



# **EARLY STAGE DISEASE**

ROSARIO GARCIA CAMPELO HEAD OF MEDICAL ONCOLOGY UNIT

University Hospital A Coruña, INIBIC

# IMPROVING LOCAL CONTROL IN NSCLC SURGERY

# PRECONDITIONING WITH MOVE FOR SURGERY SHORTENS HOSPITAL STAY AFTER LUNG CANCER SURGERY

Data from orthopedic, cardiac, and abdominal surgery has shown that **preconditioning <u>BEFORE</u>** surgery can:







# - Wearable technology-enhanced

Preoperative

Home-based

Preconditioning program

Aerobic exercise

Deep breathing



### Primary:

 Determine if preconditioning with MFS will affect LOS in hospital after surgical lung resection

#### Secondary:

- Compare the differences in the complication rates
- Compare the differences in patient-reported HRQOL outcomes Baseline
  - Day of Surgery
  - Postoperative Day 1 (POD1)
  - 3-Week Follow-Up
  - 12-Week Follow-Up

IASLC 2021 World Conference on Lung Cancer SEPTEMBER 8 - 14, 2021 I WORLDWIDE VIRTUAL EVENT



# LOS for MFS and Control



# Intraoperative Complications & Adverse Events (AEs)



•

## Chest Tube Duration



# Patient-Reported Pain/Discomfort on POD1



#### **Overall Health at Different Time Points**



Patel Y, OA04.01

# ONCOLOGIC OUTCOMES OF PATIENTS WITH RESECTED T3N0M0 NON-SMALL CELL LUNG CANCER

- Notable aspects of their study group:
  - >290 patients (!)
  - Majority received mediastinal staging with EBUS and/or mediastinoscopy (>80%)
  - Majority received lobectomy (>90%)
  - Majority did not go on for adjuvant chemotherapy (85%)
- From this group they analyzed patients by subtype of T3N0 disease:
  - Size >5cm but ≤7cm
  - Chest wall invasion
  - Satellite nodule ≤5cm
  - Parietal pleural invasion
  - Tumors with any combination of the above

# Results

 Table 1 : Patients, tumor and resection characteristics

Characteristics (n=293)	n (%)
Age	68±8
Sex	
Male	152 (51.9%)
Female	141 (48.1%)
Imaging	
PET scan	231 (78.8%)
IMS	
EBUS/EUS	54 (18.4%)
Mediastinoscopy	155 (52.9%)
Both	37 (12.6%)
None	47 (16.0%)
Surgical resection type	
Lobectomy	268 (91.5%)
Sub lobar	13 (4.4%)
Pneumonectomy	12 (4.1%)
Histology	
Adenocarcinoma	164 (56.0%)
Squamous carcinoma	99 (33.8%)
Others	30 (10.2%)

Single T3 classifying features	n (%)
Size	157 (53.6%)
SN	81 (27.6%)
CWI	15 (5.1%)
PPI	13 (4.4%)
Multiple T3 classifying features	
Size and CWI	12 (4.1%)
Size and PPI	7 (2.4%)
Size and SN	7 (2.4%)
Size, PPI, and parietal pericardium	1 (0 3%)
invasion	1 (0.570)
Completeness of resection	
RO	283 (96.6%)
R1-2	10 (3.4%)
R1-2 resection per T3 feature	
Size and CWI	5 (50 %)
CWI	2 (20 %)
PPI	1 (10 %)
Size and PPI	1 (10 %)
Size	1 (10 %)
Adjuvant Chemotherapy	
Yes	43 (14.7%)
No	250 (85.3%)



- Male gender, age > 65, CWI, larger tumors and incomplete resection were identified as poorer oncologic factors to OS and DFS (p < 0,05). (Except a trend for DFS in R1/R2 resection, p = 0,067).
- Patients with CWI T3 feature have a high rate of incomplete resections and recurrences.
- Patients in the SN-PG tumors had a superior OS than patients in the CWI-PG or Size-PG in pair-wise comparisons (p = 0,036 and p < 0,001).</p>
- Should chest wall invasion be an indication for adjuvant therapy?
- Does pT3 need to be further differentiated in future AJCC staging?

# ADJUVANT

# WHO WILL BENEFIT FROM ADJUVANT CHEMOTHERAPY/IO

IO + chemotherapy clearly benefits SOME patients with resectable NSCLC.

