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Rare Thoracic Malignancies: Mesothelioma and Thymoma Update

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Oct 2025

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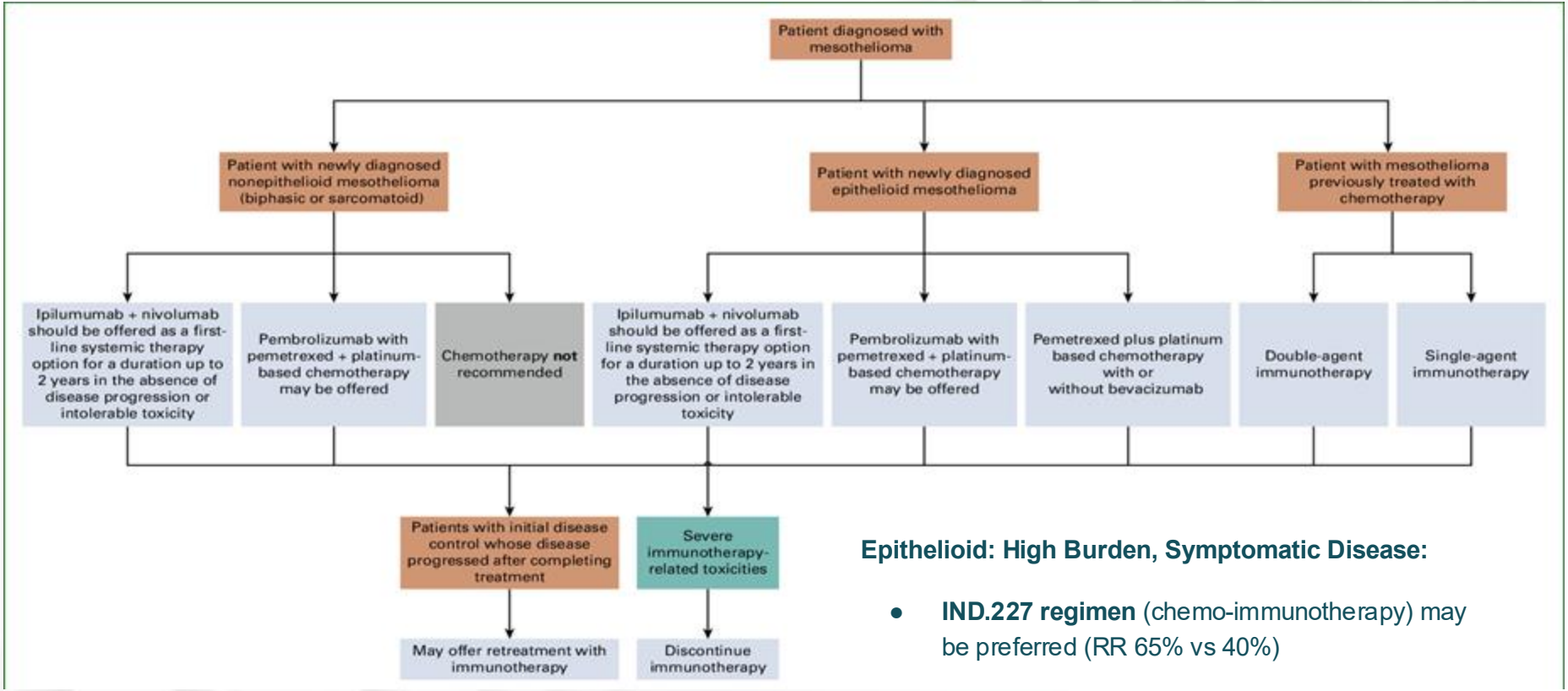
First Line Treatment in Unresectable Mesothelioma



Epithelioid: High Burden, Symptomatic Disease:

- **IND.227 regimen** (chemo-immunotherapy) may be preferred (RR 65% vs 40%)

ASCO Mesothelioma Guideline, 2025

CheckMate-743: Nivolumab + Ipilimumab vs standard platinum + pemetrexed

Randomized phase III trial of **dual immunotherapy** vs chemotherapy in untreated, unresectable Pleural Mesothelioma.

At ~3-year follow up:

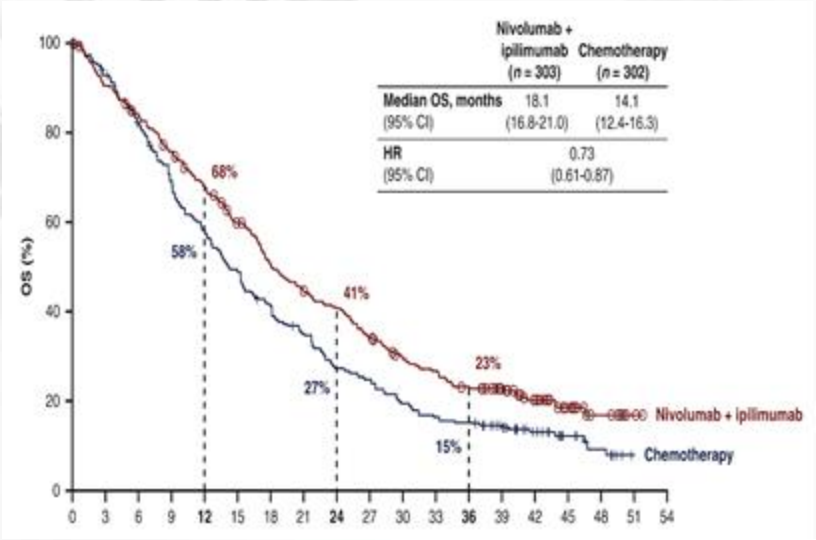
Median OS: **18.1 months** vs **14.1 months** (HR ~0.74).

