Lung Cancer UPDATES
ESMO HIGHLIGTHS
19-21 SEPTIEMBRE 2020

VIRTUAL

Iniciativa científica de: GECP lung cancer research

CARCINOMA DE PULMÓN NO MICROCÍTICO. ESTADIOS INICIALES

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DEFINICIÓN DE ESTADIOS INICIALES Y LOCALMENTE AVANZADO

- Iniciales:
  - CPCNP resecables (estadios I, II y IIIA quirúrgicos)
  - Estados del arte:
    - Cirugía +/- QT adyuvante (estadios IB > 4 cm, II y IIIA operables) (pT2B pN0-2 M0)
    - RT en pacientes no operables
    - RT adyuvante si N2, bordes quirúrgicos, infiltración, multiestación, afectación extracapsular
- Localmente avanzados:
  - CPCNP estadios IIIA voluminosos o IIIB
  - Estados del arte:
    - Quimio-radioterapia concomitante + ITP
    - Quimioterapia neoadyuvante → Cirugía +/- QT adyuvante (Tratamiento perioperatorio)
    - Quimio-radioterapia neoadyuvante → Cirugía +/- QT adyuvante (Tto. Perioperatorio)

ACTITUDES TERAPÉUTICAS EN ESTUDIO EN CPCPNP ESTADIOS INICIALES Y LOCALMENTE AVANZADOS

- Neoadyuvancia en estadios operables
  - Quimioterapia
  - Inmunoterapia
  - Quimio +/- inmunoterapia
  - IO + IO
  - Fármacos dirigidos en tumores con genes drivers
- Adyuvancia
  - Agentes dirigidos en tumores con genes drivers
  - Inmunoterapia
- Confirmación del beneficio de la RT en estadios resecables N2
- Posible beneficio de combinaciones de agentes dirigidos y RT en estadios irresecables con genes drivers
- Optimización de la inmunoterapia en estadios localmente avanzado
- Etc, etc

PRESENTACIONES RELEVANTES EN ESMO DE CPCNP, ESTADIOS INICIALES

- SAKK 16/14: QT + Durvalumab neoadyuvante en estadios resecables
- IONESCO: Durvalumab neoadyuvante en estadios resecables
- PRINCEPS: Atezolizumab neoadyuvante en estadios resecables

- ADAURA – SNC: Osimertinib adyuvante en CPCNP resecable con mutaciones de EGFR (SNC)

- LUNG-ART: PORT vs No PORT en CPCNP resecables con afectación N2

SAKK 16/14: Anti PD-L1 Antibody Durvalumab in Addition to Neoadjuvant Chemotherapy in Patients with Stage III (N2) Non-Small Cell Lung Cancer (NSCLC) – A Multicenter Single-Arm. Phase II Trial. S. I. Rothschild. 1237MO

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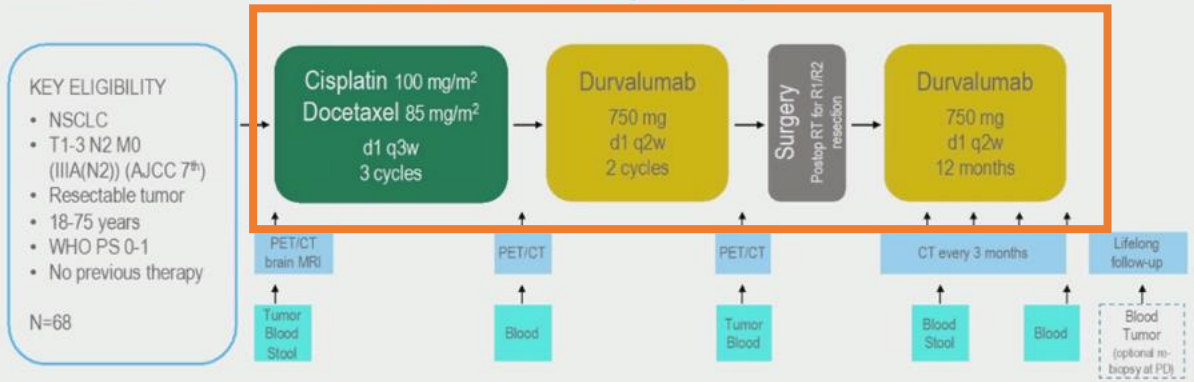
SAKK 16/14 – Study Design



1° endpoint: Event-free survival (EFS) at 12 months
2° endpoints: EFS, OS, ORR, pCR, MPR, nodal downstaging, complete resection, AEs

Statistical hypothesis: improve EFS at 12 months from ≤ 48% (SAKK 16/00[1]) to ≥ 65%

[1]Pless M, et al. Lancet 2015;386:1049-56

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SAKK 16/14 – Patient Demographics and Treatment

	N=67	%
Age, median (range)	61 (41-74)	
Gender		
- Male	35	52.2%
- Female	32	47.8%
WHO PS		
- 0	52	77.6%
- 1	15	22.4%
Histology		
- Adenocarcinoma	37	55.2%
- Squamous cell carcinoma	22	32.8%
- Large cell carcinoma	1	1.5%
- NOS	7	10.4%
T stage		
- T1	15	22.4%
- T2	33	49.3%
- T3	19	28.4%

	N	%
Neoadjuvant Chemotherapy	67	
- Completed	60	89.6%
- Not completed	7	10.4%
Neoadjuvant Immunotherapy	62	
- Completed	58	86.6%
- Not completed	4	13.4%
Surgery	55	
- Pneumonectomy	5	9.1%
- Bilobectomy	7	12.7%
- Lobectomy	43	78.2%
- R0/R1/R2	50/3/2	90.9%/5.5%/3.6%
Postoperative Radiotherapy	6	10.9%
Adjuvant Immunotherapy	50	
- Completed	25	50.0%
- Still on treatment	5	10.0%
- Not completed	20	40.0%

SAKK 16/14: Anti PD-L1 Antibody Durvalumab in Addition to Neoadjuvant Chemotherapy in Patients with Stage III (N2) Non-Small Cell Lung Cancer (NSCLC) – A Multicenter Single-Arm. Phase II Trial. S. I. Rothschild. 1237MO

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SAKK 16/14 – Radiographic and Pathologic Response

Radiographic response

Response	Total (N=62) N (%)
CR	4 (6.5%)
PR	32 (51.6%)
SD	16 (25.8%)
PD	4 (6.5%)
NE	4 (6.5%)
Missing[1]	2 (3.2%)

[1] Tumor assessment not done (N=2)

Pathologic response

Response	Total (N=55) N (%)
Pathological complete response (pCR)	10 (18.2%)
Major pathological response (MPR)[1]	33 (60.0%)
Nodal downstaging - ypN0 - ypN1	37 (67.3%) 26 (47.3%) 11 (20.0%)

[1] Defined as ≤10% viable tumor cells
MPR significantly associated with PD-L1 positivity (> 1%), p=0.038

