VII SIMPOSIO GETTHI

Sesión 3: Vías de desarrollo de la oncología transversal (I)

2 de diciembre de 2021 - *Formato virtual*

GETTHI

Grupo Español de Oncología Transversal y Tumores Huérfanos e Infrecuentes

Immunotherapy in rare tumours

Jesús Corral, MD

Clínica Universidad de Navarra, Madrid

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Immunotherapy in rare (thoracic) tumours

Jesús Corral, MD

Clínica Universidad de Navarra, Madrid

Disclosure

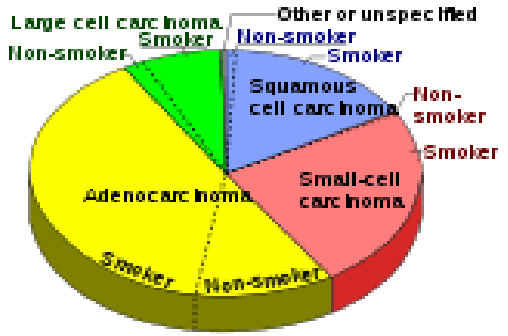
- I have received education grants, provided consultation, attended advisory boards and/or provided lectures for the following organizations:

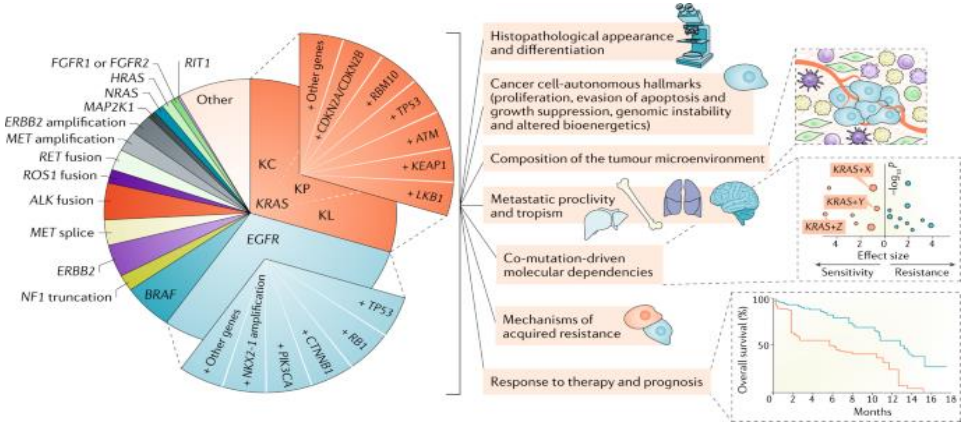
  AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, F. Hoffmann-La Roche, Eli Lilly, Merck Serono, Takeda and Pfizer.

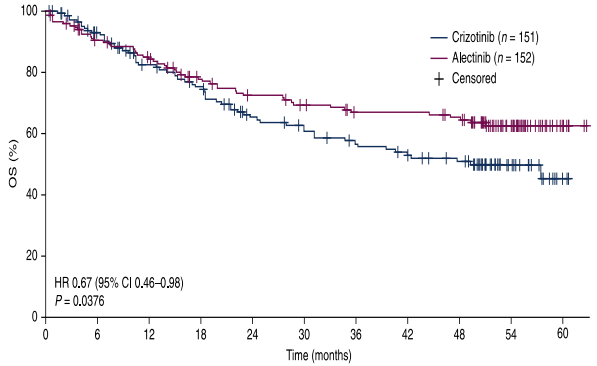
- I declare no conflict of interest.

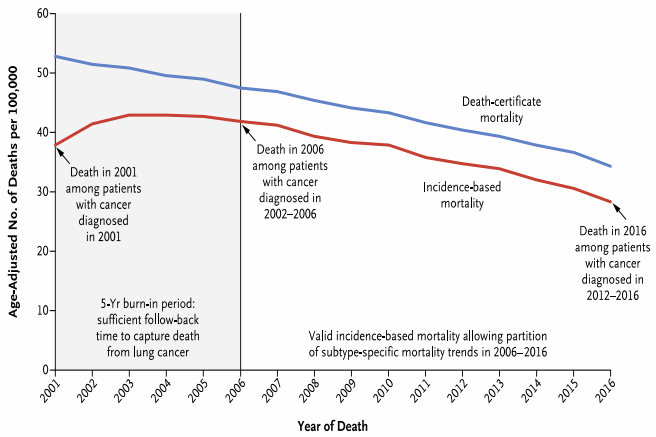
Introduction

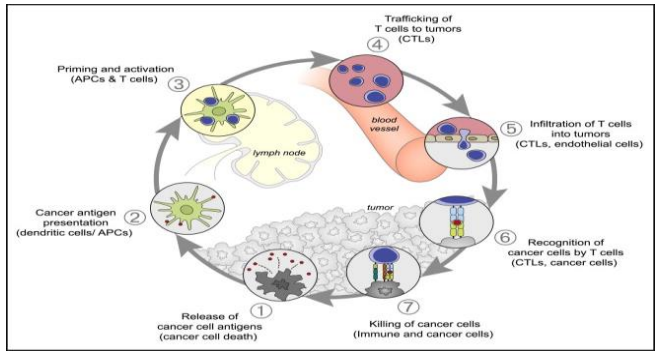
Thoracic malignancies

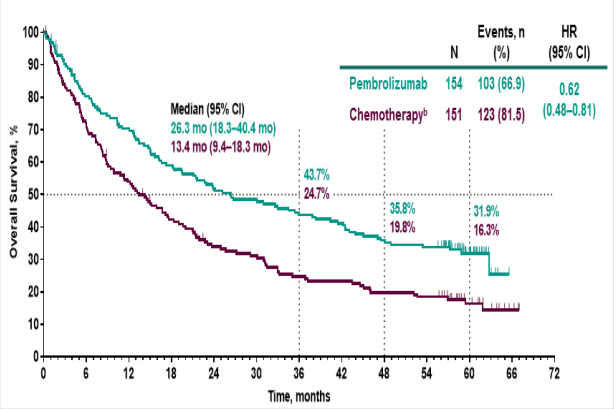








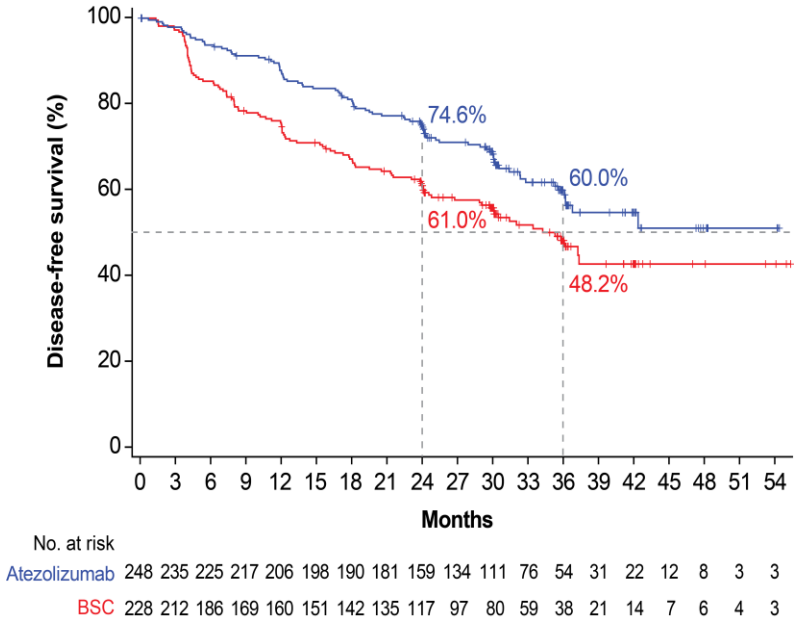


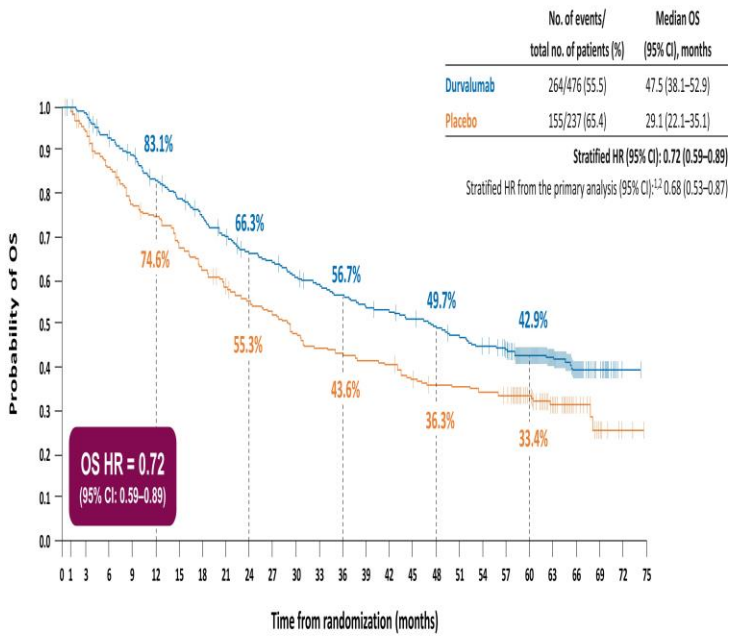


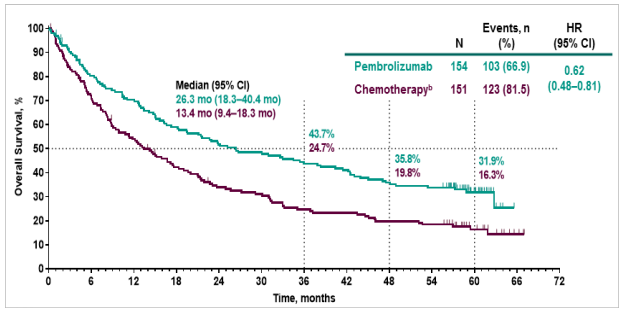
Howlander N, et al. NEJM 2020; Lawrence M, et al. Nature 2013; Chen DS, et al. Cell 2013; Mok T, et al. Ann Oncol 2020; Brahmer J, et al. ESMO 2020

