Lung Cancer UPDATES
IASLC HIGHLIGHTS
08-14 SEPTIEMBRE 2021

Iniciativa científica de:
GECP lung cancer research

Inmunoterapia en 2a linea y posteriores de CNMP avanzado

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Estudio fase 2: Quimio-immuno en EGFR/ALK tratados

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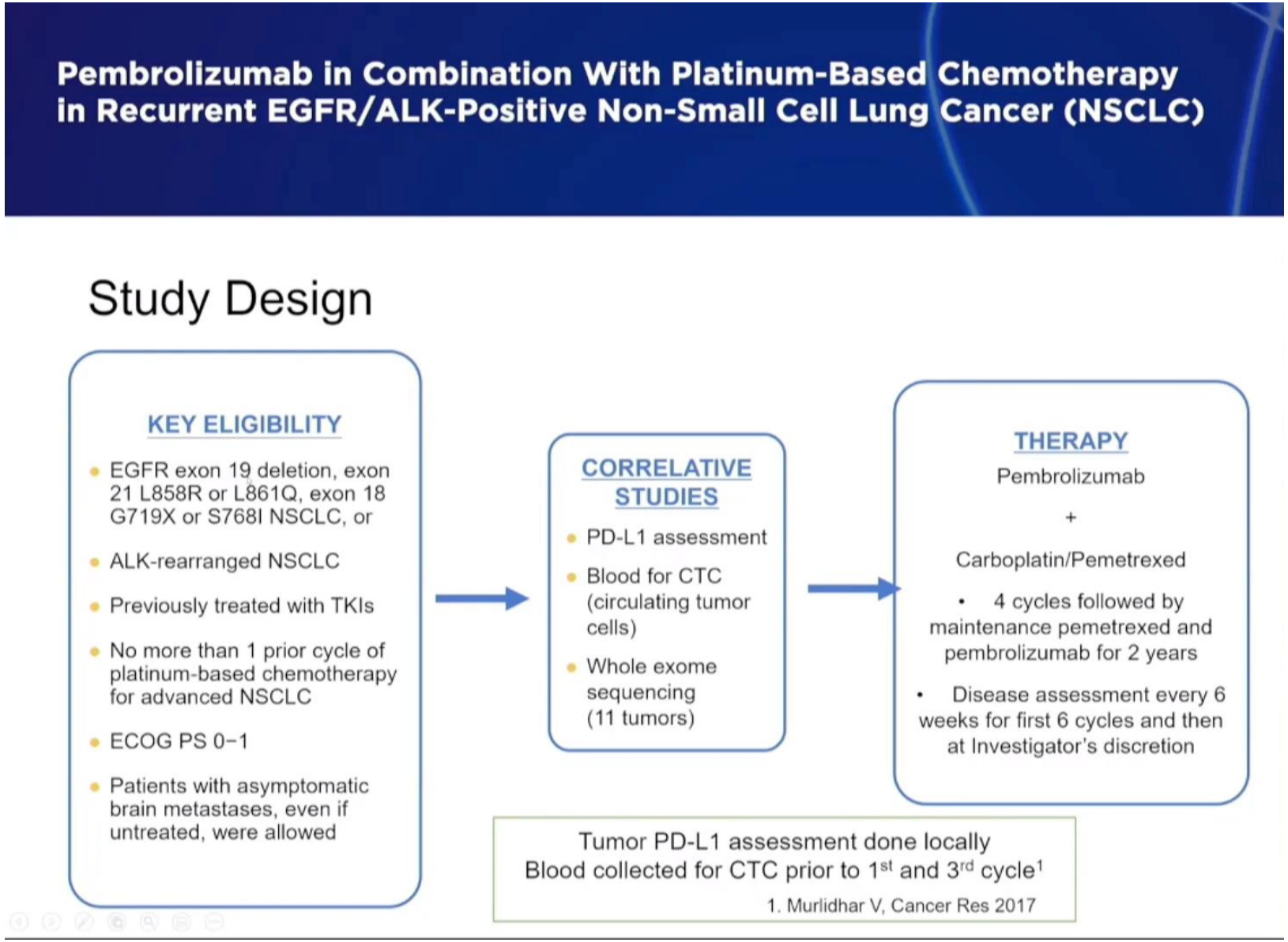


Estudio fase 2: Quimio-immuno en EGFR/ALK tratados

- Paciente pre-tratados.
- Mayor incidencia de M1 cerebrales
- El estudio se cerró antes de tiempo por bajo reclutamiento.

Pembrolizumab in Combination With Platinum-Based Chemotherapy in Recurrent EGFR/ALK-Positive Non-Small Cell Lung Cancer (NSCLC)

Baseline Characteristics

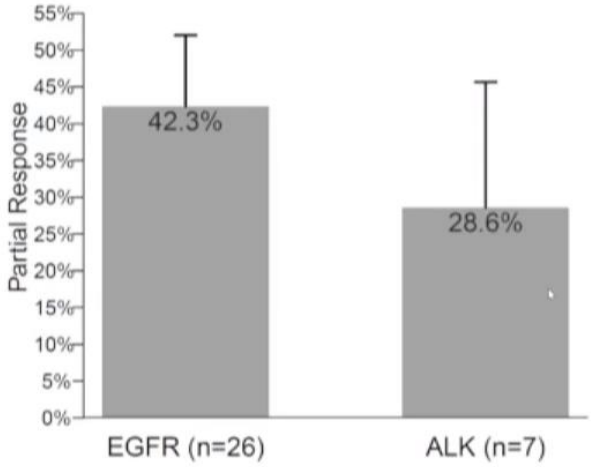
Characteristic	EGFR N = 26	ALK N=7
Age- Median (range)	68 (36-71)	66 (45-80)
Sex, Female (%)	17 (74)	4 (57)
Male (%)	9 (26)	3 (43)
Race- White (%)	17 (65)	6 (86)
Black (%)	4 (15)	0
Other (%)	5 (20)	1 (14)
Brain Metastases- Yes (%)	12 (46)	2 (28)
No (%)	14 (54)	5 (72)
EGFR mutation- exon 19 del	13 (59)	-
L858R	9 (34)	-
Number of Prior Treatments- 1	16 (61)	5 (71)
≥2	10 (39)	2 (29)
Prior Osimertinib	22 (85)	-

Estudio fase 2: Quimio-immuno en EGFR/ALK tratados

- ORR en EGFR del 42% y del 28.6% en ALK.