-OS 3-year rates: ~23% vs ~15%

-PFS 3-year rates: ~14% vs ~1%

-ORR: ~40% with IO vs ~44% with chemo early, but "ongoing responses" more durable with IO.

Quality of life / symptom burden: immunotherapy arm delayed deterioration and maintained or improved symptom burden

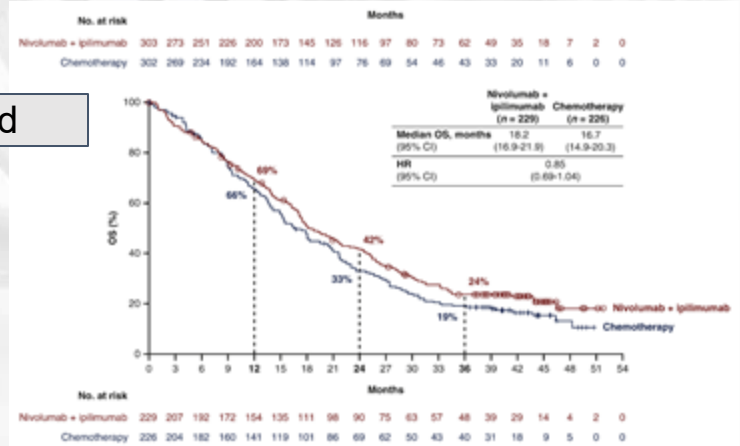


Baas et al., The Lancet, 2021

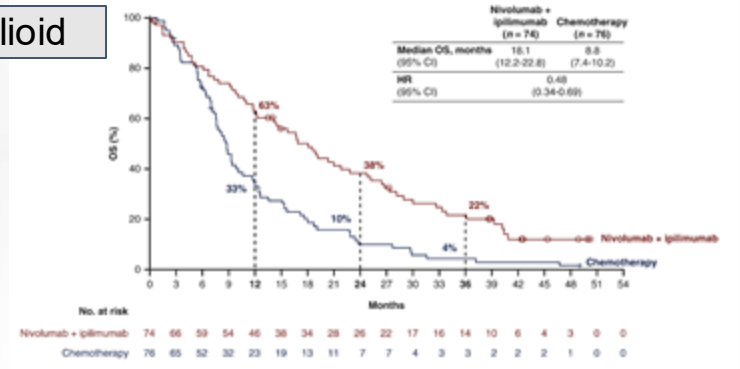
Non-epithelioid subtype had a significantly worse outcome with chemo only

- **Both Epi/Non-Epi had benefit from Ipi/Nivo**
- At 3-yr, OS rate of dual-IO: 24%
- At 3-yr, OS rate of chemo:
- -Epi: 19%
- -Non-Epi:4%
- mPFS: 6.3m (5.3-7.5)
- mOS: 18.9 (17.6–NR)

A. Epithelioid



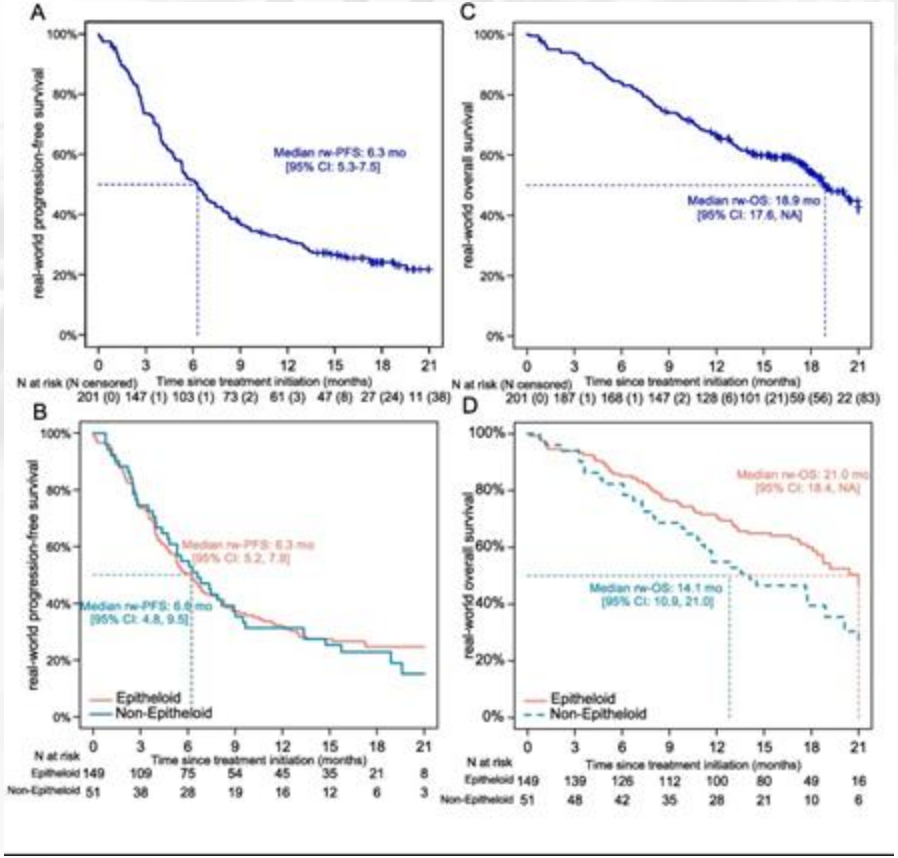
B. Non-Epithelioid



- In a subgroup analysis pts who received Ipi/Nivo and experienced treatment-related AEs leading to discontinuation had a higher 3-year OS rate of 37% compared with 23% in all randomized patients.