Understanding who should receive IO in addition to chemo and when remains an unmet need.

## IMpower010: Characterization of Stage IB-IIIA NSCLC Patients by Type and Extent of Therapy Prior to Adjuvant Atezolizumab

# IMpower010 study design



IC, tumor-infiltrating immune cells. <sup>a</sup> Per SP142 assay. <sup>b</sup> Two-sided α=0.05.

Hierarchical statistical testing

# Patient disposition and reasons for discontinuation prior to randomization

- A total of 1280 patients were enrolled
  - 1269 patients received chemotherapy
  - 275 patients discontinued prior to randomization
  - 1005 patients were subsequently randomized to atezolizumab or BSC

Study discontinuation reason, n (%)	Patients (n=275)		
Withdrawal by subject	86 (31.3)		
Disease relapse	54 (19.6)		
Other	41 (14.9)		
Adverse event	34 (12.4)		
Death	19 (6.9)		
Physician decision	18 (6.5)		
Protocol deviation	18 (6.5)		
Lost to follow-up	4 (1.5)		
Symptomatic deterioration	1 (<1)		

# Patient, disease and treatment characteristics (ITT)

Characteristic	Atezolizumab (n=507)	BSC (n=498)	All patients (n=1005)
Median age (range), y	62 (33-83)	62 (26-84)	62 (26-84)
Sex, male, n (%)	337 (66.5)	335 (67.3)	672 (66.9)
ECOG PS 0 / 1, n (%)	273 (53.8) / 232 (45.8)	283 (56.8) / 214 (43.0)	556 (55.3) / 446 (44.4)
Histology, non-squamous, n (%)	328 (64.7)	331 (66.5)	659 (65.6)
PD-L1 by SP263, TC ≥1%, n (%)ª	283 (57.4)	252 (51.9)	535 (54.6)
Stage, n (%)			
IB	65 (12.8)	58 (11.6)	123 (12.2)
IIA	147 (29.0)	148 (29.7)	295 (29.4)
IIB	90 (17.8)	84 (16.9)	174 (17.3)
IIIA	205 (40.4)	208 (41.8)	413 (41.1)
Mediastinal lymph node dissection, n (%)	402 (79.3)	409 (82.1)	811 (80.7)
Mediastinal lymph node sampling, n (%)	93 (18.3)	88 (17.7)	181 (18.0)
Regional lymph node status (pN), n (%)			
NO	183 (36.1)	169 (33.9)	352 (35.0)
N1	170 (33.5)	178 (35.7)	348 (34.6)
N2	154 (30.4)	151 (30.3)	305 (30.3)
Type of surgery, n (%) <sup>b</sup>			
Lobectomy	394 (77.7)	391 (78.5)	785 (78.1)
Pneumonectomy	77 (15.2)	83 (16.7)	160 (15.9)
Bilobectomy	31 (6.1)	19 (3.8)	50 (5.0)
Median (range) time from surgery to first atezolizumab treatment or BSC, mo	5.2 (2.4-7.7)	5.1 (2.3-8.0)	5.2 (2.3-8.0)
Chemotherapy treatment, n (%)			
Cisplatin-docetaxel	77 (15.2)	75 (15.1)	152 (15.1)
Cisplatin-gemcitabine	88 (17.4)	77 (15.5)	165 (16.4)
Cisplatin-vinorelbine	152 (30.0)	151 (30.3)	303 (30.1)
Cisplatin-pemetrexed	190 (37.5)	195 (39.2)	385 (38.3)

Clinical cutoff: January 21, 2021. <sup>a</sup> 26 patients in the ITT population had unknown PD-L1 status as assessed by SP263. <sup>b</sup> Subgroups with <10 patients are not shown.

