten Haaf, H.J.M. Groen, and M. Oudkerk

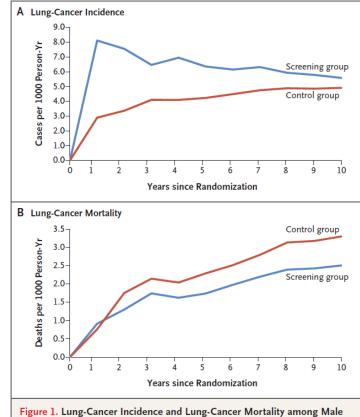


Figure 1. Lung-Cancer Incidence and Lung-Cancer Mortality among Male Participants.

Panel A shows the cumulative lung-cancer incidence (per 1000 person-years) according to follow-up year since randomization. Panel B shows the cumulative lung-cancer mortality (per 1000 person-years) according to follow-up year since randomization. Cause of death (with known date of lung-cancer diagnosis) was defined by the cause-of-death committee, if available, or by vital-statistics registries.



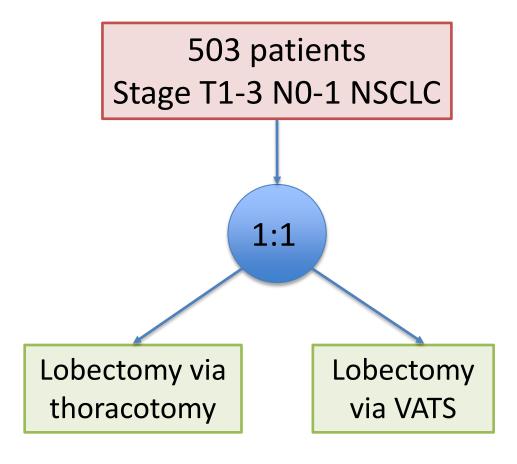
# Violet Trial – VATS v Open Lobectomy





In Hospital Clinical Efficacy, Safety and Oncologic Outcomes from VIOLET: A UK Multi-Centre RCT of VATS Versus Open Lobectomy for Lung Cancer

Eric Lim, Tim Batchelor, Joel Dunning, Michael Shackcloth, Vladimir Anikin, Babu Naidu, Elizabeth Belcher, Mahmoud Loubani, Vipin Zamvar, Tim Brush, Lucy Dabner, Rosie Harris, Dawn Phillips, Chloe Beard, Holly McKeon, Sangeetha Paramasivan, Daisy Elliott, Alba Realpe Rojas, Elizabeth Stokes, Sarah Wordsworth, Jane Blazeby, Chris Rogers, The Violet Trialists