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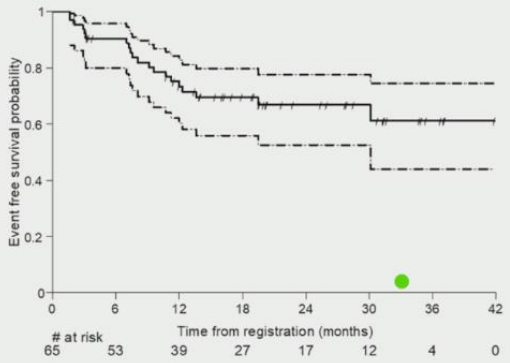
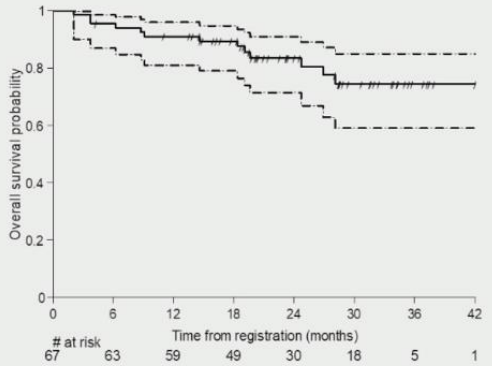
SAKK 16/14 – EFS and OS





EFS at 12 months: 73.4% (90% CI: 62.7 – 81.5)

Median EFS: not reached (95% CI: 27.6 – NR)

Median OS: not reached (NR) (95% CI: NR – NR)

Median follow-up: 28.6 months. Time point of analysis: July 10, 2020

SAKK 16/14: Anti PD-L1 Antibody Durvalumab in Addition to Neoadjuvant Chemotherapy in Patients with Stage III (N2) Non-Small Cell Lung Cancer (NSCLC) – A Multicenter Single-Arm. Phase II Trial. S. I. Rothschild. 1237MO

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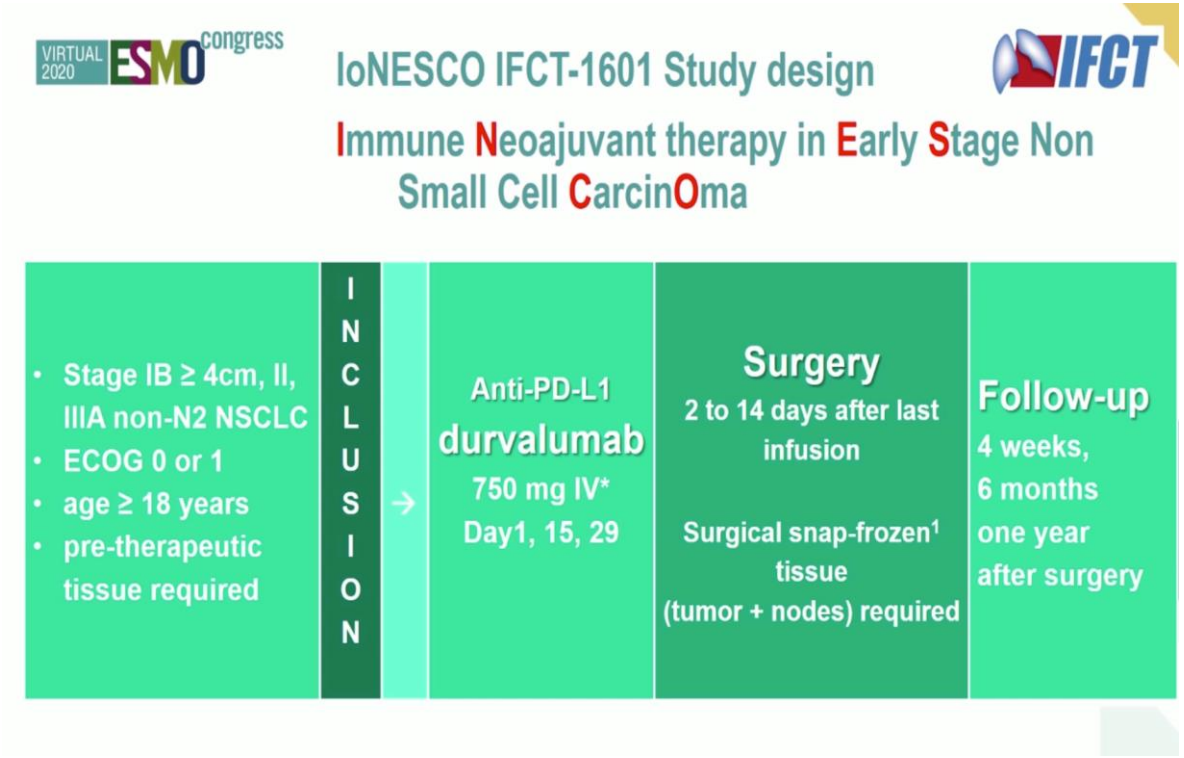
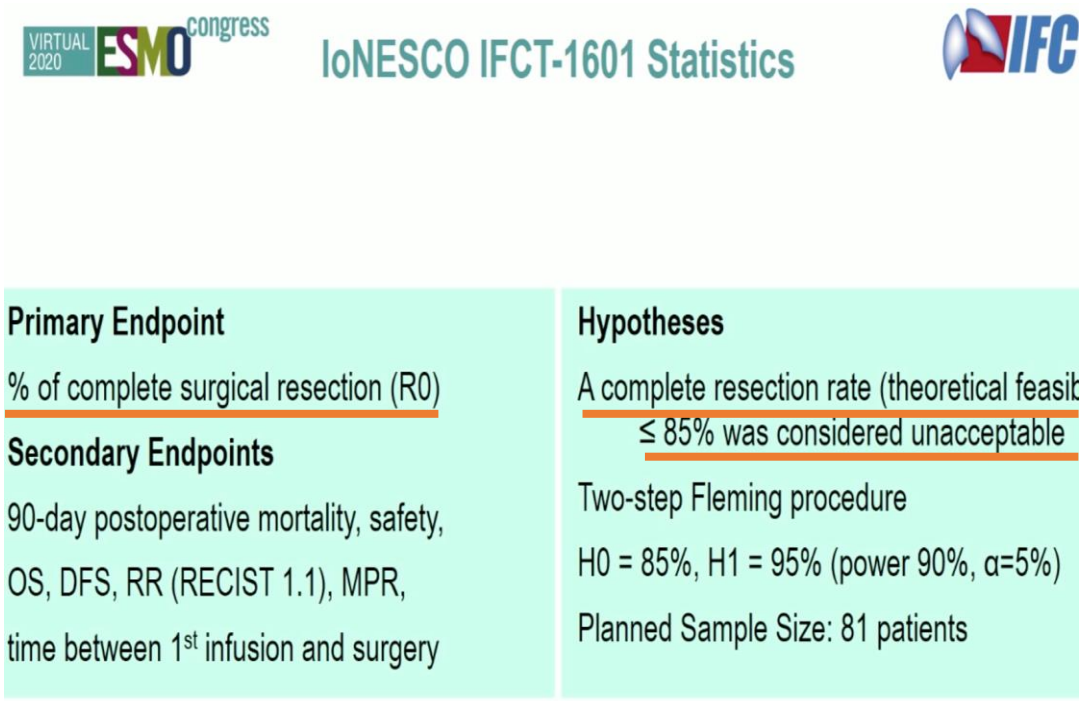
SAKK 16/14 – Conclusion