# DFS in the PD-L1 TC ≥1%<sup>a</sup> stage II-IIIA, all-randomized stage II-IIIA and ITT populations (primary endpoint)



Atezolizumab 248 235 225 217 206 198 190 181 159 134 111 76 54 31 22 12 8 3 3 Atezolizumab 442 418 384 367 352 337 319 305 269 225 185 120 84 48 34 16 11 5 3 Atezolizumab 507 47 BSC 228 212 186 169 160 151 142 135 117 97 80 59 38 21 14 7 6 4 3 BSC 440 412 366 331 314 292 277 263 230 182 146 102 71 35 22 10 8 4 3 BSC 498 46

Atezolizumab 507 478 437 418 403 387 367 353 306 257 212 139 97 53 38 19 14 8 4 BSC 498 467 418 383 365 342 324 309 269 219 173 122 90 46 30 13 10 5 4

	Atezolizumab (n=248)	BSC (n=228)		Atezolizumab (n=442)	BSC (n=440)		Atezolizumab (n=507)	BSC (n=498)
Median DFS (95% Cl), mo	NE (36.1, NE)	35.3 (29.0, NE)	Median DFS (95% CI), mo	42.3 (36.0, NE)	35.3 (30.4, 46.4)	Median DFS (95% CI), mo	NE (36.1, NE)	37.2 (31.6, NE)
Stratified HR (95% CI)	0.66 (0.5	50, 0.88)	Stratified HR (95% CI)	0.79 (0.6	54 <i>,</i> 0.96)	Stratified HR (95% CI)	0.81 (0.6	67, 0.99)
<i>P</i> value <sup>b</sup>	0.0	04 <sup>c</sup>	<i>P</i> value <sup>b</sup>	0.0	)2 <sup>c</sup>	P value <sup>b</sup>	0.0	)4 <sup>d</sup>

Clinical cutoff: January 21, 2021. <sup>a</sup> Per SP263 assay. <sup>b</sup> Stratified log-rank. <sup>c</sup> Crossed the significance boundary for DFS. <sup>d</sup> The statistical significance boundary for DFS was not crossed.

# Stage and nodal status



HRs were similar in stage and nodal status in either PD-L1 TC ≥1%<sup>a</sup> stage II-IIIA, or in all stage II-IIIA population.



0.63 (0.45, 0.87)

0.83 (0.43, 1.58

0.78 (0.18.3.33)

33.4

NE

NF

36.7



hemotherapy regimen Cisplatin-docetaxel Cisplatin-gencitabine Cisplatin-vinoreibine	71 75 161	↓↓ ↓↓	, ,	0.60 (0.30, 1.23) 1.14 (0.50, 2.61) 0.55 (0.33, 0.92)	36.1 36.1 NE	18.0 NE 34.2
	Favo	ors ATZ 🔶 🚽		Favors BS	C	• 11
						_
Regimens CDDP/DOC CDDP/GEM	Atezo BS (15.2 vs. 15.4 (17.4 vs. 15.4	sc 1%) 5%)	Seems to b	e BSC favo	r	

#### WHO BENEFITS FROM THE ADJUVANT IMMUNOTHERAPY ?

- Patients who underwent lobectomy (not pneumonectomy).
- Patients with tumor expressiing PD-L1.
- Patients who received proper regimens of adjuvant chemotherapy.....to be examined

Type of surgery

Type of surgery

Lobectomy

Bilobectomy

Pneumonectomy

# Circulating tumor DNA for monitoring minimal residual disease and early detection of recurrence in early-stage lung cancer



### **Study Cohort**

Patient Characteristics (N=57)	N (%)
Median age – years (range)	60 (43-83)
Male	34 (60)
Non-smoker	31 (54)
Histology Adenocarcinoma Squamous cell Other*	48 (84) 4 (7) 5 (9)
EGFR mutated	27 (47)
Stage I II III	39 (68) 9 (16) 9 (16)
Adjuvant chemotherapy	15 (26)
Median follow-up – mths (range)	33.0 (9.8-72.1)
Relapsed	11 (19)

#### \*Sarcomatoid carcinoma, LCNEC, LELC

### **Tumour-informed ctDNA assay**

- Resected tumour & PBMC DNA exome sequenced
- Patient-specific multiplex-PCR assays (Signatera<sup>™</sup> ctDNA assay) to track 16 clonal SNVs in plasma samples



- Plasma samples total (N=336)
  - Baseline: all (57/57) patients
  - MRD/Longitudinal: median 2 (1-4) per patient

## ctDNA detection pre-surgery associated with shorter RFS



ctDNA status prior to surgery

ctDNA positivity pre-surgery also correlated with

- Higher stage (p<0.0001) ٠
- Lymph node positivity (p<0.0001)

