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Progress in the systemic treatment of advanced small cell lung cancer and mesothelioma

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BSMO

UZA

European Reference Network
for rare or low prevalence complex diseases
Network Adult Cancers (ERN EURACAN)

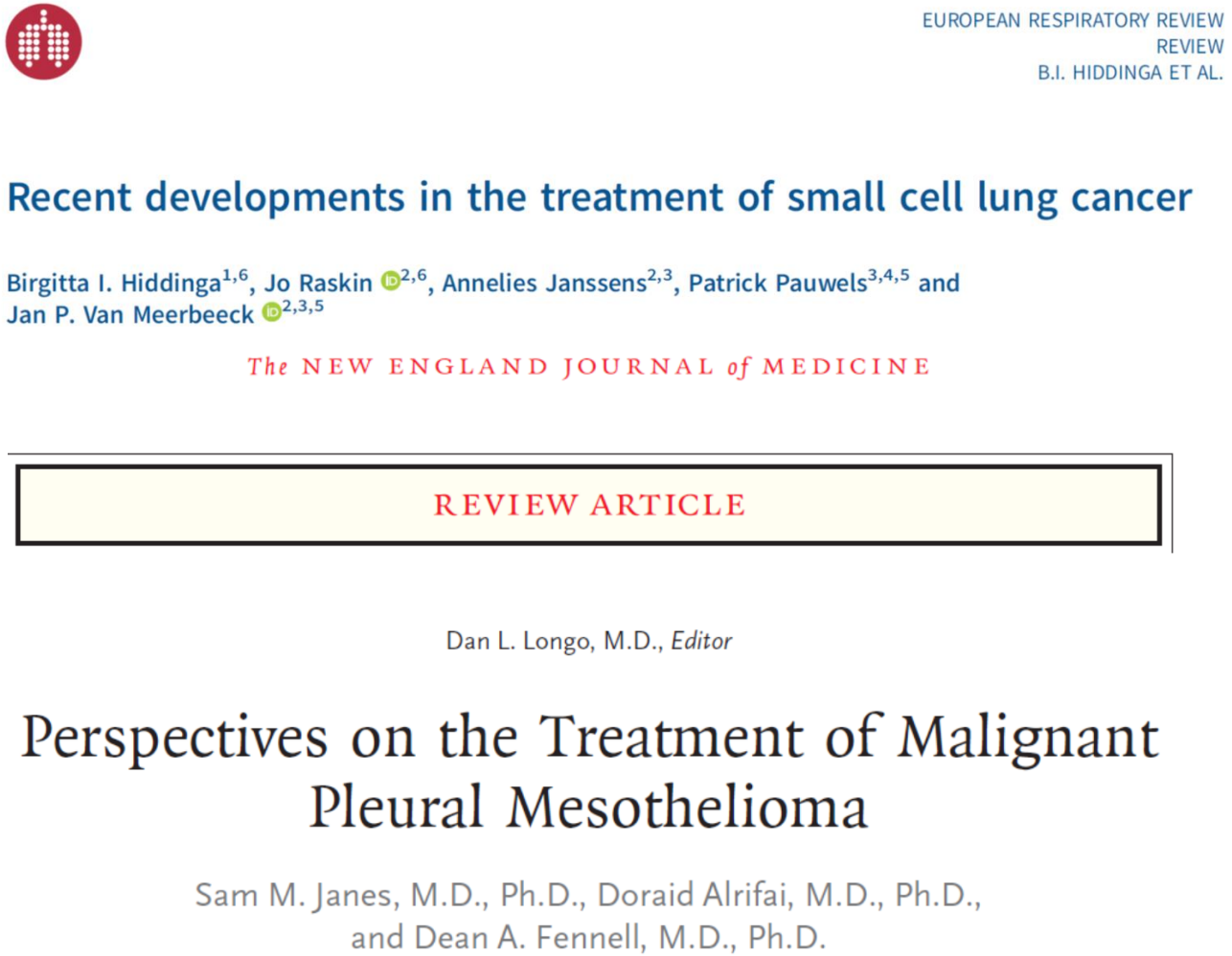
Disclosures & acknowledgements

- https://betransparent.be

- **PI in CM 743: BMS**

Outline

- **Advanced small cell lung cancer**
  - State of the art
  - Immunotherapy
  - Targeted (molecular) therapy
  - Clinical implications
- **Advanced mesothelioma**
  - State of the art
  - Immunotherapy
  - Targeted (molecular) therapy
  - Clinical implications



EUROPEAN RESPIRATORY REVIEW
REVIEW
B.I. HIDDINGA ET AL.

Recent developments in the treatment of small cell lung cancer

Birgitta I. Hiddinga[1,6], Jo Raskin[2,6], Annelies Janssens[2,3], Patrick Pauwels[3,4,5] and Jan P. Van Meerbeeck[2,3,5]

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Perspectives on the Treatment of Malignant Pleural Mesothelioma

Sam M. Janes, M.D., Ph.D., Doraid Alrifai, M.D., Ph.D., and Dean A. Fennell, M.D., Ph.D.