- This is to our knowledge the largest cohort of patients with resectable stage IIIA(N2) NSCLC receiving perioperative immune checkpoint inhibitor therapy
- The addition of perioperative durvalumab to standard of care cisplatin/docetaxel
  - is safe
  - results in a very encouraging 1-year EFS rate that exceeds historical data of chemotherapy alone
  - leads to high major pathological response rate and rate of nodal downstaging
- Exploratory analyses of tissue and blood biomarkers are ongoing
- Perioperative PD-L1 inhibition in addition to standard neoadjuvant chemotherapy forms the backbone of our next study investigating the additional benefit of neoadjuvant immune-modulatory radiotherapy (SAKK 16/18; NCT04245514)

Neoadjuvant Durvalumab in resectable non-small cell lung cáncer (NSCLC): Preliminary results from a multicenter study (IFCT-1601 IONESCO). M. Wislez. 1240





Neoadjuvant Durvalumab in resectable non-small cell lung cáncer (NSCLC): Preliminary results from a multicenter study (IFCT-1601 IONESCO). M. Wislez. 1240

Patient demographics & treatment

	N=50 (ITT)
Age (median, range)	61.0 [46 -80]
Male / female	35 (70%) / 15 (30%)
Smokers / never smokers	47 (94%) / 3 (6%)
ECOG 0 / 1	40 (80%) / 10 (20%)
Histology adenocarcinoma squamous other	 25 (50%) 21 (42%) 4 (8%)
Stage IB / IIA / IIB / IIIA	 5 (10%) / 14 (28%) / 29 (58%) / 2 (4%)
Surgical procedures lobectomy bilobectomy pneumonectomy	 32 (72.7%) 3 (6.8%) 9 (20.5%)
Number of pts receiving 3 durvalumab doses	44 (88%)

Primary endpoint:

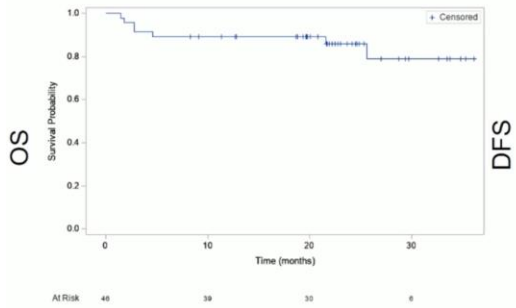
% of complete surgical resection (R0)

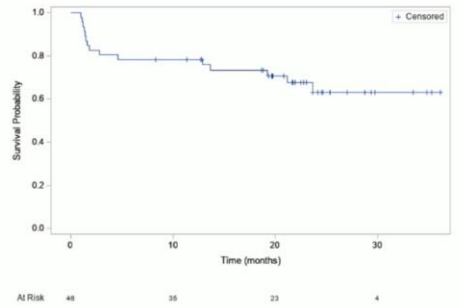
	N=46 (Eligible Population)
Complete resection (R0)	41 (89.1%)
Microscopically incomplete resection (R1)	2 (4.3%)
Not evaluable	3* (6.5%)

Time between 1st infusion and surgery (mean ± SD): 37 ± 4 days

* : 1 not operated (progression before surgery), 2 exploratory thoracotomies (pleural/oesophagial invasion)

Secondary endpoints : OS and DFS





	Population (N=46)
Event : N (%)	7 (15.2)
Median OS: months [95% CI]	NR
12-m OS: % [95% CI]	89.1 [75.8-95.3]

	Population (N=46)
Event: N (%)	15 (32.6)
Median DFS: months [95% CI]	NR [23.7-NR]
12-m DFS: % [95% CI]	78.2 [63.3-87.6]

Neoadjuvant Durvalumab in resectable non-small cell lung cáncer (NSCLC): Preliminary results from a multicenter study (IFCT-1601 IONESCO). M. Wislez. 1240

Secondary endpoints : Radiographic and Pathological Response

RECIST 1.1

	N	%
CR	0	0
PR	4	8.7
SD	36	78.3
PD	6*	13
	46	100

*One patient had pseudoprogression

PR: 8.7%

Major Pathologic Response (MPR)
defined as less than 10% of RVT

	N=43*
RVT (Mean±SD)	34.7% ± 22
RVT	
0%	3 (7)
0-10%	5 (11.6)
>10%	35 (81.4)

*Ongoing analysis *n=1 and n=2* not operated

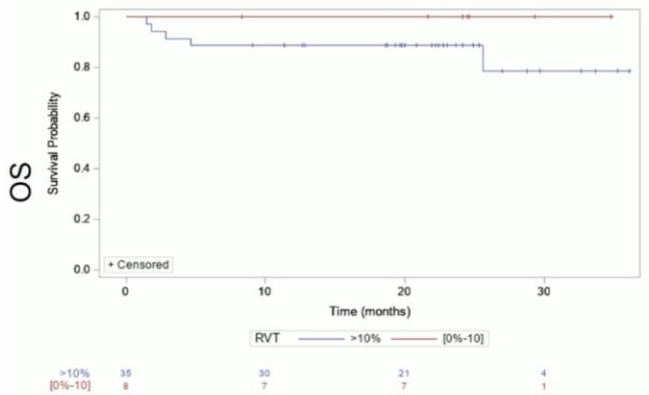
MPR: 8 (18.6%)

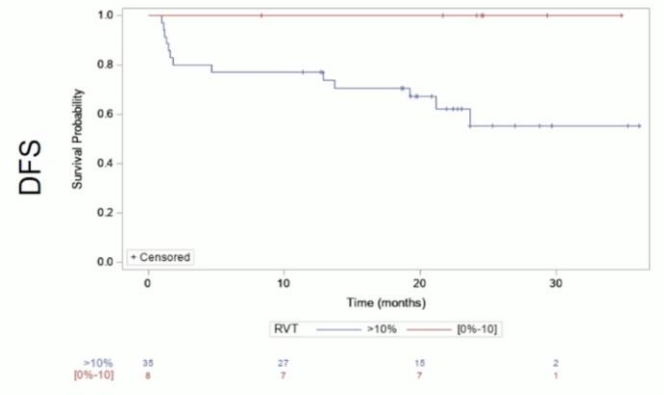
Association between pathological and radiographic response

	RVT		P value
	0-10%	>10%	
PR	3 (37.5%)	1 (2.9%)	0.028
SD	4 (50%)	29 (82.9%)	
PD	1 (12.5%)*	5 (14.3%)	

*This patient had pseudoprogression with mediastinal nodal flare-up (granulomas)

MPR and outcome : OS and DFS





RVT	0%-10%, N=8	> 10%, N=35
Event : N (%)	0 (0)	5 (14.3%)
Median OS: mo [95% CI]	NR	NR
12-m OS: % [95% CI]	100%	88.6 [72.4-95.5]
p=0.2777		

RVT	0%-10%, N=8	> 10%, N=35
Event: N (%)	0 (0)	13 (37.1%)
Median DFS: mo [95% CI]	NR	NR
12-m DFS: % [95% CI]	100%	77.1 [59.5-87.9]
p=0.0450		

Neoadjuvant Durvalumab in resectable non-small cell lung cáncer (NSCLC): Preliminary results from a multicenter study (IFCT-1601 IONESCO). M. Wislez. 1240

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Reason for premature termination of trial: 90-day postoperative mortality

