IASLC
2023 World Conference on Lung Cancer
SEPTEMBER 9-12, 2023 | SINGAPORE

Best of WCLC San Francisco 2023: Mesothelioma and Thymic Malignancies

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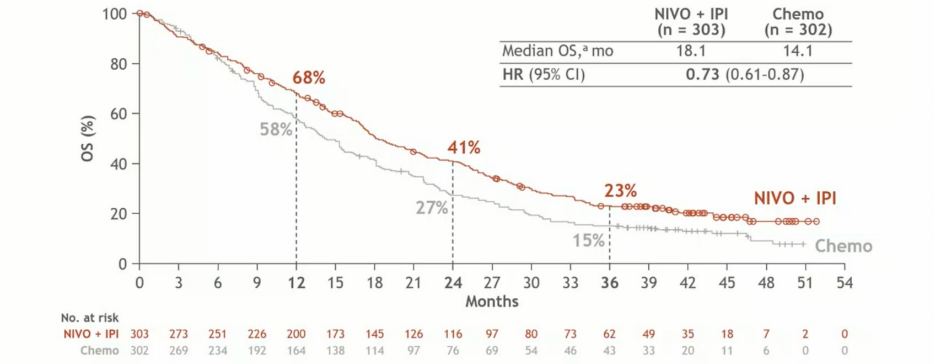
September 29, 2023

CheckMate 743: Nivolumab + ipilimumab– 3 year update

3-year update: overall survival in all randomized patients



	NIVO + IPI (n = 303)	Chemo (n = 302)
Median OS,[a] mo	18.1	14.1
HR (95% CI)	0.73 (0.61-0.87)	

Minimum follow-up: 35.5 months.
Subsequent systemic therapy was received by 45% of patients in the NIVO + IPI arm and 42% in the chemo arm; subsequent immunotherapy was received by 4% and 22%; subsequent chemotherapy was received by 43% and 33%, respectively.
[a]95% CIs were 16.8-21.0 (NIVO + IPI) and 12.4-16.3 (chemo).

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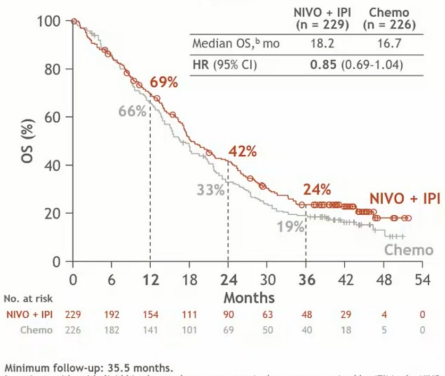
CheckMate 743 (1L NIVO + IPI in MPM): 3-year update

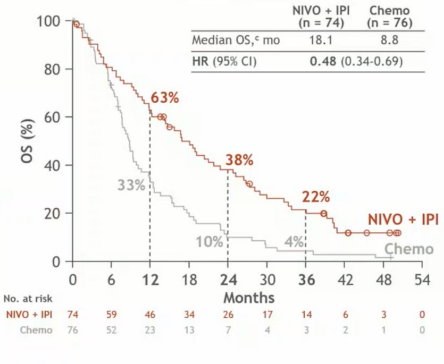
3-year update: OS by histology[a]

Epithelioid



	NIVO + IPI (n = 229)	Chemo (n = 226)
Median OS,[b] mo	18.2	16.7
HR (95% CI)	0.85 (0.69-1.04)	

Non-epithelioid



	NIVO + IPI (n = 74)	Chemo (n = 76)
Median OS,[c] mo	18.1	8.8
HR (95% CI)	0.48 (0.34-0.69)	

Minimum follow-up: 35.5 months.
In patients with epithelioid histology, subsequent systemic therapy was received by 47% in the NIVO + IPI arm vs 44% in the chemo arm; subsequent immunotherapy was received by 4% vs 22%; subsequent chemotherapy was received by 45% vs 35%, respectively. In patients with non-epithelioid histology, subsequent systemic therapy was received by 39% in the NIVO + IPI arm vs 37% in the chemo arm; subsequent immunotherapy was received by 5% vs 20%; subsequent chemotherapy was received by 38% vs 26%, respectively.
[a]Histology per CRF; [b]95% CIs were 16.9-21.9 (NIVO + IPI) and 14.9-20.3 (chemo); [c]95% CIs were 12.2-22.8 (NIVO + IPI) and 7.4-10.2 (chemo).

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Mesothelioma and thymoma systemic therapy @ WCLC

- Mesothelioma
  - Mesothelin-targeted therapy
    - Anetumab ravtansine (Mansfield)
  - Dendritic cells as maintenance
    - DENIM (Aerts)
- Thymoma
  - Chemoimmunotherapy
    - Chemo+PD-1 inhibitor vs chemo (Liu)