Real-world data of Dual IO vs Chemo in Mesothelioma

- Confirms that OS is improved with IO in different histology
- Early exposure to dual-IO improved OS compared to the historical control



Bylicki et al., Lung Cancer, 2024

IND227: Pembrolizumab plus chemotherapy versus chemotherapy in untreated advanced pleural mesothelioma in Canada, Italy, and France: a phase 3, open-label, randomized controlled trial

Phase II/III (N=440): Updated OS

Additional year of follow-up

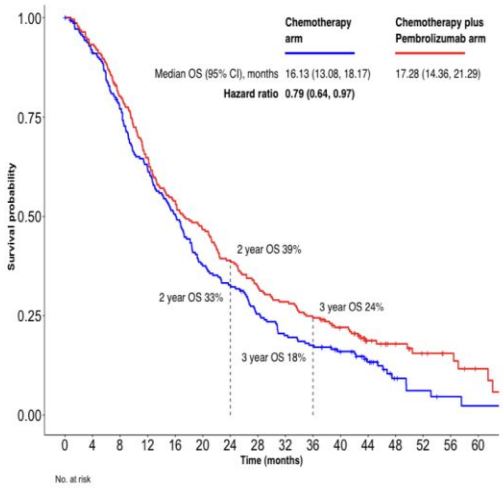
Median follow-up 16.2 months (range 0.03 – 69.9)

Additional 29 deaths occurred

- 11 in the chemotherapy alone arm
- 18 in the pembrolizumab arm

Hazard Ratio for OS unchanged (0.79)

Log-rank p-value decreased to 0.022



Median follow-up: 16.2 months

HR for OS: 0.79 [CI: 0.64–0.97], **p = 0.022**

- **21% reduction in risk of death** with pembrolizumab

3-yr OS: 24% (combo) vs 18% (chemo alone)

5-yr OS: 12% (combo) vs 2% (chemo alone)

Subgroup Analyses:

Epith OS: HR = 0.85 [0.67–1.08]

Non-Epi OS: HR = 0.65 [0.42–1.00]

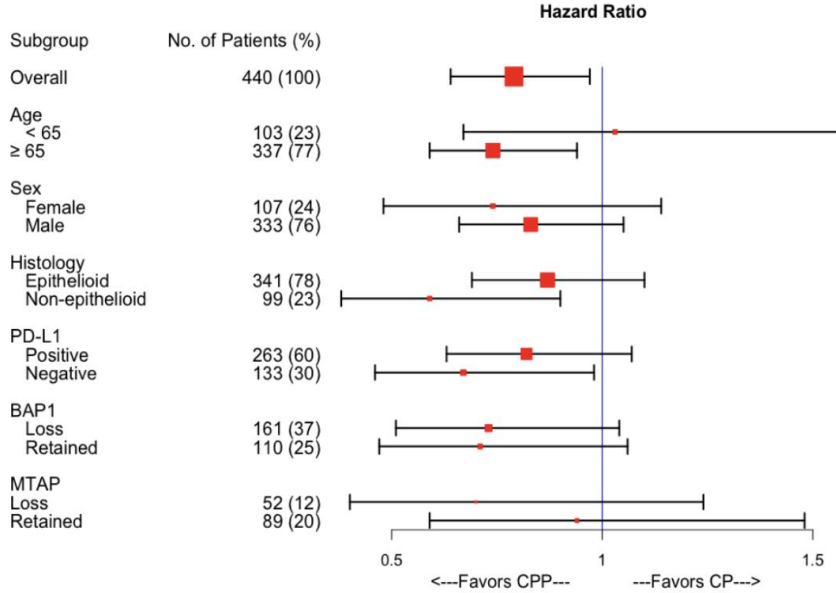
Greater benefit seen in **non-epithelioid** patients

Toxicity

Grade 3-4: 27% (chemo-IO) vs 15% (Chemo)

IND227 Trial subgroup analysis

II/III (N=440): Overall Survival: Major Subgroups



MTAP loss was observed in 39 of 118 (33%) epithelioid cases and 13 of 23 (57%) non epithelioid cases (p= 0.06).

MTAP loss was associated with Worse overall survival (p = 0.035):

➢Median OS was 15.7 months (95% CI: 11.9 22.4) in the MTAPloss group.

➢Compared to 19.2 months (95% CI: 14.1 –27.6) in the MTAP retained group.

MTAP loss was not predictive of treatment effect (p = 0.82).

There was no significant cooccurrence of MTAP loss and BAP1 loss (p = 0.76)

Summary of first-line therapy

Study	Regimen	N	ORR (inv arm)	mPFS (inv arm)	mOS (inv arm)
EMPHACIS	Cis/Pem vs Cis	226	41%	6.7m	12.1m
PrE0505	Cis/pem/durva vs Cis/Pem	55	56%	6.7m	20.4m
DREAM	Cis/pem/durva vs Cis/Pem	54	48%	6.9m	18.4m
CM743	Ipi/nivo vs Cis/Pem	605	40%	6.8m	18.1m
IND227	Platinum chemo/Pem/Pem vs Chemo/Pemetrexed	121	61%	7.1m	17.3m