Study was stopped because of an excess in 90-day postoperative mortality (4 deaths, 9%)

age	gender	smoking	stage	comorbidities	surgical procedure	surgical resection / histology	RVT	cause of death* (time from surgery)
63	F	Yes	IIB	Arterial hypertension Severe COPD	Lobectomy	R0 adeno	>10%	Sudden death at home (40 days)
49	F	Yes	IIB	No	Lobectomy	R0 squamous	>10%	Surgical procedure complication (45 days
76	M	Yes	IIA	Arterial hypertension Diabetes	Pneumonectomy	R0 squamous	>10%	Tracheal Fistula (8 days)
78	M	Yes	IIB	Arterial hypertension, Ischemic Heart disease Peripheral arterial disease	Lobectomy	R0 squamous	>10%	Respiratory Distress (21 days)

These deaths are not related to durvalumab

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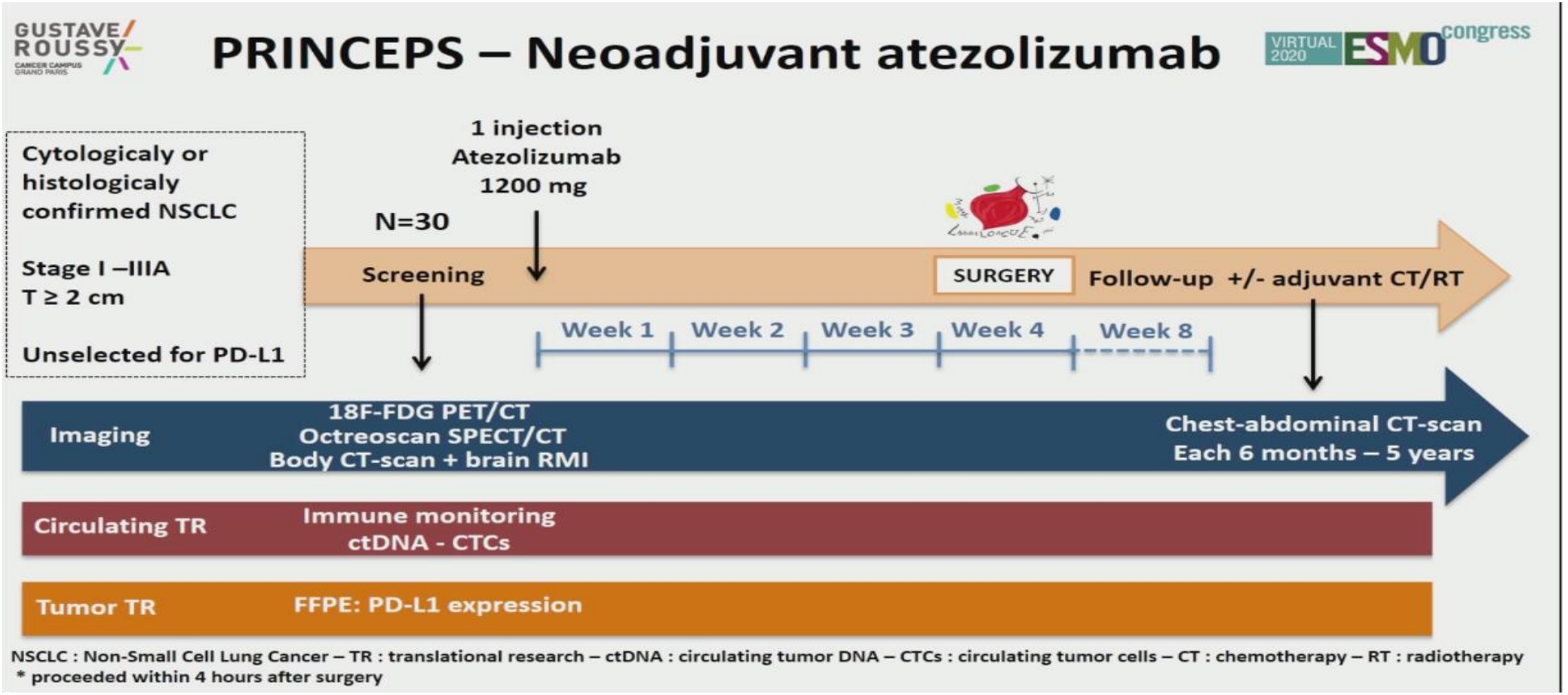
Summary

- The Ionesco Study was stopped because of an excess in 90-day post-operative mortality (4 deaths, 9%)
- Mortality was due to postoperative complications most likely related to comorbidities, and not to direct durvalumab toxicity
- Durvalumab was well tolerated with no grade 3 to 5 AE
- % of complete surgical resection (R0) was 89% that is considered as a pre-specified trial efficacy boundary
- Partial response (8.7%) and Major Pathological Response (18.6%) rates are in the range of those observed in the largest neoadjuvant trial using anti-PD-L1monotherapy (7 and 18%, respectively)
- A significant association between radiographic and pathological response was observed
- Major Pathological Response was significantly associated with best DFS
- Ancillary studies are ongoing to determine whether PD-L1 expression is predictive or not and to better analyze immune cell infiltration response

Neoadjuvant atezolizumab for resectable non-small cell lung cáncer: results from the phase II PRINCEPS TRIAL. B. BESSE. 1250



Neoadjuvant atezolizumab for resectable non-small cell lung cáncer: results from the phase II PRINCEPS TRIAL. B. BESSE. 1250

Primary endpoint

- **Primary endpoint : 2-month tolerance rate**
  Rate of patients without major toxicities or morbidities during the period defined as the start of treatment and 1 month after the surgery.
- Major toxicities or morbidities include:
  - a) treatment toxicity leading to a delay of at least 15 days of the surgery,
  - b) grade ≥ 3 toxicity occurring within 2 months after atezolizumab infusion,
  - c) major postoperative morbidities,
  - d) any death related to the experimental treatment and occurring in the period from the day of injection of atezolizumab to the 30 postoperative days,
  - e) patients that did not have surgery because of early progression.

Characteristics

Patients and tumors	N=30 N (%)
Age (Years)	
Median	64
Sex	
Male	15 (50)
Female	15 (50)
ECOG performance status	
0	23 (77)
1	7 (23)
Smoking status	
Never	2 (7)
Ever	28 (93)
Pathological stage	
I	15 (50)
II	6 (20)
III	9 (30)

Mutations	N=24 N (%)
BRAF	2
EGFR	3
KRAS	8
TP53	13
PI3KCA	1
STK11	1
ESR1	1
WT	1

Baseline PD-L1 (clone SP142)	N=29 N (%)
<1%	18 (62)
≥1%	6 (21)
≥50%	5 (17)

Neoadjuvant atezolizumab for resectable non-small cell lung cancer: results from the phase II PRINCEPS TRIAL. B. BESSE. 1250