Pembrolizumab in Combination With Platinum-Based Chemotherapy in Recurrent EGFR/ALK-Positive Non-Small Cell Lung Cancer (NSCLC)

Response Rate



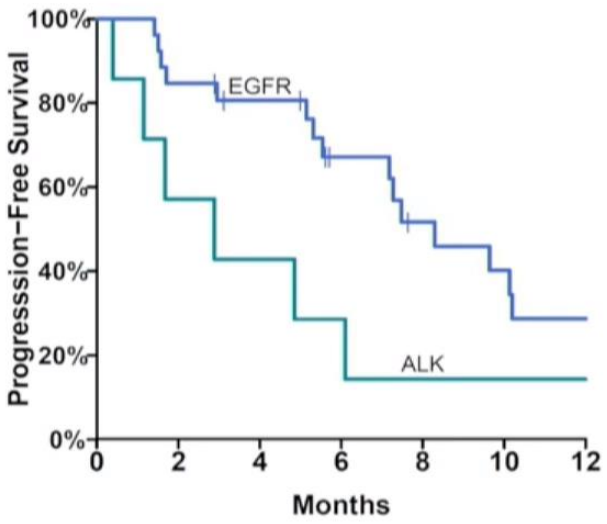
Group	RR	95% CI
EGFR	11/26	23%-63%
ALK	2/7	4%-71%

Estudio fase 2: Quimio-immuno en EGFR/ALK tratados

- PFS de 2.9 meses en pacientes ALK y de 8,3 meses en EGFR.

Pembrolizumab in Combination With Platinum-Based Chemotherapy in Recurrent EGFR/ALK-Positive Non-Small Cell Lung Cancer (NSCLC)

Progression-Free Survival



Group	Median (95%CI)	12-month PFS (95%CI)
EGFR	8.3 months (7.2-16.5)	29% (14-59)
ALK	2.9 months (1.1-NE[1])	14% (2-88)

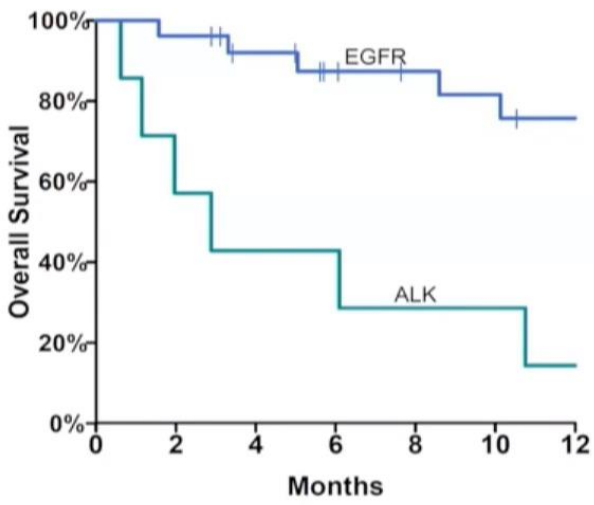
1. Not evaluable

Estudio fase 2: Quimio-immuno en EGFR/ALK tratados

- OS de 22.2 meses en pacientes EGFR, mientras que tan sólo 2,9 meses en ALK.

Pembrolizumab in Combination With Platinum-Based Chemotherapy in Recurrent EGFR/ALK-Positive Non-Small Cell Lung Cancer (NSCLC)

Overall Survival



Group	Median (95% CI)	12-month OS (95% CI)
EGFR	22.2 months (20.6-NE[1])	76% (59-97)
ALK	2.9 months (1.1-NE[1])	14% (2-88)

1. Not evaluable

Estudio fase 2: Nivo + ipi + nintedanib

Phase II Study of Nivolumab and Ipilimumab Combined With Nintedanib in Recurrent Non-Small Cell Lung Cancer

IASLC 2021 World Conference on Lung Cancer

Phase II study of Nivolumab and Ipilimumab combined with Nintedanib in Recurrent Non-small Cell Lung Cancer.

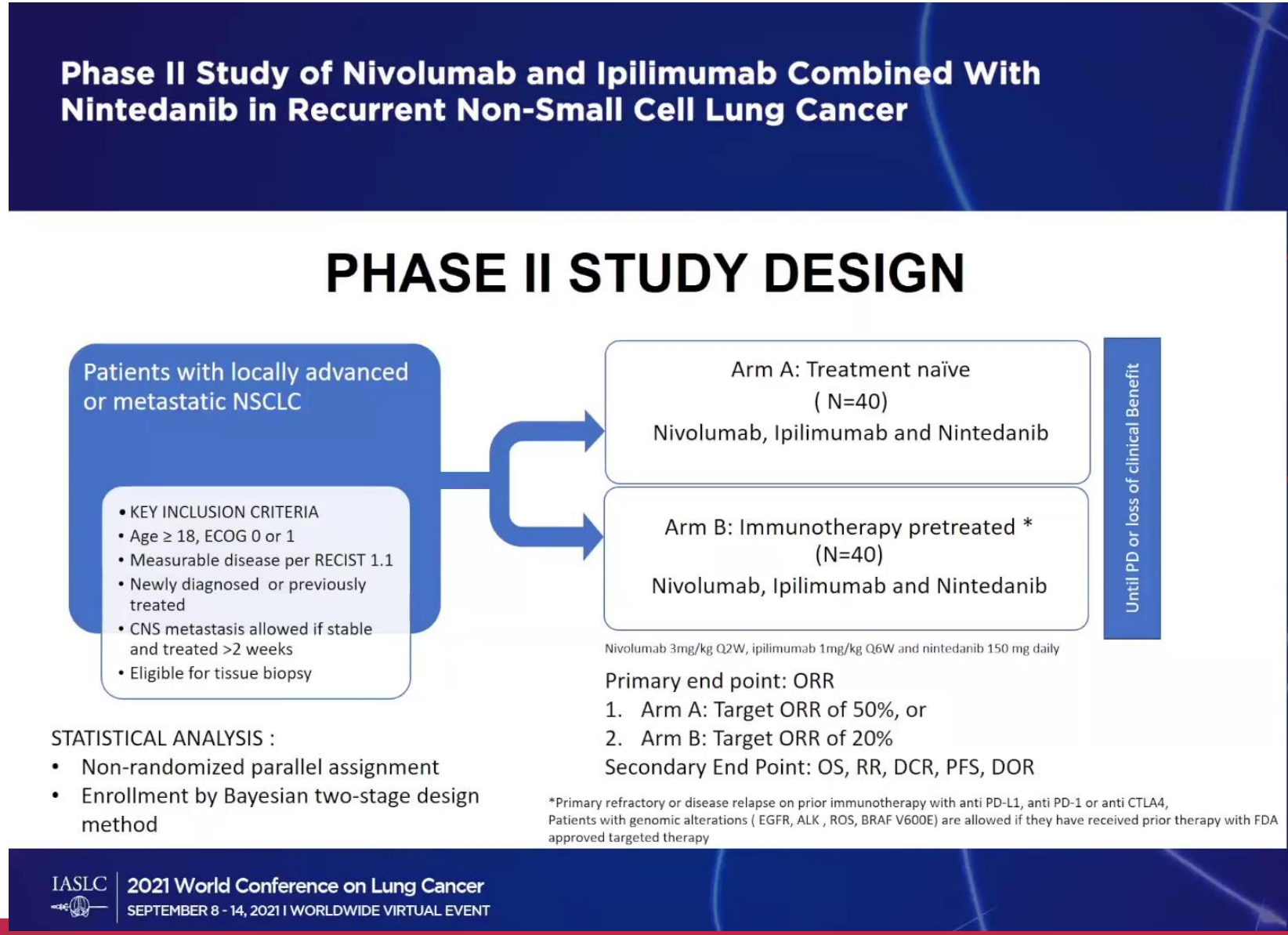
Sonam Puri [1], Tawee Tanvetyanon [2], Benjamin Creelan [2], Michael Shafique [2], Andreas Saltos [2], Alberto Chiappori [2], Eric Haura [2], Ram Thapa [2], Dung-Tsa Chen [2], Scott Antonia [3], Jhanelle E. Gray [2]

1. Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT, USA
2. Moffitt Cancer Center, Tampa, FL, USA
3. Duke Cancer Institute, Durham, NC, USA

Sonam Puri
MD

Estudio fase 2: Nivo + ipi + nintedanib

- Dos grupos, uno naive de tratamiento, otro que ha recibido IO previamente



Estudio fase 2: Nivo + ipi + nintedanib

- Datos preliminares de 18 pacientes.
- **Tasa respuesta: 22%, DCR 61%**

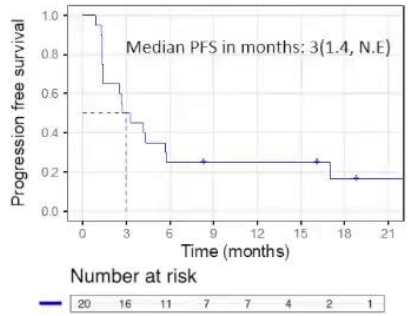
Phase II Study of Nivolumab and Ipilimumab Combined With Nintedanib in Recurrent Non-Small Cell Lung Cancer

EFFICACY ANALYSIS

Table 2: Response Evaluation: N=18*	
CR	0
PR**	4 (22%)
SD	7 (39%)
PD	7 (39%)
ORR	4 (22%)
DCR	11 (61%)

CR: Complete response; PR: Partial Response; SD: Stable Disease; PD: Progressive Disease ORR: Overall Response Rate; DCR: Disease Control Rate
* 2 patients were not evaluable for response.
** 2 PRs were confirmed

Figure 1: Kaplan-Meir curve of Progression Free Survival on Arm B



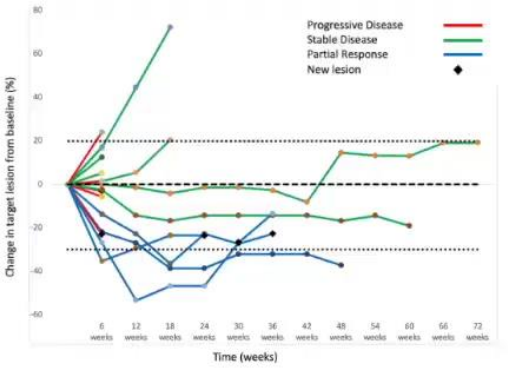
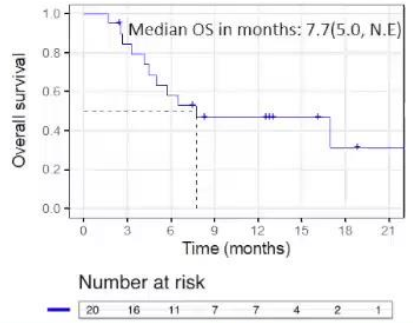


Figure 3: Spider plot of tumor response

Figure 2: Kaplan-Meir curve of Overall Survival on Arm B



Estudio fase 2: Nivo + ipi + nintedanib

- Seguridad manejable, toxicidad hepática, diarrea y prurito la más frecuente

Phase II Study of Nivolumab and Ipilimumab Combined With Nintedanib in Recurrent Non-Small Cell Lung Cancer

SAFETY ANALYSIS

Table 3: Incidence of Treatment Related Adverse Events *

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Total
Alanine aminotransferase increased	3 (15%)	0	2 (10%)	0	5 (25%)
Aspartate aminotransferase increased	2 (10%)	1 (5%)	1 (5%)	0	4 (20%)
Diarrhea	2 (10%)	1 (5%)	1 (5%)	0	4 (20%)
Pruritis	4 (20%)	0	0	0	4 (20%)
Nausea	1 (5%)	0	2 (10%)	0	3 (15%)
Rash: Acneiform	3 (15%)	0	0	0	3 (15%)
Anorexia	1 (5%)	1 (5%)	0	0	2 (10%)
Rash: Maculo-papular	1 (5%)	1 (5%)	0	0	2 (10%)
Vomiting	0	0	2 (10%)	0	2 (10%)
Abdominal Pain	1 (5%)	0	0	0	1 (5%)
Adrenal insufficiency	0	0	1 (5%)	0	1 (5%)
Alkaline phosphatase increased	0	1 (5%)	0	0	1 (5%)
Arthralgia	1 (5%)	0	0	0	1 (5%)
Bloating	1 (5%)	0	0	0	1 (5%)
Dehydration	0	0	1 (5%)	0	1 (5%)
Eye disorders -Other **	1 (5%)	0	0	0	1 (5%)
Fatigue	0	1 (5%)	0	0	1 (5%)
Hyponatremia	0	0	0	1 (5%)	1 (5%)
Investigations-Other	1 (5%)	0	0	0	1 (5%)
Pneumonitis	1 (5%)	0	0	0	1 (5%)
Skin and subcutaneous tissue disorders- Other ^	1 (5%)	0	0	0	1 (5%)
Total	24	6	10	1	41

Most common TRAEs

* Incidence of treatment related adverse events (TRAEs) from any component of treatment
** Eye disorders -Other (Eye rash) ; ^Skin and subcutaneous tissue disorders- Other (eczema)