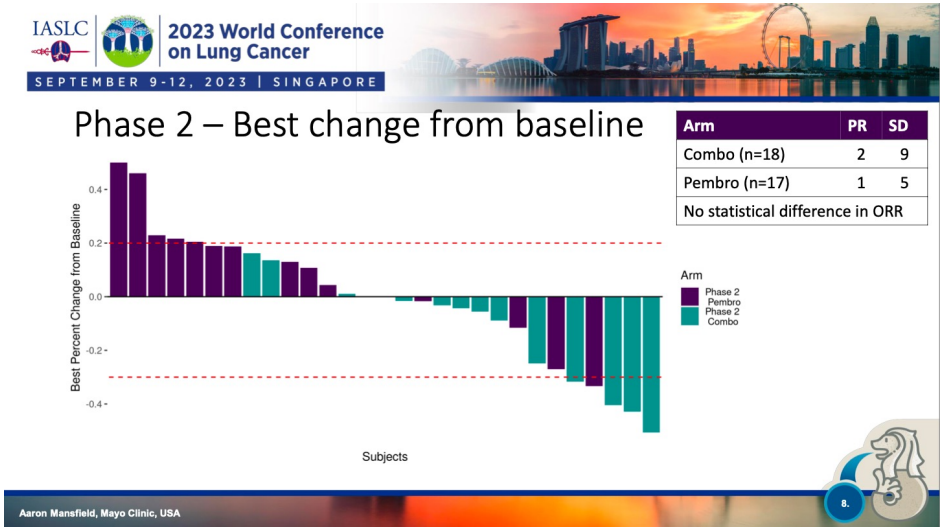
Mesothelioma and thymoma systemic therapy @ WCLC

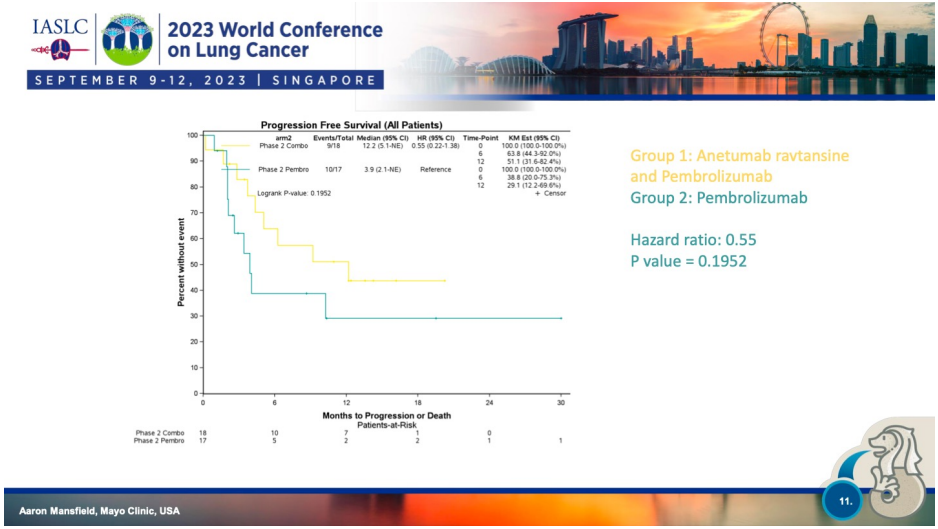
- Mesothelioma
  - Mesothelin-targeted therapy
    - Anetumab ravtansine (Mansfield)

- Mesothelin overexpressed in pleural mesothelioma
- Anetumab ravtansine is an IgG1 ADC– recognizes mesothelin and bound to DM4
  - Phase 1/2, phase 1 with pembro + anetumab ravtansine (n=13) phase 2 randomized to pembro (n=17) vs pembro + anetumab ravtansine (n=18)
    - Enrolled epithelioid pts with no prior immunotherapy, phase 2 >= 30% mesothelin expression by tumor cells

Mansfield et al. WCLC 2023 OA02.04

Pembrolizumab +/- Anetumab ravtansine





- No statistical difference in ORR or PFS
- (Might be related to smaller then planned sample size)
- Anetumab ravtansine not moving forward for further development

Mesothelioma and thymoma systemic therapy @ WCLC

- Mesothelioma
  - Dendritic cells as maintenance
    - DENIM (Aerts)

- Dendritic cells among the most efficient antigen presenting cells, and function suppressed in meso
  - DC therapy with allogenic lysate is feasible, safe, and induces immune activation in pleural meso
  - Randomized phase 3 to eval allogenic DC vaccination as maintenance therapy
    - N=176, pts with at least SD after 1L treatment, randomized 1:1 to DC therapy vs BSC alone, primary endpoint OS

Aerts et al. WCLC 2023 OA02.05

Dendritic cells vs BSC as maintenance after 1L meso tx

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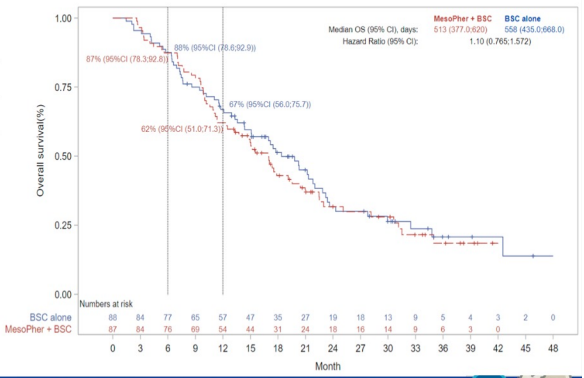
Overall Survival
(Intention to treat analysis)

	DC + BSC (n=88)	BSC alone (n=88)
Median OS (95% CI), months	16,9 (12.4; 20.4)	18,3 (14.3; 21.9)