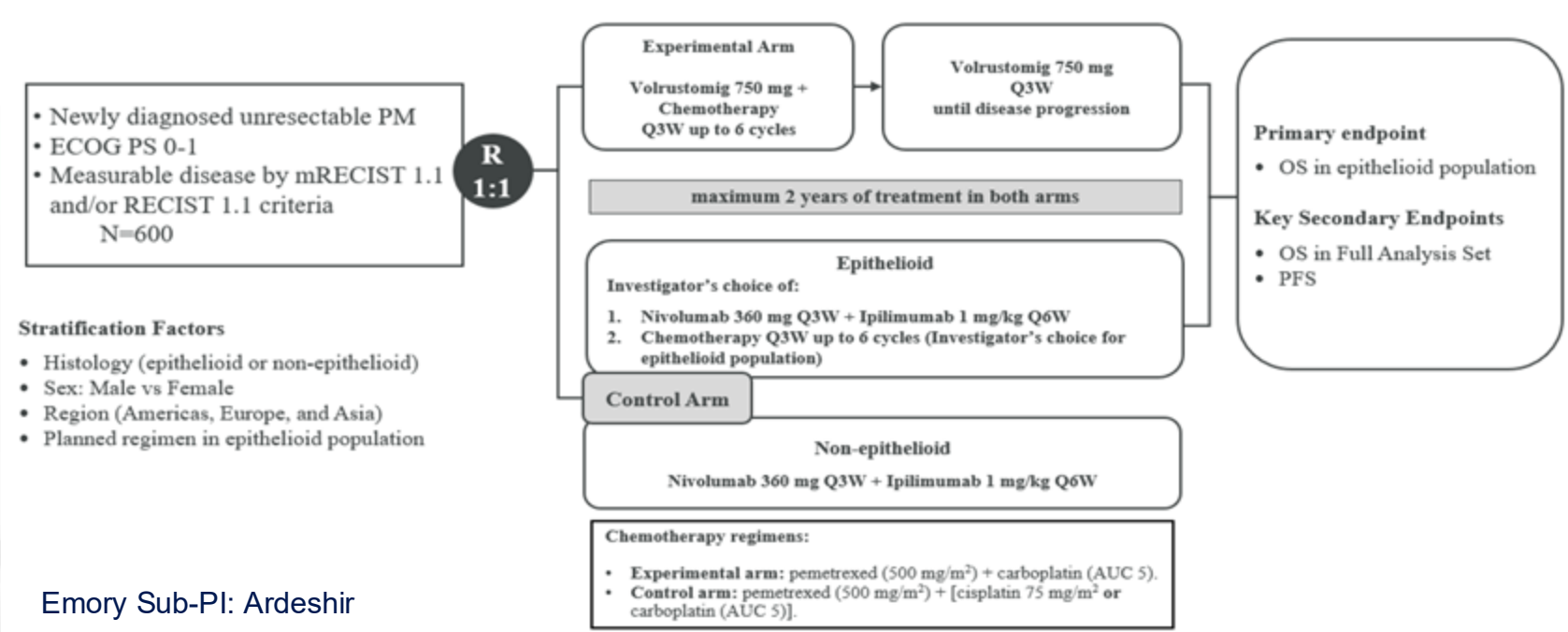
Volgerlzang et al., JCO 2003
Forde et al., Nat Medicine 2021
Nowak et al., Lancet Oncol 2020
Baas et al., Lancet, 2021
Chu et al.,The Lancet, 2023

Addition of VEGF inh to chemo improved clinical outcome

Study	N	Regimen	Primary Endpoint	ORR	PFS	OS
MAPS Trial (IFCT-GFPC-0701)	448	**Bevacizumab + Pemetrexed + Cisplatin**	**OS**	**41.3%**	**6.7 m**	**18.8 vs 16.1 m (p=0.01)**
BEAT Meso (NCT02991468)	268	**Atezolizumab + Bevacizumab + Pemetrexed + Cisplatin**	**PFS**	**46.4%**	**7.0 m**	**Data not mature**

Zalcman et al., *The Lancet*, 2016
Fennell et al., *Annals of Oncology,* ASCO 2024

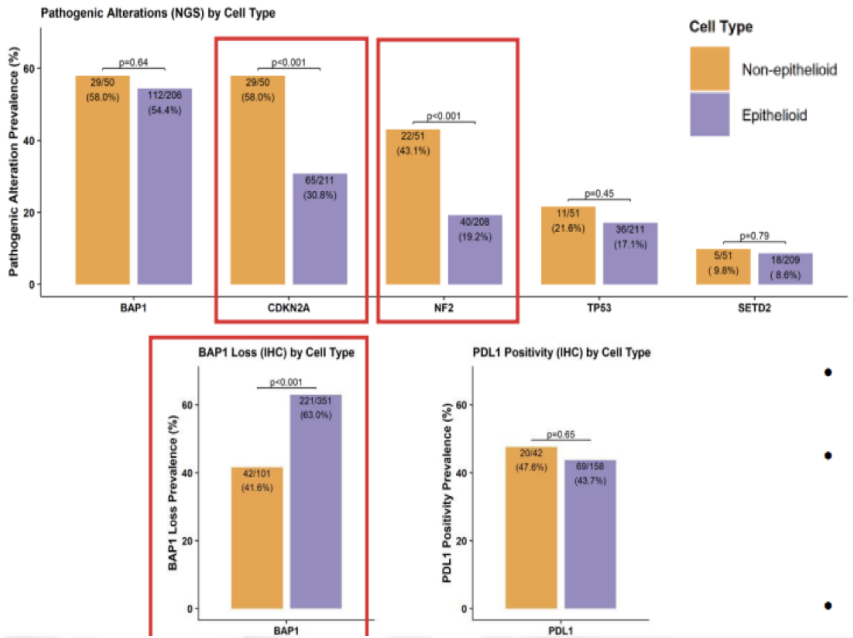
Phase III, Randomized, Multicenter, Global Study of Volrustomig in Combination with Carboplatin plus Pemetrexed Versus Platinum plus Pemetrexed or Nivolumab plus Ipilimumab in Participants with Unresectable Pleural Mesothelioma (eVOLVE-Meso)