Estudio fase 2: atezo + bevacizumab

Combination of Bevacizumab + Atezolizumab (A) Who Progressed On A In Pretreated NSCLC Patients: An Open-Label, Two-Stage, Phase II Trial

IASLC 2021 World Conference on Lung Cancer

ML40243
Combination of bevacizumab plus atezolizumab who progressed on atezolizumab monotherapy in pretreated NSCLC patients : an open-label, two-stage, phase II trial

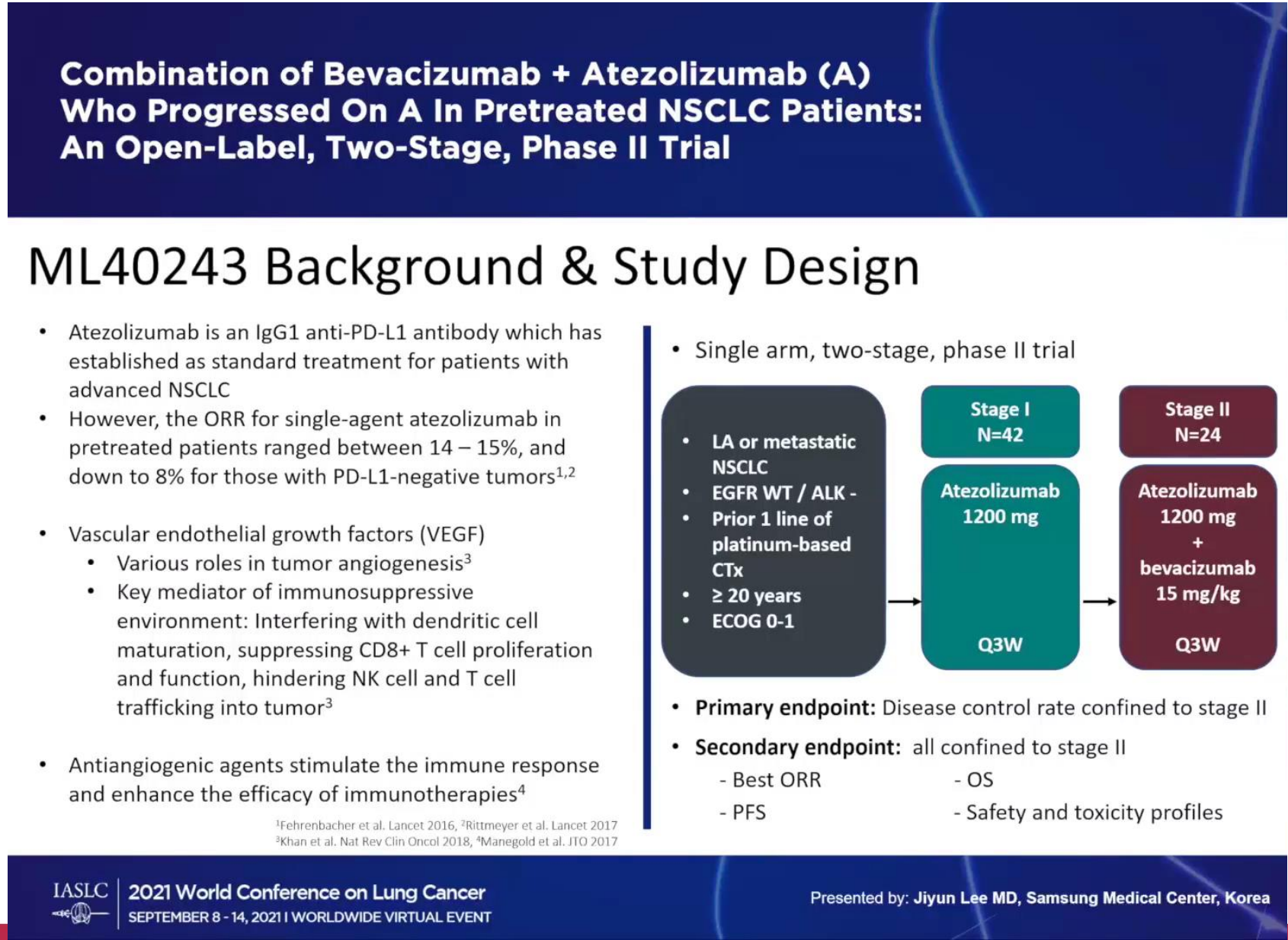
Jiyun Lee[1], Sehhoon Park[1], Hyun Ae Jung[1], Jong-Mu Sun[1], Se-Hoon Lee[1], Jin Seok Ahn[1], Keunchil Park[1], Myung-Ju Ahn[1]
[1]Samsung Medical Center
Korea

Jiyun Lee
MD

Presented by: Jiyun Lee MD, Samsung Medical Center, Korea

Estudio fase 2: atezo + bevacizumab

- Atezo + bevacizumab tras progresión a atezolizumab



Estudio fase 2: atezo + bevacizumab

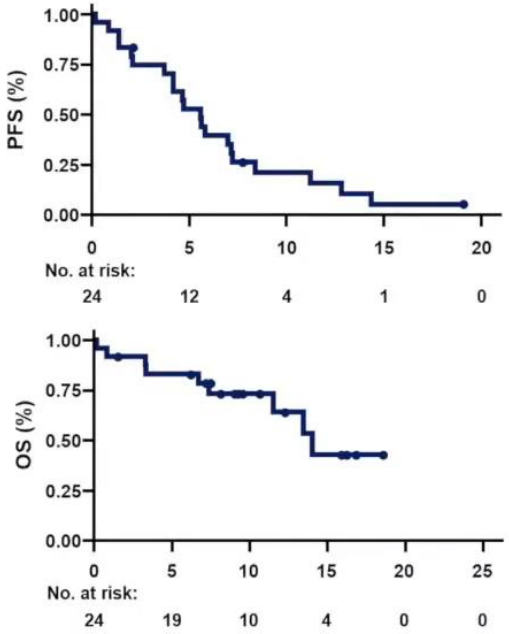
- Control de la enfermedad en el 35.7% en la parte 1, pero con una respuesta del 12.5% y control enfermedad del 87.5% al añadir bevacizumab

Combination of Bevacizumab + Atezolizumab (A) Who Progressed On A In Pretreated NSCLC Patients: An Open-Label, Two-Stage, Phase II Trial