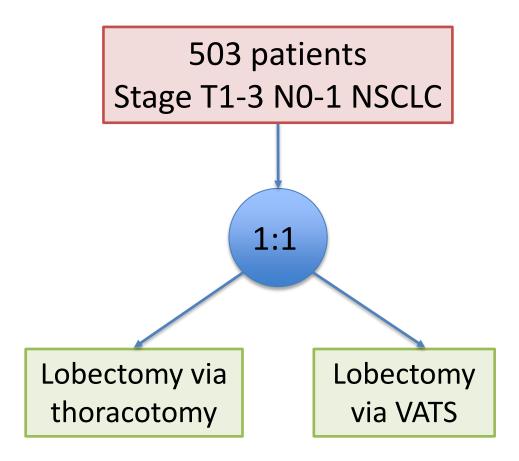
#### **Primary endpoint:**

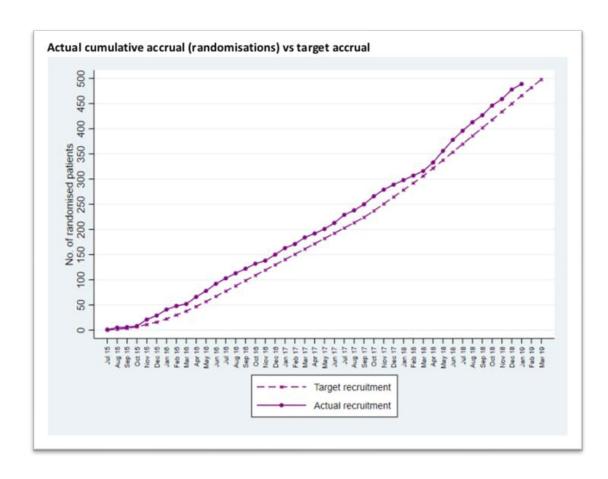
Quality of life at 5 weeks postop

#### **Secondary endpoints:**

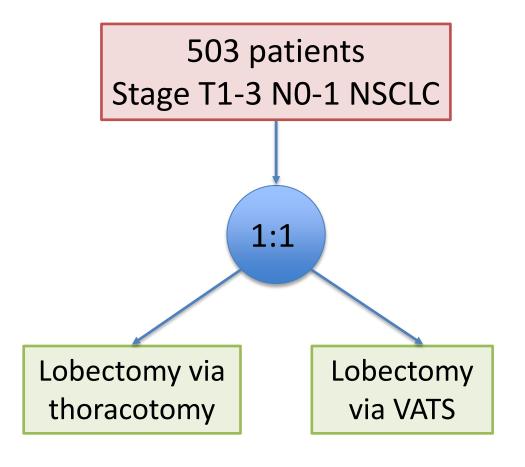
- Pain
- Complications
- Length of stay
- Nodal upstaging
- Quality of life at 1 year













#### In hospital results:

Pain

Complications

Length of stay

Nodal upstaging

Little difference

32.8% VATS vs. 44.3%

4 days VATS vs. 5 days

No difference

Adaura Trial – Adjuvant Osimertinib (EGFR inhibitor) for Resected IB – IIIA Lung Cancer



CONQUERING THORACIC CANCERS WORLDWIDE

### Postoperative chemotherapy use and outcomes from ADAURA: Osimertinib as adjuvant therapy for resected EGFR mutated NSCLC

<u>Yi-Long Wu</u><sup>1</sup>, Thomas John<sup>2</sup>, Christian Grohe<sup>3</sup>, Margarita Majem<sup>4</sup>, Jonathan W Goldman<sup>5</sup>, Sang-We Kim<sup>6</sup>, Terufumi Kato<sup>7</sup>, Konstantin Laktionov<sup>8</sup>, Huu Vinh Vu<sup>9</sup>, Zhijie Wang<sup>10</sup>, Shun Lu<sup>11</sup>, Kye Young Lee<sup>12</sup>, Charuwan Akewanlop<sup>13</sup>, Chong-Jen Yu<sup>14</sup>, Filippo de Marinis<sup>15</sup>, Laura Bonanno<sup>16</sup>, Manuel Domine<sup>17</sup>, Frances A Shepherd<sup>18</sup>, Lingmin Zeng<sup>19</sup>, Ajlan Atasoy<sup>20</sup>, Roy S Herbst<sup>21</sup>, Masahiro Tsuboi<sup>22</sup>

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Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China; "Lung Cancer Center, Shanghai Chest Hospital, Shanghai Jiao Tong
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Haven, CT, USA; "Department of Thoracic

#### ADAURA Phase III double-blind study design

Patients with completely resected stage\* IB, II, IIIA NSCLC, with or without adjuvant chemotherapy\*

#### Key inclusion criteria:

≥18 years (Japan / Taiwan: ≥20)

WHO PS 0 / 1

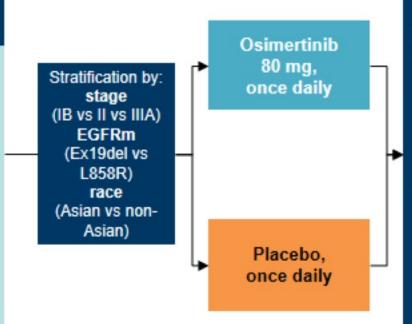
Confirmed primary non-squamous NSCLC Ex19del / L858R‡

MRI or CT scan of the brain prior to surgery or randomization

Complete resection with negative margins<sup>1</sup>
Maximum interval between surgery and randomization:

- 10 weeks without adjuvant chemotherapy
- 26 weeks with adjuvant chemotherapy

Adjuvant chemotherapy use was per physician and patient choice, and should have consisted of a platinum-based doublet for ≤4 cycles



<u>Planned treatment duration: three</u> <u>years</u>

#### Treatment continues until:

- Disease recurrence
- Treatment completed
- Discontinuation criterion met

#### Follow up:

- Until recurrence: Week 12 and 24, then every 24 weeks to 5 years, then yearly
- After recurrence: every 24 weeks for 5 years, then yearly
- The primary and key secondary endpoints of DFS<sup>§</sup> in stage II / IIIA patients and the overall population, respectively, have been reported previously<sup>1</sup>
- Here we report an exploratory analysis of adjuvant chemotherapy use and outcomes in ADAURA

Wu et al. N Engl J Med 2020;383:1711–23. NCT02511108; ADAURA data cut-off: January 17, 2020.