Treatment

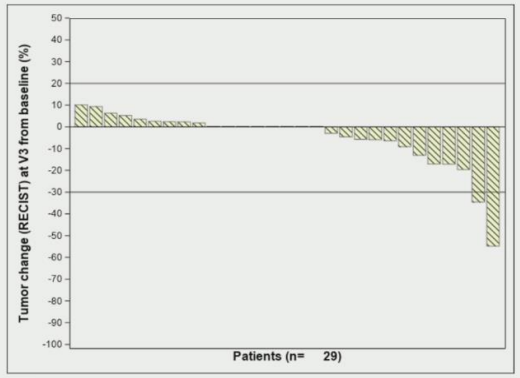
Treatments	N=30 N (%)
Time between atezolizumab and surgery (days)	
Median	24
Resection delayed > 15 days	0 (0)
Type of resection	
Pneumonectomy	2 (7)
Lobectomy	28 (93)
Quality of resection	
RO	29 (97)
R1	1 (3)
Adjuvant radiotherapy	19 (29.7)

Dindo Classification	N=30 Grade
Respiratory Distress* Septic Shock*	Grade III Grade III - a
Paresthesia	Grade I
Heart Block Atrioventricular	Grade III
Atrial Fibrilation	Grade II
Bronchial Congestion	Grade II
Atrial Fibrilation* Air leak*	Grade I Grade I
Cardiac Decomponsation secondary to Atrial Fibrilation	Grade I

Dindo D et al. Ann Surg. 2004

- There were no grade 4-5 complications
- 7/30 patients (23%) had complication within 1 month after surgery

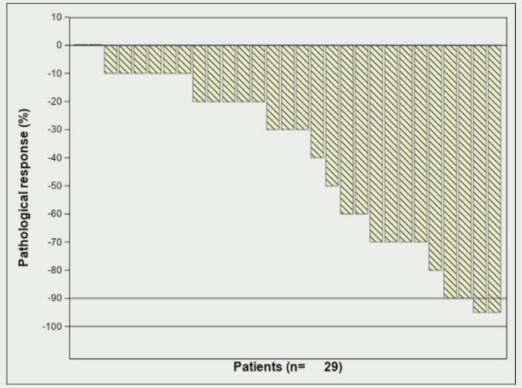
Response according to RECIST 1.1



- 29 patients evaluable
- 1 additional SD, central review pending

Objective response	N=29 N (%)
Complete response	0 (0)
Partial response	2 (7)
Stable disease	27 (93)
Progression	0 (0)

Pathological response



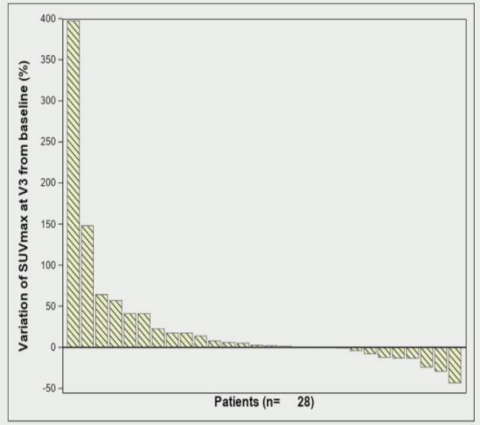
- irPRC criteria, centrally reviewed

Cotterell et al. Ann Oncol 2018

Pathological response	N=29 N (%)
Complete response	0 (0)
Major pathological response	4 (14)
Pathological response ≥ 50%	12 (41)

Major pathological response: less than 10% residual tumor cells
Pathological response ≥ 50%: less than 50% residual tumor cells

Metabolic response

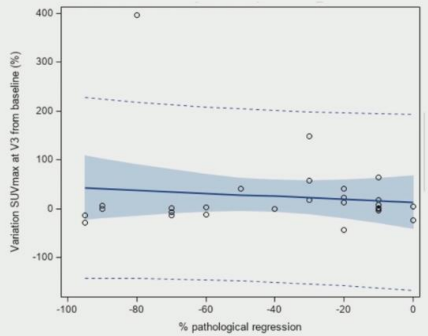


- 18F-FDG PET/CT
- Variation between baseline and week 3 post atezolizumab

Variation of SUVmax	N=28 N (%)
+20% or more	7 (25)
Stable (between +20% and -20%)	18 (64)
-20% or more	3 (11)

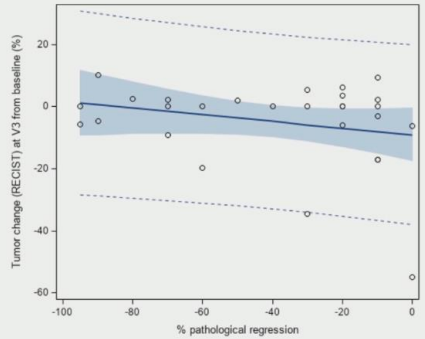
Neoadjuvant atezolizumab for resectable non-small cell lung cáncer: results from the phase II PRINCEPS TRIAL. B. BESSE. 1250

Correlation between pathological response and metabolic response



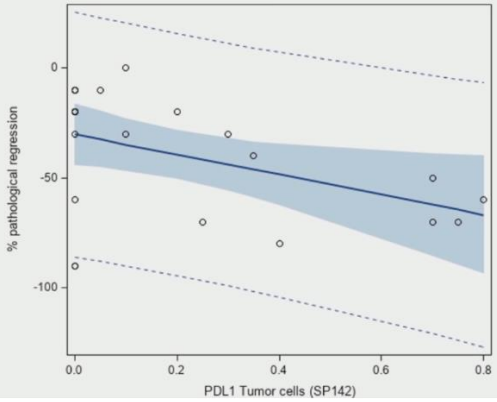
- 18F-FDG PET/CT
- 27 patients evaluable
- Pearson correlation= -0.12, pvalue=0.55
- No correlation observed between percentage of pathological regression and variation of SUVmax at week 3 post atezolizumab

Correlation between pathological response and response by RECIST



- 28 patients evaluable
- Pearson correlation=-0.24 p value=0.2
- No correlation observed between percentage of pathological regression and variation of SDM at week 3 post atezolizumab

Correlation between pathological response and PD-L1 expression at baseline



- 23 patients evaluable
- PD-L1 assessed on tumor cells
- Pearson correlation= -0.45, pvalue=0.0311
- An increased level of PD-L1 tumor cells status before treatment is associated to a larger pathological regression

Osimertinib adjuvant therapy in patients with resected EGFR mutated (EGFRm) NSCLC (ADAURA): central nervous system (CNS) disease recurrence. M. Tsuboi. LBA1

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 performance status 0 / 1
Confirmed primary non-squamous NSCLC Ex19del / L858R‡
MRI or CT scan of the brain prior to surgery or randomisation
Complete resection with negative margins§
Max. interval between surgery and randomisation:
- 10 weeks without adjuvant chemotherapy
- 26 weeks with adjuvant chemotherapy

Stratification by:
stage (IB vs II vs IIIA)
EGFRm (Ex19del vs L858R)
race (Asian vs non-Asian)

Osimertinib 80 mg, once daily

Randomisation 1:1 (N=682)