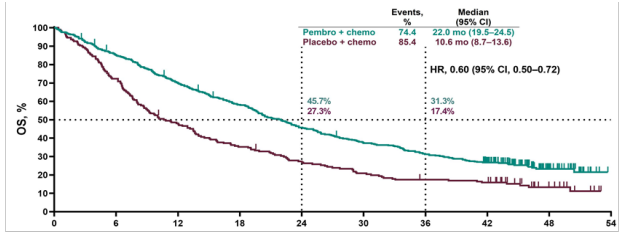
Introduction

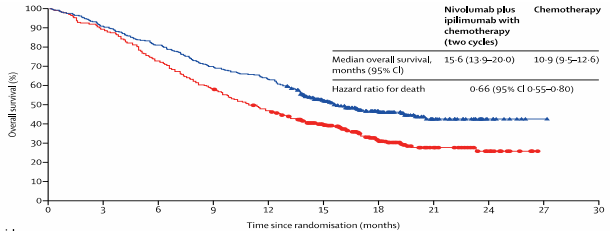
NSCLC IO approach







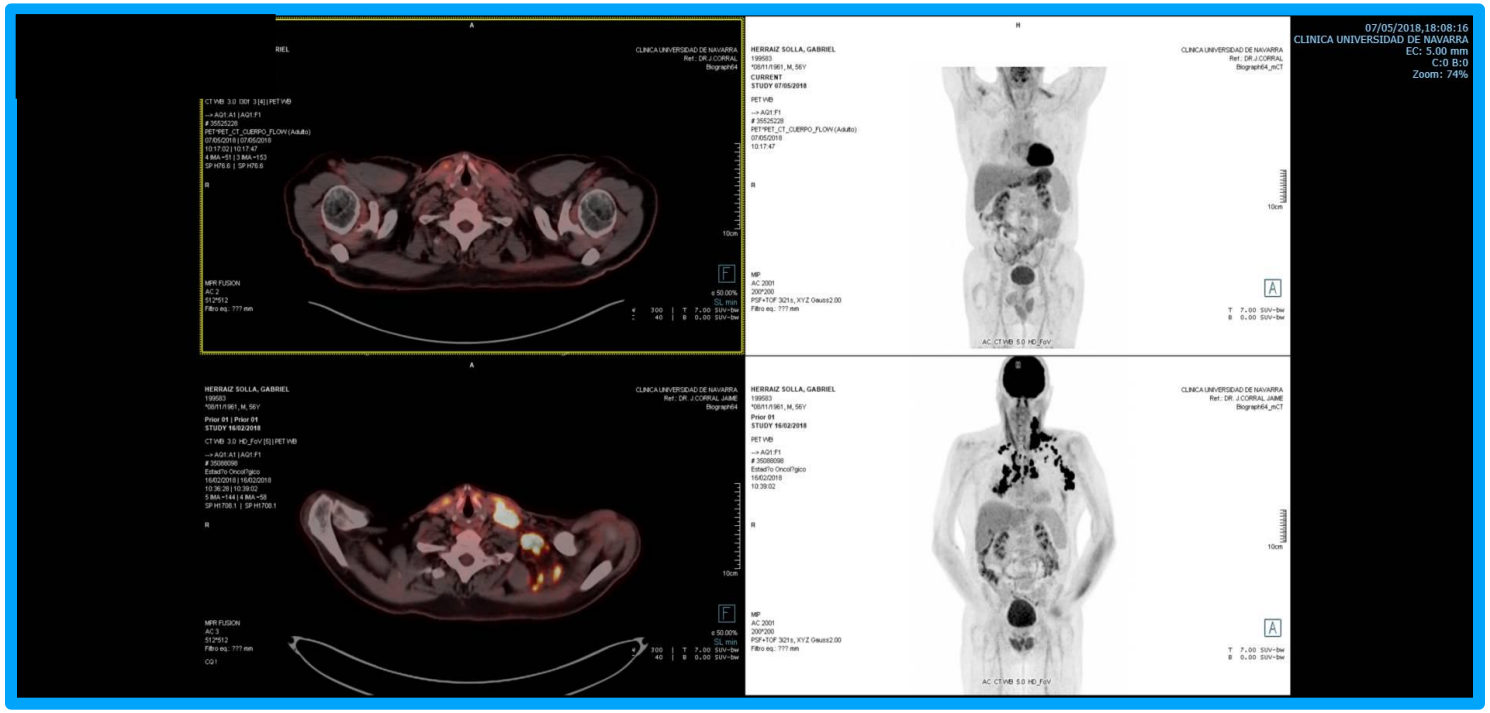




Felip E, et al. ESMO 2021; Spigel D, et al. ESCO 2021; Brahmer J, et al. ESMO 2020; Gray J, et al. IASLC 2020; Paz Ares L, et al. Lancet Oncol 2021

Introduction

Long term survivors

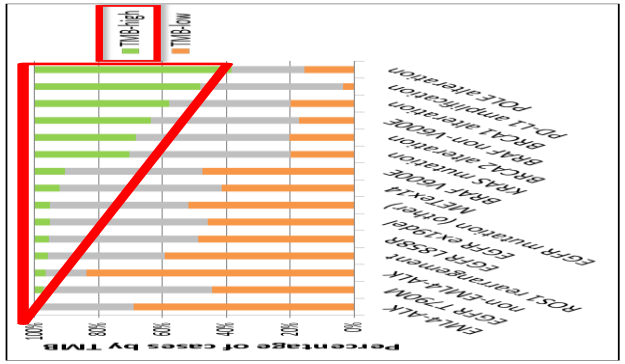


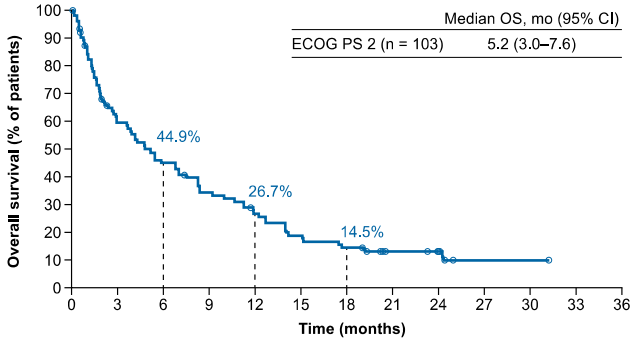
56 yo, male, past light smoker, Stage IV NSCLC Adeno NGS WT PD-L1 90% 1L Pembro (CR ongoing; PFS 4y)

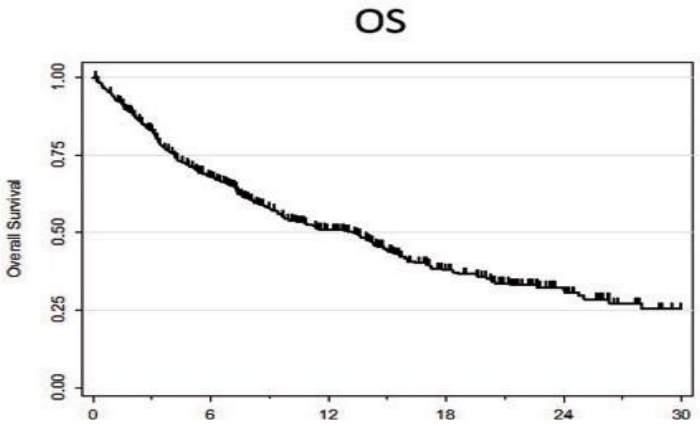
Introduction

No everyone benefits

	Leonardi et al	Khozin et al	Danlos et al	Cortellini et al
N/Tumor types	56 NSCLC	2402 NSCLC	397(16% lung)	751(66% lung)
Pts with AID	56	531	45 (13% lung)	85
Active AID	18%	NR	56%	17%
Rx for AID	20%	NR	16%	17%
AID flare	23%	NR	24.4%	47.1%
Ir-	38%/11%	27%/NR	44%/11%	66%/9.4%
Discontinued	14%	NR	11.1%	7%
RR	22%	NR	38% - similar	38-50%
PFS (mos)	NR	P=0.74	NR	6.8-14.4







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

Califano R, et al. Eur J Cancer 2020; Dudnik E, et al. ASCO 2018; Mazieres J, et al. Ann Oncol 2019; Havel M, et al. Nar Rev Cancer 2019

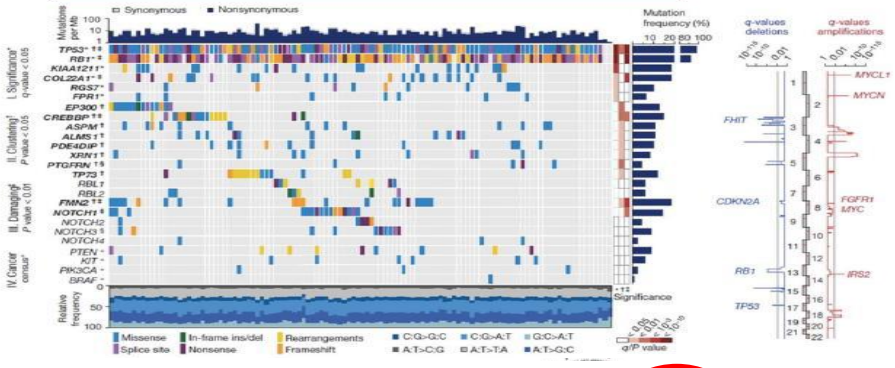
SCLC
Introduction

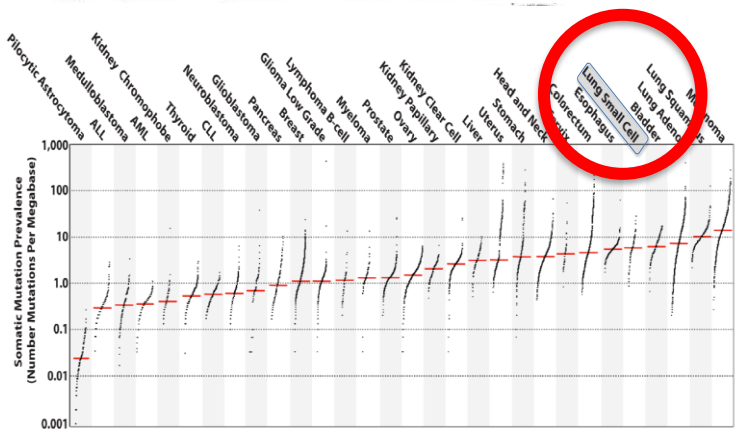
- ✓ 13% of all newly diagnosed lung cancers (decreasing incidence)
- ✓ Association with tobacco exposure (98%) and multiple genetic alterations (*p53*, *Rb1*, …)
- ✓ More agressive than NSCLC: high growth fraction, rapid double time and association with paraneoplastic syndromes (SIADH, Cushing syndrome, hypercalcemia, Eaton-Lambert syndrome, peripheral neuropathy)
- ✓ 70-80% of patients have extensive disease at diagnosis with a median OS < 12 months
- ✓ CT based on platinum/etoposide remains SoC, with no major treatment advances during the last decade, unless consolidation chest RT +/- PCI