\*AJCC 7th edition; disease staging based on electronic case report forms for baseline characteristics data, and interactive voice response system for efficacy data (per statistical analysis plan);

†Prior, post, or planned radiotherapy was not allowed; †Centrally confirmed in tissue; †Patients received a CT scan after resection and within 28 days prior to treatment; †By investigator assessment.

AJCC, American Joint Committee on Cancer; CT, computed tomography; Ex19del, exon 19 deletion; IDMC, Independent Data Monitoring Committee; MRI, magnetic resonance imaging; PS, performance status;

WHO, World Health Organization.

#### **Baseline characteristics**

Patients, %	Osimertinib (n=339)	Placebo (n=343)
Sex: male / female	32 / 68	28 / 72
Age: median (range), years	64 (30-86)	62 (31–82)
Smoking status*: smoker / non-smoker	32 / 68	25 / 75
Race: Asian / non-Asian	64 / 36	64 / 36
WHO PS: 0 / 1	64 / 36	64 / 36
Brain imaging at randomization†: MRI / CT / neither	54 / 45 / <1	48 / 52 / 0
AJCC staging at diagnosis (7th edition)‡: IB / II / IIIA	32 / 34 / 35	32 / 34 / 34
Histology: adenocarcinoma / other¶	96 / 4	97 / 3
EGFR mutation at randomization§: Ex19del / L858R	55 / 45	55 / 45
Adjuvant chemotherapy: yes / no	60 / 40	60 / 40

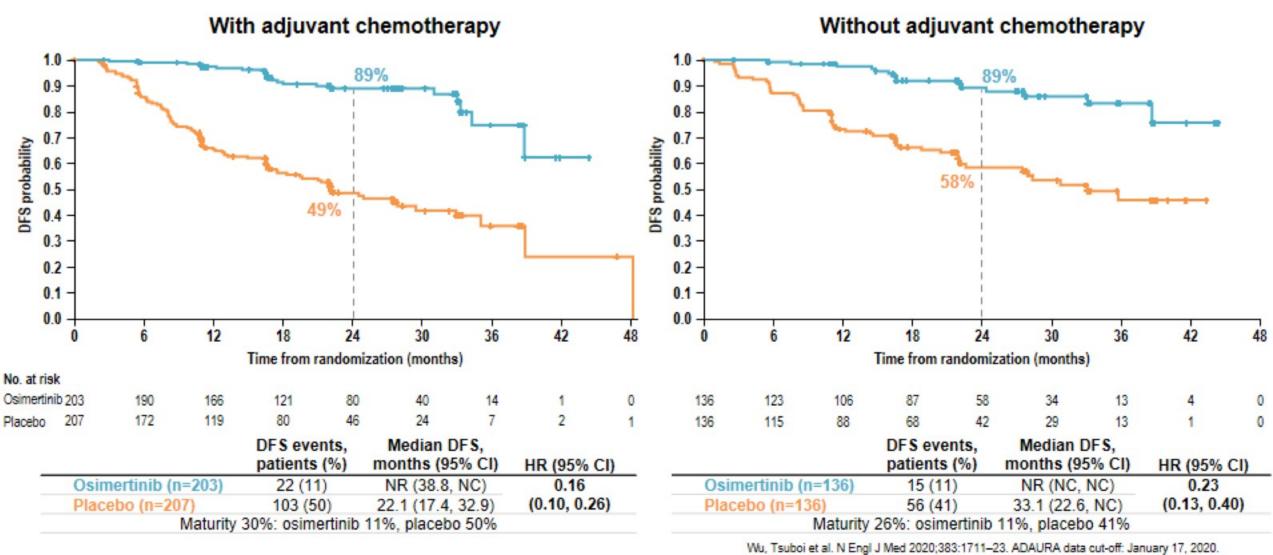
Wu, Tsuboi et al. N Engl J Med 2020;383:1711–23. ADAURA data cut-off: January 17, 2020.

\*Former: osimertinib n=104, placebo n=83; current: osimertinib n=4, placebo n=3; never: osimertinib n=231, placebo n=257;

\*If not performed prior to surgery, brain MRI or CT scans were performed prior to randomization. Imaging methods used at baseline (MRI or CT) were required to be used at each subsequent follow-up assessment;

\*Tumor size data were not collected; \*Includes bronchial gland carcinoma (NOS): osimertinib n=1; placebo n=2; malignant adenosquamous carcinoma: osimertinib n=4; placebo n=5; other: osimertinib n=8; placebo n=4; \*Central test. Column percentages may sum to greater than 100%.

# DFS in patients with and without adjuvant chemotherapy (overall population)



Tick marks indicate censored data. NC, not calculable, NR, not reached.