Emory Sub-PI: Ardeshir

Impact of Molecular Alterations on Survival in a Cohort From 9th Edition Database

Landscape of genomic alterations and biomarker status according to histologic subtypes



Integrated BAP1 analysis by IHC and NGS

	BAP1 by IHC		
	Retained	Lost	Total
BAP1 by NGS, n (%)	(N=67)	(N=122)	(N=189)
Wild type	**58 (86.6%)**	21 (17.2%)	79 (41.8%)
Pathogenic	7 (10.4%)	**101 (82.8%)**	108 (57.1%)
VUS	2 (3.0%)	0 (0.0%)	2 (1.1%)

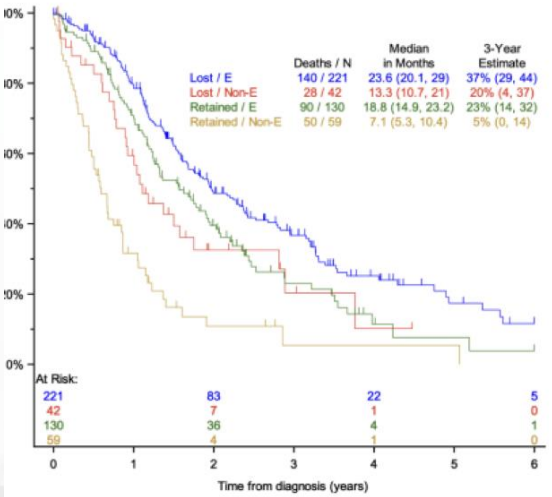
- **Pearson's correlation coefficient calculated based on WT and pathogenic: 0.6943**
- **Both IHC and NGS have limitations in detecting the full spectrum of BAP1 alterations; each assay can pick up alterations missed by the other method**
- **Combined IHC/NGS approach may be optimal**

Yang et al., WCLC 2025

OS analysis by genomic/biomarker result and histologic subtype (epithelioid vs. non-epithelioid)

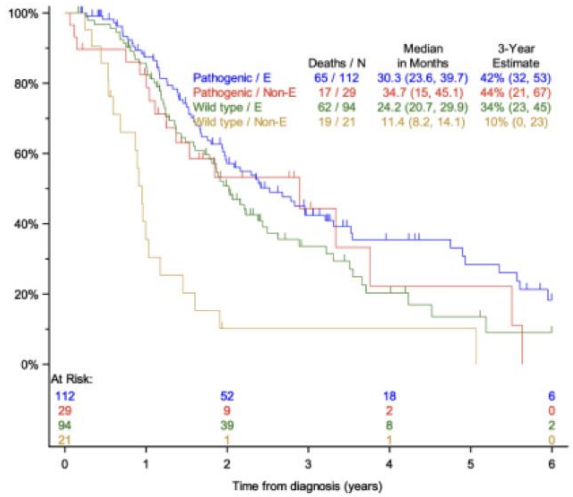
BAP1 IHC (lost vs. retained)

HR=0.60 (95% CI: 0.48, 0.75) p<0.001



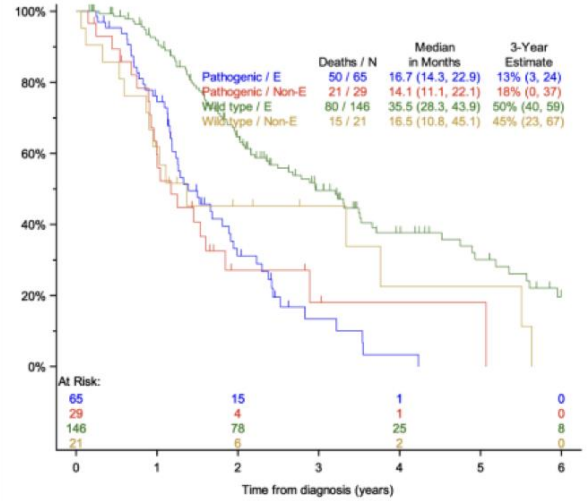
BAP1 NGS (pathogenic vs. WT)

HR=0.63 (95% CI: 0.46, 0.85) p=0.003



CDKN2A NGS (pathogenic vs. WT)

HR=2.67 (95% CI: 1.93, 3.69) p<0.001

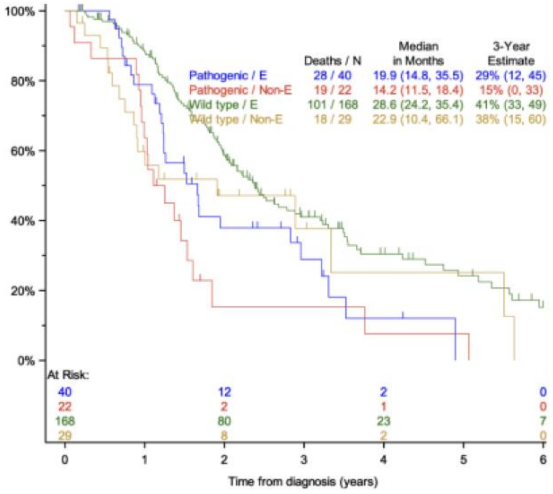


Yang et al., WCLC 2025

OS analysis by genomic/biomarker result and histologic subtype (epithelioid vs. non-epithelioid)