Joachim Aerts, Erasmus MC University Hospital Rotterdam, the Netherlands

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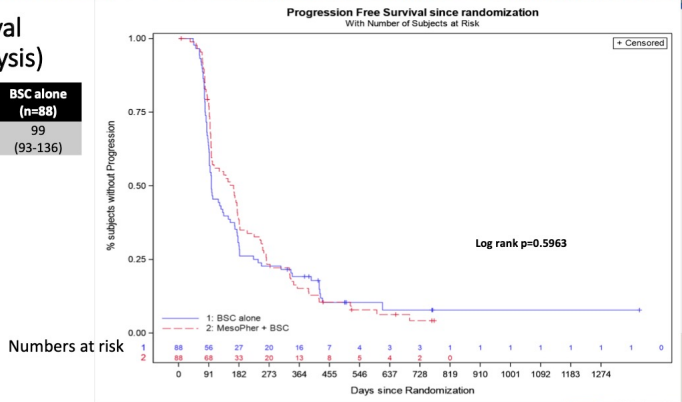
Progression Free Survival
(intention to treat analysis)

	DC+ BSC (n=88)	BSC alone (n=88)
Median PFS (95% CI), days	166 (99-178)	99 (93-136)



Joachim Aerts, Erasmus MC University Hospital Rotterdam, the Netherlands

- No statistical difference in OS or PFS
- (Noted that median OS in BSC better than expected, and long interval between chemo and DC vaccination)
- Negative trial, but safe– combinations?

Aerts et al. WCLC 2023 OA02.05

Thymoma systemic therapy @ WCLC

- Immunotherapy role
  - In thymoma, excess irAE toxicity– would not do off study
  - In thymic carcinoma, more akin to other carcinomas
- Liu et al: Retrospective evaluation of first-line PD-1 inhibitor + chemo vs chemo alone in thymic carcinoma
  - N=62 pts at Sun Yat-Sen University Cancer Center 2018-2023
    - N=24 with ICI+platinum-based chemo, n=38 with platinum-based chemo alone
    - PFS 8.7 vs 4.0 mo (HR 0.46, p=0.029)
    - ORR 50 vs 34%, p=0.44
    - No new safety signals, though small numbers
  - Conclusion: Warrants prospective randomized study

Liu et al. WCLC 2023 MA08.08

Mesothelioma and thymoma systemic therapy @ WCLC

- Mesothelioma
  - Mesothelin-targeted therapy
    - Anetumab ravtansine (Mansfield) — Negative phase 1/2.N ot being developed
  - Dendritic cells as maintenance
    - DENIM (Aerts) — Negative phase 3. But safe. Combos?
- Thymoma
  - Chemoimmunotherapy
    - Chemo+PD-1 inhibitor vs chemo (Liu) — Retrospective. Promising, safe. Future trials?

Future directions in meso systemic treatment

- Chemoimmunotherapy
  - DREAM3R phase 3: Cis/pemetrexed +/- durvalumab
  - ETOP 13-18 BEAT-meso: Carbo/pemetrexed/bev +/- atezolizumab
  - CCTG IND227/IFCT1901: Platinum/pemetrexed +/- pembrolizumab
- Cellular therapies
  - Intra-pleural or systemic mesothelin and FAP-directed CARs
  - Anti-mesothelin T cell receptor fusion construct (TRuC)
- Targeted therapy
  - Mesothelin-targeted drugs (other than cellular therapy)
    - ADCs (eg anetumab ravtansine, BMS-986148, BAY2287411)
    - Immunotoxins (eg LMB-100)
    - Vaccines

Mesothelioma surgical therapy @ WCLC

- MARS2: A multicentre randomised trial comparing (extended) pleurectomy/decortication versus no (extended) pleurectomy decortication for patients with malignant pleural mesothelioma

Extra-pleural pneumonectomy versus no extra-pleural pneumonectomy for patients with malignant pleural mesothelioma: clinical outcomes of the Mesothelioma and Radical Surgery (MARS) randomised feasibility study

Tom Treasure, Loic Lang-Lazdunski, David Waller, Judith M Bliss, Carol Tan, James Entwisle, Michael Snee, Mary O'Brien, Gill Thomas, Suresh Senan, Ken O'Byrne, Lucy S Kilburn, James Spicer, David Landau, John Edwards, Gill Coombes, Liz Darlison, Julian Peto, for the MARS trialists*

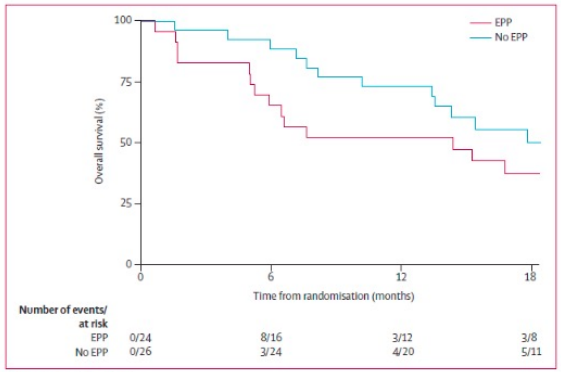
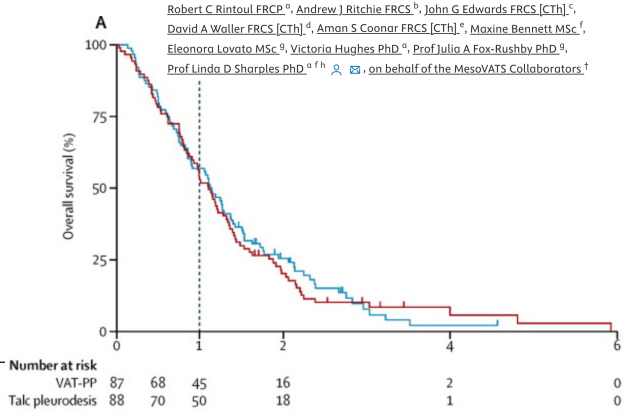


Figure 4: Overall survival
EPP=extra-pleural pneumonectomy.