Stage	
I	7 (47)
II	2 (13)
III	6 (40)
Relapsed	7 (47)
No adjuvant therapy	3 out of 7

### Longitudinal ctDNA+ preceded radiological recurrence



Longitudinal ctDNA monitoring

Free Survival

.75

.5

Becurrence F

Number at risk

ctDNA-positive

ctDNA-negative 50

favourable outcomes with NPV of 94% (45/49)

ctDNApositivity (baseline & longitudinal) was associated with relapse in early-stage NSCLC Molecular recurrence (ctDNA) preceded radiological findings by a median of 3.9 months

# NEOADJUVANT





### Neoadjuvant pembrolizumab for early stage non-small cell lung cancer

<u>Jair Bar</u><sup>1</sup>, Damien Urban<sup>1</sup>, Ilanit Redinsky<sup>1</sup>, Aliza Ackerstein<sup>1</sup>, Sameh Daher<sup>1</sup>, Iris Kamer<sup>1</sup>, Amir Onn<sup>2</sup>, Tiberiu Shulimzon<sup>2</sup>, Michael Peled<sup>2</sup>, Nona Zeitlin<sup>3</sup>, Ran Kremer<sup>3</sup>, Stephen Raskin<sup>4</sup>, Alon Ben-Nun<sup>3</sup>, Marina Perelman<sup>5</sup>, Efrat Ofek<sup>5</sup>

<sup>1</sup>Institute of Oncology, Sheba Medical Center, Tel HaShomer, Ramat Gan, Israel, <sup>2</sup>Institute of Pulmonology, Sheba Medical Center, Ramat Gan, Israel, <sup>3</sup>Thoracic Surgery, Sheba Medical Center, Ramat Gan, Israel, <sup>4</sup>Radiology Department, Sheba Medical Center, Ramat Gan, Israel, <sup>5</sup>Pathology Department, Sheba Medical Center, Ramat Gan, Israel

## Study conduct

#### Study initiation: Janury 2017.

Expansion cohort target increased to 29 total to maximize trial validity (January 2020) Closed enrolment with 26 patients in November 2020 due to slowed recruitment during COVID-19 pandemic.



\*SAE= Severe Adverse Event; Myositis grade 3 (n=1), Acute cardiac event – not related (n=1)

#### Primary endpoints:

- 1) Safety, Recommended Phase 2 Dose/Schedule
- 2) Pathologic response
- Secondary endpoints: Recurrence Free Survival, Overall Survival

Exploratory endpoints: Exploration of the mechanism of response and resistance to pembro in early NSCLC



# Recommended Phase 2 Dose/Schedule

- No DLT in the escalation cohorts
- MPR was observed only in patients with a time interval from treatment initiation to surgery  $\geq$  5 weeks
- Recommended dose/schedule:



- Exploratory: among the patients treated by this dose/schedule (n=16)
  - MPR 44% (7 of 16)
  - pCR 19% (3 of 16)

Relapse Free Survival

# **Overall Survival**



Median follow up: 23 months (95% CI 13-32)

Bar K, et al. OA 11.01

unrelated sepsis (at 32.4 m)

# **IDENTIFYING EARLY NSCLC POPULATIONS**

# INTEGRATING GENOMIC AND TRANSCRIPTOMIC FEATURES PREDICT THE RECURRENCE RISK OF STAGE I NON-SMALL CELL LUNG CANCER





- USH2A mutation and chromosome 2q31.1 amplification might be clinical indicators of recurrent stage I NSCLC.
- Recurrent patients have defected antigen processing and presentation orchestrated by dendritic cells.

Zhang S, et al. MA 08.05

# INMUNE CELL PROFILES AS PREDICTORS OF SURVIVAL IN SURGICALLY TREATED NSCLC

### Methods & Outcomes

- Tissues collected:
  - Tumor
  - Affected lymph nodes
  - Unaffected N1 lymph nodes
  - Unaffected N2 lymph nodes
- Investigation of morphology and gene expression analysis
- Outcomes: OS and/or PFS



 ${\tt Source: https://www.minimed.at/medizinische-themen/krebs/lungenkrebs/}$ 



 Sinus histiocytosis and TiL density are associated with PFS and OS, respectively



Overall survival (in months)

Results

•

CD4 expression in N1 and N2 lymph nodes is associated with PFS and OS, respectively

# **Driver mutations in non-metastatic NSCLC**

# Presence of High-Grade Subtype Predicts Recurrence of Stage I Lung Adenocarcinoma Only in EGFR-Mutated Patients

The OS and RFS of 721 patients with pStage I lung Ad were compared according to EGFR mutation status and presence of > 5% high-grade subtype (solid or micropapillary) component.