Advanced small cell lung cancer: state of the art

- **Rare disease**
  - 15% of incident cases of lung cancer: ~ 1300 cases in Belgium in 2020 (BCR)
  - Neuro-endocrine origin
  - At diagnosis 69% in stage 4: distant met's, pleural fluid, contralateral lung, …
- **Strong causal association with smoking**
- **Rapid doubling time**
  - Escapes screening by low dose Ct-scan
  - Often dramatic presentation: SVCS, brain met's, stridor, dysphagia
- **Frequently associated with paraneoplastic syndromes**
  - Endocrine: ACTH, ADH, …
  - Neurological: myasthenia, polyneuritis, …
- **SOC since 1990's: palliative chemotherapy**
  - 1st line: platinum + etoposide q 3w x 4-6 cycles RR ~50% mPS: 4-5 m
    - No benefit with maintenance, dose escalation, 3rd generation drugs, …
  - 2nd line: topotecan or CAV q3w x ?
  - Optional irradiation of brain (PCI) and thorax in responders
- **Poor prognosis:** mOS 10-12 months 2y SR 20% 3y SR 6%

Immunotherapy with ICI

- **Is SCLC immunogenic?**
  - PRO: High mutational burden, with enhanced immunogenicity
    - Chemotherapy primes tumour by exposing antigens for response to ICI
  - CON: 'immune-cold' phenotype with low PDL-1 and TILs and elevated expression of B7-H3 mediating immune evasion
- **9 RCT**
  - In 1st line with Platinum Etoposide: 5 +/- aPD(L)-1; 2 +/- aCTLA-4; 1 +/- aTIGIT
  - In maintenance: 1 +/- aPD(L)-1/aCTLA-4
  - In 2nd line with topotecan vs. aPD(L)-1

Immunotherapy with ICI in advanced SCLC

RCT/acronym	Setting	ICI	ΔRR (%)	ΔOS (m, %)	HR (95% CI)
CA184-156 *Reck, JCO 2016*	1st line	Ipilimumab		mOS: + 0,1 m	0,94 (0,81-1,09)
IMPOWER 133 *Horn, NEJM 2018*					0,70 (0,64-0,91)
CASPIAN *Goldman, TLO 2020*					0,75 (0,62-0,91)
					0,82 (0,68–1,00)
KN604 *Rudin, JCO 2020*					0,80 (0,64-0,98)
SKYSCRAPER 02 *Rudin, JCO 2022*					1,04 (0,79-1,36)
CM 451 *Owonikoko, JCO 2021*		nivolumab			0,92 (0,75-1,12)
CM 331 *Spigel, Ann Oncol 2021*	2nd line	Nivolumab	NR	- 0,9 m	0.86 (0,72-1,04)

1st line: median survival + ~2m with aPD(L)-1 ICI (IMPOWER, CASPIAN)

- Tail of survival curve suggests durable benefit in minority of pts
- Lack of significant improvement in RR suggests lack of synergism with chemotherapy

Dual ICI with either aCTLA-4 or aTIGIT not beneficial

- In 1st line (CASPIAN, SKYSCRAPER 02)
- As maintenance (CM451)

2nd line: nivolumab not better than topotecan (CM331)
Neither PD(L)-1, nor TMB are predictive factors

Targeted therapy

- **RNA polymerase II**: blocked by **lurbinectedin**
  - Promising phase 2 data as single agent in 2nd line: EMA approval
  - RCT lurbinectedin + doxorubicine vs. topotecan/CAV + G-CSF
    - ATLANTIS: *Ponce-Aix, Lancet Resp Med 2022*
    - Similar efficacy, less hematologic toxicity
- **DLL3:** overexpressed in 80% of NETs and target of ADC **rovalpituzumab-tesirine**
  - TAHOE: RCT Rova-T vs. topotecan in 2nd line (*Blackhall, JTO 2021)*
  - Inferior survival and more complications with ADC
- **DNA damage repair:** inhibited by **PARPi**
  - Ongoing trials with veliparib
  - Synergistic with temozolomide
- Potential targetable **genomic alterations**
  - Mutations in **PTEN or RET**
  - Amplifications of fibroblast growth factor receptor 1 (**FGFR1**)

Clinical implications: advanced SCLC

- Platinum-etoposide **+ aPD(L)-1** new SOC in 1st line
  - Modest benefit due to absence of synergistic effect with chemotherapy
  - No predictive biomarkers
  - BE: reimbursement by RIZIV-INAMI
    - Durvalumab: 1500 mg q 3-4w
    - Atezolizumab: 1200 mg q 3w
- Topotecan/CAV still SOC in 2nd line
- No targeted drugs in foreseeable future
- Several promising molecules in development