Lancet Oncol 2011; 12: 763–72

Efficacy and cost of video-assisted thoracoscopic partial pleurectomy versus talc pleurodesis in patients with malignant pleural mesothelioma (MesoVATS): an open-label, randomised, controlled trial

Robert C Rintoul FRCP [a], Andrew J Ritchie FRCS [b], John G Edwards FRCS [CTh] [c], David A Waller FRCS [CTh] [d], Aman S Coonar FRCS [CTh] [e], Maxine Bennett MSc [f], Eleonora Lovato MSc [g], Victoria Hughes PhD [a], Prof Julia A Fox-Rushby PhD [g], Prof Linda D Sharples PhD [a f h], on behalf of the MesoVATS Collaborators [t]



Lancet 2014; 384: 1118-1124

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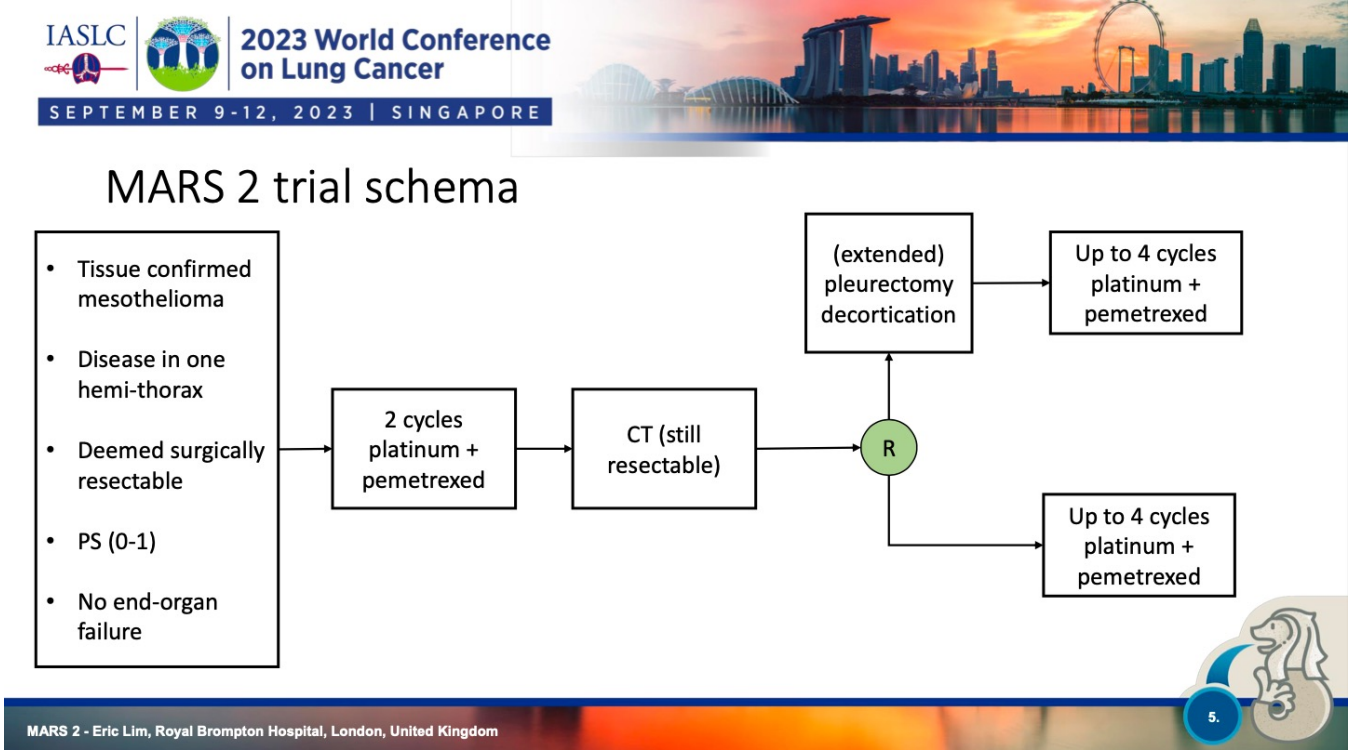

- Primary endpoint: OS
  - N=328 with alpha = 0.05, power 0.80, to test hypothesis that P/D + chemo superior to chemo alone with 30% relative improvement
- Secondary: PFS, safety, HRQoL, cost-effectiveness

Lim et al. WCLC 2023 PL03.10

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MARS2: Meso P/D+chemo vs chemo alone

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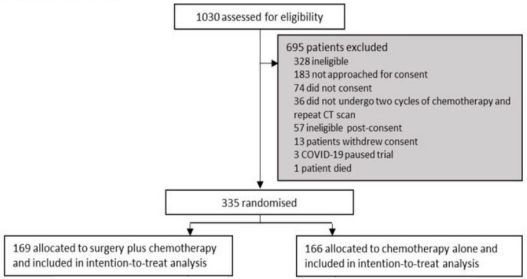
Participant flow