ML40243 Results

Efficacy

	Atezolizumab n=42 (%) [a]	Atezolizumab + Bevacizumab n=24 (%)
Response rates, n(%)		
Complete response	0 (0.0)	0 (0)
Partial response	1 (2.4)	3 (12.5)
Stable disease	14 (35.7)	18 (75.0)
Progressive disease	24 (57.2)	1 (4.2)
Not evaluable	3 (7.1)	2 (8.3)
Objective response rate, % (95% CI)	2.4 (0.1–12.6)	12.5 (2.7–32.4)
Disease control rate, % (95% CI)	35.7 (21.6–52.0)	87.5 (67.6–97.3)
Duration of response		
Median, months (95% CI)	NR [b]	4.4 (NA–NA) [c]
Range	NR	0.6–17.6
No. of cycles, median (range)	2 (1–28)	8 (1–25)
Duration of treatment, median, months (95% CI)	0.7 (0.7–0.7)	5.2 (1.2–9.2)
Progression-free survival		
Patients with event, n(%)	40 (95.2)	21 (87.5)
Median, months (95% CI)	1.4 (1.4–1.5)	5.6 (4.1–7.1)
Overall survival		
Patients with event	22 (52.4)	9 (37.5)
Median, months (95% CI)	12.9 (5.8–20.1)	14.0 (10.7–17.4)



Biomarcadores para eficacia inmunoterapia

Discussant

IASLC

2021 World Conference on Lung Cancer

Solange Peters
MD, PhD

The essentials
PD-L1 and TMB

The host
T cell repertoire, HLA and microbiome

The microenvironment

The genetic oncongenic contexture

Factor	Association with favourable clinical outcome	Validated in phase III clinical trial?	Predictive versus prognostic[a]	Cancer type	Tissue type for biomarker assessment[b]	Possible assay type for biomarker assessment
Tumour mutation burden	Positive	Yes	Predictive	Multiple cancer types	Blood or tumour tissue	NGS WES or targeted gene panel sequencing
PDL1 expression	Positive	Yes	Predictive	Multiple cancer types	Tumour tissue	Immunohistochemistry
Copy number variation	Negative	TBD	Prognostic, predictive or both	Multiple cancer types	Tumour tissue	NGS WES or targeted gene panel sequencing
HLA class I diversity	Positive	TBD	Predictive	Melanoma and NSCLC	Blood	NGS WES or PCR-based typing
LOH at HLA class I alleles	Negative	TBD	Predictive	Melanoma	Tumour tissue	TBD
T cell repertoire clonality change	Positive	TBD	Predictive	Melanoma	Tumour tissue or blood	TBD
T cell-inflamed microenvironment	Positive	TBD	Prognostic, predictive or both	Multiple cancer types	Tumour tissue	NGS RNA-seq or immunostaining
SERPINB3 or *SERPINB4* mutations	Positive	TBD	Predictive	Melanoma	Tumour tissue	NGS WES
Gut microbial diversity	Positive	TBD	Predictive	Melanoma	Oral or gut	PCR or NGS
Specific gut microbial species	Positive or negative	TBD	Predictive	Melanoma	Oral or gut	PCR or NGS
TGFβ expression	Negative	TBD	Predictive	Colon cancer and urothelial cancer	Tumour tissue	NGS RNA-seq or expression panel
Mutations in the β-catenin pathway	Negative	TBD	Predictive	Melanoma	Tumour tissue or blood	NGS WES, targeted gene panel sequencing or RNA-seq
JAK2 mutations (rare)[c]	Negative	TBD	Predictive	Melanoma	Tumour tissue or blood	NGS WES or targeted gene panel sequencing
B2M mutations (rare)[c]	Negative	TBD	Predictive	Melanoma	Tumour tissue or blood	NGS WES or targeted gene panel sequencing
STK11 mutations (common)	Negative	TBD	Predictive	NSCLC	Tumour tissue or blood	NGS WES or targeted gene panel sequencing

FOR RESEARCH NOT DECISON

Havel, Nat Rev Cancer 2019

DNA damage response gene mutations como biomarcador

- Algunos de estos genes son analizados en NGS

DNA Damage Response (DDR) Gene Mutations and Correlation With Immunotherapy Response in NSCLC Patients

Study design

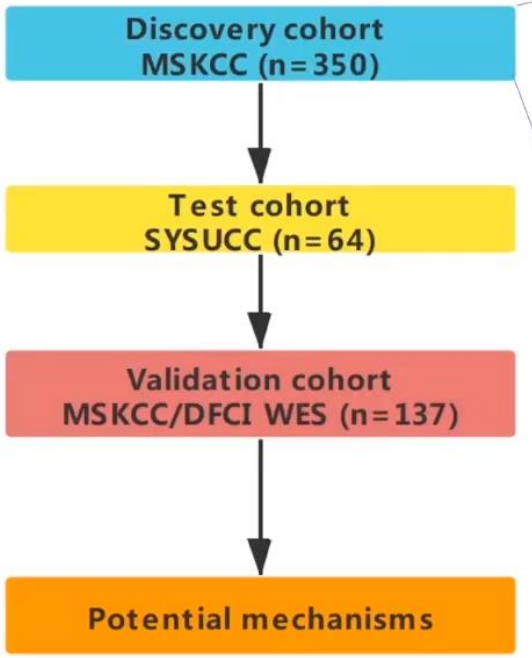


Table 2-1. List of 34 DDR genes included in MSK-IMPACT gene Panels.