Mesothelioma: state of the art

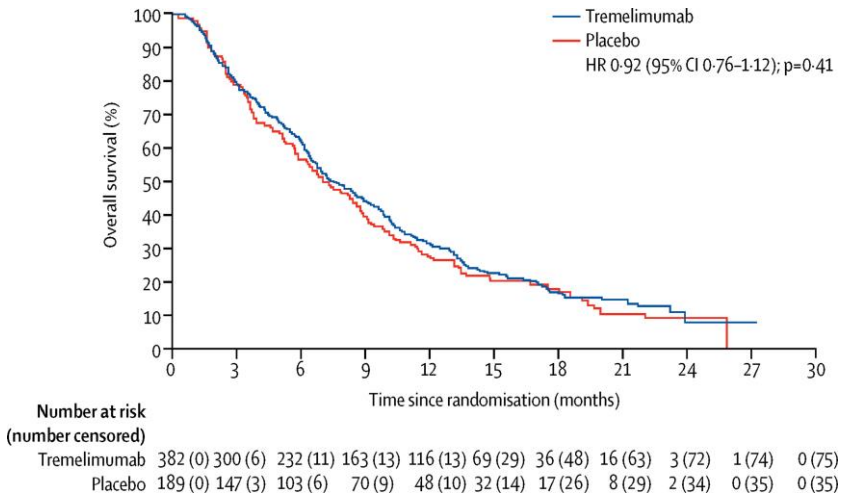
- **Rare disease:** 383 cases in Belgium in 2020 (BCR)
- **Strong causative association** with (professional) asbestos exposure, >30 years prior to diagnosis
- **Presenting symptoms:** dyspnea (pleural fluid), costopleural pain (infiltration thoracic wall + diaphragm)
- **Confident PA-diagnosis requires biopsy sample, not cytology**
- **Staging of disease extent by imaging often unaccurate:** ~60% stage 3-4 at diagnosis ('inoperable')
- **Histological subtype strong prognostic factor:** epithelioid (~70%) >> biphasic + sarcomatoid (30%)
- **SOC since 2005: palliative chemotherapy**
  - 1st line: platinum + antifolate (pemetrexed/raltitrexed) q 3w x 4-6 cycles ORR ~ 40% mPFS: 6-7 m
  - Optional + bevacizumab (mnp in BE) based on MAPS trial (*Zalcman, 2015: HR 0,77*)
  - No role for any maintenance
  - 2nd line: vinorelbine or gemcitabine: *Petrelli, Respir Med 2018* ORR: 8.63% mPFS: 3.4 m
- **Poor prognosis:** mOS 14-16 m 2 year SR: 20%

Immunotherapy with ICI

- **Is MPM immunogenic?**
  - PRO: persisting inflammatory response to asbestos: frustrated phagocytosis
  - CON: suppressive immune cells, M2-like macrophages and regulatory T cells, low TMB, paucity of activated T cells

