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LUNG CANCER SYMPOSIUM

Rare Thoracic Malignancies: Mesothelioma and Thymic Malignancies

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Disclosure:

Honoraria/Consulting: Picture Health, Jasper Colin, Binaytara, CIRB

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PACE Partners for Advancing Clinical Education

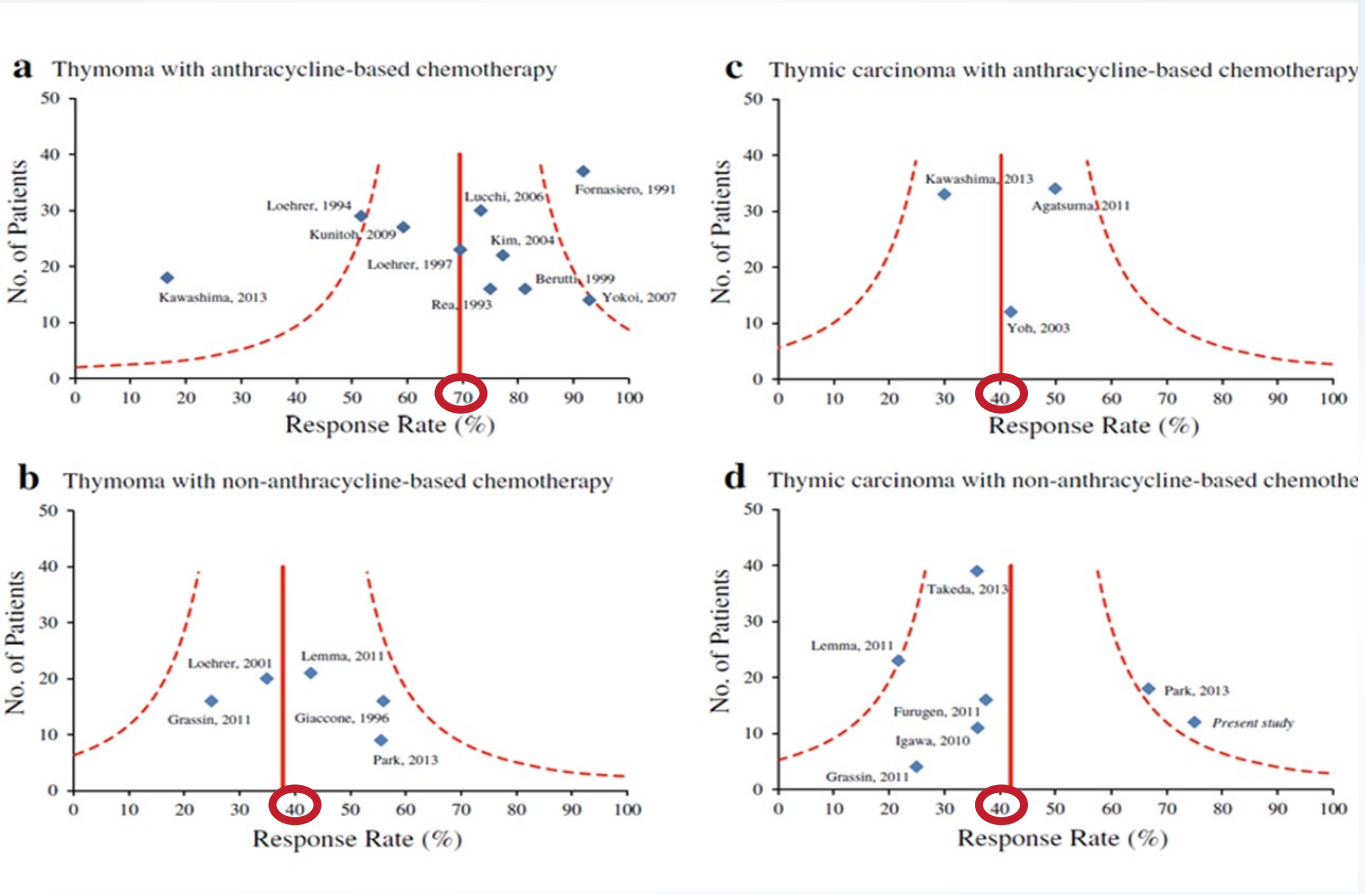
Bio Ascend™

First line treatment in thymic epithelial tumors

Thymic Carcinoma:
TC (preferred)

Thymoma:
PAC (Preferred)

CAP with prednisone
ADOC
Cis/Etop
Cis/Etop/Ifos



In thymic carcinoma, the response rate for chemotherapy, with or without anthracyclines, is 40%

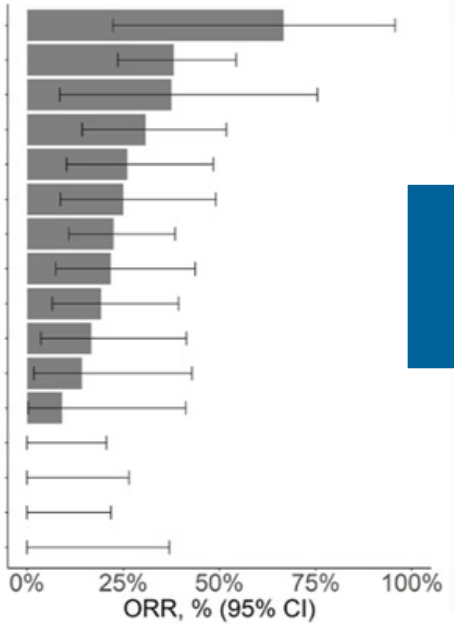
J Cancer Res Clin Oncol (2015) 141:323–331

Lemma et al., JCO, 2011
Loehrer et al, JCO, 1997

Efficacy and safety of treatments for advanced thymic carcinoma after failure of first-line platinum-based chemotherapy

(A)

Trial	Treatment	TC, N	INV/IRC	ORR, % (95% CI)
Kalra 2018	napabucasin + paclitaxel	6	NA	66.7 (22.3, 95.7)
Itoh 2019 (REMORA)	lenvatinib*	42	IRC	38.1 (23.6, 54.4)
Palmieri 2014	capecitabine + gemcitabine*	8	INV	37.5 (8.5, 75.5)
Okuma 2020	S-1	26	INV	30.8 (14.3, 51.8)
Thomas 2015	sunitinib*	23	INV	26.1 (10.2, 48.4)
Tsukita 2020 (NJLCGS 1203)	S-1	20	IRC	25 (8.7, 49.1)
Giaccone 2018	pembrolizumab*	40	IRC	22.5 (10.8, 38.5)
Kim 2018 (KOSMIC)	sunitinib*	23	NA	21.7 (7.5, 43.7)
Cho 2018	pembrolizumab*	26	INV	19.2 (6.6, 39.4)
Zucali 2018	everolimus*	18	NA	16.7 (3.6, 41.4)
Inoue 2014 (NJLCGS 0803)	amrubicin + carboplatin	14	IRC	14.3 (1.8, 42.8)
Gbolahan 2018	pemetrexed*	11	NA	9.1 (0.2, 41.3)
Giaccone 2011	belinostat	16	IRC	0 (0, 20.6)
Rajan 2014	cixutumumab	12	INV	0 (0, 26.5)
Katsuya 2019 (PRIMER)	nivolumab	15	IRC	0 (0, 21.8)
Perrino 2018 (RESOUND)	regorafenib	8	INV	0 (0, 36.9)