#### Conclusions

- In ADAURA, adjuvant chemotherapy use prior to randomization was balanced across treatment arms, and in line with uptake observed in previous studies and clinical practice<sup>1,2</sup>
- As expected, younger age (<70 years) and higher disease stage were associated with increased chemotherapy use, compared with older age (≥70 years) and lower disease stage
- A clinically meaningful DFS benefit with osimertinib was observed in patients with and without adjuvant chemotherapy (DFS HR of 0.16 and 0.23, respectively), regardless of disease stage
- Higher disease recurrence rates observed among patients in the placebo arm who received adjuvant chemotherapy compared with those who did not were likely driven by the large proportion of patients with stage II / IIIA disease, as disease stage is a prognostic factor for clinical outcome<sup>3</sup>

DFS benefit with osimertinib versus placebo was observed irrespective of whether patients received prior chemotherapy or not, supporting that adjuvant osimertinib will provide a highly effective treatment for patients with stage IB / II / IIIA EGFRm NSCLC after resection, with or without adjuvant chemotherapy as indicated



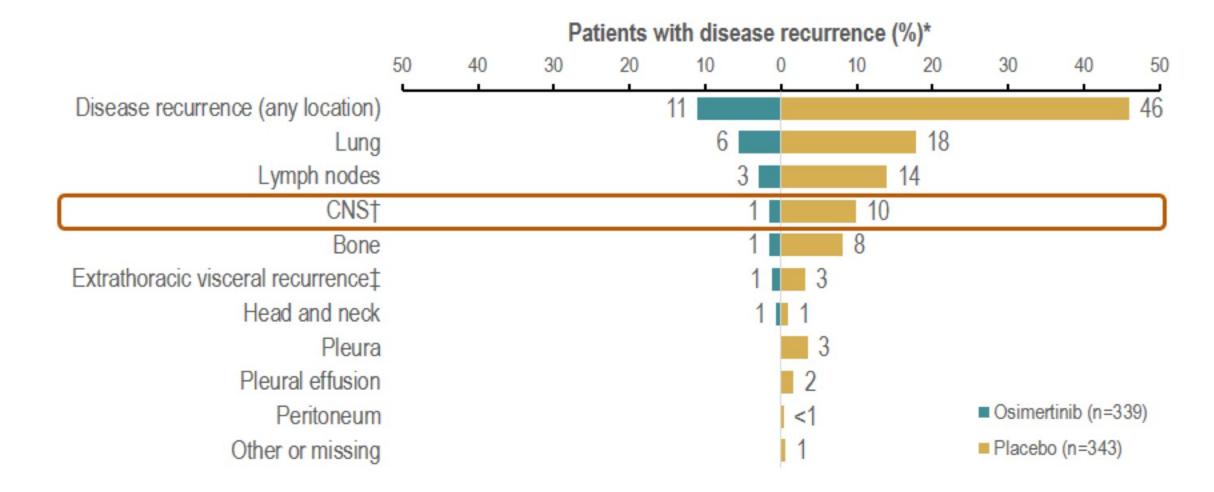
# Osimertinib adjuvant therapy in patients with resected EGFR mutated NSCLC (ADAURA): CNS disease recurrence

Masahiro Tsuboi,<sup>1</sup> Yi-Long Wu,<sup>2</sup> Jie He,<sup>3</sup> Thomas John,<sup>4</sup> Christian Grohe,<sup>5</sup> Margarita Majem,<sup>6</sup> Jonathan W Goldman,<sup>7</sup> Konstantin Laktionov,<sup>8</sup> Sang-We Kim,<sup>9</sup> Terufumi Kato,<sup>10</sup> Huu Vinh Vu,<sup>11</sup> Charuwan Akewanlop,<sup>12</sup> Chong-Jen Yu,<sup>13</sup> Filippo de Marinis,<sup>14</sup> Manuel Domine,<sup>15</sup> Frances A Shepherd,<sup>16</sup> Chris Yan,<sup>17</sup> Ajlan Atasoy,<sup>18</sup> Roy S. Herbst<sup>19</sup>

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#### Sites of disease recurrence





#Includes disease recurrence in liver, renal and adrenal systems and pancreas.