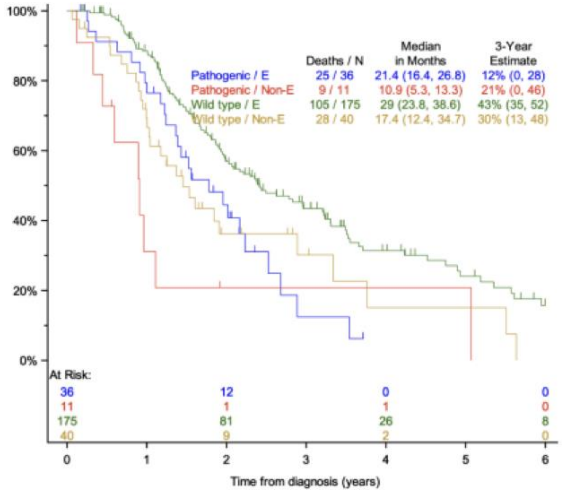
NF2 NGS (pathogenic vs. WT)

HR=1.89 (95% CI: 1.34, 2.67) p<0.001



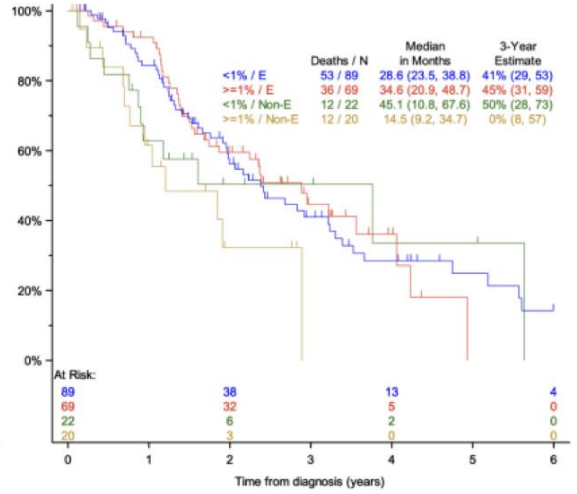
TP53 NGS (pathogenic vs. WT)

HR=1.86 (95% CI: 1.27, 2.73) p=0.001



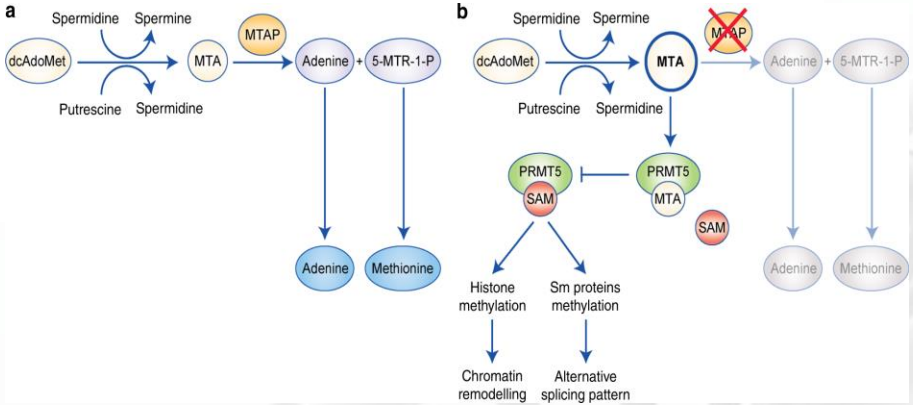
PD-L1 IHC (<1 vs. ≥1%)

HR=1.09 (95% CI: 0.75, 1.60) p=0.645



Yang et al., WCLC 2025

Novel Approach: Targeting MTAP loss with PRMT5 inh

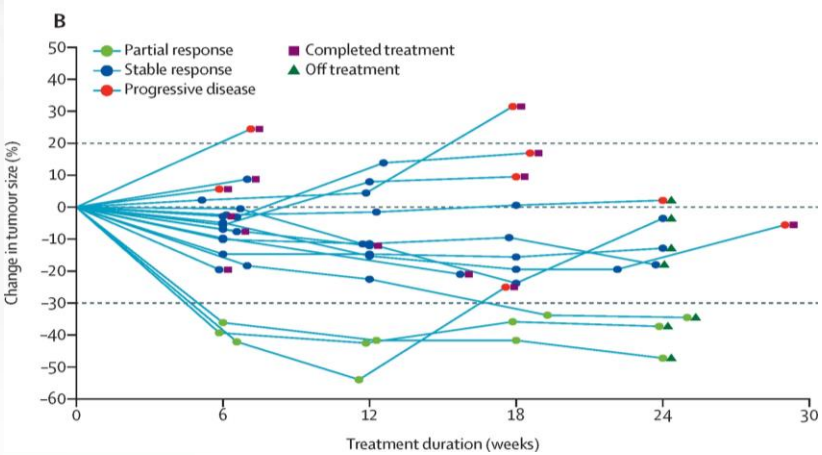


MTAP loss: 70% to 90% of mesothelioma

MTAP Loss: MTA accumulation, dependence on PRMT5

PRMT5 inhibitors in NSCLC

- BMS-986504 presented at WCLC 2025
- ORR 29%, DCR 80%
- Included patients with EGFR or ALK alterations