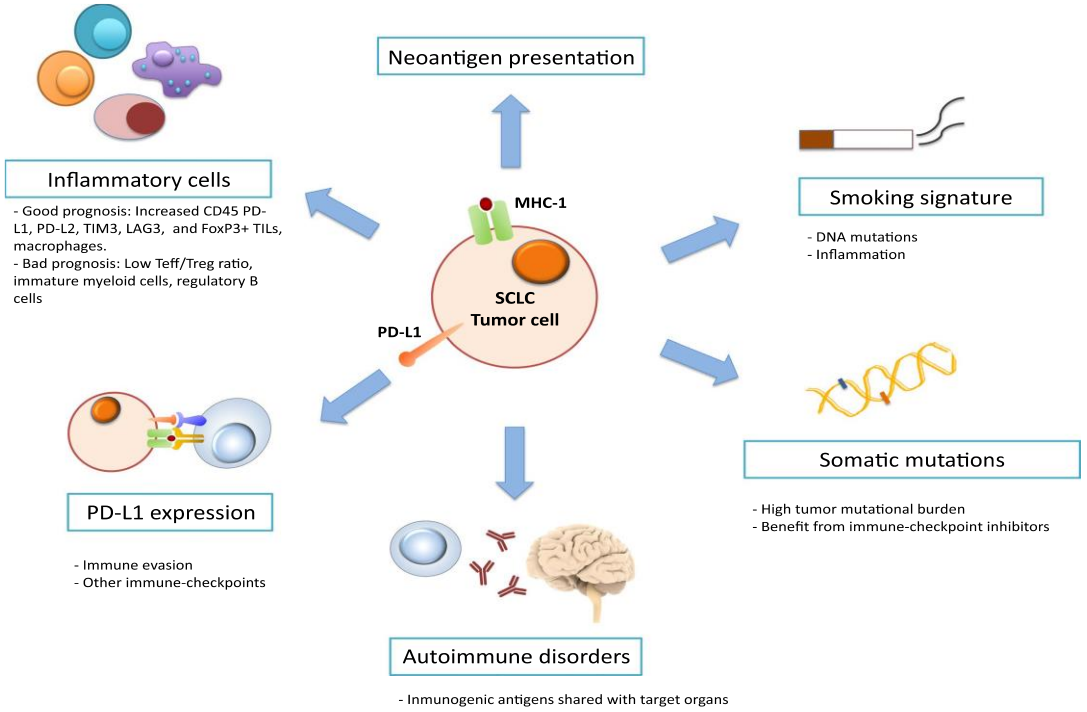
Arriola E, et al. CTO 2010; Rudin C, et al. Nat Gen 2012 ;Fruh M, et al. Ann Oncol 2013; Demedts IK, et al. Eur Respir J 2010; Tiseo M, et al. JCO 2017
Ready NE, et al. JCO 2015; Reck M, et al. JCO 2016; Zhang X, et al. Oncotarget 2017; Slotman B, et al. NEJM 2007; Takayashi T, et al. Lancet Oncol 2017

SCLC

Rationale







Jia H, et al. BMC Medical Genomics 2014; Lawrence M, et al. Nature 2013 ;Bunn P, et al. JTO 2016; Hendriks LE and Besse B. Nature 2018; Calles A, et al. CTO 2019

SCLC

IO approach

IMPower 133

Patients with (N = 403):
- Measurable ES-SCLC (RECIST v1.1)
- ECOG PS 0 or 1
- No prior systemic treatment for ES-SCLC
- Patients with treated asymptomatic brain metastases were eligible

Stratification:
- Sex (male vs. female)
- ECOG PS (0 vs. 1)
- Brain metastases ([illegible])[a]

R 1:1

Induction (4 x 21-day cycles)
- Atezolizumab (1200 mg IV, Day 1) + carboplatin + etoposide
- Placebo + carboplatin + etoposide

Carboplatin: AUC 5 mg/mL/min IV, Day 1
Etoposide: 100 mg/m² IV, Days 1–3

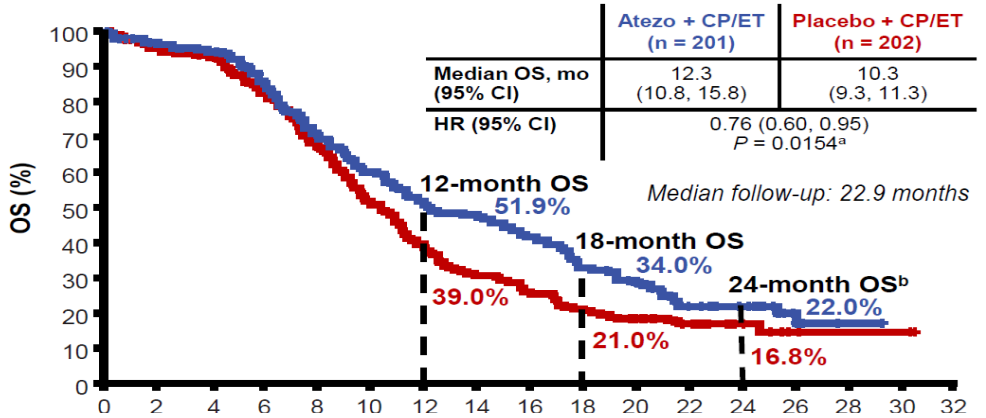
Maintenance
- Atezolizumab
- Placebo

PCI per local standard of care

Treat until PD or loss of clinical benefit → Survival follow-up

Co-primary end points:
- Overall survival
- Investigator-assessed PFS

Key secondary end points:
- Objective response rate
- Duration of response
- Safety



CASPIAN

Treatment-naïve ES-SCLC
- WHO PS 0 or 1
- Asymptomatic or treated and stable brain metastases permitted
- Life expectancy ≥12 weeks
- Measurable disease per RECIST v1.1

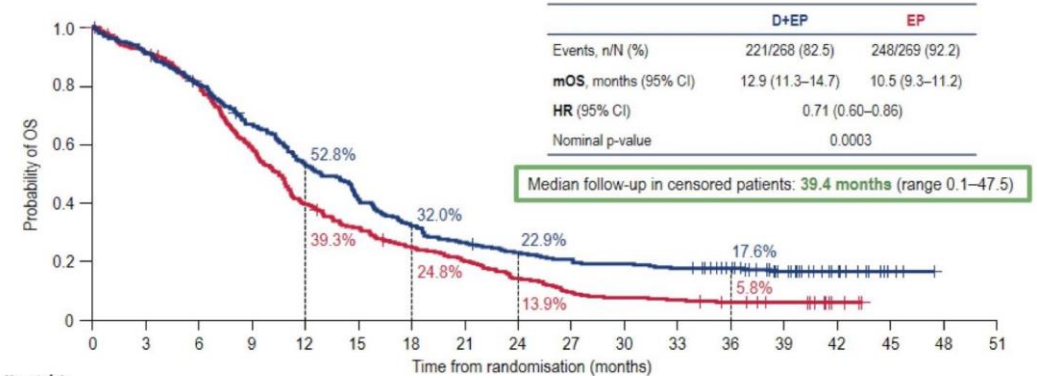
N=805 (randomized)

1:1:1 R — Stratified by planned platinum (carboplatin vs cisplatin)

- Durvalumab + tremelimumab + EP* (q3w for 4 cycles) → Durvalumab‡ (q4w until PD)
- Durvalumab + EP* (q3w for 4 cycles) → Durvalumab (q4w until PD)
- EP* (q3w for up to 6 cycles†) → Optional PCI†

Primary endpoint
- OS

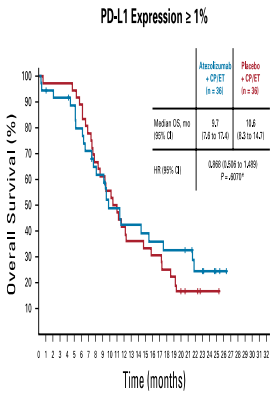
Secondary endpoints
- PFS§
- ORR§
- Safety & tolerability
- PROs

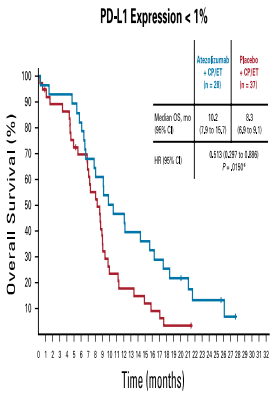


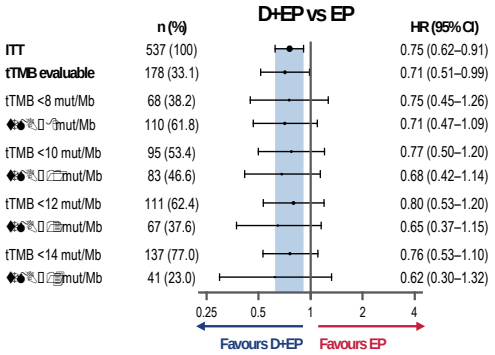
Socinski M, et al. NEJM 2019; Paz Ares L, et al. Lancet 2019; Liu SV, et al. JCO 2021; Paz Ares L, et al. ESMO 2021

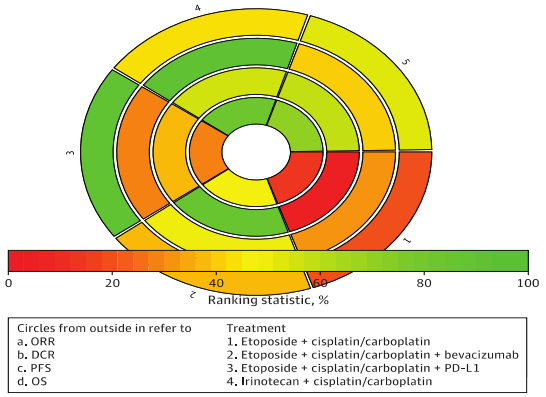
SCLC

Future

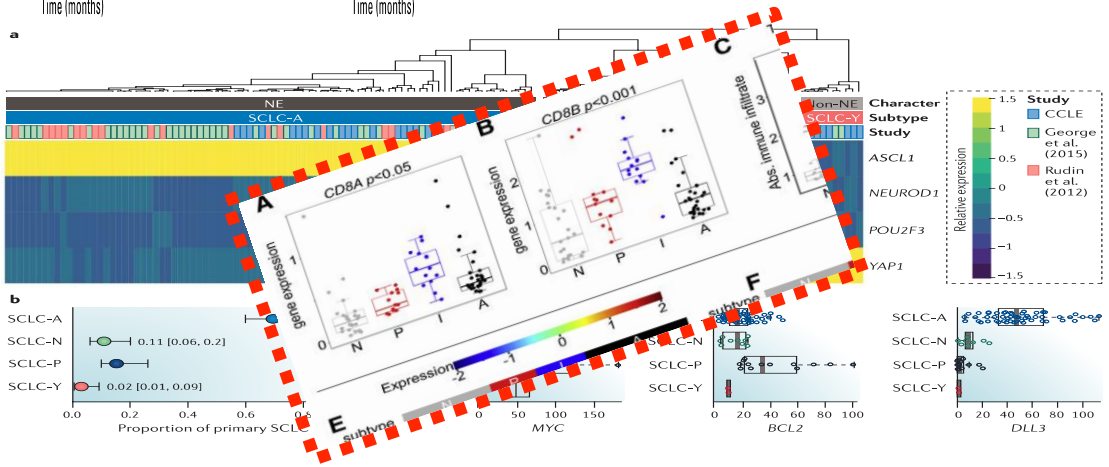






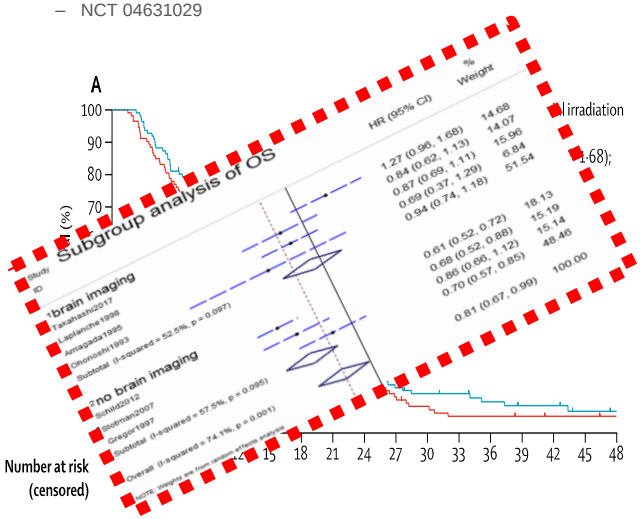


- SKYSCRAPER-02: Phase III trial of carboplatin + etoposide + atezolizumab with either tiragolumab or placebo
  - NCT 04256421
- PRIO: Olaparib and durvalumab with carboplatin, etoposide and/or radiation therapy
  - NCT 04728230
- ETCTN 10399: Phase I study of entinostat in combination with atezolizumab / carboplatin / etoposide in previously untreated ES-SCLC
  - NCT 04631029