#### Conclusions

- In ADAURA, adjuvant osimertinib demonstrated a highly statistically significant and clinically meaningful improvement in DFS in patients with stage IB—IIIA EGFRm NSCLC<sup>1</sup>
- Patients who received osimertinib had fewer local / regional and distant relapses than those who received placebo, with a lower incidence of metastatic disease in those patients with recurrence, including fewer CNS recurrence events
- Adjuvant osimertinib demonstrated a clinically meaningful improvement in CNS DFS compared with placebo
  - HR: 0.18 (95% CI: 0.10, 0.33; p<0.0001), equating to an 82% reduction in risk of CNS disease recurrence or death</li>
- CNS disease recurrence was less likely with osimertinib compared with placebo, with a conditional probability of <1% at 18
  months with osimertinib</li>

The reduced risk of local and distant recurrence and improved CNS DFS reinforce adjuvant osimertinib as a highly effective, practice changing treatment for patients with stage IB / II / IIIA EGFRm NSCLC following complete tumour resection



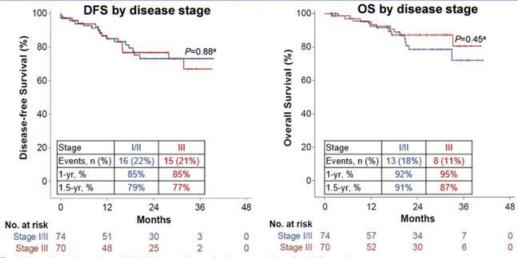
# LCMC3 – Neoadjuvant Atezolizumab for stage IB-IIIB Lung Cancer



# LCMC3 – World Lung 2021, Jay Lee, MD

- Phase II Neoadjuvant Atezolizumab (PD-L1 inhib) for resectable Stage 1B-IIIB NSCLC
- 181 patients
- 2 cycles atezo 3 weeks apart, resection
   8-28 days later
- 21% Major PR, 7% cPR
- 43% downstaged
- 54% VATS/RATS, 46% open
- 15% conversion rate
- 92% R0 resection rate
- Safe/feasible

### Exploratory endpoints: efficacy outcomes in the primary efficacy population



P-values are based on a log-rank test between the survival curves and are descriptive only.

Median follow-up for OS: 2.1 years

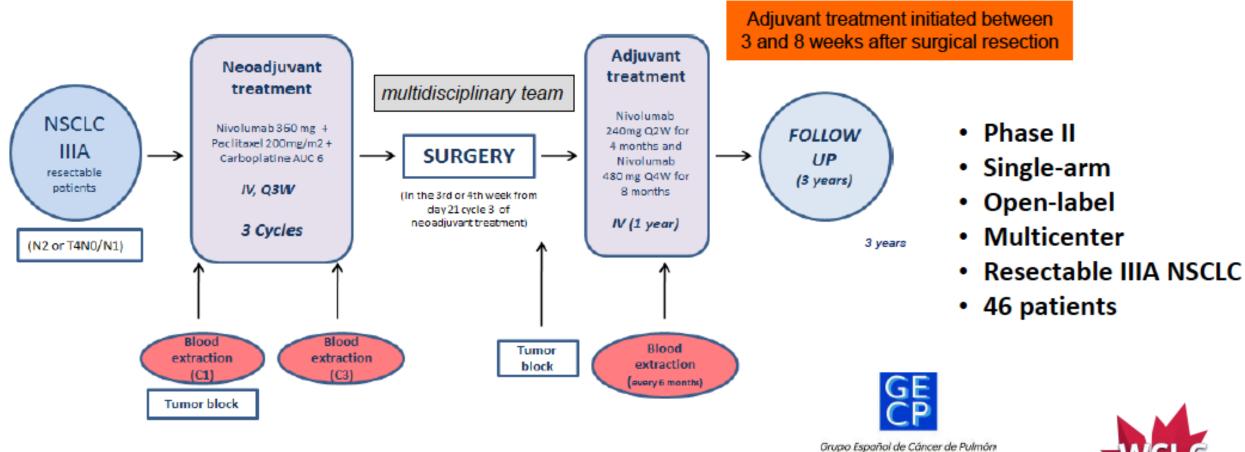
Presented by Dr Jay M. Lee LCMC3: Neoadjuvant Atezolizumab in Resectable NSCLC JANUARY 28-31, 2021 | WORLDWIDE VIRTUAL EVENT