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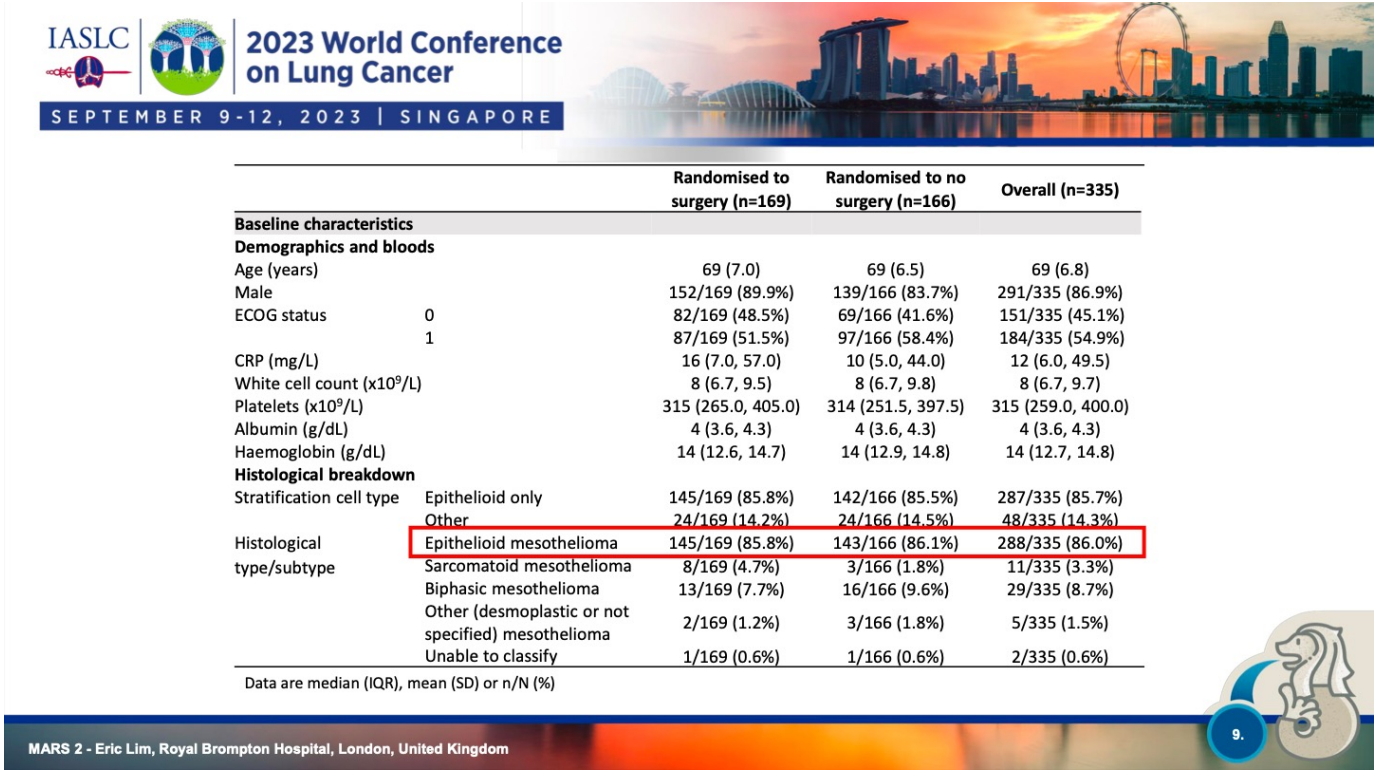
Protocol deviations and withdrawals

	Randomised to surgery (n=169)	Randomised to no surgery (n=166)	Overall (n=335)
Protocol deviation			
Participant did not receive allocated treatment	13/169 (7.7%)	2/166 (1.2%)	15/335 (4.5%)
Post-randomisation withdrawal	**14/169 (8.3%)**	**11/166 (6.6%)**	**25/335 (7.5%)**
Patient choice	8/14 (57.1%)	9/11 (81.8%)	17/25 (68.0%)
Clinician choice	6/14 (42.9%)	2/11 (18.2%)	8/25 (32.0%)

MARS2: Meso P/D+chemo vs chemo alone



		Randomised to surgery (n=169)	Randomised to no surgery (n=166)	Overall (n=335)
Baseline characteristics				
Demographics and bloods				
Age (years)		69 (7.0)	69 (6.5)	69 (6.8)
Male		152/169 (89.9%)	139/166 (83.7%)	291/335 (86.9%)
ECOG status	0	82/169 (48.5%)	69/166 (41.6%)	151/335 (45.1%)
	1	87/169 (51.5%)	97/166 (58.4%)	184/335 (54.9%)
CRP (mg/L)		16 (7.0, 57.0)	10 (5.0, 44.0)	12 (6.0, 49.5)
White cell count (x10^9/L)		8 (6.7, 9.5)	8 (6.7, 9.8)	8 (6.7, 9.7)
Platelets (x10^9/L)		315 (265.0, 405.0)	314 (251.5, 397.5)	315 (259.0, 400.0)
Albumin (g/dL)		4 (3.6, 4.3)	4 (3.6, 4.3)	4 (3.6, 4.3)
Haemoglobin (g/dL)		14 (12.6, 14.7)	14 (12.9, 14.8)	14 (12.7, 14.8)
Histological breakdown				
Stratification cell type	Epithelioid only	145/169 (85.8%)	142/166 (85.5%)	287/335 (85.7%)
	Other	24/169 (14.2%)	24/166 (14.5%)	48/335 (14.3%)
Histological type/subtype	Epithelioid mesothelioma	145/169 (85.8%)	143/166 (86.1%)	288/335 (86.0%)
	Sarcomatoid mesothelioma	8/169 (4.7%)	3/166 (1.8%)	11/335 (3.3%)
	Biphasic mesothelioma	13/169 (7.7%)	16/166 (9.6%)	29/335 (8.7%)
	Other (desmoplastic or not specified) mesothelioma	2/169 (1.2%)	3/166 (1.8%)	5/335 (1.5%)
	Unable to classify	1/169 (0.6%)	1/166 (0.6%)	2/335 (0.6%)