NRG-LU007 (RAPTOR)

- ES-SCLC after chemo-immunotherapy, randomized to maintenance atezolizumab +/- consolidative thoracic radiation
- NCT 04402788

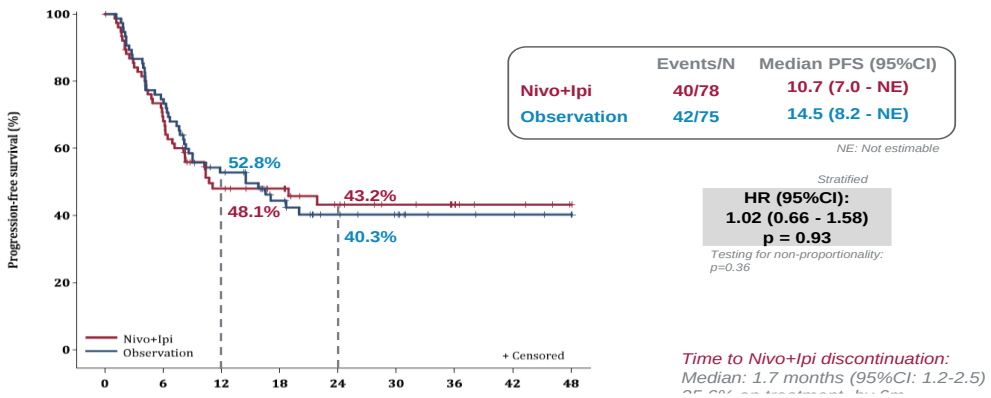


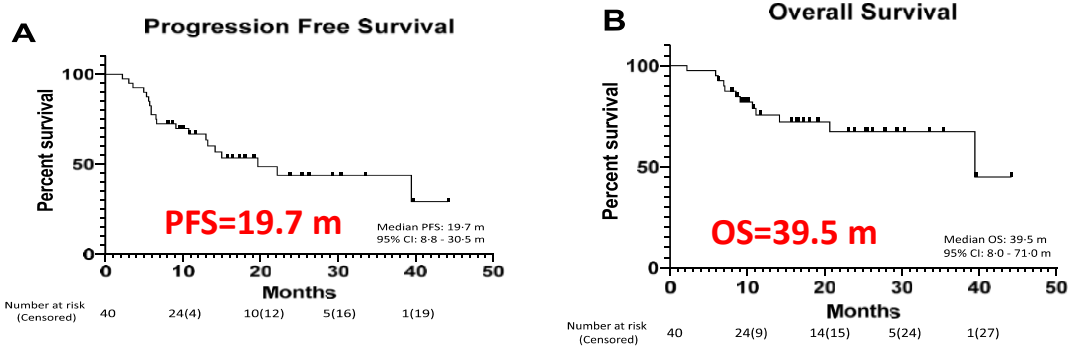
Liu SV, et al. JCO 2021; Goldman JW, et al. ESMO 2020; Gay CM, et al. Cancer Cell 2021; Rudin C, et al. Nature 2019; Takahashi T, et al. Lancet Oncol 2017

SCLC

Next step

Immunotherapy for LD-SCLC	Study name	Study phase	Number of patients	Primary endpoints	ClinicalTrials.gov study identifier	Status
ICI Consolidation after chemoradiation						
Nivolumab + ipilimumab -> nivolumab vs observation	STIMULI	II	260	PFS, OS	NCT02046733	Active, not recruiting
Durvalumab ± tremelimumab vs placebo	ADRIATIC	III	600	PFS, OS	NCT03703297	Recruiting
Atezolizumab	ACHILES	II	212	2-year OS	NCT03540420	Recruiting
ICI + concurrent chemoradiation						
Atezolizumab + cisplatin/etoposide vs CRT	NRG-LU005	II/III	506	PFS, OS	NCT03041311	Recruiting
Pembrolizumab + CRT (EP/ECb)	NCI-2015-00598	I	80	Safety	NCT02402920	Recruiting
Durvalumab ± tremelimumab + CRT (EP)	CLOVER	I	30	Safety	NCT03540420	Recruiting
Durvalumab + CRT (EP)	2018-01-103	II	51	PFS	NCT03585998	Recruiting

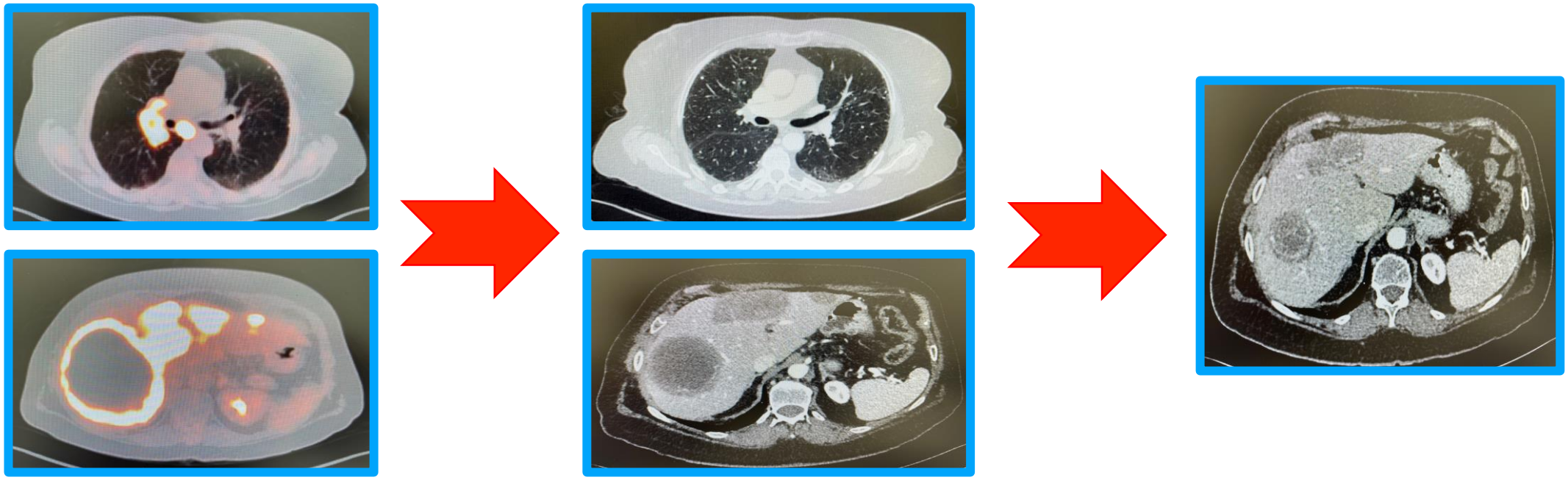




Wang Y, et al. CCR 2018; Calles A, et al. CTO 2019; Peters S, et al. ESMO 2020; Welsh JW, et al. JTO 2020

SCLC

Experience



64 yo female, past smoker (PYI=20), Dec 2019 ED-SCLC (liver metastases), CNS MRI free
Cb/VP-16/Atezolizumab x 4 cycles (PR) followed by Atezolizumab maintenance (increase PR!)
Toxicity: G1 fatigue and skin rash; PFS 15 m (ongoing)

MPM

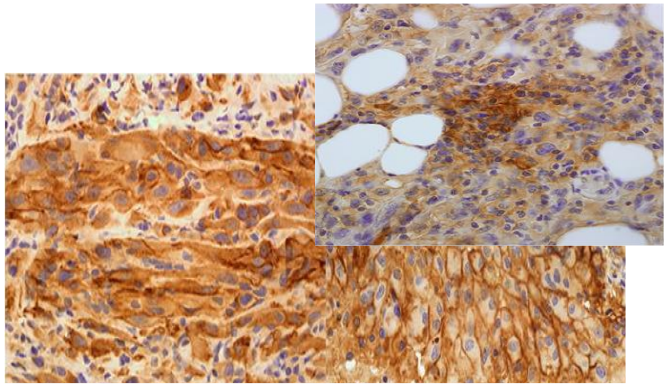
Introduction

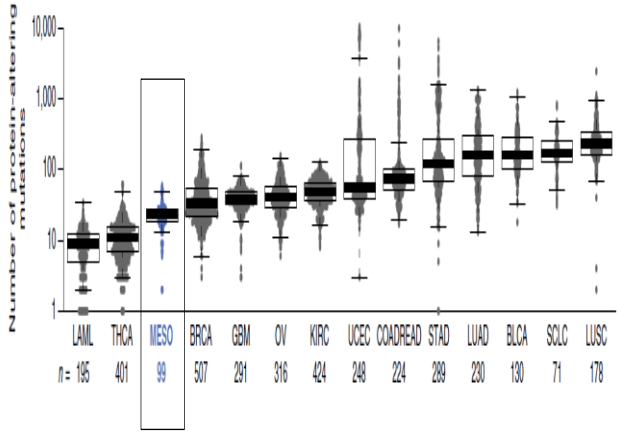
- ✓ Mesothelioma is rare disease (2.1 cases/100000 people/year) caused by asbestos exposure
- ✓ It comprises 3 histological subtypes: epithelioid (50-70%), sarcomatoid (7-20%, poor prognosis) and biphasic
- ✓ MDT management should be recommended with a multimodality treatment approach, although most of patients have metastatic disease at diagnosis
- ✓ Following the approval of CT based on cisplatinum/pemetrexed (OS 12.1m), no randomised phase 3 trial assesing any novel drug or combinations has yet shown a survival improvement, unless Bevacizumab addiction (OS 18.8 m, no FDA/EMA approved)

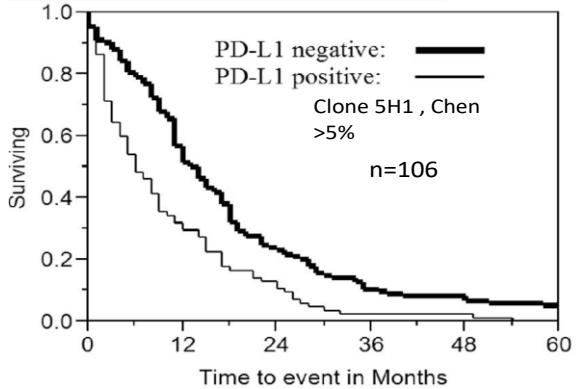
Remon J, et al. Cancer Treat Rev 2013; Elliott D, et al. Surg Pathol Clin 2020; Vogelzang NJ, et al. JCO 2003; Zalcman G, et al. Lancet 2016