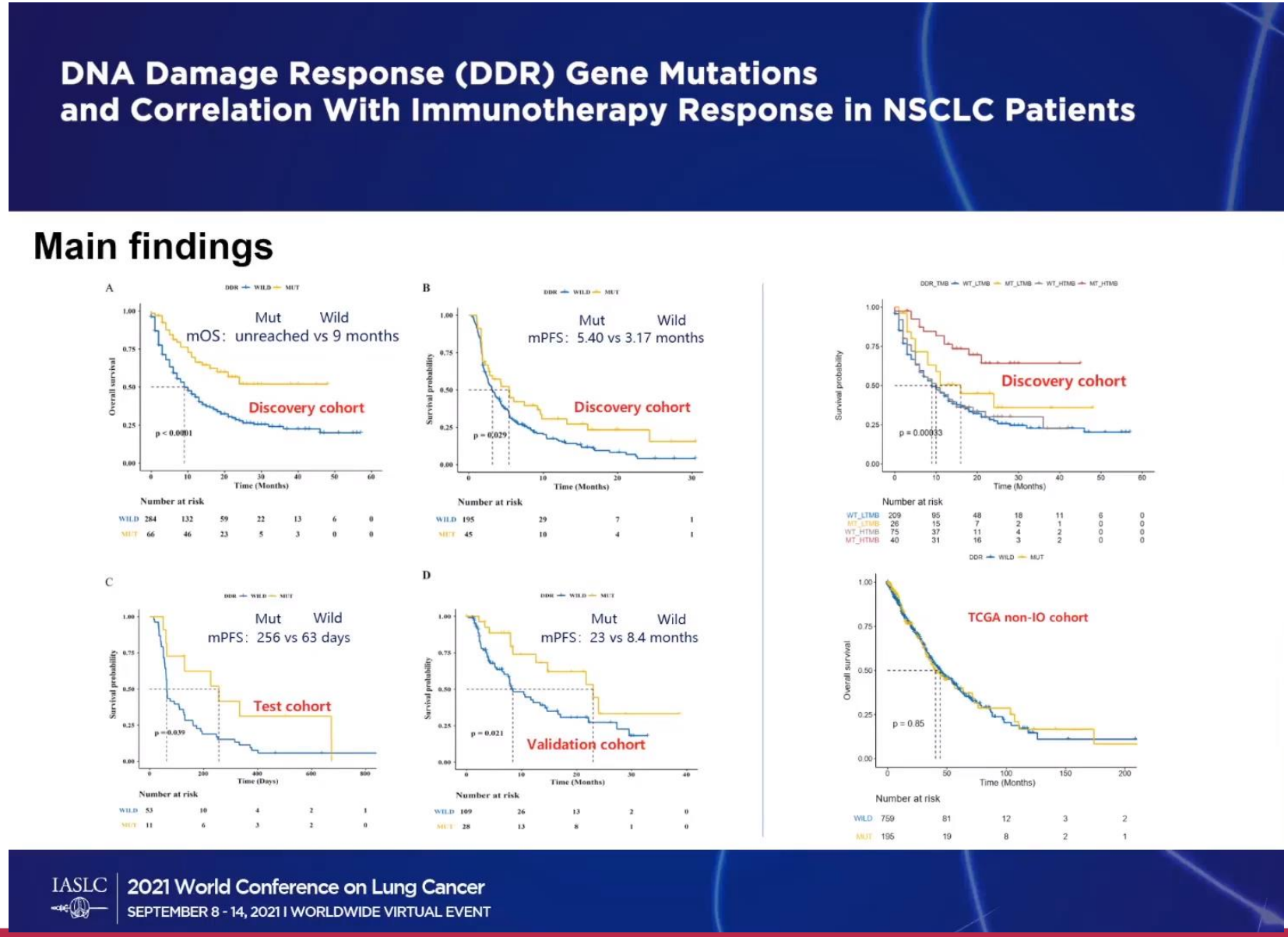
MMR	HR	NER	Checkpoint	FA	Others
MLH1	BRCA1	ERCC2	ATM	BRCA2	POLE
MSH2	MRE11	ERCC3	ATR	BRIP1	MUTYH
MSH6	NBN	ERCC4	CHEK1	FANCA	PARP1
PMS1	RAD50	ERCC5	CHEK2	FANCC	RECQL4
PMS2	RAD51		MDC1	PALB2	
	RAD51B			RAD51C	
	RAD51D			BLM	
	RAD52				
	RAD54L				

DDR: DNA damage response; MMR: Mismatch repair; HR: Homologous recombination; NER: Nucleotide excision repair; FA: Fanconi anemia

Identification of DDR-IO gene set

DNA damage response gene mutations como biomarcador

- Mutaciones en estos genes podrían relacionarse con mayor respuesta a immunoterapia