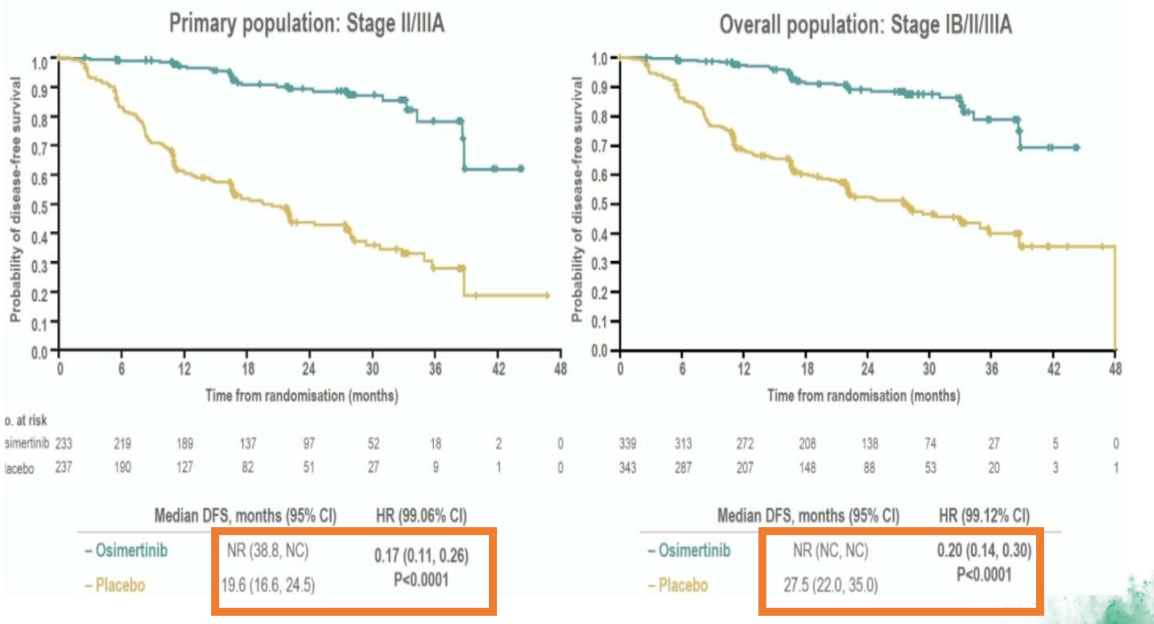
Placebo, once daily

Planned treatment duration: 3 years
Treatment continued until:
- Disease recurrence
- Treatment completed
- Discontinuation criterion met

Assessments:
- For recurrence: Weeks 12 and 24, then every 24 weeks to 5 years, then yearly (brain scans not mandated)
- All sites of NSCLC and post-relapse cancer treatments were recorded at recurrence
- Patients received regular CT scans,# with additional imaging as indicated by signs and symptoms

- The primary and key secondary endpoints of DFS¶ in stage II/IIIA patients and the overall population, respectively, have been reported previously[1]
- **Here we report results from a pre-specified exploratory analysis of disease recurrence patterns in ADAURA, including CNS**

ADAURA: Osimertinib improves DFS versus placebo in resected EGFRm NSCLC



Osimertinib adjuvant therapy in patients with resected EGFR mutated (EGFRm) NSCLC (ADAURA): central nervous system (CNS) disease recurrence. M. Tsuboi. LBA1

Baseline patient characteristics

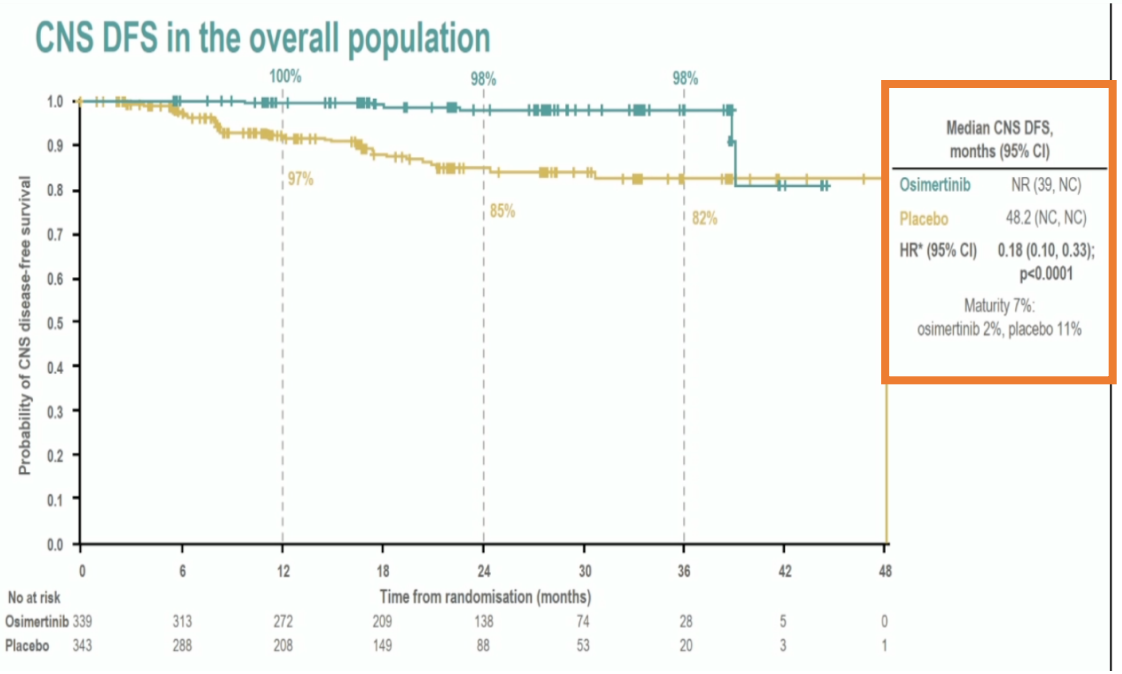
Characteristic	Osimertinib n=339	Placebo n=343
Sex: male / female, %	32 / 68	28 / 72
Age, median (range), years	64 (30–86)	62 (31–82)
Race*: Asian / non-Asian, %	64 / 36	64 / 36
Smoking status: never / current or former, %	68 / 32	75 / 25
WHO performance status: 0 / 1, %	64 / 36	64 / 36
Histology: adenocarcinoma / other, %	96 / 4	97 / 3
EGFR mutation at randomisation: Ex19del / L858R, %	55 / 45	55 / 45
Adjuvant chemotherapy: yes / no, %	60 / 40	60 / 40

CNS DFS events

- Overall, 45 patients (osimertinib n=6, placebo n=39) had CNS DFS events*

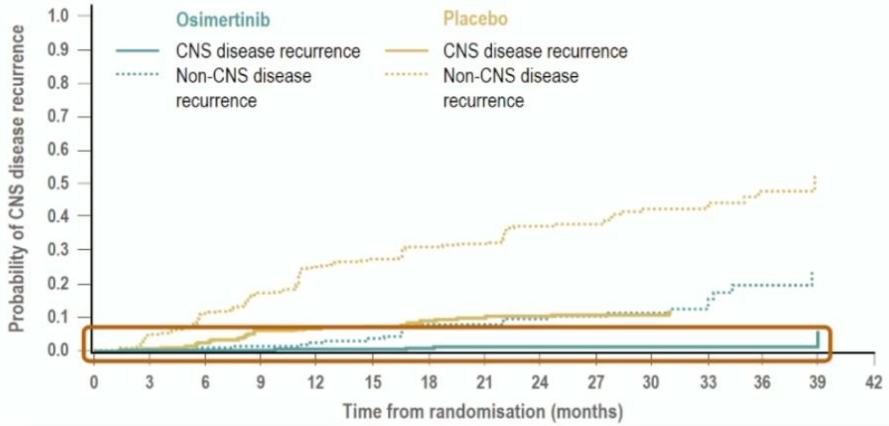
	Overall population	
Patients, n (%)	Osimertinib n=339	Placebo n=343
CNS DFS events:	6 (2%)	39 (11%)
CNS recurrence	4 (1%)	33 (10%)
Death†	2 (1%)	6 (2%)