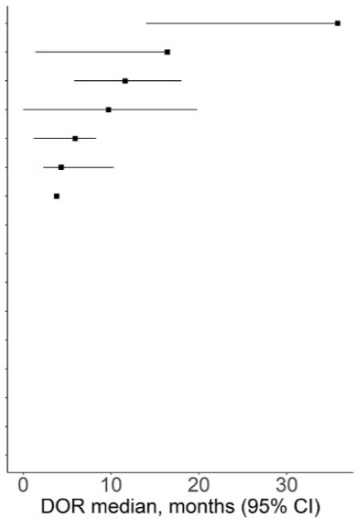
ORR (0-66.7%)

Arunachalam, et al., Lung Cancer, 2024

(B)

Trial	Treatment	TC, N	DOR median months (95% CI)
Giaccone 2018	pembrolizumab*	9	35.8 (14, NR)
Thomas 2015	sunitinib*	6	16.4 (1.4, 16.4)**
Itoh 2019 (REMORA)	lenvatinib*	16	11.6 (5.8, 18)
Cho 2018	pembrolizumab*	5	9.7 (0, 19.8)
Zucali 2018	everolimus*	3	5.9 (1.2, 8.3)**
Okuma 2020	S-1	8	4.3 (2.3, 10.3)
Gbolahan 2018	pemetrexed*	1	3.8
Inoue 2014 (NJLCGS 0803)	amrubicin + carboplatin	2	NA
Giaccone 2011	belinostat	0	NA
Palmieri 2014	capecitabine + gemcitabine*	3	NA
Tsukita 2020 (NJLCGS 1203)	S-1	5	NA
Rajan 2014	cixutumumab	0	NA
Katsuya 2019 (PRIMER)	nivolumab	0	NA
Kalra 2018	napabucasin + paclitaxel	4	NA
Perrino 2018 (RESOUND)	regorafenib	0	NA
Kim 2018 (KOSMIC)	sunitinib*	5	NA

*NCCN guideline recommended intervention.
**Range reported instead of 95% CI.



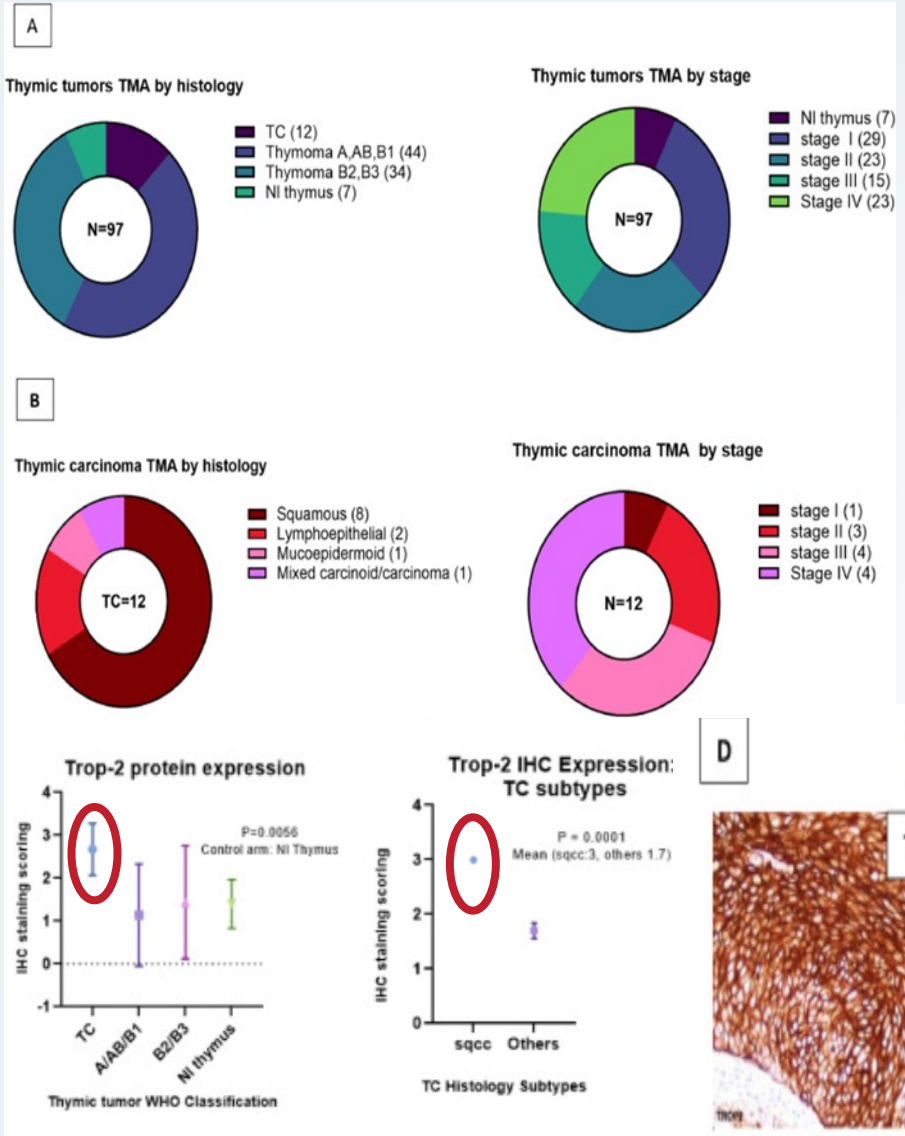
mDOR (3.8 -35.8m)

Summary of trials in thymic epithelial tumors

Setting	Treatment	N	Histology	Phase	Primary Endpoint(s)	Region	NCT
Resectable TET (Neoadjuvant/Perioperative)	Platinum-based chemotherapy/toripalimab	15	Stage III-IVA T/TC	2	Rate of severe AEs mPR	China	NCT04667793
	Cisplatin/docetaxel/pembrolizumab	40	Stage III-IVA T/TC	2	mPR	South Korea	NCT03858582
	Radiation/envolizumab	25	Stage III-IVA TC	2	ORR	China	NCT06019468
Advanced TET (First-line)	Carboplatin/taxane/pembrolizumab	40	T/TC	4	ORR	China	NCT04554524
	Carboplatin/taxol/lenvatinib/pembrolizumab	35	TC	2	ORR	Japan	NCT05832827
Advanced TET (Second-line and beyond)	Avelumab	55	T/TC	2	Safety, tolerability ORR	USA	NCT03076554
	Atezolizumab	34	TC	2	ORR	China	NCT04321330
	Pembrolizumab	37	T/TC	1	Incidence of AEs	USA	NCT03295227
	Pembrolizumab/lenvatinib	43	B3 T/TC	2	5-month PFS	France, Italy, Spain	NCT04710628
	Pembrolizumab/sunitinib	40	TC	2	ORR	USA	NCT03463460
	Nivolumab +/- ipilimumab	55	B3 T/TC	2	6-month PFS	Europe	NCT03134118
	Bintrafusp Alfa (Anti-PD-L1/TGFβ Trap fusion protein)	38	T/TC	2	ORR	USA	NCT04417660
	KN046 (PD-L1/CTLA-4 bispecific antibody)	66	TC	2	ORR	China	NCT04469725
	XmAb20717						
	KFA115 +/- tislelizumab	220	TC among other cancers	1	DLT Dose intensity	International	NCT05544929
	SO-C101 (IL-15 superagonist) +/- pembrolizumab	200	TC among other cancers	1	DLT	International	NCT04234113

Chul Kim, TTLC24

TROP-2 Expression in TETs



TROP-2 has highest expression in TC

Sacituzumab (NCT06248515)
- Phase II non-randomized (n=18)
- Second line+, thymoma/TC