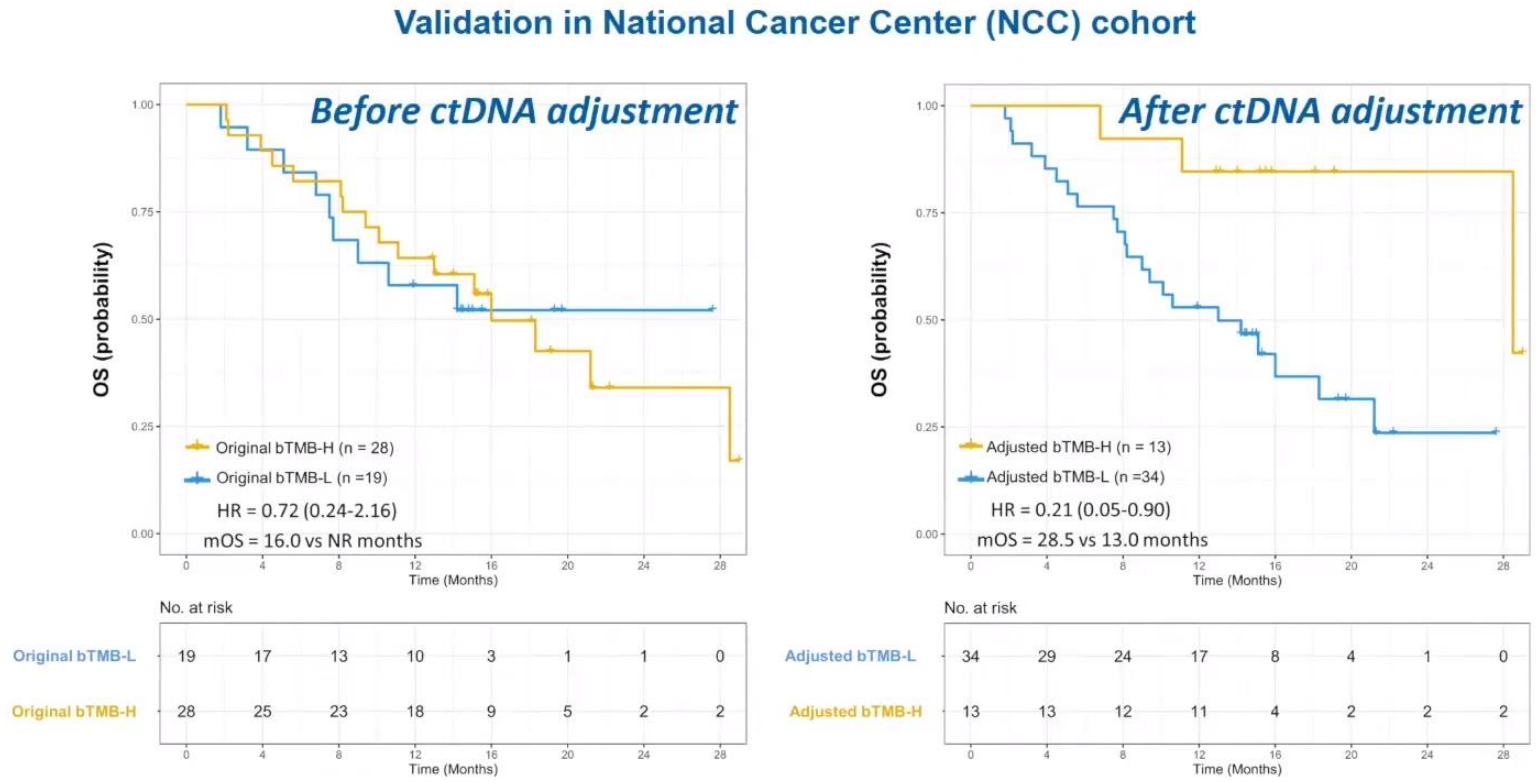


TMB como biomarcador, papel del ctDNA

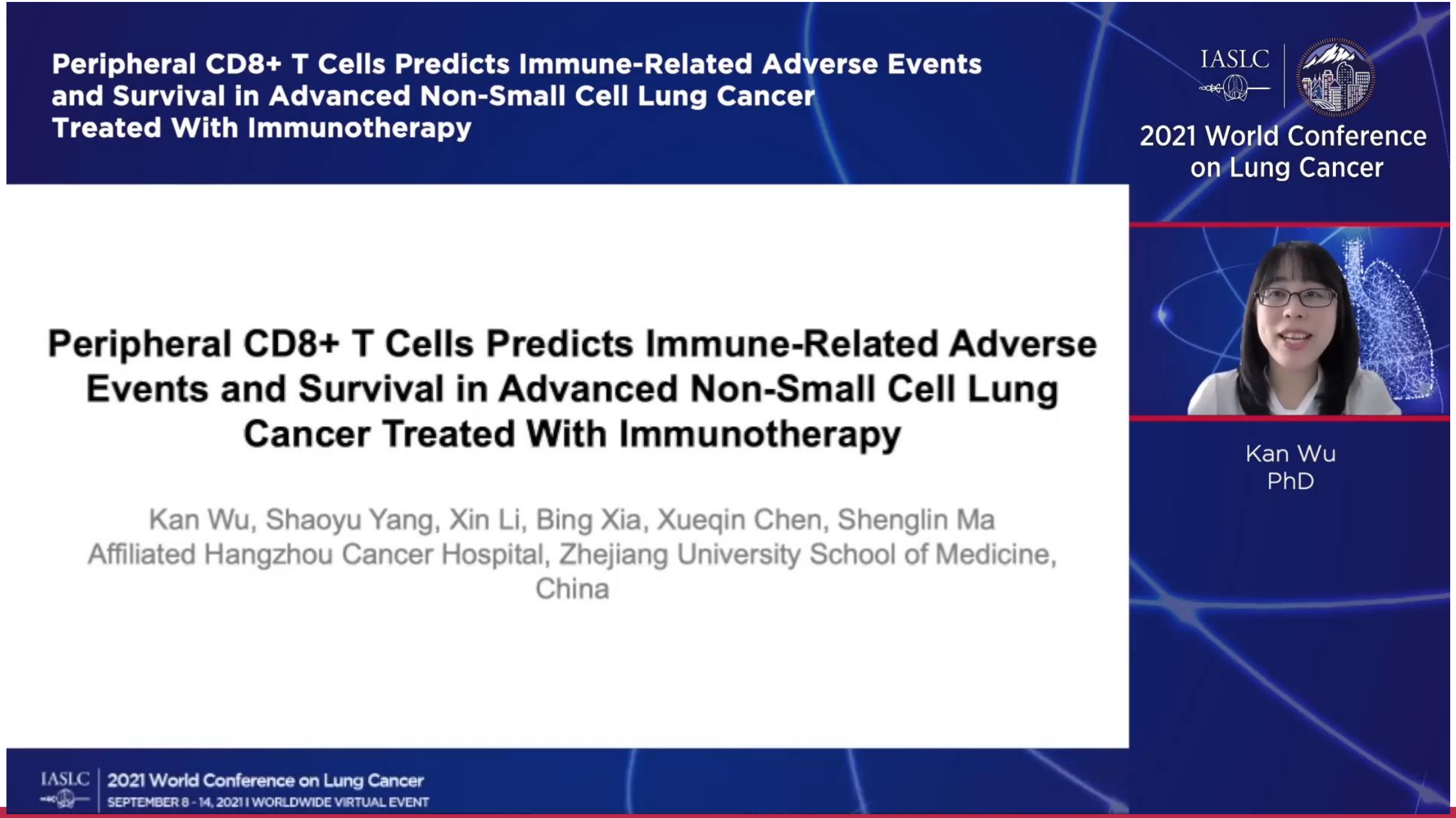
- Podría obtenerse mayor información pronóstica de bTMB cuando se ajusta con el ctDNA (más real de carga de neo-antígenos)

ctDNA Mass-Adjusted bTMB as a Predictive Biomarker in NSCLC Patients Receiving PD-(L)1 Inhibitors

Nie W, et al. WCLC2021, Abstract No.386



Linfocitos T CD8+ periféricos como biomarcador



Linfocitos T CD8+ periféricos como biomarcador

- Se incluyen 109 pacientes de CNMP, 37% 1ª L, 39% 2ª L y 14% 3 o más lineas

Peripheral CD8+ T Cells Predicts Immune-Related Adverse Events and Survival in Advanced Non-Small Cell Lung Cancer Treated With Immunotherapy

Baseline characteristics

Table 1. Baseline characteristics of 109 advanced NSCLC patients

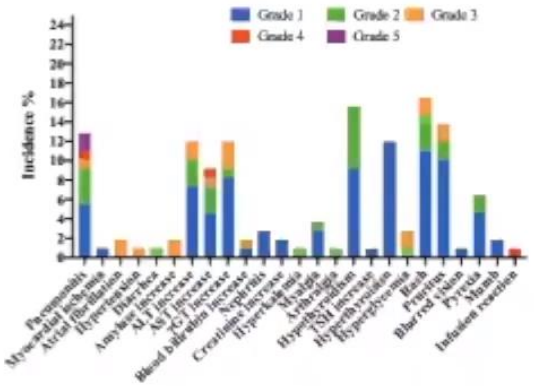
Characteristics	Subset	No	%
Age (years)	Median	65.6	
	Range	36-85	
ECOG PS score	0-1	92	84.4%
	2	17	15.6%
Smoking status	Current/Former	63	57.8%
	Never	46	42.2%
Histology	Adenocarcinoma	60	55.0%
	Squamous carcinoma	46	42.2%
	Large cell carcinoma	3	2.8%
PD-L1 states test	≥50%	23	21.1%
	1-49%	33	30.3%
	< 1%	17	15.6%
	Unknown	36	33.0%
Treatment line	First	41	37.6%
	Second	39	35.8%
	Third	15	13.8%
	Fourth or later line	14	12.8%
Combination treatment	Yes	64	58.7%
	No	45	41.3%