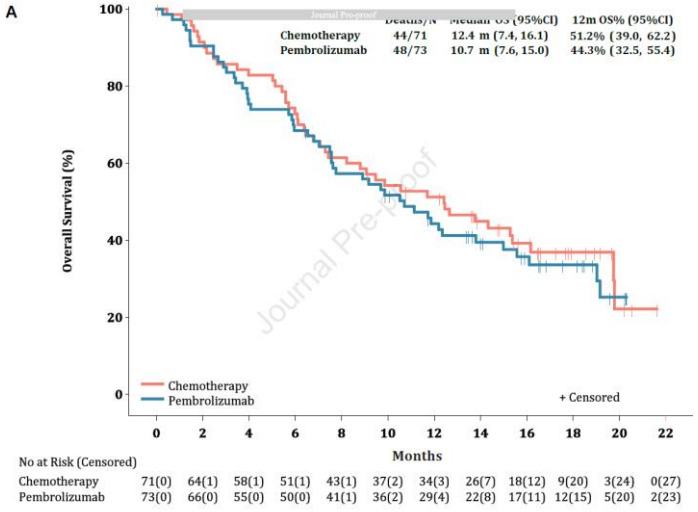
DETERMINE/tremelimumab

Maio, TLO 2017



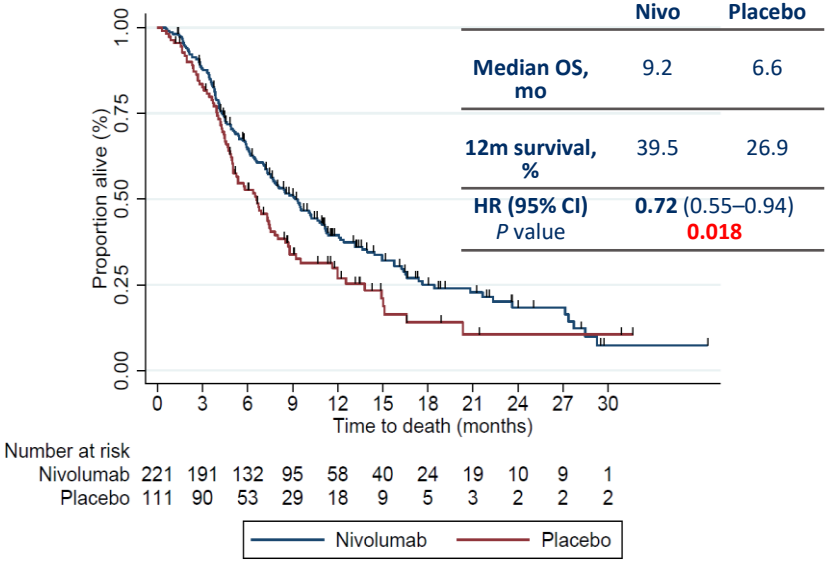
PROMISE/pembrolizumab

Popat, Ann Oncol 2020



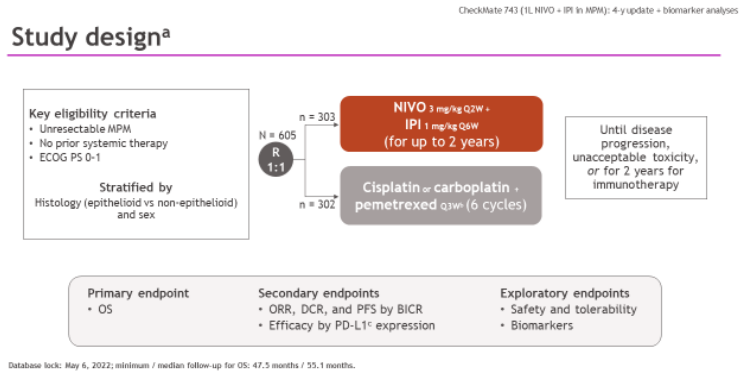
CONFIRM/nivolumab

Fennell, TLO 2021

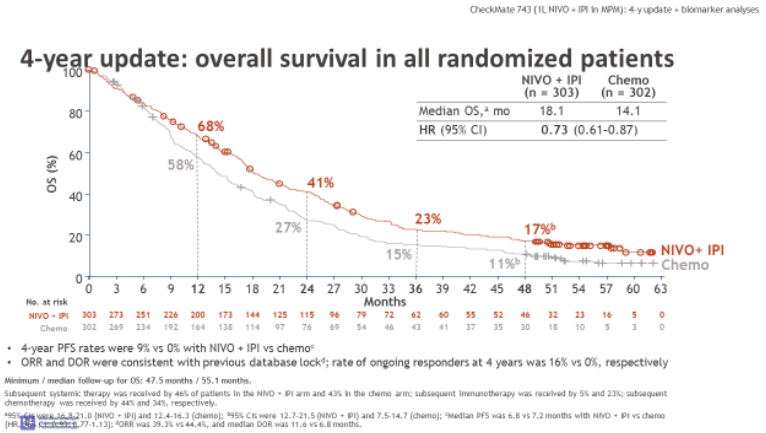


Checkmate 743: *Baas, Lancet 2021, Scherpereel, ESMO 2021 & Zalcman, ESMO 2022*

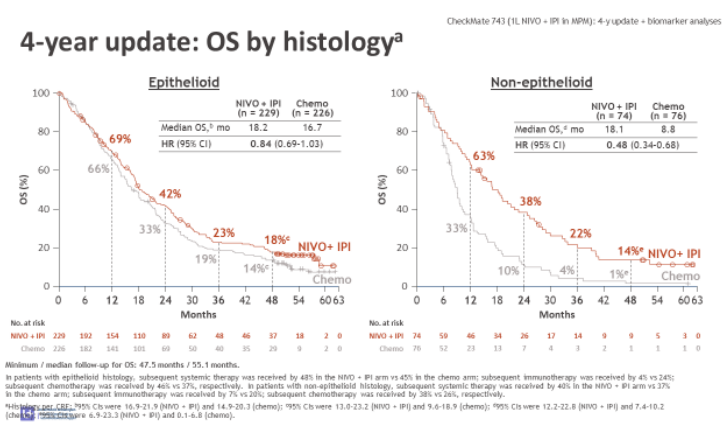
Study design



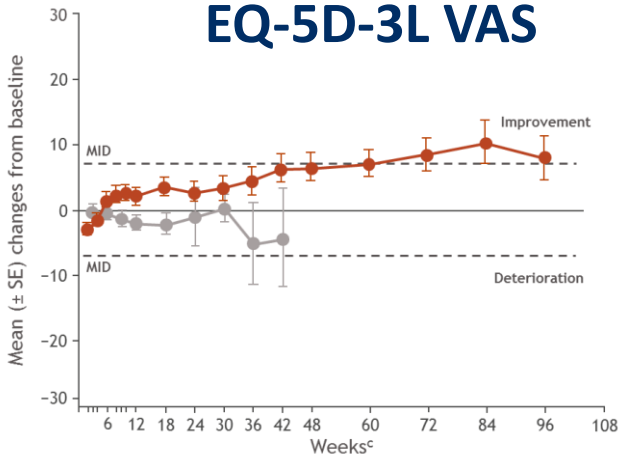
Overall survival



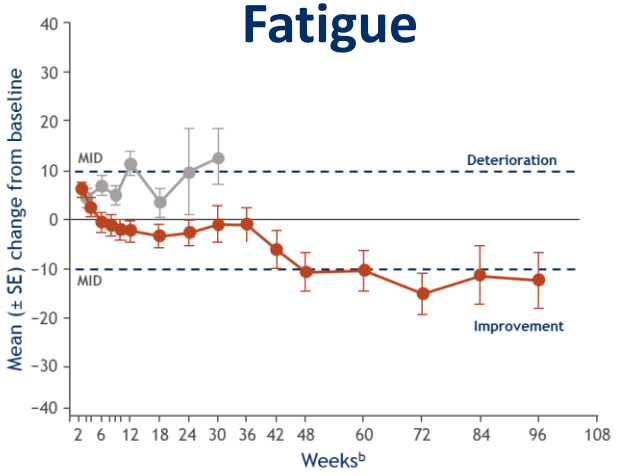
OS by histology



EQ-5D-3L VAS

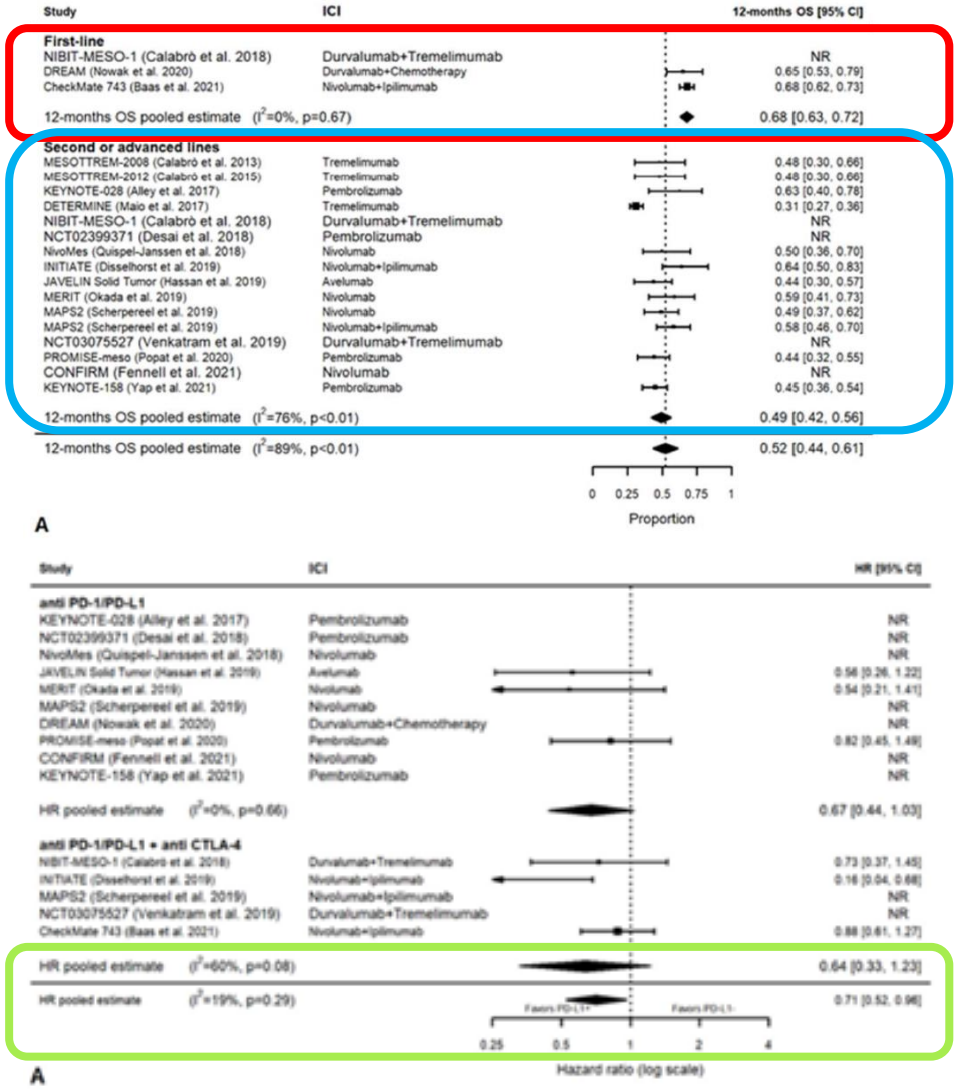


Fatigue



Immunotherapy with ICI: systematic review/meta-analysis

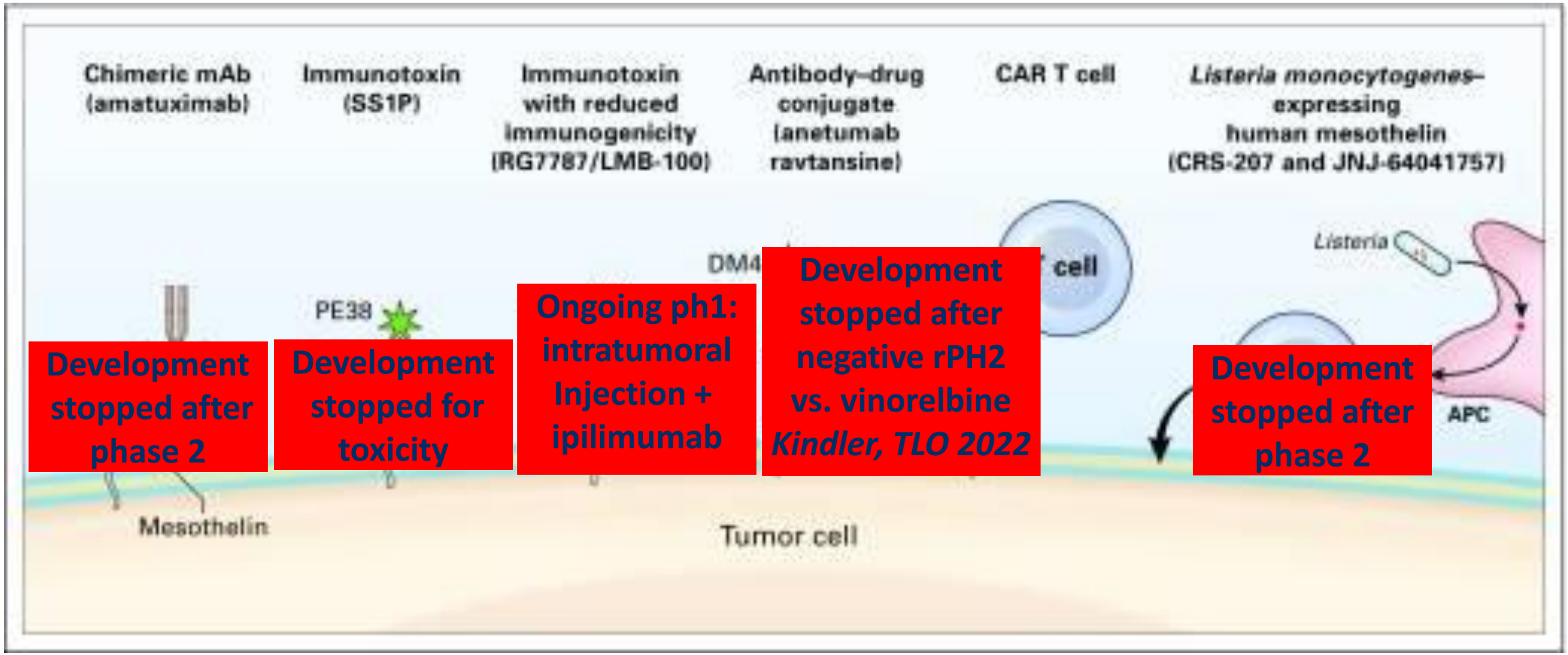
- *Gemelli et al, Cancers 2022, in press*
  - 3 phase III, 12 phase II, 2 phase I trials: **2328 patients**