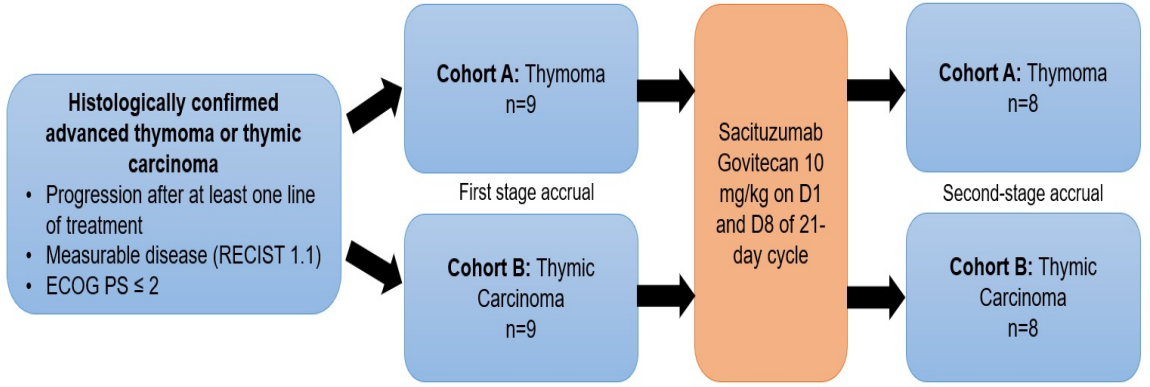
Pembrolizumab/Sac-TMT (EA-5142)- To be open
PI: Fatemeh Ardeshir, Chair: Sukhmani Pada
- Phase II non-randomized (n=30)
- Second line+, TC only

Carbo/Paclitaxel/Ram (NCT03694002)
- Phase II randomized (n=33)
- First line, thymoma/TC

Tislelizumab/Carbo/Nap-paclitaxel (China)
- Phase II non-randomized (n=18)
- First line, thymoma/TC

Fatemeh Ardeshir-Larijani, et al., Clinical Lung cancer, 2024

1) Phase II trial of Sacituzumab-Govitecan



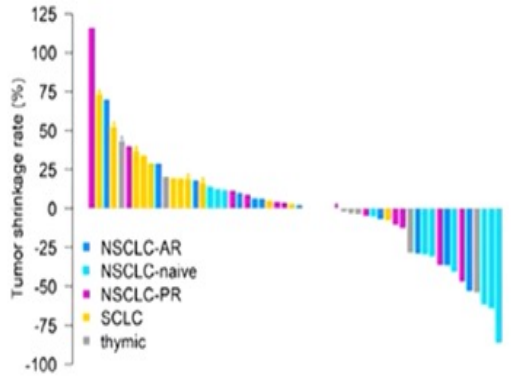
- Primary endpoint: ORR
- Secondary endpoints: DOR, PFS, OS, adverse events
- Exploratory analyses: Expression of Trop-2 in tissue and circulating tumor cells and its correlation with treatment outcomes

PI: Chul Kim

2) Phase II of Carbo/Taxol/Ram+ maintenance Ram in TC and B3 thymoma: RELEVENT trial

- N=33
- Median follow up 31.6m
- ORR (n=19, 57.6%), PR (57.6%), SD (42.4%)
- mPFS (18.1, CI :10.5-52.3), mOS (43.8, CI: 22.5-NE)

3) Phase I of Nivo/Vorolanib in refractory thymic Carcinoma



ORR 1/9 (11%)

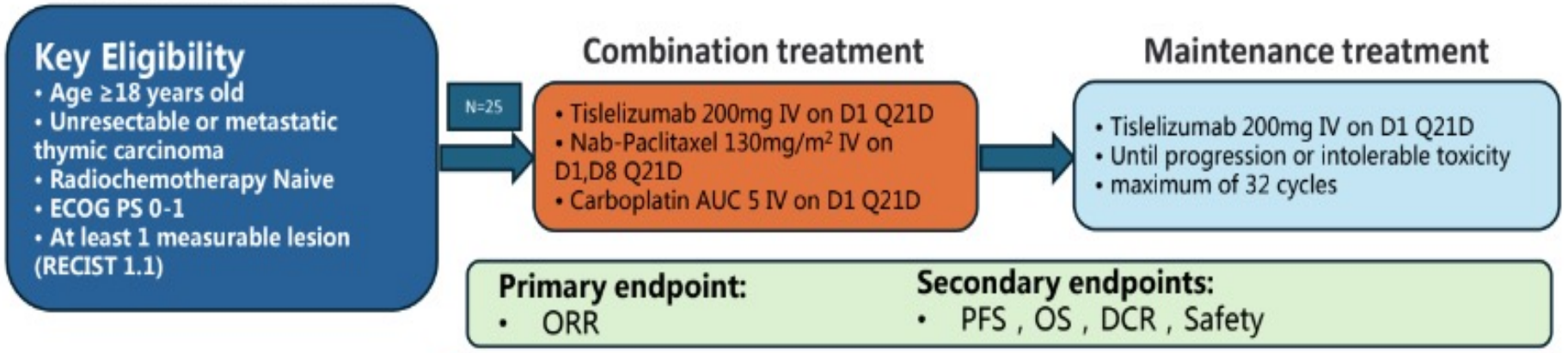
mPFS 9.1 months

mOS 21.1 months

More toxicity – 78% abnl LFTs

Beckmann, JTO CRR, 2024
WCLC-2024

4) A Phase II study of Tislelizumab with chemotherapy in patients with thymic carcinoma



Baseline characteristics

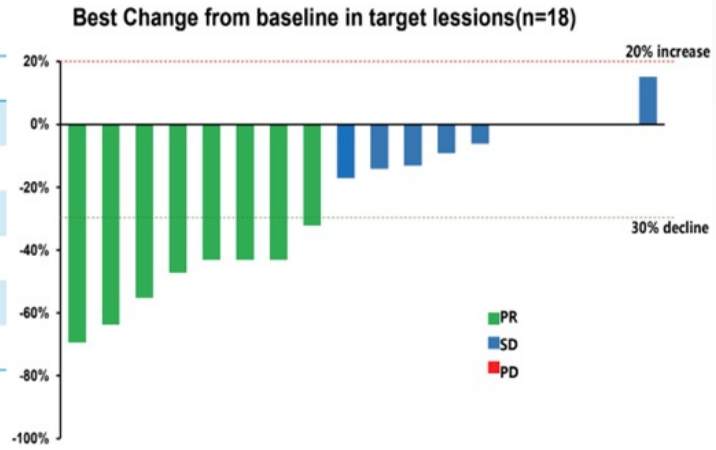
Characteristic		N=18
Age,years	Median(range)	61(42-69)
Sex	Male Female	13(72.2%) 5(27.8%)
ECOG performance status	0 1	1(5.6%) 17(94.4%)
Smoking Status	Never smoked Former smoker Current smoker	6(33.3%) 9(50.0%) 3(16.7%)
Disease stage	Ⅲ Ⅳ	2 (11.1%) 16 (88.9%)
Metastases site	>2 ≤2	5(27.8%) 13(72.2%)

Cho J, et al. J Clin Oncol. 2018 Jun 15.Lancet Oncol 2018; 19: 347–55. Isshiki T,et al.Case Rep Oncol, 2018, Oct.