'High-grade' subtype associated with worse RFS in pathological stage I, but only in *EGFR*-mutated subgroup

Median follow-up 5.2 years



- The combination of EGFR mutation and the presence of high-grade subtype predicted recurrence in stage I lung adenocarcinoma.
- Histological subtypes, including minor components, should be considered when evaluating the risk of recurrence in patients with EGFR-mutated lung adenocarcinoma.

# Adjuvant chemotherapy for patients with high-risk stage I lung adenocarcinoma stratified by epidermal growth factor receptor mutation status



Age Sex Smoking history Size of invasive part Visceral pleural invasion Lymphatic invasion Vascular invasion AdenoCa subtype



- The role of adjuvant chemotherapy for high-risk stage I lung adenocarcinoma was different by the EGFR mutation status.
- EGFR mutation status should be tested in patients with high-risk stage I lung adenocarcinoma to decide the application of adjuvant chemotherapy. Tsutani Y, et al. MA 08.03

# Treatment patterns and outcomes in early stage ALK+ NSCLC

		Patients with ALK+ NSCLC			
Covariate	Category	Overall cohort (100%)	No relapse	Relapse	
Total Count (100%)		45	15	30	
Age	Median, in years [IQR]	61.2 [13.6]	64.6 (11.7)	61.1 [16.2]	
Carr	Male	20 (44)	7 (47)	13 (43)	
Sex	Female	25 (56)	8 (53)	17 (57)	
	Caucasian	11 (37)	2 (29)	9 (39)	
Calminian	Asian	15 (50)	5 (71)	10 (44)	
Ethnicity	Other	4 (13)	0 (0)	4 (17)	
	Missing	15	8	7	
	Never	31 (66)	11 (73)	20 (67)	
Smoking history	Current/Former	14 (31)	4 (27)	10 (33)	
	Missing	0	0	0	
Stage at initial	1	19 (42)	10 (67)	9 (28)	
diagnosis	Ш	5 (11)	1 (7)	4 (13)	
	II	22 (47)	4 (27)	19 (54)	
	<1%	4 (25.0)	3 (38)	1 (13)	
	1-49%	6 (38)	2 (25.0)	4 (50.0)	
PDL1	>=50	6 (38)	3 (37.5)	3 (37.5)	
	Missing	29	7	22	
ECOG performance	0	15 (50)	6 (67)	9 (43)	
status at initial	1	14 (47)	3 (33)	11 (52)	
diagnosis	≥2	1 (3)	0 (0)	1 (5)	
uldgilosis	Missing	15	6	9	



Ξ



MA08.02 SCchmid Y. et al.

• 10 patients treated with chemoradiation alone

1 patient stopped because of toxicity

#### • 7 patients received chemoradiation + durvalumab

• All patients completed chemoradiation

• Median number of cycles of durva received: 8.5

Median time on durvalumab: 9.9 months

• Reasons to stop durvalumab were:

PFS

Chemoradiation

Time from initial diagnosis (months)

Chemoradiation

Log-rank

p = 0.34

+ Durvalumab

- Completed treatment n=2
- Disease progression n=4
- Durvalumab-related AEs n=1

16 of 17 patients relapsed:
 Median PFS 8.5 (95% CI: 5.8-18.7)

 No suggestion of inceased pulmonary toxicity in patients treated with an ALK TKI after durvalumab

MA08.02 SCchmid Y, et al.

- PFS of patients with early stage ALK+ NSCLC after initial curative intent treatment is comparable to molecularly unselected patients with NSCLC
- No significant benefit from addition of durvalumab after concurrent chemoradiation in this small cohort of patients with stage III ALK+ NSCLC was seen
- Durvalumab treatment was not associated with increased toxicity on the first ALK-TKI treatment, as pulmonary toxicity was overall rare
- 16 of 17 unresectable Stage III patients treated with chemoradiation +/-durvalumab relapsed with a short median PFS of 8.5 months.

# GRACIAS