  - 2 comparisons with chemo, 2 with placebo
  - 1 chemo+/- immuno RP2: DREAM
  - Clear benefit of ICI in 1st line, driven by CM743
  - Unclear benefit of ICI in 2nd line
  - Dual ICI PDL-1 + CTLA-4 >> single agent PD-L1
  - Dual ICI higher rate of Adverse Events: p=0.01
  - PDL-1+ (TPS >1%) predictive for better response and survival



Immunotherapy

- **Ongoing trials with chemo-immunotherapy**
  - DREAM 3R-meso: chemotherapy +/- durvalumab
  - BEAT-meso: chemotherapy + bevacizumab +/- atezolizumab
- **Adaptive immunotherapy**
  - DENIM: consolidation with allogeneic tumorlysate loaden DC's/placebo: results pending
  - Mesothelin-targeted CAR-T cells:
    - Intravenous injection of lentiviral transduced huCART-meso cells (*Haas, Mol Ther 2019)*
      - Well tolerated, but limited penetration in tumour → limited clinical benefit
      - Ongoing NCT03054298 (Upen, USA)
    - Intra-pleural injection of chimeric antigen receptor T-cell (*Adusumilli , Cancer Discovery 2021*)
      - +/- PD-1 ICI: ORR 63% in 18 pts, 37% of which pretreated with ≥ 3 lines of therapy
      - Ongoing NCT02414269 (MSK, USA)

Mesothelin-targeted therapy



Hassan, JCO 2016

Targeted therapies in development *(clintrials.gov)*

Mutation	Target	Drug	Trial	Reference
MTAP	CDKN2A	AMG193	Phase 1	
YAP-TEAD	Merlin	Small molecule TEAD-i	Phase 1	
	Hsp-90	Ganetespib = small molecule blocker of Hsp90	Phase 1b	*Fennell, Clin Cancer Res. 2020*
BAP1	EZH2	Tazemetostat = oral EZH2-i	Phase 2	*Zauderer, TLO 2022*
NF2	FAK	Defactinib = oral FAK-i	RCT COMMAND	*Fennell, JCO 2019*
ASS1-	Arginine, essential AA	ADI-PEG 20 = enzyme degrading arginine	RCT ATOMIC with chemo backbone	*Beddowes, JCO 2017*