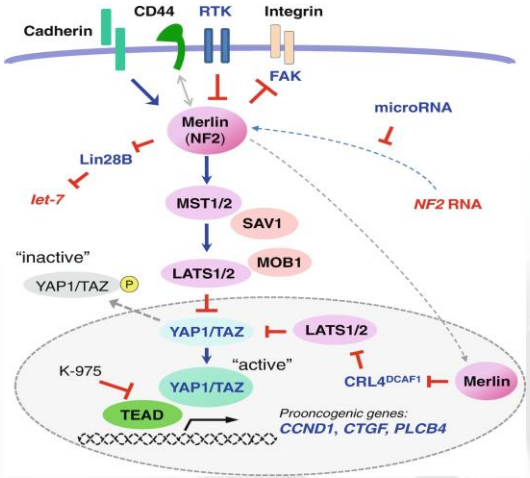


Fennell et al., Lancet Onc, 2022
Janne et al., WCLC 2025

Ongoing Studies On MTAP Loss

ClinicalTrials.gov ID	Study Drug/Intervention	Phase	Title/Focus	Status (General)
NCT05245500	MRTX1719 (PRMT5-MTA Inhibitor)	1/1b	Study of the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and anti-tumor activity of MRTX1719 in patients with advanced solid tumors with homozygous deletion of the MTAP gene, including mesothelioma.	Active, Recruiting
NCT05275478	TNG908 (Selective PRMT5 Inhibitor)	1/2	Safety, Tolerability, and Preliminary Anti-tumor Activity of TNG908 in Patients With MTAP-deleted Advanced or Metastatic Solid Tumors, which includes mesothelioma.	Active, Not Recruiting (Phase 1/2)
NCT05094336	AMG 193 (MTA-Cooperative PRMT5 Inhibitor)	1	Dose-Exploration/Dose-Expansion Study of AMG 193 in Participants With MTAP-Deleted Solid Tumors. Preliminary data has shown promising activity.	Active, Not Recruiting (Expansion Phase)

Novel Approach: Targeting NF2 with TEAD inh



NF2/Merlin loss: Frequent in Mesothelioma

Hypo pathway:

- Inactive: YAP1/TAZ underphosphoylated interacts with TEAD → Mesothelioma

VT3989-001, Oral 100mg daily two w on and two w off

Phase 1/2, solid tumors

Response Rate: 25%

Disease Control Rate: 92%

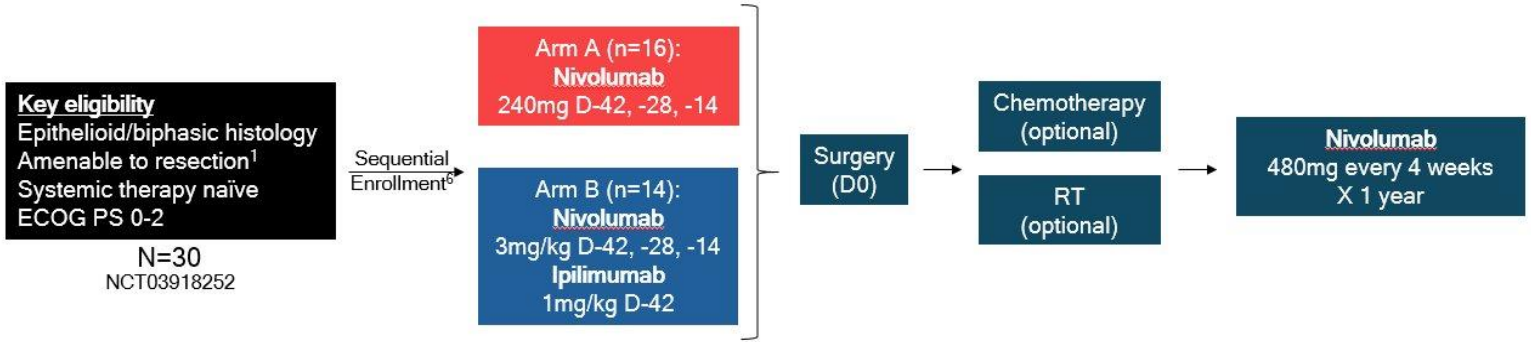
Median Progression-Free Survival: 39 weeks

Responses were durable

NCT06566079	ISM6331; TEADi	Mesothelioma, solid tumors
NCT04857372	IAG933; YAP/TEAD inhibitors	156 pts, solid tumors
NCT04665206	VT3989; TEAD inhibitor	80 pts, solid tumors, NF2 loss

Slides content from Dr. Marmarelis

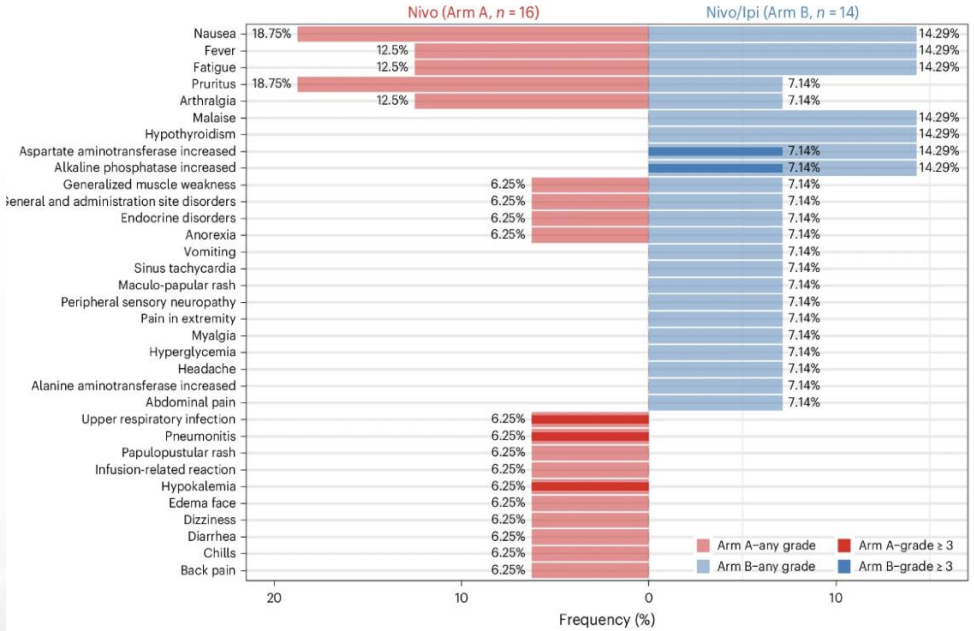
Phase 2 Trial of Neoadjuvant Nivolumab and Nivolumab/Ipilimumab in Resectable Pleural Mesothelioma along with Tumor-Informed Liquid Biopsy Residual Disease Assessments