# Nadim Trial – Neoadjuvant Chemo + IO in Resectable Stage IIIA NSCLC



# NADIM: Study design & Flow-chart







Spanish Luna Cancer Group

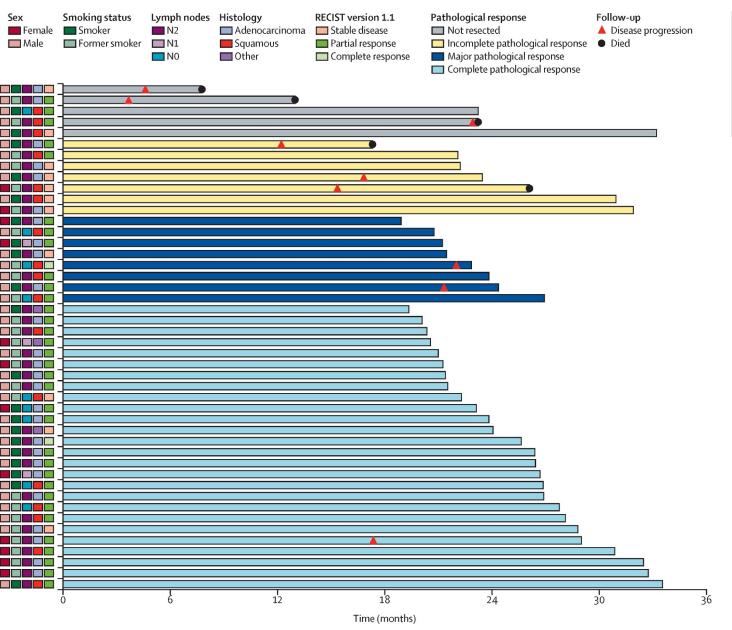
### Nadim trial

Patients with stage IIIA (N2 or T4N0) are potentially curable but median overall survival has been only 15 months

46 patients enrolled
41 went to surgery
85% major path response
61% path CR
Too early to assess survival

Historically - std chemo: 36-39 would go to surgery major response not defined 2-12% path CR





#### Nadim Trial – Neoadjuvant Chemo/Nivo in Resectable NSCLC; Phase 2 trial

#### **Progression Free Survival**

Figure 1. Swimmer plot of progression-free survival in the modified intention-to-treat population (n=46)

Each bar represents one patient. The left column shows clinical characteristics and radiological responses. Nine (20%) of 46 patients had disease progression or died; three (7%) patients who did not undergo surgery had disease progression and died, and six (13%) patients who underwent surgery had disease progression, two (4%) of whom died. Of the 26 patients who achieved a complete pathological response, one patient (4%) had disease progression, and this patient had an *EGFR* mutation (exon 19 deletion;  $Glu746\_Ala750del$ ) in the baseline biopsy that was not known at the trial inclusion. Of the seven patients with a major pathological response, two (29%) had disease progression and harboured baseline mutations in *STK11* (465-2A $\rightarrow$ T) and *KEAP1* (Lys287 $\_Gln292dup$ , 876 $\_877insLysCysGlulleLeuGln$ ). RECIST=Response Evaluation Criteria in Solid Tumors.

Provencio M, Lancet Oncology, Nov 2020

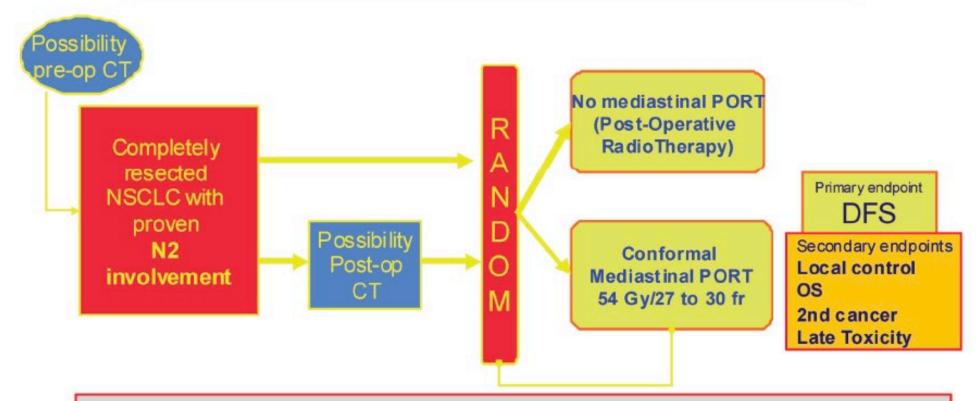


# Lung ART – Use of Adjuvant Radiation in Resected Stage IIIA



#### **Lung ART: Trial Design**





Stratification factors: Center, Administration of CT (no CT vs Post-op CT vs pre-op CT alone), Histology (SCC vs other), Extent of mediastinal lymph node involvement (0 vs 1 vs 2+), Histology (SCC vs others), use of pre-treatment PET-scan (yes/no)

Statistical considerations: 700 pts necessary to show a 10% DFS difference at 3 years (from

Power of 80%, Type one error of 5%, 2-sided log-rank test

30% in the control arm to 40%)



### Lung ART – ESMO Sept 2020

- 501 IIIA/N2 patients randomized to Postoperative Radiation Therapy (PORT) or no PORT, for known N2 disease after resection
  - Most had preop chemo, then resection, some got postop chemo
- No difference in DFS (47.1% vs 43.8%) or OS (3 year 66.5% vs 68.5%)
   p=NS
- Did decrease mediastinal relapse by 50%
- Late cardiopulmonary toxicity 20% with PORT vs 7.7%
- "PORT cannot be recommended for all NSCLC patients with mediastinal nodal involvement. No benefit, and potential harm."