CNS DFS in the overall population



Conditional probability of CNS* and non-CNS recurrence

- The estimated probability of observing CNS recurrence (in the absence of non-CNS recurrence or death) at 18 months was <1% (95% CI: 0.2%, 2.5%) with osimertinib versus 9% (95% CI: 5.9%, 12.5%) with placebo
- The cumulative incidence† of CNS recurrence was consistently lower in the osimertinib arm than in the placebo arm



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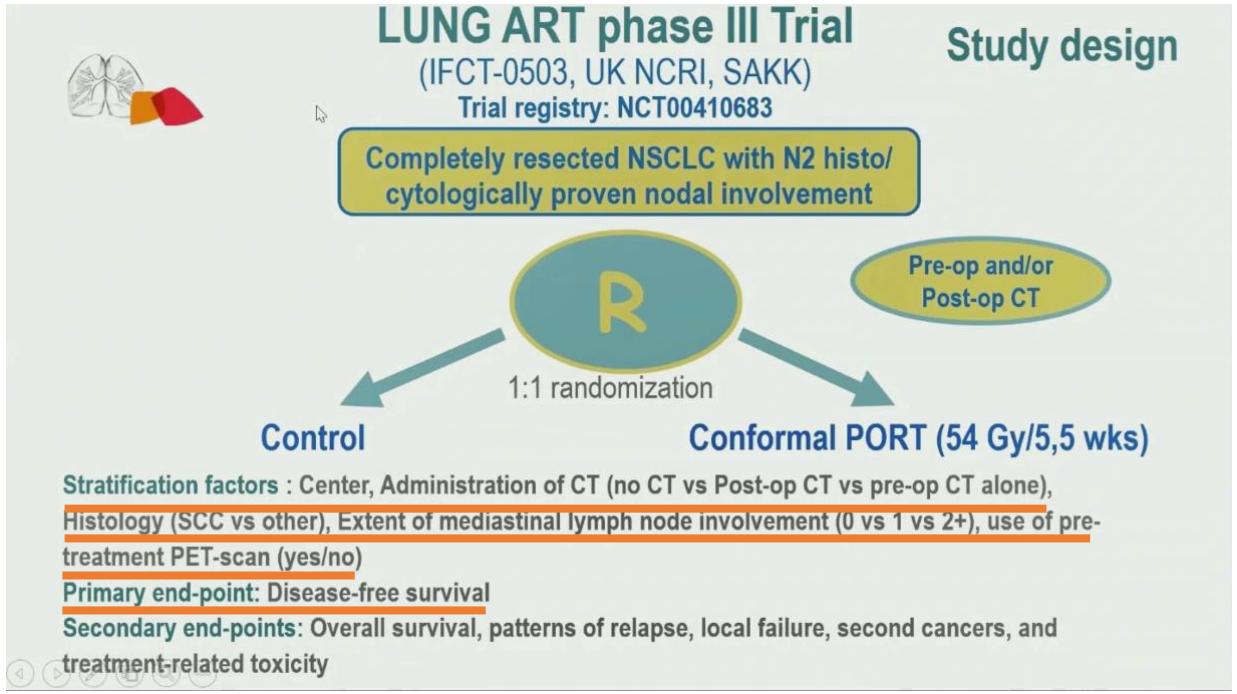

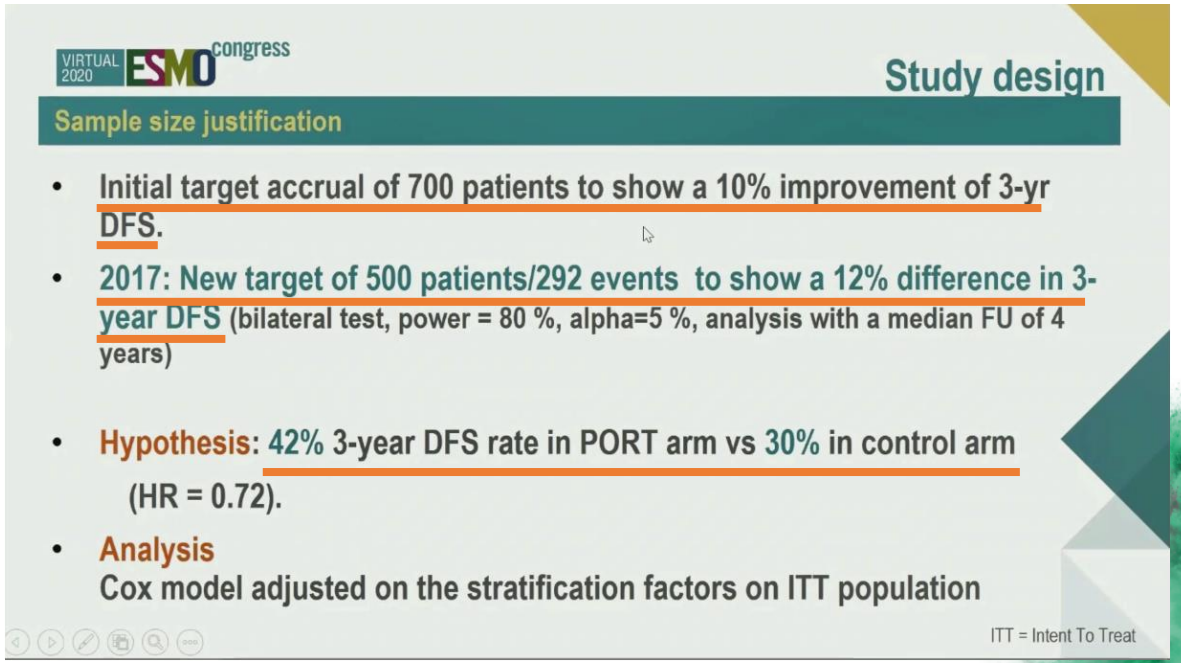

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Baseline Characteristics (ITT)

	Control arm (n = 249)	PORT arm (n = 252)
Gender male (%)	66%	66%
Age (median [min;max])	61 [38;85]	61 [36;79]
Smoking status: Current-former/ Never	90% / 10%	92%) / 8,0%
cTNM Unforeseen N2/Single St N2 / Multiple N2	41% / 34% / 25%	42%/ 35% / 23%
Histology: AdenoC / SCC	76% / 20%	70% / 23%
Adjuvant chemoT: Pre or postop/Preop	96%/12%	96%/14%
Pre-treatment PET scan	90%	92%
pTNM or ypTNM Number of N2 stations involved: 0/1/ ≥ 2	2% / 45% / 52%	4% / 45% / 52%