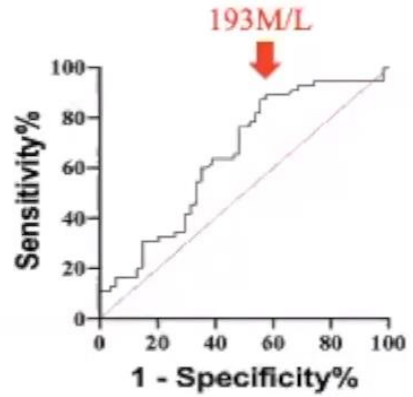
Linfocitos T CD8+ periféricos como biomarcador

- Tanto en análisis univariante como multivariante, los niveles de CD8+ fue un factor predictor de aparición de irAES

Peripheral CD8+ T Cells Predicts Immune-Related Adverse Events and Survival in Advanced Non-Small Cell Lung Cancer Treated With Immunotherapy

Relationship between irAEs and CD8⁺ T lymphocytes





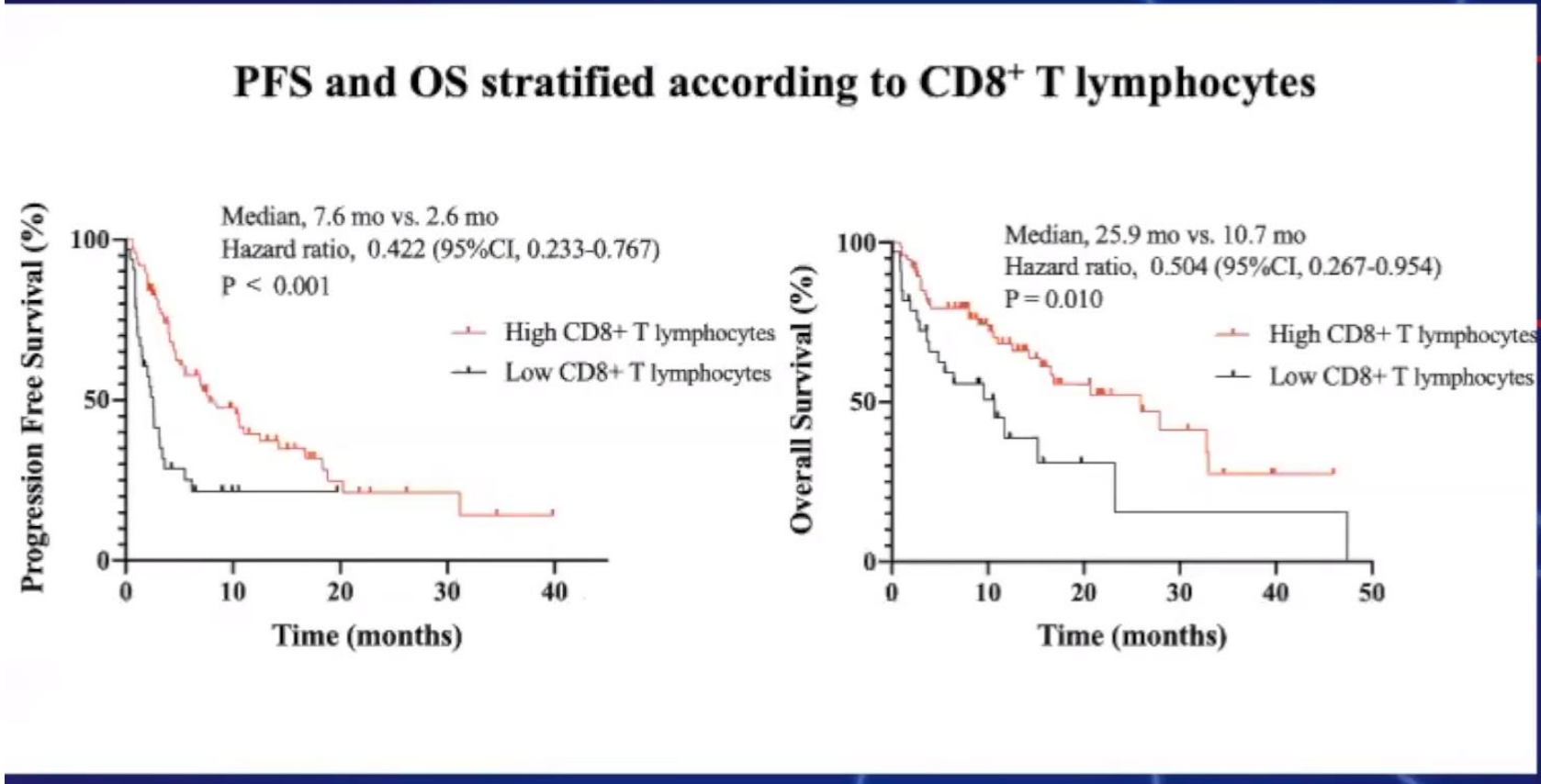
- At least one type of irAEs: 55 patients (50.5%)
- Multiple irAEs: 38 patients (34.9%)
- Severe irAEs (grade ≥ 3) : 16 patients (14.7%)
- 70.3% irAEs were resolved by the end of the observation
- Most commonly irAEs: skin-related, endocrine-related
- Most common severe irAEs (grade ≥ 3): pulmonary-related.

- Univariate and multivariate analysis, the level of CD8+T lymphocytes was the independent predictor for the onset of irAEs.

Linfocitos T CD8+ periféricos como biomarcador

- Los pacientes con mayores niveles de CD8+ presentaron mayor PFS (HR 0.42) y OS (HR 0.504)

Peripheral CD8+ T Cells Predicts Immune-Related Adverse Events and Survival in Advanced Non-Small Cell Lung Cancer Treated With Immunotherapy



Principales conclusiones

- Actividad de quimio-inmuno + pembrolizumab en pacientes con driver mutations post TKI: limitada actividad en ALK+, algo más de actividad en EGFRmut

- Estudios de inmuno + antiangiogénico muestran actividad en pacientes pre-tratados con inmunoterapia.

- Seguimos buscando biomarcadores para predecir respuesta a inmunoterapia:
  - DNA damage response gene mutations como biomarcador (NGS)
  - Linfocitos T CD8+ periféricos como biomarcador de toxicidad y eficacia
  - Mejorar valor pronóstico de bTMB ajustando con ctDNA.