A Phase II study of Tislelizumab with chemotherapy in patients with thymic carcinoma

Primary endpoint:ORR

Best overall response,n (%)	N=18
CR	0
PR	8 (44.4%)
SD	10 (55.6%)
PD	0
ORR , (95%CI)	44.4% (41.7-47.1)
DCR , (95%CI)	100%



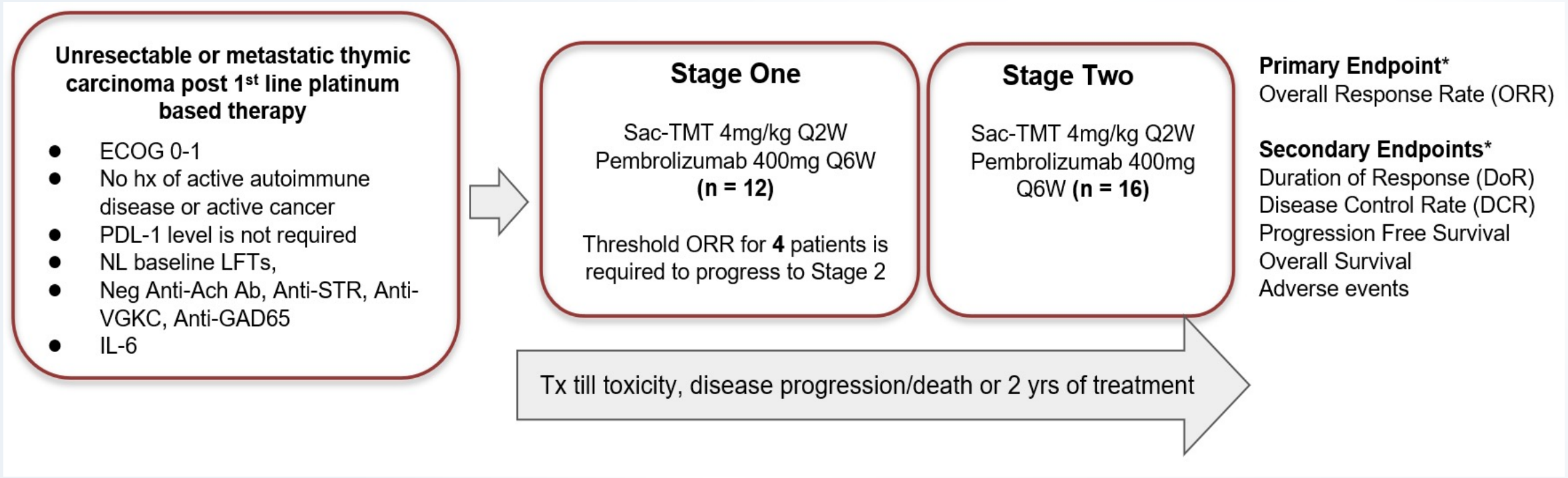
NO CR, DCR 100%
No myocarditis, Hepatitis

Safety

	Treatment-related AEs		
	Grade1-2	Grade 3	Grade 4
Any treatment-related AEs(n,%)	8(44.4%)	2(11.1%)	0
Hematological toxicity(n,%)			
Leukopenia	5(27.8%)	1(5.6%)	0
Thrombocytopenia	4(22.2%)	0	0
Anemia	2(11.1%)	0	0
Non-hematological toxicity(n,%)			
Creatinine increased	1(5.6%)	0	0
Skeletal related events(SREs)	1(5.6%)	0	0
Hyperthyroidism	1(5.6%)	0	0
Tropnin increased	1(5.6%)	0	0
Myocarditis*	0	1(5.6%)	0
Hepatitis*	0	1(5.6%)	0

*1 patient occurred immune related myocarditis and hepatitis and the treatment response was PR（63.5%decline）.

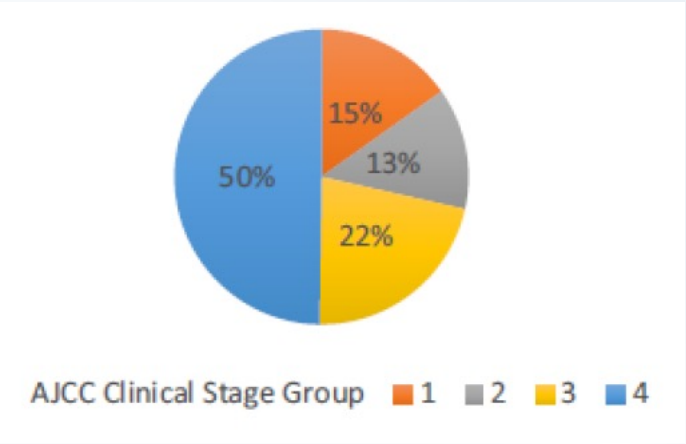
5) EA-5241: A Single Arm, Phase 2 Study of Pembrolizumab plus Sacituzumab Tirumotecan (Sac-TMT) in Unresectable or Metastatic Thymic carcinoma After Progression on First Line Therapy

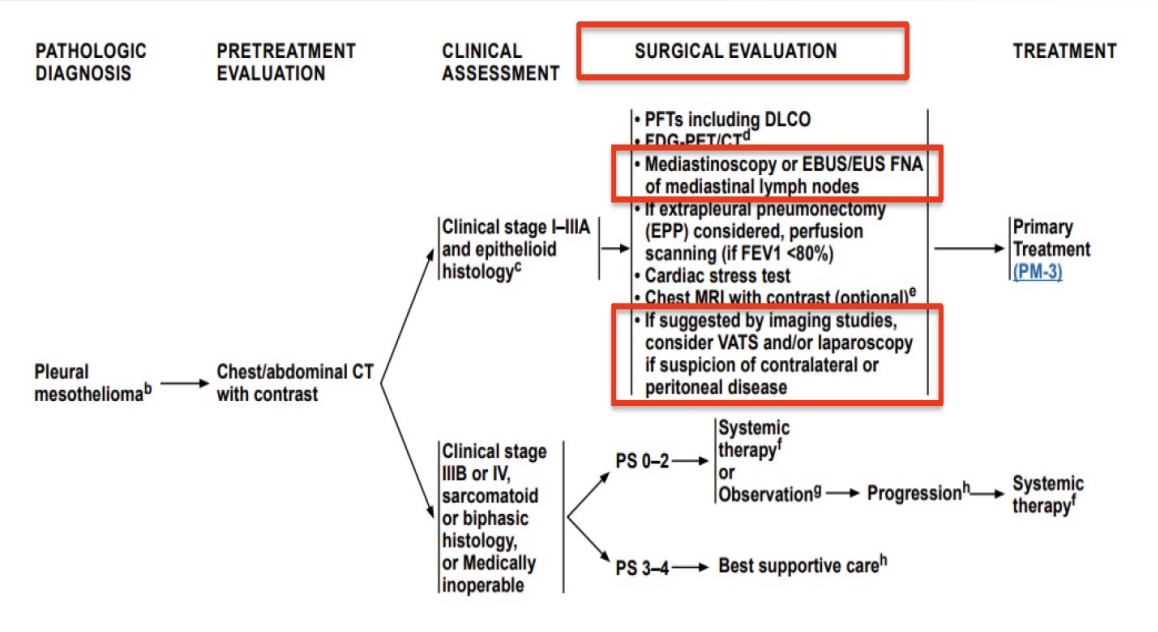


PI: Fatemeh Ardeshir, MD, Co-Chair: Padda, MD

Pleural Mesothelioma Background

- The incidence rate per 100 000 people has been reported as 0·9 for men and 0·3 for women in the USA
- The average reported lifespan from diagnosis of 9–12 months
- Main stay of treatment is platinum and pemetrexed chemotherapy w/wo surgery