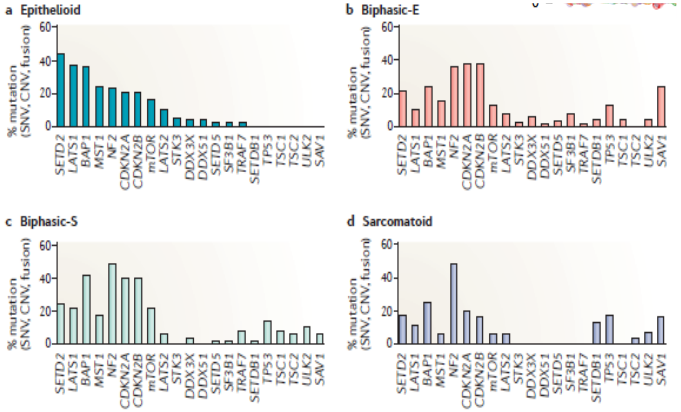
MPM

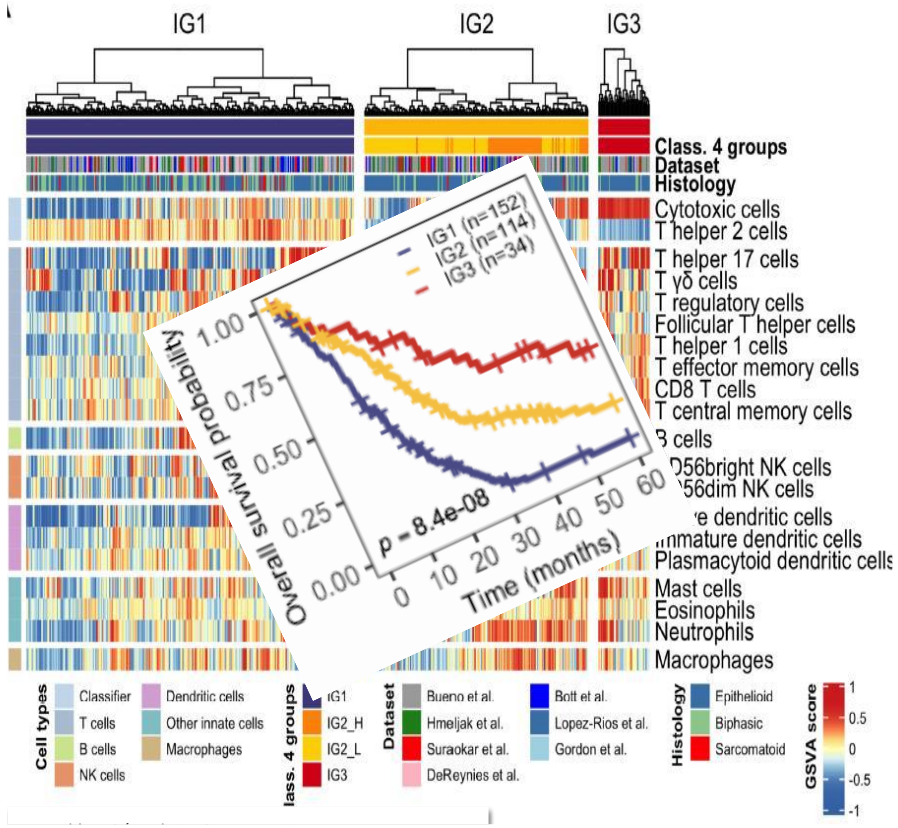
Rationale











Mansfield AS, et al. JTO 2014; Yap TA, et al. Nature Rev Cancer 2017; Zalcman G, et al. ELCC 2021; Alay A, et al. J Immunother Cancer 2021

MPM

IO approach

CheckMate 743

Key Eligibility Criteria
- Unresectable pleural mesothelioma
- No prior systemic therapy
- ECOG performance status 0-1

Stratified by:
histology (epithelioid vs non-epithelioid) and gender

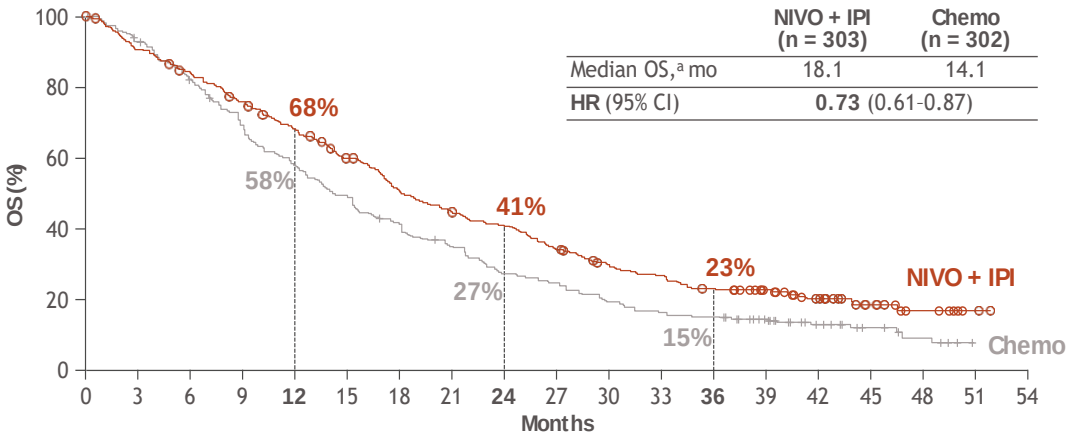
N = 605 → R 1:1

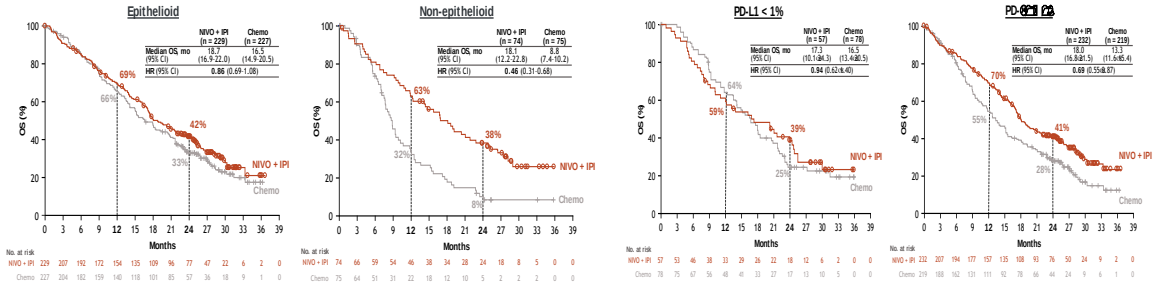
- n = 303 → NIVO 3 mg/kg Q2W + IPI 1 mg/kg Q6W (for up to 2 years)
- n = 302 → Cisplatin or carboplatin + pemetrexed Q3W[b] (6 cycles)

Until disease progression, unacceptable toxicity or for 2 years for immunotherapy arm

Primary Endpoint
- OS

Secondary Endpoints
- ORR, DCR, and PFS by BICR
- PD-L1[c] expression as a predictive biomarker





Baas P, et al. Lancet 2021; Peters S, et al. ESMO 2021

MPM

IO approach

IO	Treatment line	N	ORR (%)	DCR (%)	PFS (m)	OS (m)
Pembrolizumab (KN-028)	2L	25	20	72	5.4	18
Pembrolizumab	2L	35	21	77	6.2	NR
Nivolumab (NivoMES)	Beyond 1L	33	24	50	3.6	NR
Nivolumab (MERIT)	2/3L	34	29	68	6.1	17.3
Avelumab (JAVELIN)	Any	53	9.4	57	4.3	NR
Nivolumab/Ipilimumab vs Nivolumab (MAPS-2)	2/3L	125 (62 vs 63)	25.9 18.5	50 44.1	5.6 4	NR 13.6

Key eligibility criteria:
Mesothelioma
> 1 prior line of therapy
ECOG status 0 or 1

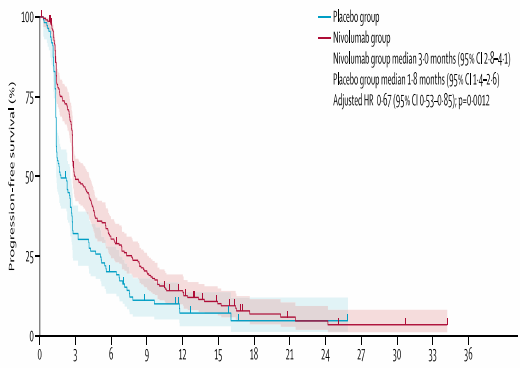
Randomised 2:1
Stratified by histology
(epithelioid or non-epithelioid)

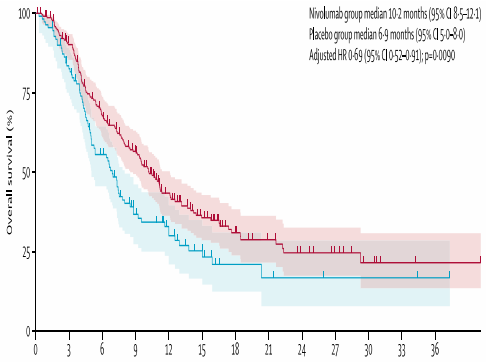
Recruited
April 2017 – March 2020

Nivolumab (n=221)
240mg in 30-min IV infusion on day 1 of 14-day cycle

Placebo (n=111)
240mg sterile solution in 30-min IV infusion on day 1 of 14-day cycle

Administered until progression, unacceptable toxicity, withdrawal or 12m



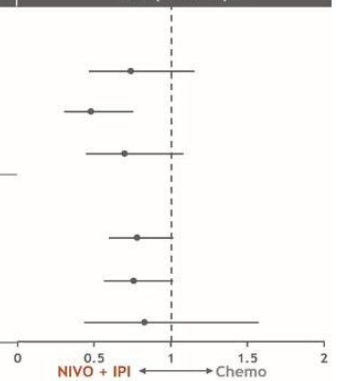


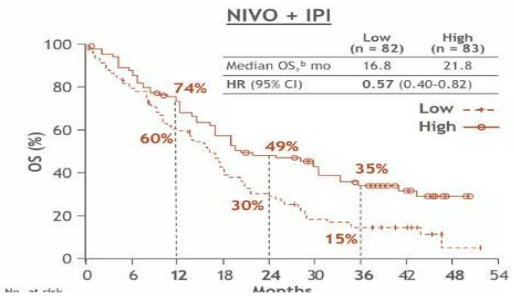
Alley EW, et al. Lancet Oncol 2017; Scherpereel A, et al. Lancet Oncol 2019; Okada M, et al. CCR 2019; Fennell DA, et al. Lancet Oncol 2021