Data are median (IQR), mean (SD) or n/N (%)

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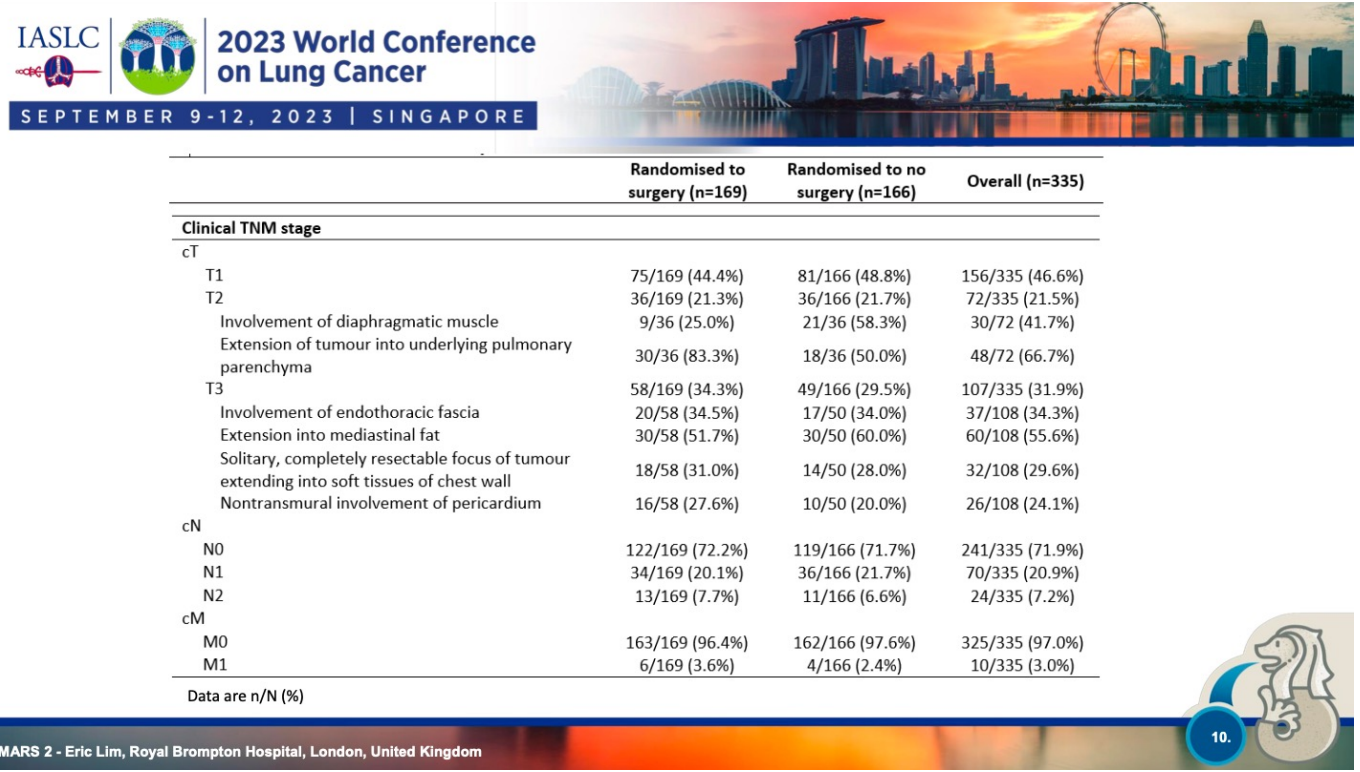
MARS2: Meso P/D+chemo vs chemo alone



	Randomised to surgery (n=169)	Randomised to no surgery (n=166)	Overall (n=335)
Clinical TNM stage			
cT			
T1	75/169 (44.4%)	81/166 (48.8%)	156/335 (46.6%)
T2	36/169 (21.3%)	36/166 (21.7%)	72/335 (21.5%)
Involvement of diaphragmatic muscle	9/36 (25.0%)	21/36 (58.3%)	30/72 (41.7%)
Extension of tumour into underlying pulmonary parenchyma	30/36 (83.3%)	18/36 (50.0%)	48/72 (66.7%)
T3	58/169 (34.3%)	49/166 (29.5%)	107/335 (31.9%)
Involvement of endothoracic fascia	20/58 (34.5%)	17/50 (34.0%)	37/108 (34.3%)
Extension into mediastinal fat	30/58 (51.7%)	30/50 (60.0%)	60/108 (55.6%)
Solitary, completely resectable focus of tumour extending into soft tissues of chest wall	18/58 (31.0%)	14/50 (28.0%)	32/108 (29.6%)
Nontransmural involvement of pericardium	16/58 (27.6%)	10/50 (20.0%)	26/108 (24.1%)
cN			
N0	122/169 (72.2%)	119/166 (71.7%)	241/335 (71.9%)
N1	34/169 (20.1%)	36/166 (21.7%)	70/335 (20.9%)
N2	13/169 (7.7%)	11/166 (6.6%)	24/335 (7.2%)
cM			
M0	163/169 (96.4%)	162/166 (97.6%)	325/335 (97.0%)
M1	6/169 (3.6%)	4/166 (2.4%)	10/335 (3.0%)