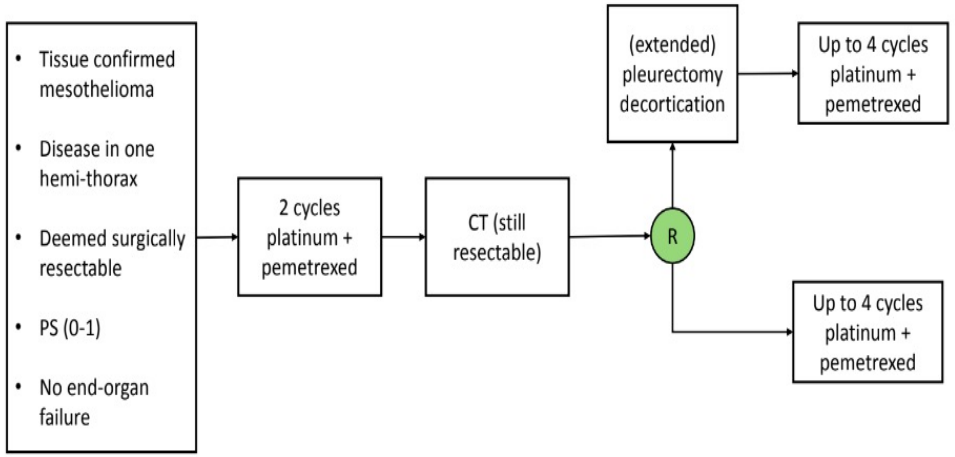


- There are different types of surgical techniques:
  - Extra pleural pneumonectomy (EPP): En bloc resection of the parietal and visceral pleura with the ipsilateral lung, pericardium, and diaphragm.
  - Extended Pleurectomy decortication (EPD): Parietal and visceral pleurectomy to remove all gross tumor and, where required, the additional resection of the diaphragm or pericardium (Lung sparing)
  - Pleurectomy decortication (PD): Parietal and visceral pleurectomy to remove all gross tumor

EPP has higher mortality competed to EPD/PD

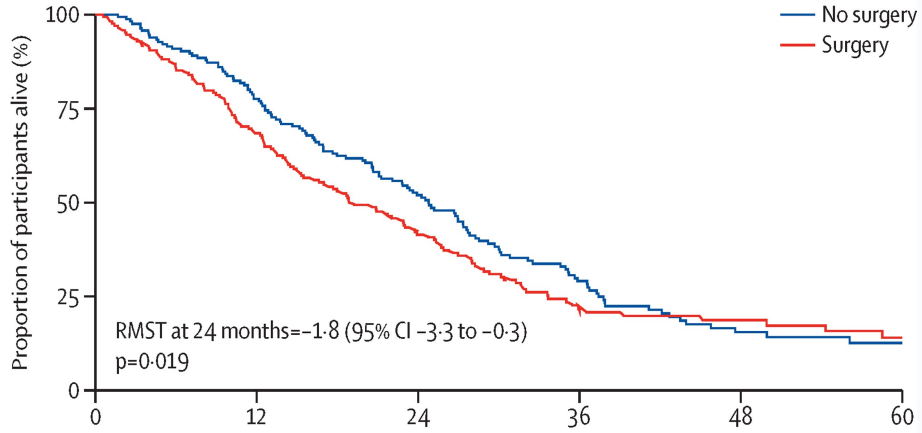
Naomi Alpert et al., translational lung cancer Res, 2022
NJ Vogelzang et al., JCO 2003

MARS 2 trial schema

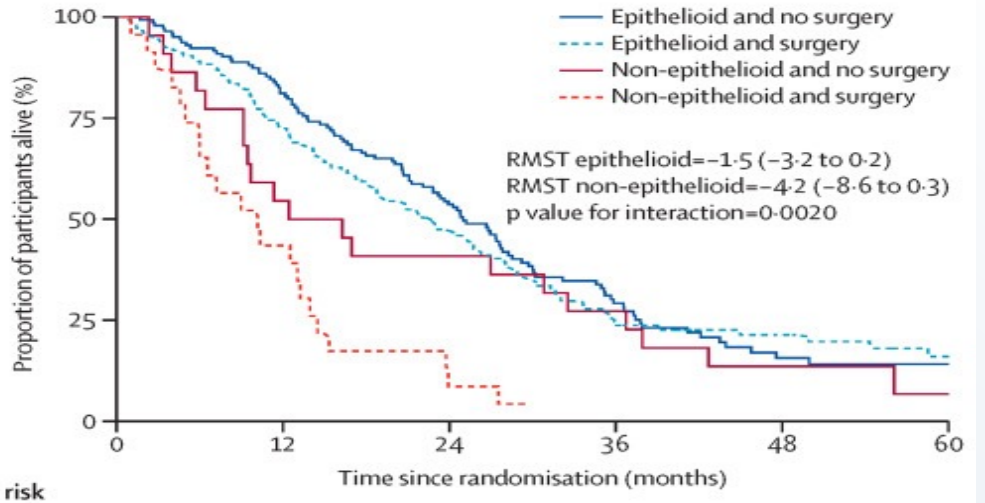


Lim E et al, 2023/24

- Phase III RCT conducted in UK (26 hospitals) evaluating Superiority of **chemotherapy alone** vs **Pleurectomy decortication + chemotherapy**
- The primary objective was OS
- Median OS in surgery vs chemotherapy group **(19.3m vs 24.8m)**
- Surgery with 3.6x higher rate of serious adverse events
- Increased Incidence rate of cardiac (30 vs12), Respiratory (84 vs 34) and infection(124 vs 53)



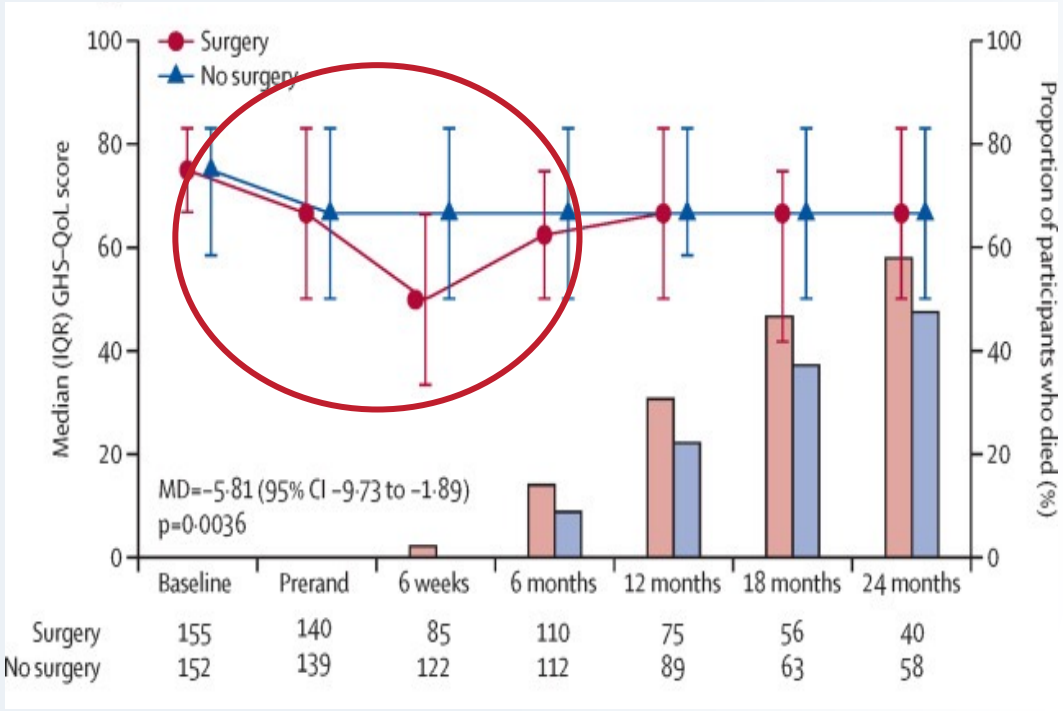
Number at risk (number censored)						
No surgery	166	129	82	37	15	6
	(1)	(4)	(14)	(7)	(7)	(6)
Surgery	169	115	64	24	15	7
	(1)	(6)	(14)	(6)	(5)	(7)