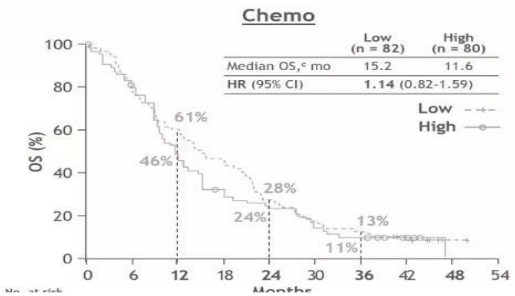
MPM

Future

Subgroup	Median OS, mo		Unstratified HR
	NIVO + IPI	Chemo	
Tissue TMB tertile[a]			
Low[b] (n = 103)	19.3	18.0	0.74
Intermediate[c] (n = 97)	17.9	9.9	0.48
High[d] (n = 95)	17.1	14.1	0.70
LIPI score[e]			
Good[f] (n = 293)	21.6	16.3	0.78
Intermediate[g] (n = 233)	17.1	14.1	0.76
Poor[h] (n = 47)	6.1	6.0	0.83







Exploratory biomarker analyses: OS by 4-gene inflammatory signature score

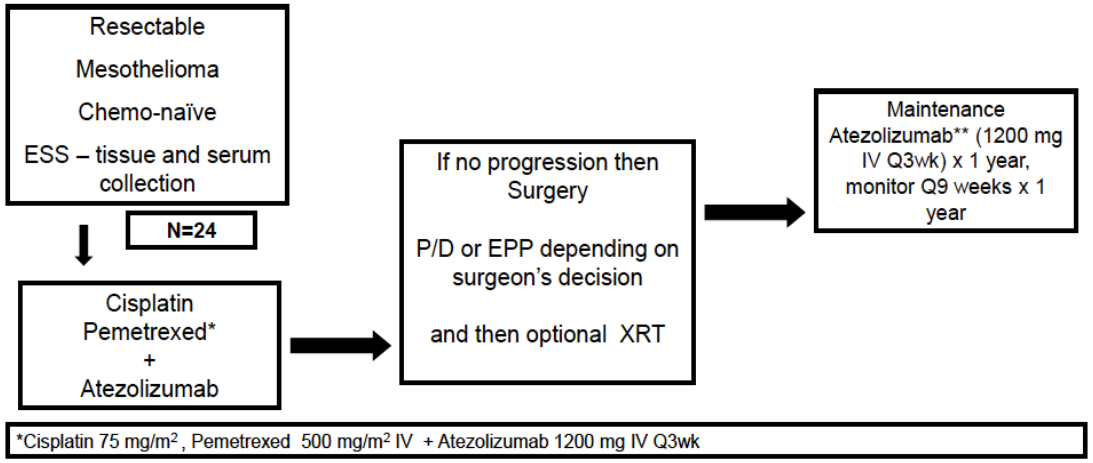
- 4-gene inflammatory signature score includes CD8A, STAT1, LAG3 and CD274 (PD-L1) genes
- Performed via RNA sequencing on baseline formalin-fixed, paraffin-embedded tumor samples

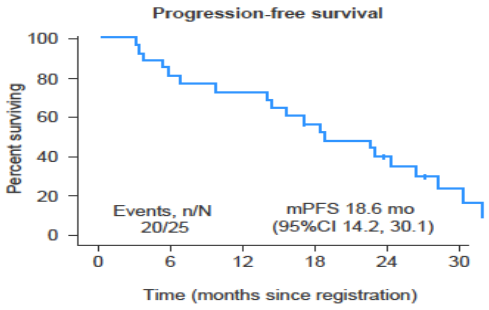
Durvalumab + cisplatin-pemetrexed (PrE0505)	II	02899195	PD-L1 inhibitor + chemo	Frontline	55	OS
Durvalumab + cisplatin-pemetrexed (DREAM – Australia ALTG)	II	-	PD-L1 inhibitor + chemo	Frontline	54	6 month PFS
ONCOS-102 + cisplatin-pemetrexed (Spain)	Ib/II	02879669	Immune-priming GM-CSF coding oncolytic adenovirus + chemo	Frontline	30	Safety Toxicity
Pembrolizumab + cisplatin-pemetrexed vs cisplatin-pemetrexed vs pemetrexed alone (Canadian Cancer Trials Group)	II	02784171	PD-1 inhibitor + chemo	Frontline	126	PFS
BEAT-Meso	III	03762018	Chemo-antiangiogenic +/- PD-L1 inhibitor	Frontline	320	PFS and OS
DREAMR3	III	04334759	Chemo +/- PD-L1 inhibitor	Frontline	480	OS

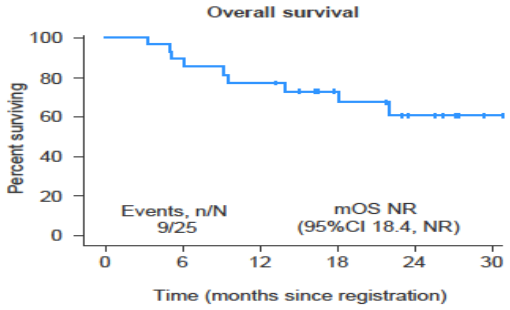
Peters S, et al. ESMO 2021; Tsao AS , et al. ELCC 2021; Danlos FX, et al. ESMO 2021

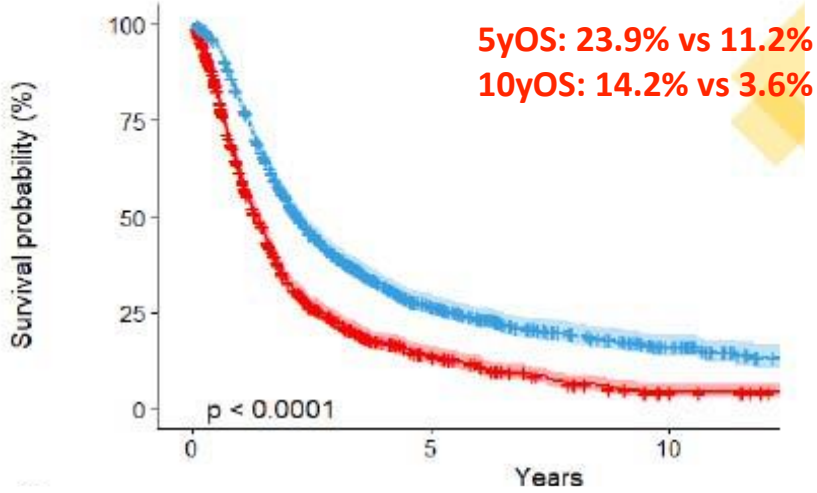
MPM

Next step







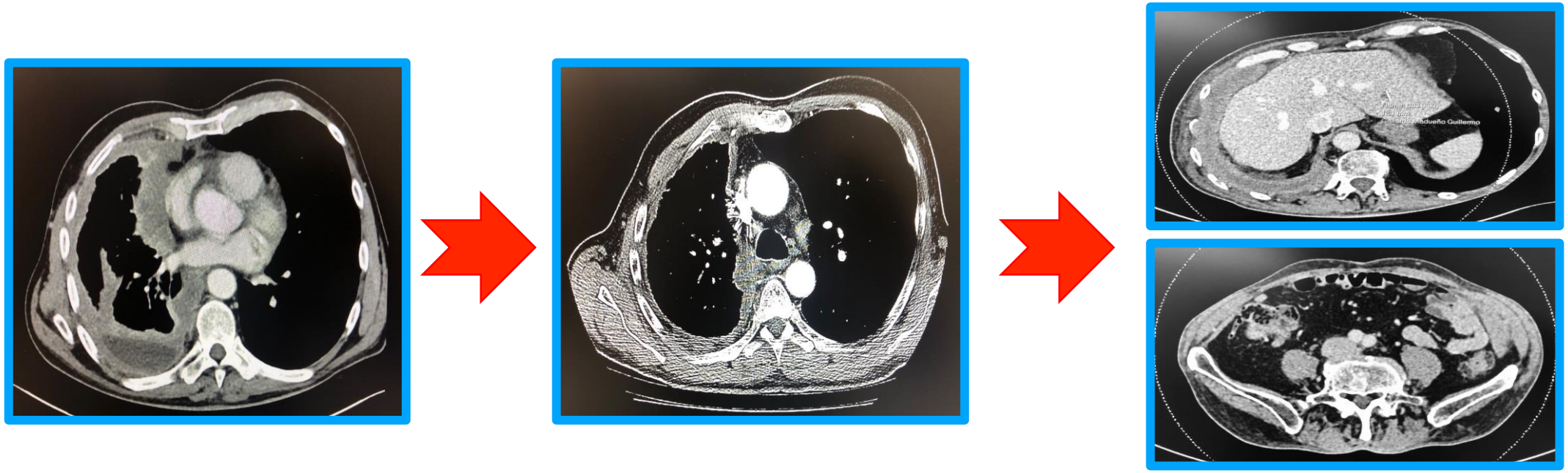


Treatment Factors	MVA Cox	
	HR	p-value
Multiagent Chemotherapy alone	Ref	-
Chemo + radiotherapy	1.272	0.0604
Surgery with chemotherapy	0.606	<.0001
Surgery + chemo + radiotherapy	0.728	<.0001

Tsao A, et al. IASLC 2021; Alnajar A, et al. IASLC 2021

MPM

Experience



67 yo male, past smoker (PYI=7), Feb 2020 Epitelioid Mesothelioma
1L Cis/Pemetrexed x 6 cycles (PD) followed by 2L Clinical Trial IO (PFS 13 m)
Toxicity: G2 HypoT and G1 Colitis…slow signs of asymptomatic PD