Stratification factors

Percents calculated on non missing data

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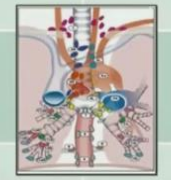
Baseline Characteristics : Surgery

	Control arm (n = 249)	PORT arm (n = 252)
Type of surgery (n(%)) - Lobectomy - Bilobectomy - Pneumonectomy - Sublobar resection	 81% 7% 10% 2%	 78% 8% 12% 2%
Largest T size (Median [min;max],mm	34 [0;110]	33 [5;150]
pTNM pN0/pN1 (down staging after preop CT) pN2	 pN0: 1% pN1: 2% pN2: 98%	 pN0: 2% pN1: 1% pN2: 96%
In pN2 patients N2 stations most frequently involved on Surgical pathological exam 4R / 5 / 7	 St4 R: 66% / St 5 L: 43% St7 R Tum: 66% / L Tum: 34%	 St 4R: 55% / St 5 L: 31% St7 R Tum: 65% / L Tum: 35%



IASLC Nodal Map (Rusch et al, JTO 2009 TNM 7)

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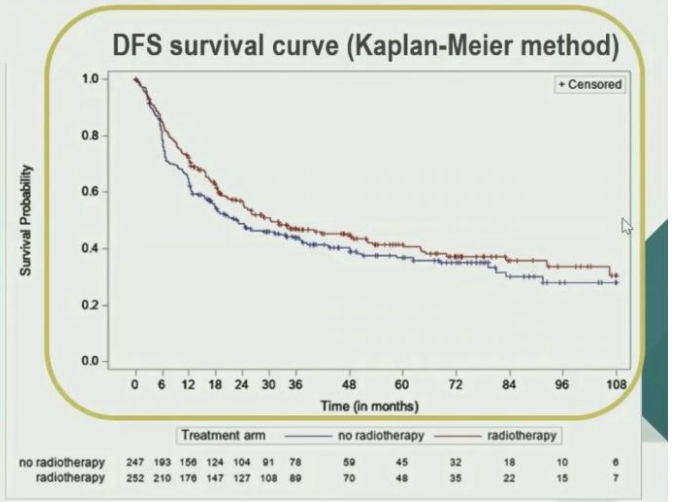
Disease-Free Survival 1/3 (Primary Endpoint; ITT)

Main analysis (Adjusted Cox Model)

HR = 0.85
95% CI = [0.67;1.07]
p value = 0.16

	Control	PORT
Median DFS	22.8 mo (95% CI = [17;37])	30.5 mo (95% CI = [24;49])
3-yr DFS	43.8% (95% CI = [37;51])	47.1 % (95% CI = [40;54])

95%CI = 95% bilateral Confidence Interval



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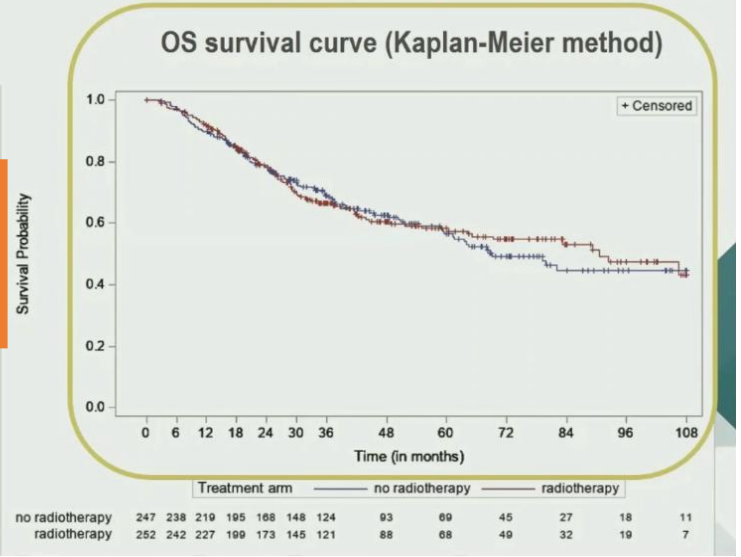
Overall Survival (Secondary Endpoint; ITT)

n_{events} = 201 events

Overall Survival rates at 3 years

Control arm: 68.5% (95% CI = [61;75])

PORT arm: 66.5% (95% CI = [59;73])



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Disease-Free Survival 2/3 (Primary Endpoint; ITT)

DFS components (First Event)

	Control	PORT
All DFS events*	152	144
Mediastinal relapse	70 (46.1 %)	36 (25.0%)
Brain metastasis	27 (17.8%)	34 (23.6%)
Other metastasis	71 (46.7%)	71 (49.3%)
Death	8 (5.3%)	21 (14.6%)

* Patients can have more than one event at the same time
Causes of death:
Control arm: 2 2nd Primary,1 vascular,4 unknown, 1 non cancer related
PORT arm: 11 cardio-pulmonary;2 PORT toxicity;4 2nd Primary;1 progression,3 unknown.

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Results

Causes of death

	Control arm (n = 249)	PORT arm (n = 252)
Deaths	102 (41.5%)	99 (39.6%)
Cause of death		
- Progression or recurrence	87 (86.1%)	68 (69.4%)
- Cardio-pulmonary	2 (2.0%)	16 (16.2%)
- Second primary	1 (1.0%)	5 (5.1%)
- RT or CT related toxicity	0 (0%)	3 (3.0%)
- Other	11 (10.9%)	6 (6.1%)
- Unreported	1	1

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Safety Summary

n(%)	Control arm (n = 246)	PORT arm (n = 241)
At least one toxicity*	200 (81.3%)	222 (92.1%)
At least one toxicity gr 3-4	37 (15.0%) 62 events	57 (23.7%) 112 events
At least one EARLY** TOXICITY gr 3-4	19 (7,7%)	28 (11,6%)
At least one LATE TOXICITY gr 3-4	22 (8,9%)	36 (14,6%)
EARLY** TOXICITY gr 5	0 (0%)	3 (1.2%)
LATE TOXICITY gr 5	2 (0.8%)	3 (1.2%)

Toxicities are censored at DFS date if any
* Many grade (gr) I-2 Adverse Events (AEs), heterogeneity in reporting
** reported at first visit = in the first 3 months after randomization

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Results

Second cancers and possible late cardio-pulmonary toxicities

	Control arm (n = 249)	PORT arm (n = 252)
At least one LATE CARDIAC /PULMONARY TOXICITY gr 3-4	12 (4,9%)	26 (10,8%)
Second cancers (n(%)) - Second Lung cancers (n(% among 2nd cancers))	18 (7.2%) - 4/18 (22.2%)	28 (11.1%) - 11/28 (39.3%)

Gr 3-4 Late Toxicity	CA	PORT
Cardiac rythm disorders	1	4
Cardiac ischemia/infaction	2	3
HTA	2	2
Pericarditis	0	3
Cardiac failure	1	1
Pneumonitis	3	12
Cough		2
Dyspnea/Resp failure	5	8
Pulmonary embolism		1
Pleural Effusion		2
Thoracic Pain	1	1
Sleep apnea syndrome		1

These issues clearly need further analysis:

- Side of second tumour?
- Location of tumour and involved N2 stations
- Radiotherapy Plan
- Patterns of failure with competing events
- etc...

Percents calculated on non missing data