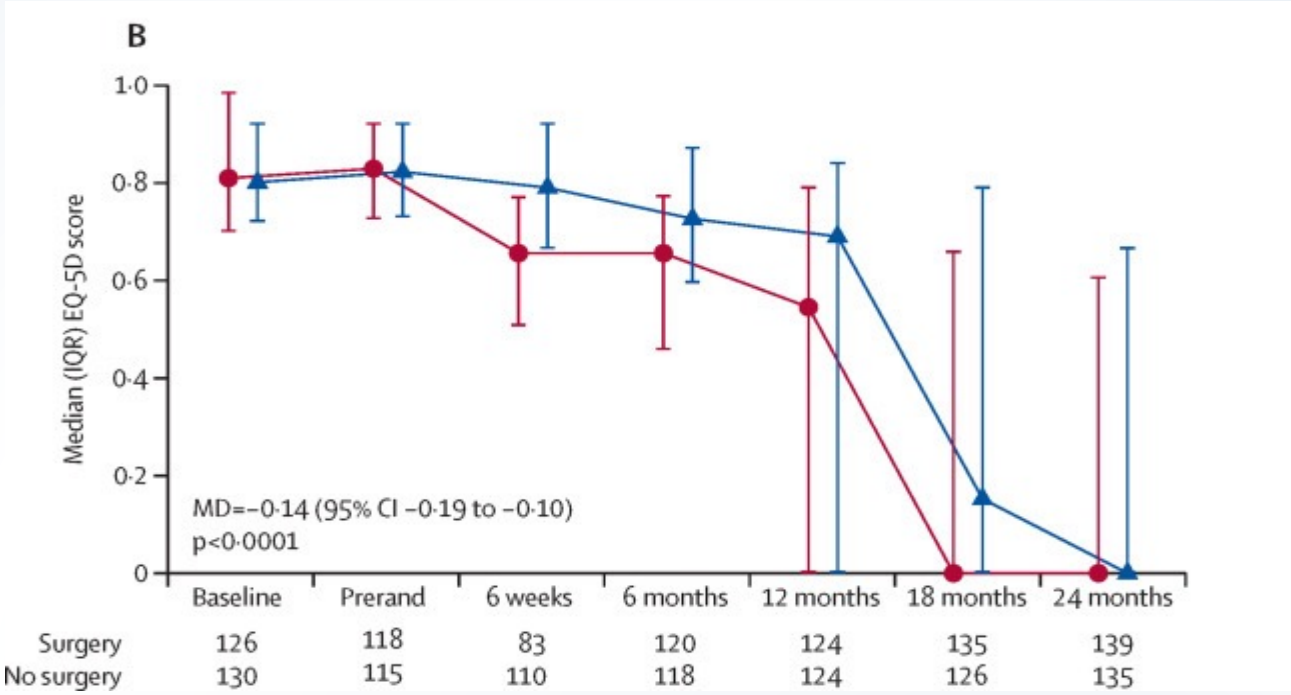
Number at risk (number censored)						
Epithelioid and no surgery	144 (1)	116 (4)	73 (14)	31 (7)	12 (6)	5 (5)
Epithelioid and surgery	146 (1)	105 (6)	62 (13)	24 (6)	15 (5)	7 (7)
Non-epithelioid and no surgery	22 (0)	12 (0)	9 (0)	6 (0)	3 (1)	1 (1)
Non-epithelioid and surgery	23 (0)	10 (0)	2 (1)	0 (0)	0 (0)	0 (0)

MARS-2 study- Patient reported Quality of life

Epithelioid



Non-Epithelioid



Epithelioid pts had better QOL soccer in the first 6m post surgery.
Non-Epithelioid pts had significantly worse outcome and lower QOL in both short- and long-term follow-up.

Eric Lim, David Waller et al,. The Lancet, June 2024

MARS-2 was practice changing with some considerations….

- Staging was based on the CT scan and not PET or mediastinal LN bx
- There were 89% Extended PD, which has been associated in higher mortality compared to PD
- About 50% of surgeries were performed in low volume center
- 90-day mortality: 9% (~doubled compared to high volume center)
- **MARS 2 population:**
  - Biphasic: 8.7% (N=29)
  - Sarcomatoid : 3.3% (N=11)
  - Other non epithelioid: 2.1% (N=7)

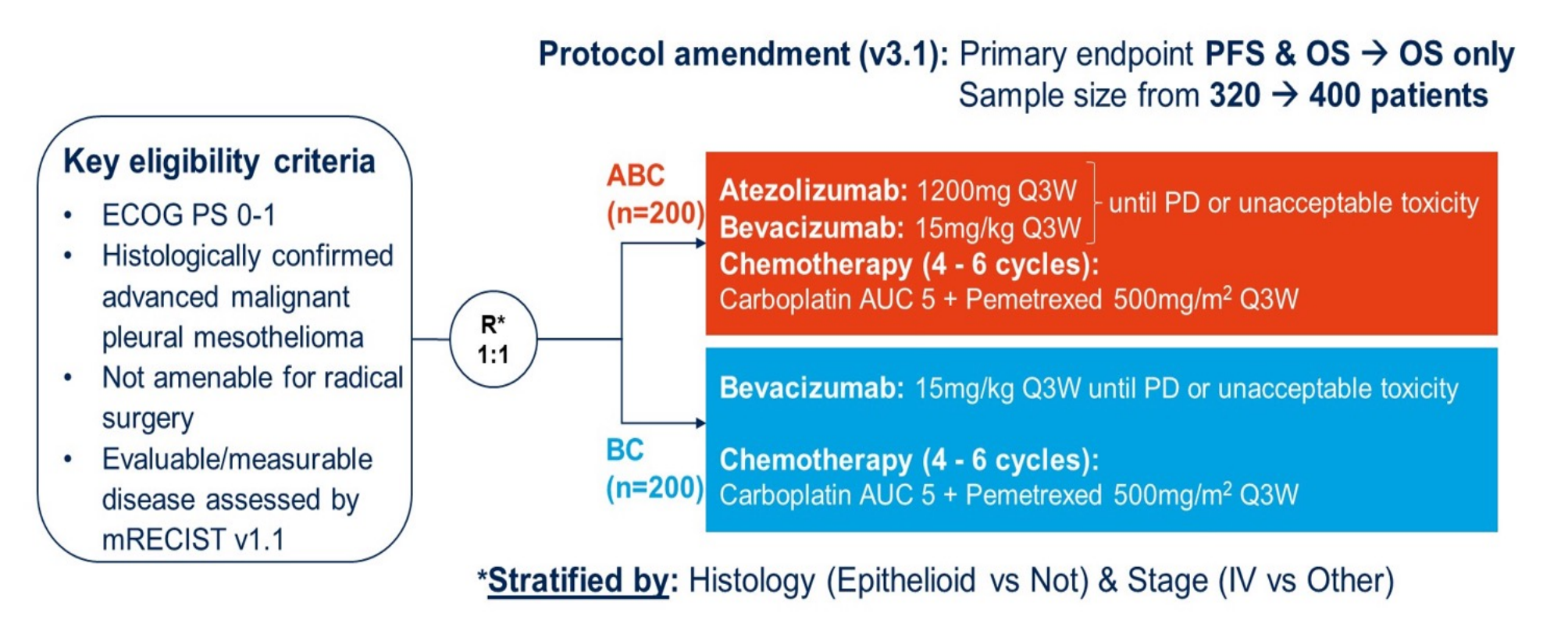
Surgery in mesothelioma:

- higher risk of death
- more serious complications
- worse quality of life
- higher cost of $41877 vs. $15805