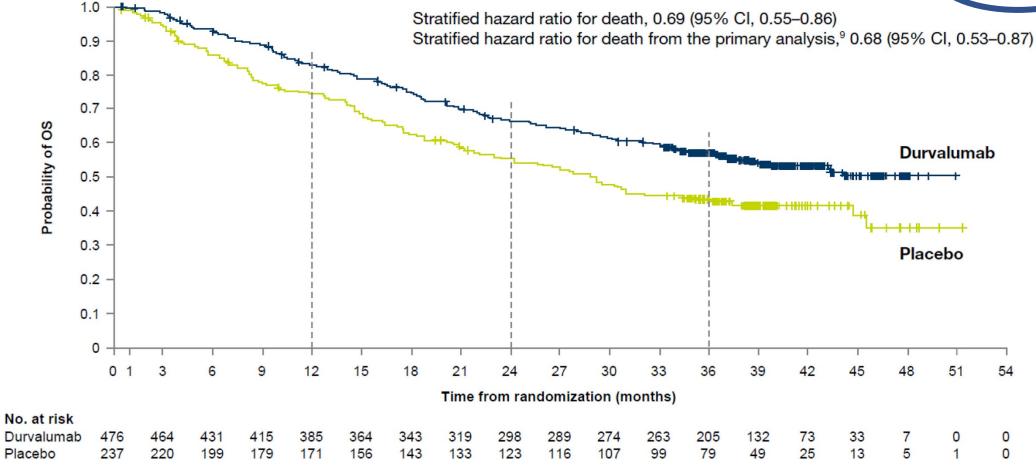
# PACIFIC Trial – 3 year survival data



### PACIFIC 3 year Overall Survival

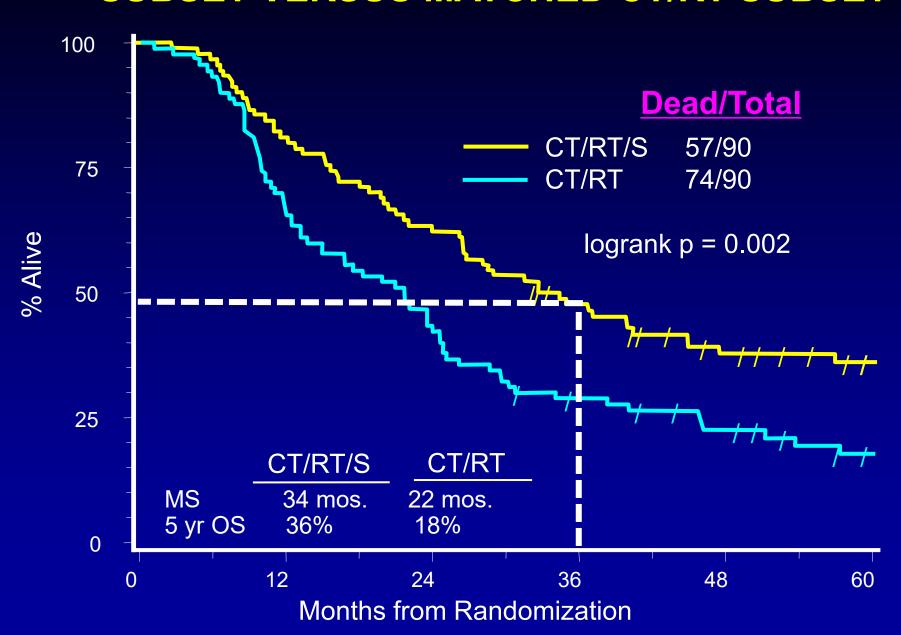
#### Figure 1







# INT0139 OVERALL SURVIVAL OF THE LOBECTOMY SUBSET VERSUS MATCHED CT/RT SUBSET



# RTOG 1010 – Use of Trastuzumab in Resectable Her2+ Esophageal Adenocarcinoma



# Trastuzumab with trimodality treatment for esophageal adenocarcinoma with HER2 overexpression: *NRG Oncology/RTOG 1010.* (ASCO 2020)