Clinical implications: advanced mesothelioma

- Dual ICI **aPD(L)-1 + aCTLA-4** new SOC
  - Equipoise with chemotherapy in epithelioid subtype but improved QoL with ICI
  - PDL-1 TPS is a (weak) predictive factor
  - BE: nivolumab (360 mg q 3w) and ipilimumab (1 mg/kg q 6w) both reimbursed
  - Pending results of RCT's with chemo-IO
- Platinum pemetrexed = new SOC in 2nd line for fit pts
  - Promising data with nivolumab rechallenge in third line
- Mesothelin-targeted therapies did not deliver (yet)
- No role yet for molecular/targeted agents outside clinical trials
  - Refer to reference centers cfr KCE Report 219 (2014)

16th INTERNATIONAL CONFERENCE OF THE INTERNATIONAL MESOTHELIOMA INTEREST GROUP

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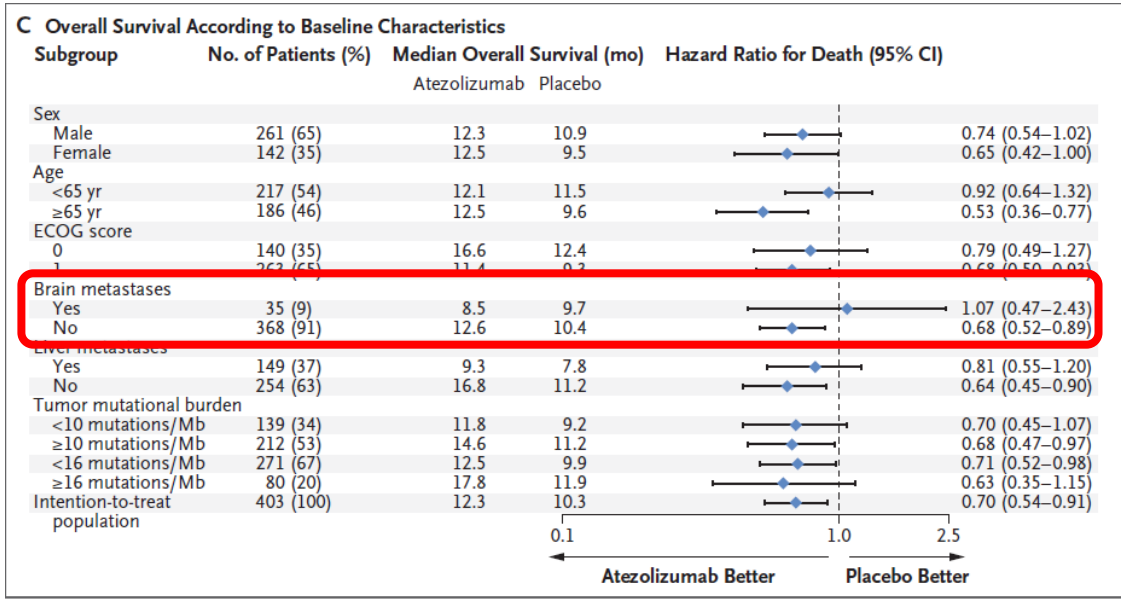
Immunotherapy with ICI in advanced SCLC (2)

IMPOWER 133



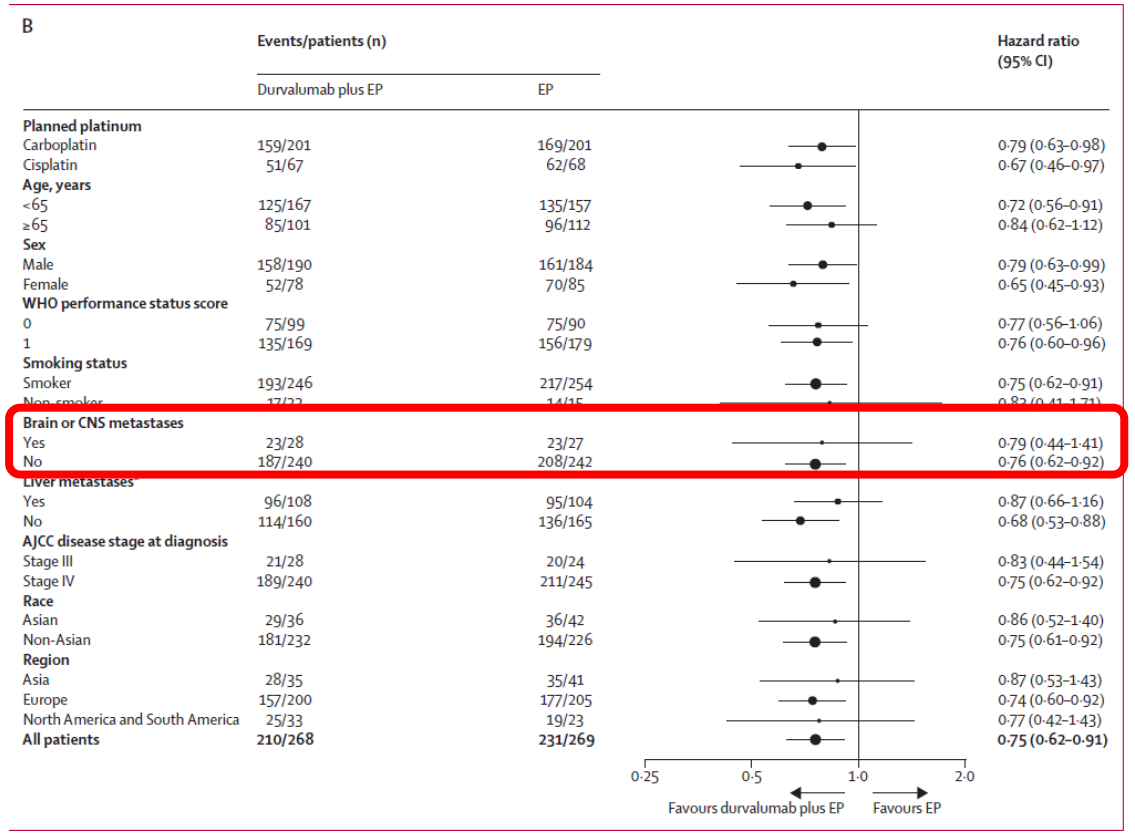
C Overall Survival According to Baseline Characteristics