TET

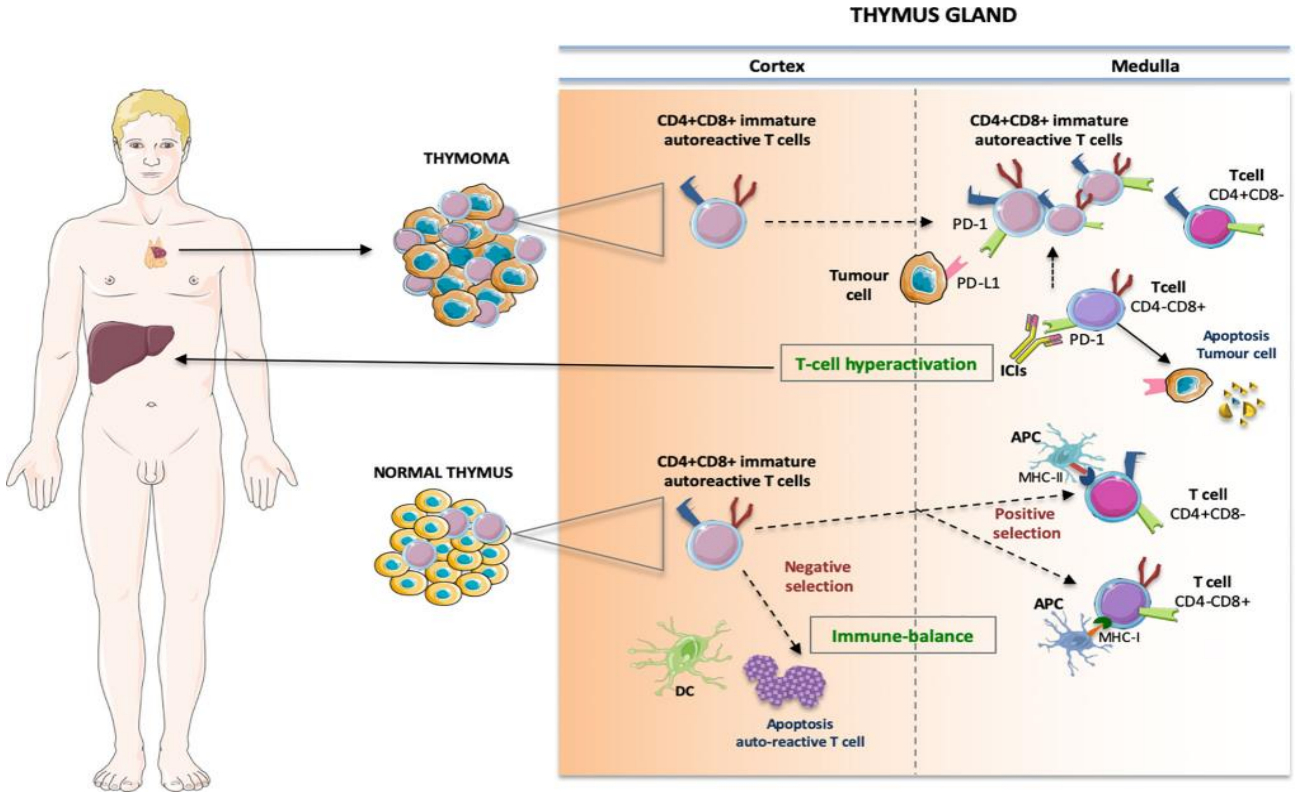
Introduction

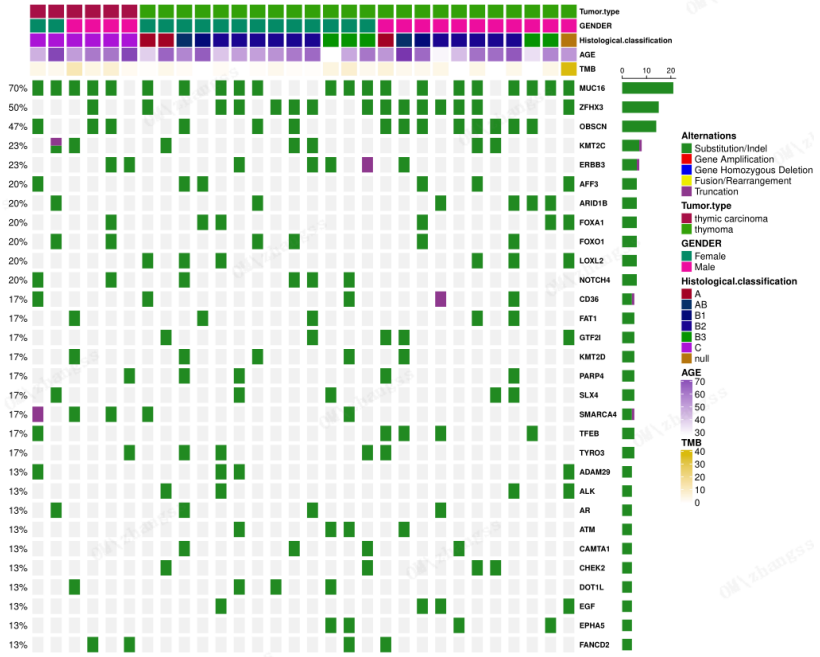
- ✓ Thymic epithelial tumours (TET) remain rare disease (1,3-3,2 cases/million) with high prevalence of AI disease, mostly myasthenia
- ✓ It comprises 6 histological subtypes, no molecular classification
- ✓ Classification: Masaoka-Koga (surgical stage) + TNM (complete resection)=main prognostic factors!
- ✓ Treatment strategy based on tumor resectability, followed by adjuvant RT (R1 or Stage IIA-B2, Stage IIB-B2/3, Stage III/IV and thymic carcinomas). CT plays a role in locally advanced +/- metastastatic disease into a multimodality treatment approach (OS 10y 64-32%)

Engels EA. JTO 2010; Girard N, et al. Ann Oncol 2015

TET

Rationale

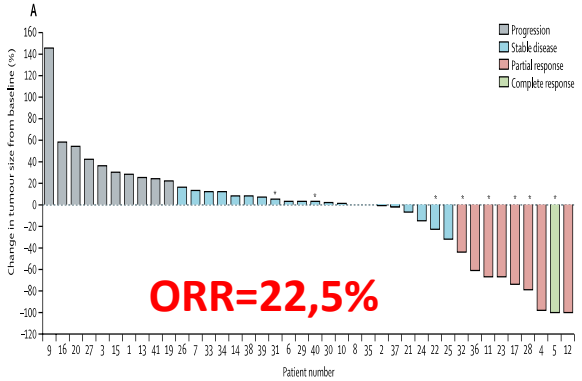




Jakopovic M, et al. J Thorac Dis 2020; Rajan A, et al. Medistinum 2019; Argentiero A, et al. Frontiers in Oncol 2020

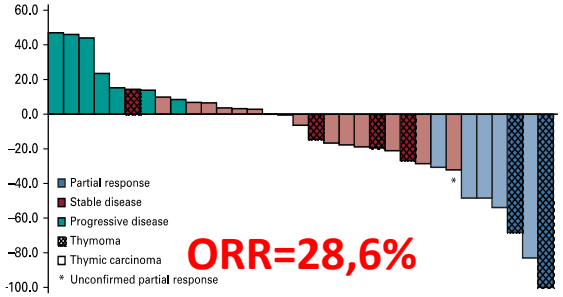
TET

IO approach



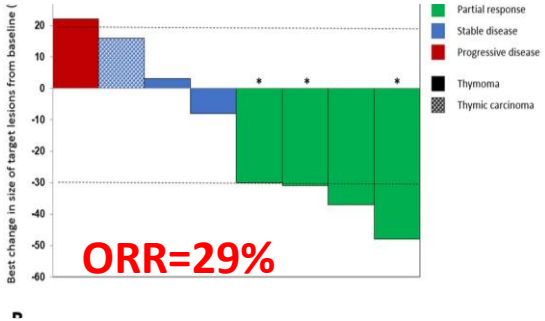
ORR=22,5%

Grade>3 Tox=15%



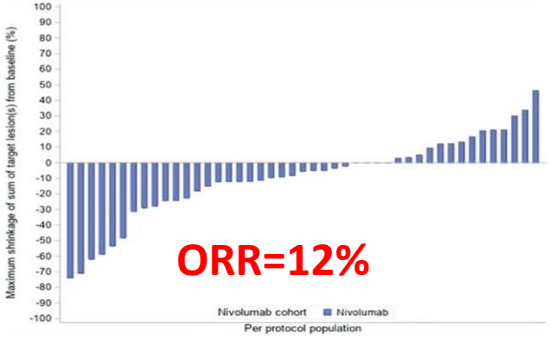
ORR=28,6%

Grade>3 Tox=71,4%



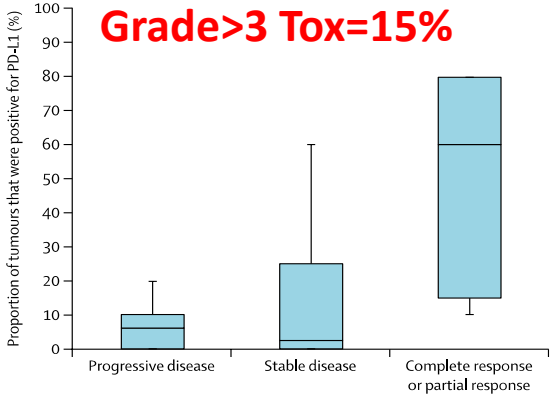
ORR=29%

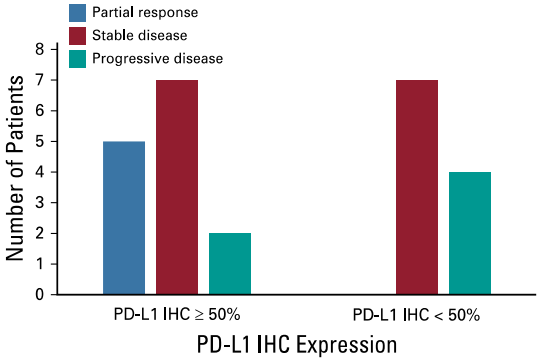
Grade>3 Tox=63%

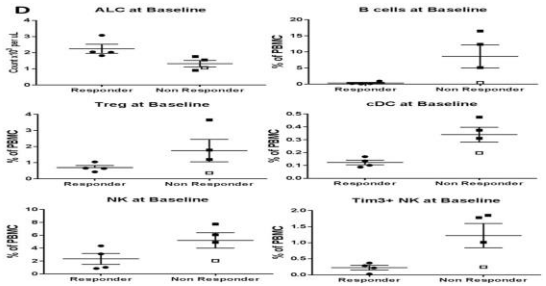


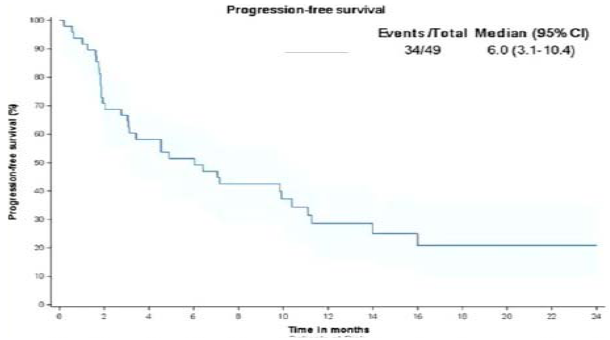
ORR=12%

Grade>3 Tox=59%





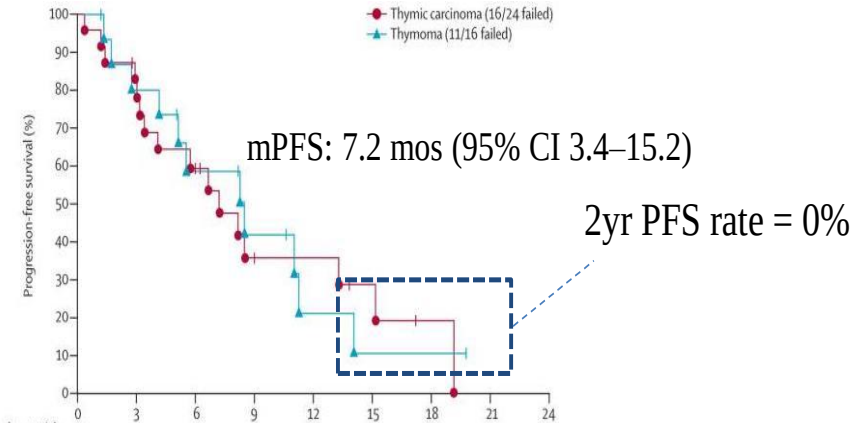


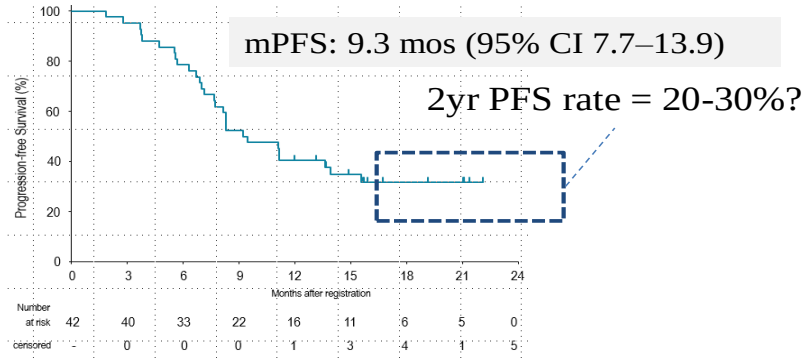


Giaccone G, et al. Lancet Oncol 2018; Cho J, et al. JCO 2018; Rajan A, et al. BMC 2019; Girard N, et al. ESMO 2021