- Randomized phase III trial for T1N1-2, T2-3N0-2 adenocarcinoma
- Carbo/taxol + 50.4Gy, with or without trastuzumab, followed by resection, then trastuzumab q3 weeks x13 doses postop
- 203 patients
- DFS 19.6 mo with trastuzumab vs 14.2 mo (NS)
- HR 0.97 (0.69, 1.47)
- No increase in toxicity but also no increase in DFS



# Checkmate 577 – Adjuvant IO in Completely Resected Esophageal Cancer



# CheckMate 577 – ESMO Sept 2020 – Ronan Kelly

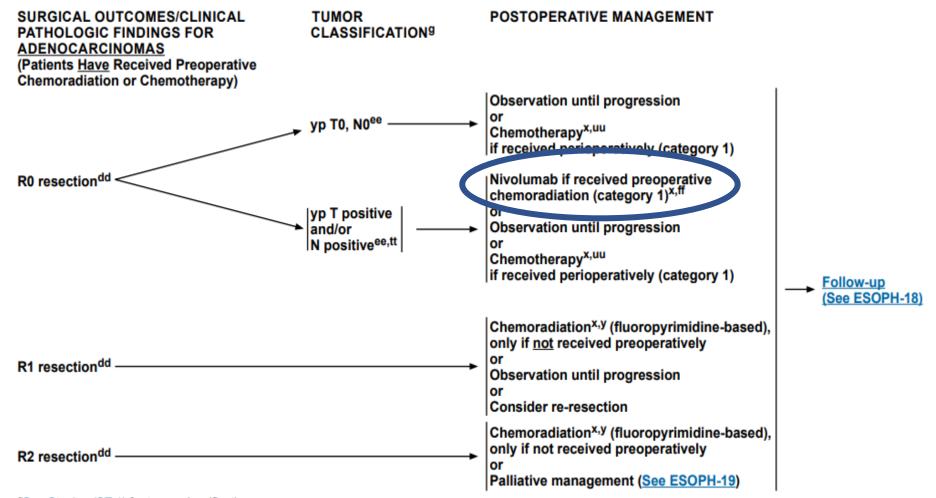
- Randomized phase III
- Adjuvant Nivolumab up to 1 yr in resected Stage 2/3 Eso/GEJ cancer who received preop CRT with ANY residual disease
- 794 patients
- 70% adeno; 60% were >= ypN1
- DFS HR was 0.69 (0.56-0.86) p=0.0003; median DFS 22.4 vs 11 mo
- Low toxicity





#### NCCN Guidelines Version 1.2021 Esophageal and Esophagogastric Junction Cancers

NCCN Guidelines Index
Table of Contents
Discussion





### Links to Papers and Abstracts

- NELSON
  - https://pubmed.ncbi.nlm.nih.gov/31995683/
- Violet Trial
  - <a href="https://oncology.medicinematters.com/surgery/early-stage-lung-cancer/researcher-comment--violet-supports-vats-lung-cancer-resection/17168600">https://oncology.medicinematters.com/surgery/early-stage-lung-cancer/researcher-comment--violet-supports-vats-lung-cancer-resection/17168600</a>
- Adaura Trial
  - https://pubmed.ncbi.nlm.nih.gov/32955177/
- LCMC3
  - https://www.iaslc.org/iaslc-news/ilcn/lcmc3-findings-indicate-neoadjuvant-atezolizumab-safe-efficacious-resectable-stage
- NADIM
  - https://pubmed.ncbi.nlm.nih.gov/32979984/
- Lung ART
  - <a href="https://oncologypro.esmo.org/meeting-resources/esmo-virtual-congress-2020/an-international-randomized-trial-comparing-post-operative-conformal-radiotherapy-port-to-no-port-in-patients-with-completely-resected-non-smal">https://oncologypro.esmo.org/meeting-resources/esmo-virtual-congress-2020/an-international-randomized-trial-comparing-post-operative-conformal-radiotherapy-port-to-no-port-in-patients-with-completely-resected-non-smal</a>
- PACIFIC 3 yr results
  - https://pubmed.ncbi.nlm.nih.gov/31622733/
- RTOG 1010
  - https://ascopubs.org/doi/abs/10.1200/JCO.2020.38.15 suppl.4500
- Checkmate 577
  - https://oncologypro.esmo.org/meeting-resources/esmo-virtual-congress-2020/adjuvant-nivolumab-in-resected-esophageal-or-gastroesophageal-junct cancer-ec-gejc-following-neoadjuvant-chemoradiation-therapy-crt-first-r