Subgroup	No. of Patients (%)	Median Overall Survival (mo)		Hazard Ratio for Death (95% CI)
		Atezolizumab	Placebo	
Sex				
Male	261 (65)	12.3	10.9	0.74 (0.54–1.02)
Female	142 (35)	12.5	9.5	0.65 (0.42–1.00)
Age				
<65 yr	217 (54)	12.1	11.5	0.92 (0.64–1.32)
≥65 yr	186 (46)	12.5	9.6	0.53 (0.36–0.77)
ECOG score				
0	140 (35)	16.6	12.4	0.79 (0.49–1.27)
1	262 (65)	11.4	9.3	0.68 (0.50–0.93)
Brain metastases				
Yes	35 (9)	8.5	9.7	1.07 (0.47–2.43)
No	368 (91)	12.6	10.4	0.68 (0.52–0.89)
Liver metastases				
Yes	149 (37)	9.3	7.8	0.81 (0.55–1.20)
No	254 (63)	16.8	11.2	0.64 (0.45–0.90)
Tumor mutational burden				
<10 mutations/Mb	139 (34)	11.8	9.2	0.70 (0.45–1.07)
≥10 mutations/Mb	212 (53)	14.6	11.2	0.68 (0.47–0.97)
<16 mutations/Mb	271 (67)	12.5	9.9	0.71 (0.52–0.98)
≥16 mutations/Mb	80 (20)	17.8	11.9	0.63 (0.35–1.15)
Intention-to-treat population	403 (100)	12.3	10.3	0.70 (0.54–0.91)

0.1 1.0 2.5

Atezolizumab Better Placebo Better

CASPIAN



B

	Events/patients (n)		Hazard ratio (95% CI)
	Durvalumab plus EP	EP	
Planned platinum			
Carboplatin	159/201	169/201	0·79 (0·63–0·98)
Cisplatin	51/67	62/68	0·67 (0·46–0·97)
Age, years			
<65	125/167	135/157	0·72 (0·56–0·91)
≥65	85/101	96/112	0·84 (0·62–1·12)
Sex			
Male	158/190	161/184	0·79 (0·63–0·99)
Female	52/78	70/85	0·65 (0·45–0·93)
WHO performance status score			
0	75/99	75/90	0·77 (0·56–1·06)
1	135/169	156/179	0·76 (0·60–0·96)
Smoking status			
Smoker	193/246	217/254	0·75 (0·62–0·91)
Non-smoker	17/22	14/15	0·82 (0·41–1·71)
Brain or CNS metastases			
Yes	23/28	23/27	0·79 (0·44–1·41)
No	187/240	208/242	0·76 (0·62–0·92)
Liver metastases			
Yes	96/108	95/104	0·87 (0·66–1·16)
No	114/160	136/165	0·68 (0·53–0·88)
AJCC disease stage at diagnosis			
Stage III	21/28	20/24	0·83 (0·44–1·54)
Stage IV	189/240	211/245	0·75 (0·62–0·92)
Race			
Asian	29/36	36/42	0·86 (0·52–1·40)
Non-Asian	181/232	194/226	0·75 (0·61–0·92)
Region			
Asia	28/35	35/41	0·87 (0·53–1·43)
Europe	157/200	177/205	0·74 (0·60–0·92)
North America and South America	25/33	19/23	0·77 (0·42–1·43)
All patients	**210/268**	**231/269**	**0·75 (0·62–0·91)**

0·25 0·5 1·0 2·0

Favours durvalumab plus EP Favours EP