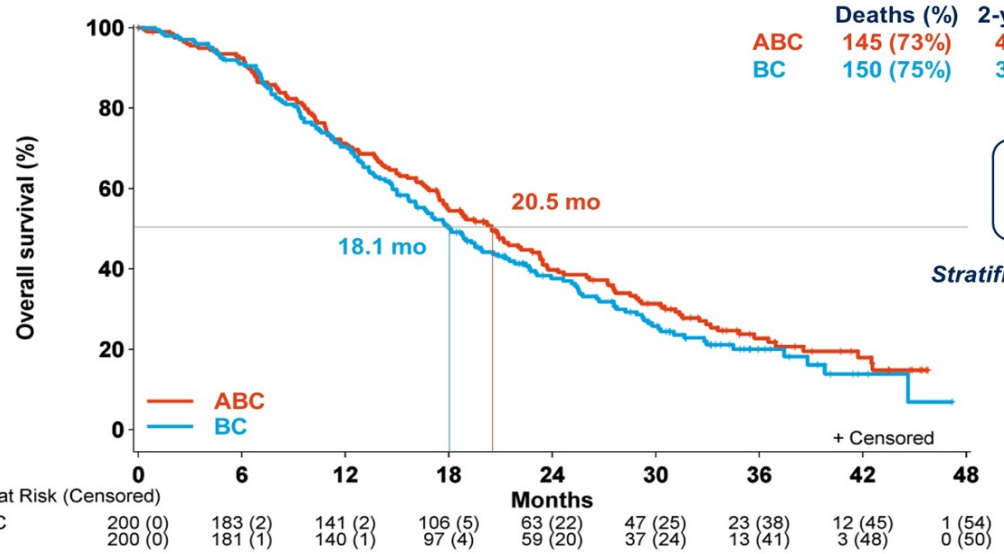
Only select patients with limited disease and good performance should be assessed for surgery

Lapidot M, et al. Ann Surg. 2022
Eric Lim, David Waller et al,. The Lancet, 2024

A randomized phase III study of bevacizumab (B) and standard chemotherapy (C) with or without atezolizumab (A), as first-line treatment (TX) for advanced pleural mesothelioma (PM)—Results from the ETOP 13-18 trial.



ETOP BEAT-meso: Primary endpoint - OS



	Deaths (%)	2-yr OS% (95% CI)
ABC	145 (73%)	40% (33%-47%)
BC	150 (75%)	38% (31%-45%)

HR (95% CI):
0.84 (0.66 – 1.06)
Log-rank p=0.14

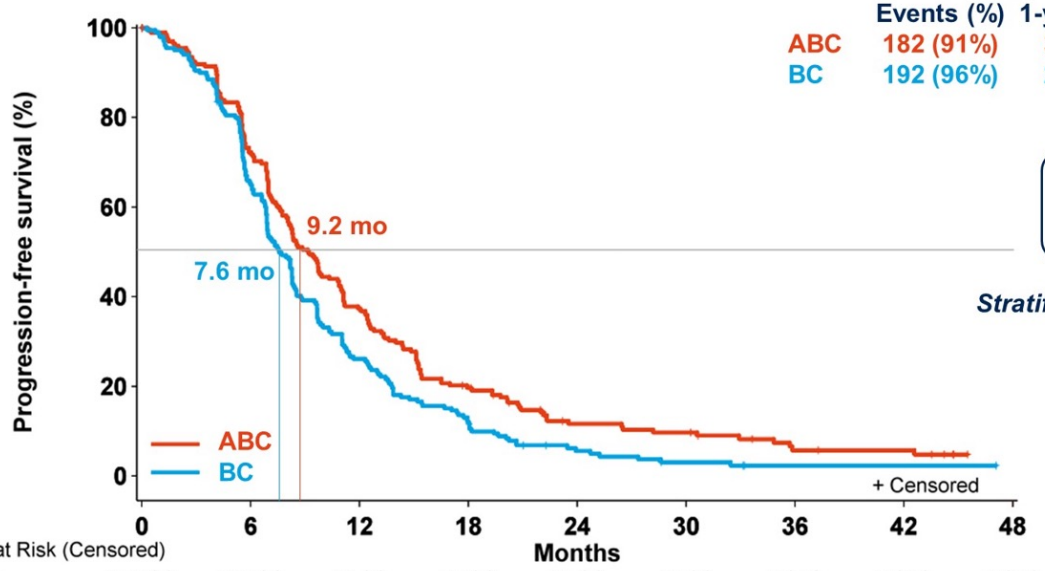
Stratified by histology & stage

No at Risk (Censored)									
ABC	200 (0)	183 (2)	141 (2)	106 (5)	63 (22)	47 (25)	23 (38)	12 (45)	1 (54)
BC	200 (0)	181 (1)	140 (1)	97 (4)	59 (20)	37 (24)	13 (41)	3 (48)	0 (50)

Interim for efficacy (previously performed):

Boundary for OS not crossed

ETOP BEAT-meso: Secondary endpoint - PFS



	Events (%)	1-yr PFS% (95% CI)
ABC	182 (91%)	37% (31%-44%)
BC	192 (96%)	26% (20%-32%)

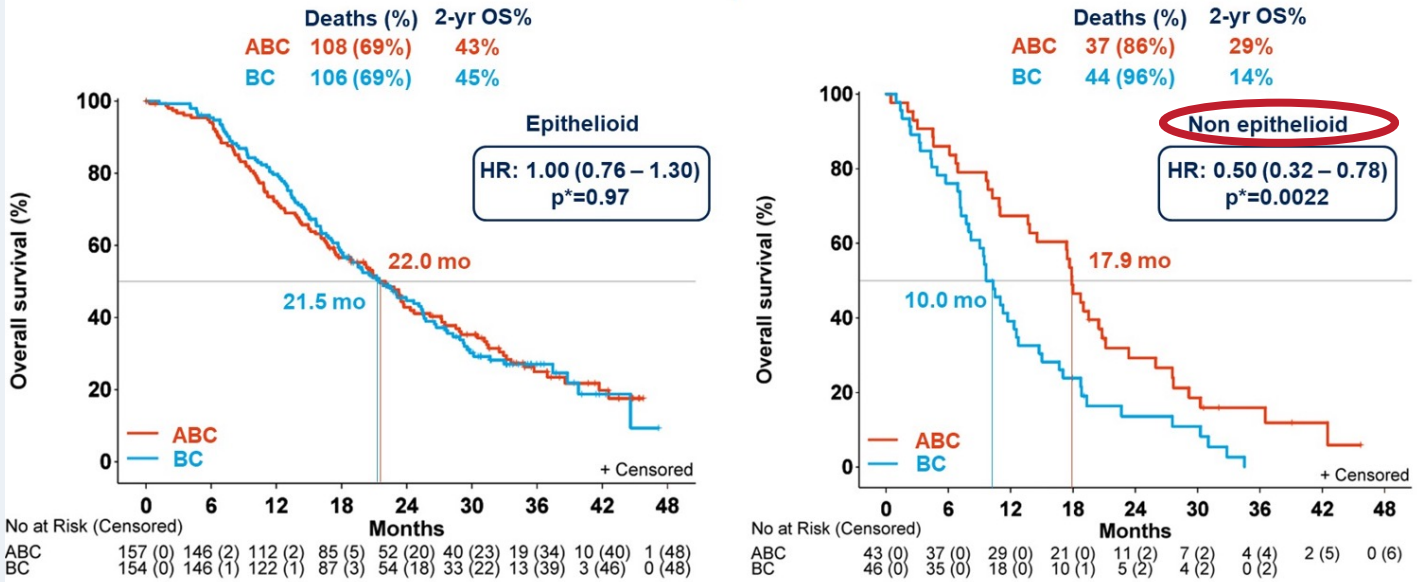
HR (95% CI):
0.72 (0.59 – 0.89)
Log-rank p=0.0020