Data are n/N (%)

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MARS2: Meso P/D+chemo vs chemo alone

Surgery

	Received surgery (n=158*)
Surgical procedure	
Extended pleurectomy/decortication	139/157 (88.5%)
Pleurectomy decortication	13/157 (8.3%)
Partial pleurectomy	3/157 (1.9%)
Exploration, no pleurodesis	1/157 (0.6%)
Other	1/157 (0.6%)
Resection and reconstruction	
Diaphragm resection	130/157 (82.8%)
Diaphragm reconstructed	128/157 (81.5%)
Pericardium resection	105/157 (66.9%)
Pericardium reconstructed	84/157 (53.5%)
Chest wall resection	19/157 (12.1%)
Chest wall reconstructed	9/157 (5.7%)
Other ipsilateral lung resection	67/157 (42.7%)
Wedge resection	64/67 (95.5%)
Bilobectomy	1/67 (1.5%)
Lobectomy	2/67 (3.0%)

Completeness of resection	
R0 (no residual tumour)	5/157 (3.2%)
R1 (microscopic residual tumour)	127/157 (80.9%)
R2 (macroscopic residual tumour)	25/157 (15.9%)
Length of hospital stay (days) §	13 (12, 14)
In-hospital mortality	6/157 (3.8%)
30 day mortality	6/157 (3.8%)
90 day mortality	14/157 (8.9%)

Data are n/N (%)
* 1 patient withdrew to receive surgery privately and operative details were unable to be obtained. § in-hospital deaths censored at maximum length of stay

Lim E, Darlison L, Edwards J *et al.* on behalf of MARS 2 Trialists. Mesothelioma and Radical Surgery 2 (MARS 2): protocol for a multicentre randomised trial comparing (extended) pleurectomy decortication versus no (extended) pleurectomy decortication for patients with malignant pleural mesothelioma *BMJ Open* 2020;**10:**e038892. doi: 10.1136/bmjopen-2020-038892

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MARS2: Meso P/D+chemo vs chemo alone

Systemic treatments

	Randomised to surgery (n=169)	Randomised to no surgery (n=166)	Overall (n=335)
Systemic treatments			
First-line chemotherapy cycles			
Completed 2 cycles	169/169 (100.0%)	166/166 (100.0%)	335/335 (100.0%)
Completed 3 cycles	101/169 (59.8%)	154/166 (92.8%)	255/335 (76.1%)
Completed 4 cycles	96/169 (56.8%)	147/166 (88.6%)	243/335 (72.5%)
Completed 5 cycles	76/169 (45.0%)	111/166 (66.9%)	187/335 (55.8%)
Completed 6 cycles	66/169 (39.1%)	93/166 (56.0%)	159/335 (47.5%)
Additional treatments			
Any additional treatment reported during trial participation	**90/169 (53.3%)**	**115/166 (69.3%)**	**205/335 (61.2%)**
Immunotherapy or other treatment known to improve overall survival ††	37/169 (21.9%)	64/166 (38.6%)	101/335 (30.1%)
Additional chemotherapy	35/169 (20.7%)	65/166 (39.2%)	100/335 (29.9%)
Radiotherapy	32/169 (18.9%)	30/166 (18.1%)	62/335 (18.5%)
Further surgery	4/169 (2.4%)	6/166 (3.6%)	10/335 (3.0%)
Other systemic treatment	10/169 (5.9%)	19/166 (11.4%)	29/335 (8.7%)

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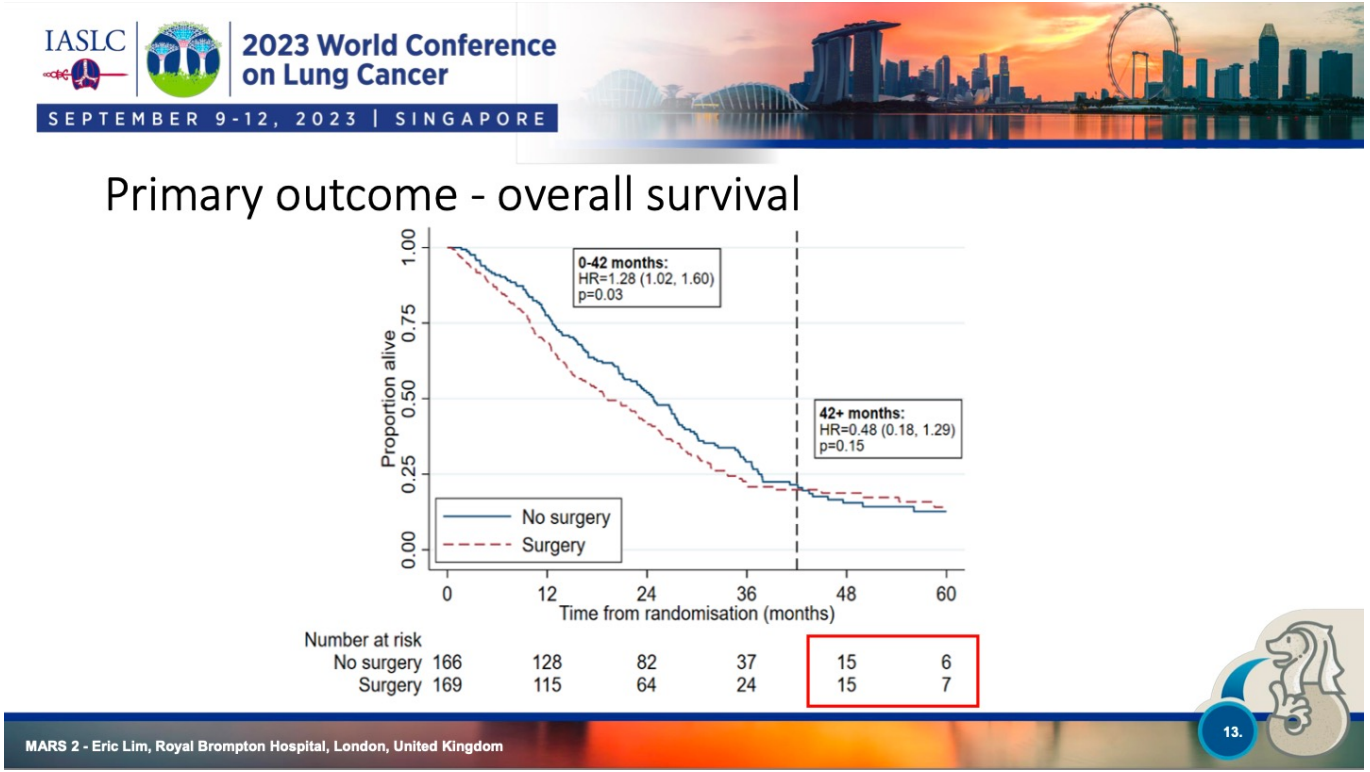