TET

Future





Strategic/Combo

NCT03921671
Carbo-paclitaxel/Nab-paclitaxel + Pembrolizumab (Phase 4)
2020.8 → 2024.7
China, Thy B3+ TC, n= up to 40
Primary endpoint = ORR

NCT03921671
CBDCA+PTX+Ramucirumab
RELEVENT
2018.11 → 2021.10
Italy, Thy B3+ TC, n=60
Primary endpoint = ORR

NCT03463460
Pembrolizumab + Sunitinib
2018.12 → 2020.12
Ohio State U. n=40 (thy B3+ TC)
Primary endpoint =ORR

NCT04710628
Pembrolizumab + Lenvatinib
PECATI
2021.4 → 2023.3
France + Spain. n=43 (thy B3+ TC)
Primary endpoint =PFS

Chemo+pembro+Len combo!?

IND

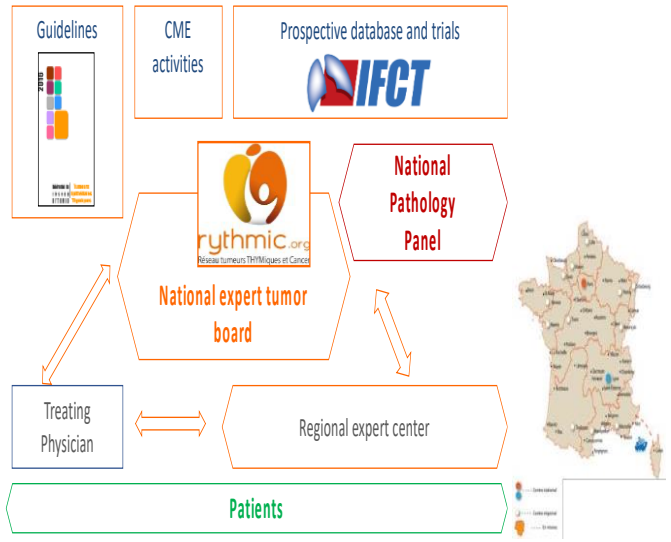
NCT04469725
KN046
(PD-L1/CTLA4 Bispecific Single Domain Fc Fusion Protein Ab)
2021.6 → 2026.1
n=29, IO PD後
Primary endpoint = PFS

NCT03193437
Selinexor (KPT-330, ONO-7705)
oral Selective Inhibitor of Nuclear Export (SINE) compound
2018.4 → 2021.12
Gerogetown U. n=50 (US=25 + EU=25), thy=25; TC=25
Primary endpoint = ORR

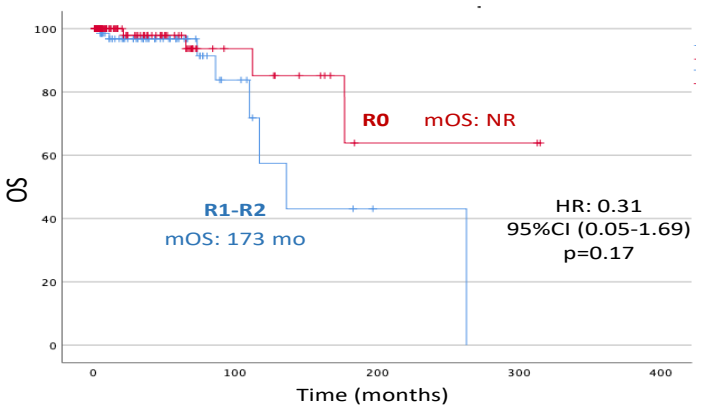
Sato J, et al. Lancet Oncol 2020; Thomas A, et al. Lancet Oncol 2015; Okumura M, et al. IASLC 2021

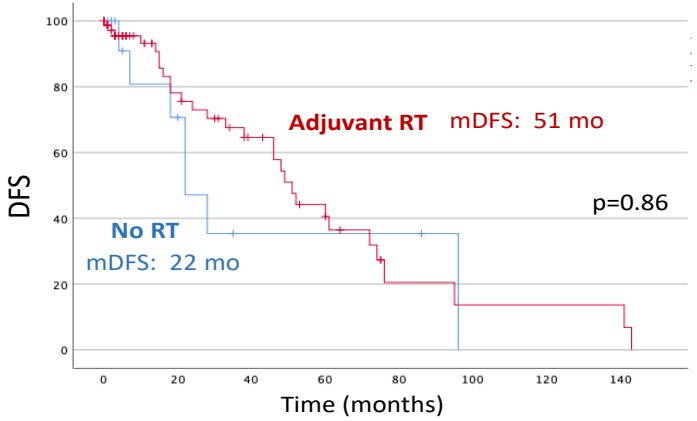
TET

Next step



DFS	HR	95% C.I. lower	95% C.I. upper	p-value
Sex (female)	4,951	2,094	11,708	<0,0001
Age	0,976	0,953	1,001	0,059
AIDs	0,791	0,295	2,123	0,642
T2	NA	NA	NA	0,046
T3	1,463	0,516	4,147	0,474
T4	10,424	1,607	67,611	0,014
Type A	7,147	0,431	118,425	0,17
Type AB	NA	NA	NA	0,982
Type B1	0,239	0,025	2,281	0,214
Type B2	2,339	0,609	8,991	0,216
Type B3	0,778	0,166	3,637	0,749
TC	43,18	7,604	245,212	<0,0001
R0	0,311	0,14	0,692	0,004
Adjuvant RT	0,771	0,236	2,518	0,666
Induction ChT	0,371	0,143	0,962	0,041

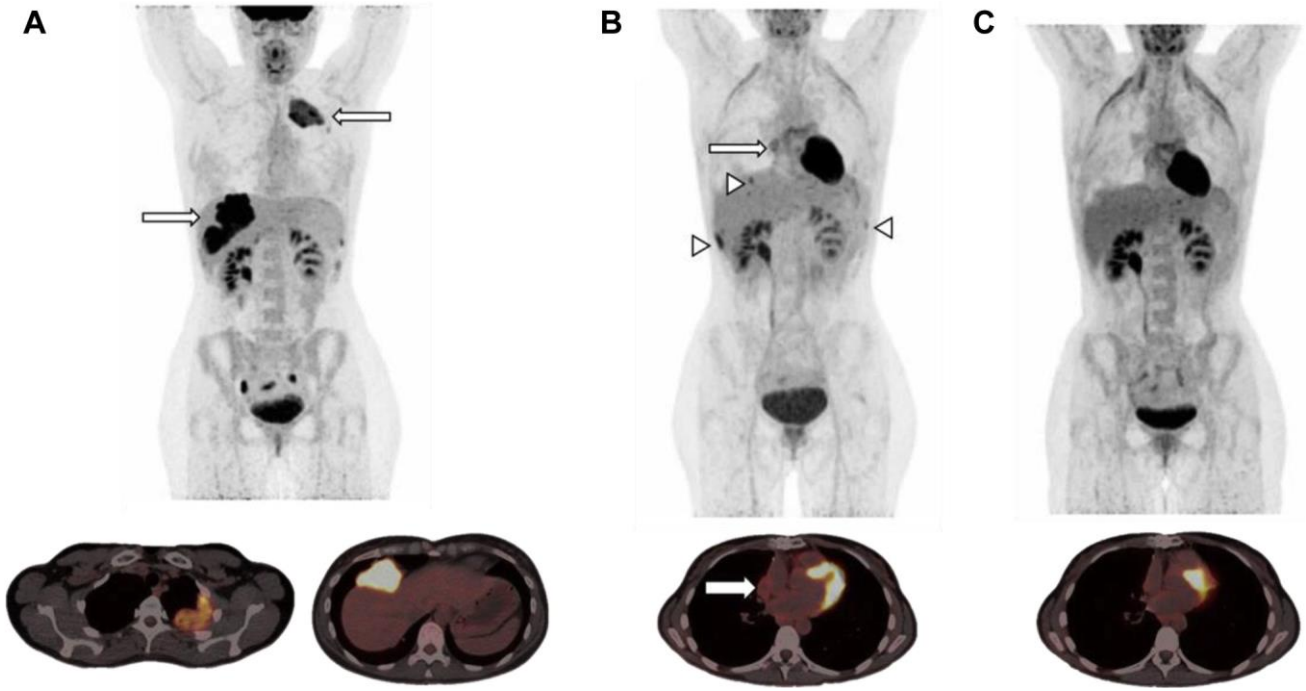




Benitez JC, et al. IASLC 2021

TET

Experience



39 yo female, Thymoma B1 after surgery + adj RT and 2 lines CT (CAP, Cb/Pem)
PD-L1 65% Pembrolizumab x 2 y (mantained CR x 24 m)

Corral J, et al. JTO 2020

Conclusions

- ✓ IO has rapidly transformed the treatment paradigm for multiple cancer types, including thoracic malignancies
- ✓ Although in NSCLC has become a new SoC worldwide based on improved OS compared with CT, it still remains some relevant clinical questions to be answered: unselected population, oncogenic addicted tumours, etc
- ✓ IO has recently modified the therapeutic strategy in first-line setting in patients with ED-SCLC and MPM: the magnitude of benefit remains modest in comparison witn NSCLC and further investigation is strongly required
- ✓ TETs are the last thoracic malignancy where IO has reported some light of efficacy, with a special focus in the risk of irAEs
- ✓ Rare tumors require an extra effort (academic + commercial + institutional) to design studies that help IO implementation into our daily clinical practice

VII SIMPOSIO GETTHI

Sesión 3: Vías de desarrollo de la oncología transversal (I)

2 de diciembre de 2021 - *Formato virtual*

GETTHI

Grupo Español de Oncología Transversal y Tumores Huérfanos e Infrecuentes

Thanks

jcorral@unav.es