Stratified by histology & stage

No at Risk (Censored)									
ABC	200 (0)	143 (2)	74 (2)	38 (3)	18 (9)	15 (9)	7 (12)	6 (13)	0 (18)
BC	200 (0)	130 (1)	52 (1)	24 (1)	9 (4)	4 (5)	1 (7)	1 (7)	0 (8)

ETOP BEAT-meso: OS by histology

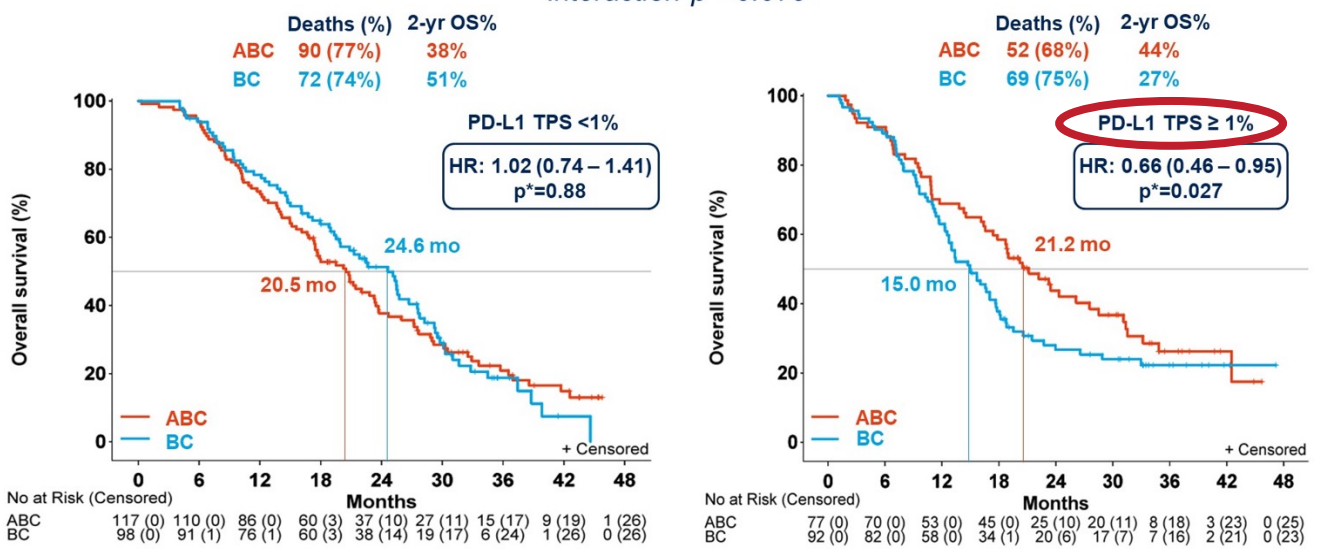
Interaction p=0.0096*



- The OS was not significantly different
- PFS is significantly prolonged
- Addition of IO is more effective in PDL+, non-Epith
- Same QOL
- Higher thrombocytopenia, AKI, rash and pruritus

ETOP BEAT-meso: OS by PD-L1 TPS

Interaction p=0.079*

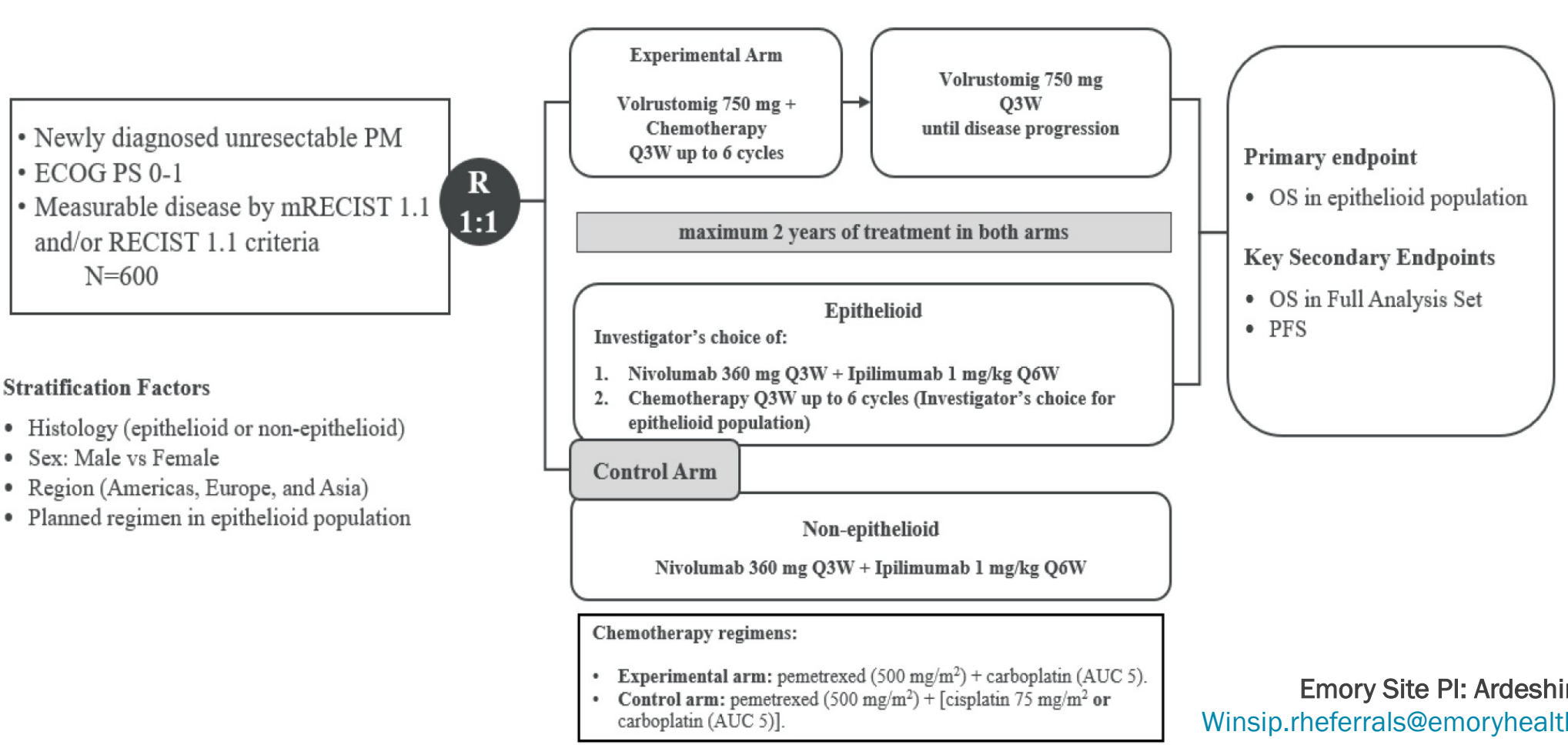


* Stratified by histology and stage

* Stratified by histology and stage

@ArdeshirFatemeh

Phase III, Randomized, Multicenter, Global Study of Volrustomig in Combination with Carboplatin plus Pemetrexed Versus Platinum plus Pemetrexed or Nivolumab plus Ipilimumab in Participants with Unresectable Pleural Mesothelioma (eVOLVE-Meso)



Volrustomig: bispecific antibody (PDL-1 & CTLA-4)

Emory Site PI: Ardeshir,
Winsip.rheferrals@emoryhealthcare.org

eVOLVE at Winship

@ArdeshirFatemeh

Thank you!