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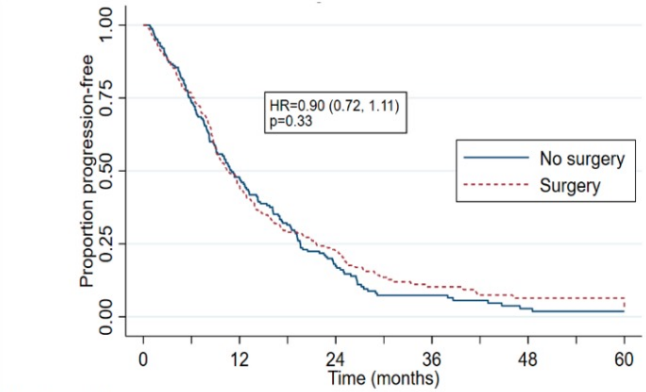
Progression-free survival



Number at risk						
No surgery	166	78	27	9	3	1
Surgery	169	76	33	11	6	3

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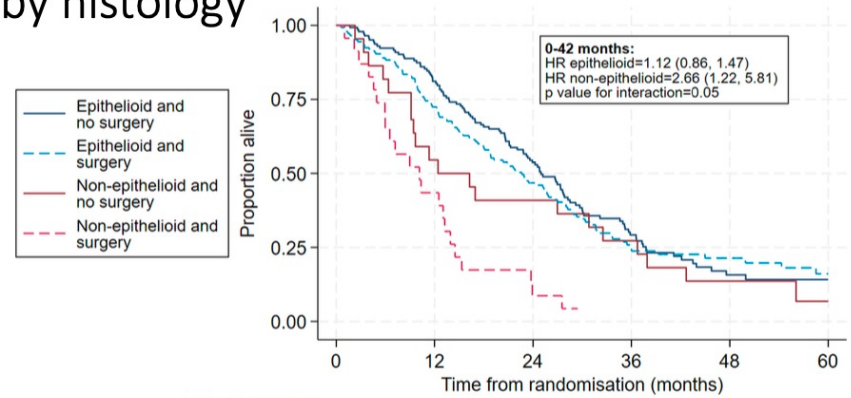
Survival by histology



Number at risk

Epithelioid and no surgery	144	116	73	31	12	5
Epithelioid and surgery	146	105	62	24	15	7
Non-epithelioid and no surgery	22	12	9	6	3	1
Non-epithelioid and surgery	23	10	2	0	0	0

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MARS2: Meso P/D+chemo vs chemo alone

- Authors' conclusions:
  - Extended pleurectomy decortication for mesothelioma had:
    - Higher risk of death
    - More serious complications
    - Poorer quality of life
    - At higher cost of 14,631 pounds ($US20,102)
      - …compared to those who were randomized to chemo alone
  - Relinquishing the concept of "resectability…"
    - Increases survival by reducing risk of death associated with surgery
    - Opens access to effective systemic treatments currently licensed for "unresectable" disease

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MARS2: Meso P/D+chemo vs chemo alone

- Criticisms by discussant:
  - Role of surgeon's experience?
  - Prior pleural effusion mgmt– pleurodesis or talc?
  - PET/CT not required?
  - Extent of burden, diaphragm infiltration, chest wall infiltration, lung infiltration? Arms well-balanced?
  - Standardization?
  - Volume at center? (noting 45% of pts were at centers that enrolled 3 or fewer pts a year on study)
- "Would the outcome be different in exclusively high-volume center?"

Summary: Mesothelioma and Thymic at WLC 2023

- No new practice-changing systemic therapies
- MARS2 might change the paradigm in mesothelioma surgery
  - At least it shifts onus to the surgeon to explain why patient factors (and/or surgeon factors) lead to recommendation for surgery
    - Especially with a well-designed phase 3 trial arguing against
  - (Manuscript forthcoming!)

ENROLL IN TRIALS!

Parnassus Heights

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Mt. Zion