Primary Endpoints: Feasibility, Safety
Secondary Endpoints: ORR[2], Safety of adjuvant nivo[3]
Exploratory Endpoints: PFS[4], OS[5], Longitudinal ctDNA assessment, genomic/immunologic analyses, gut microbiome

Joshua Ross et al., Nat Communication, 2025, WCLC 2025

Overall No new Safety Signal in NAD Nivo or Nivo/Ipi in Meso



Joshua Ross et al., Nat Communication, 2025, WCLC 2025

G3 AEs:

- Nivo: Pneumonitis, URI
- Ipi/Nivo: LFTs

Most common AEs:

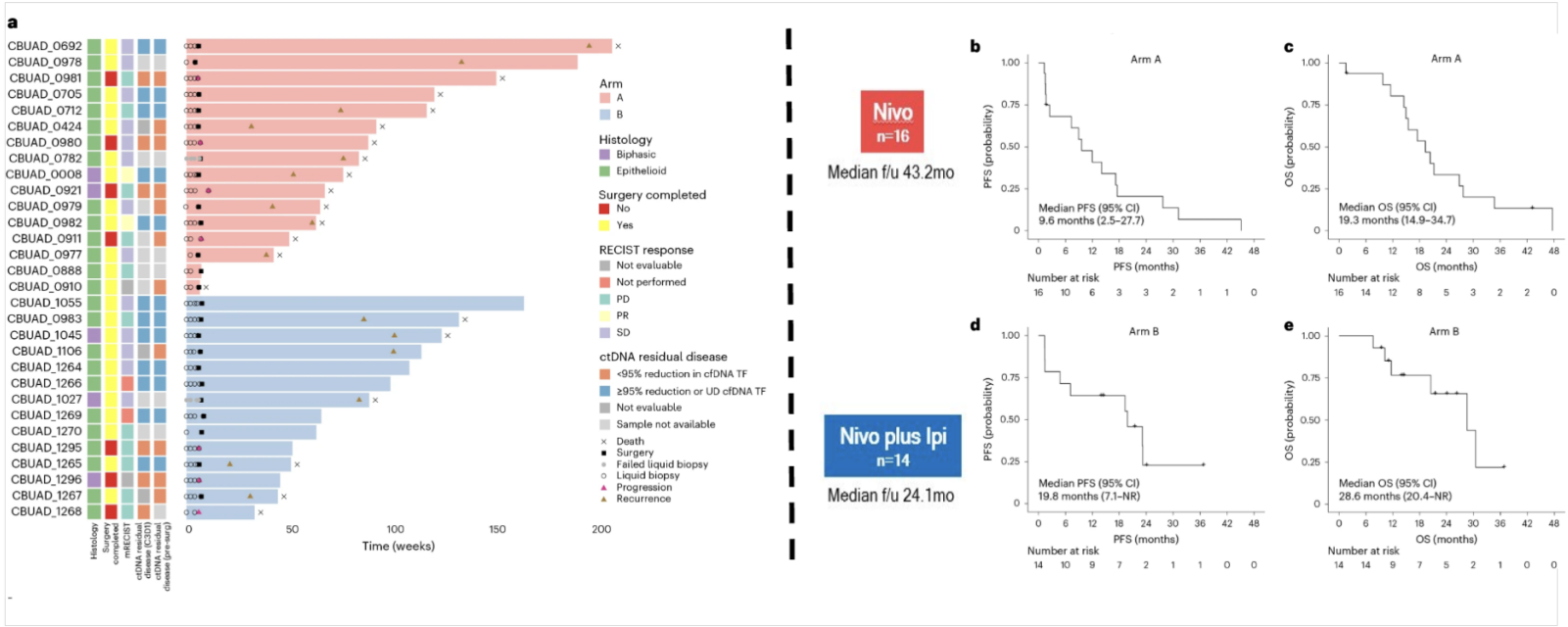
- Nausea
- Fever
- Fatigue
- Pruritus

Surgical Feasibility

	Arm A Nivo (n=16)	Arm B Nivo/Ipi (n=14)
Proceeded to Surgery, n(%)	13 (81.3%)	12 (85.7%)
Completed Surgery, n(%)	12 (75%)	11 (78.6%)
- P/D	- 10 (83.3%)	- 9 (81.8%)
- EPP	- 2 (16.7%)	- 2 (18.2%)
Posterior mean [90% credible interval]	**0.78 [0.60, 0.92]**	**0.81 [0.64, 0.94]**

P/D: pleurectomy/decortication
EPP: extrapleural pneumonectomy

PFS &OS: Nivo (Arm A)< Ipi/Nivo (Arm B) in Nadj Meso



Joshua Ross et al., Nat Communication, 2025, WCLC 2025

Summary of Neoadjuvant Ipi/Nivo in Resectable Pleural Mesothelioma

Neoadjuvant Data

1. At a median follow-up of 24.1 months in the **Ipi/Nivo arm**:
- **mPFS was 19.8 m** (95% CI: 7.1– not reached)
- **mOS was 28.6 m** (95% CI: 14.9–34.7)

2. At a median follow-up of 43.2 months in the **Nivo arm**:
- **mPFS 9.6 m** (95% CI: 2.5–27.7)
- **mOS was 19.3 m** (95% CI: 14.9–34.7)

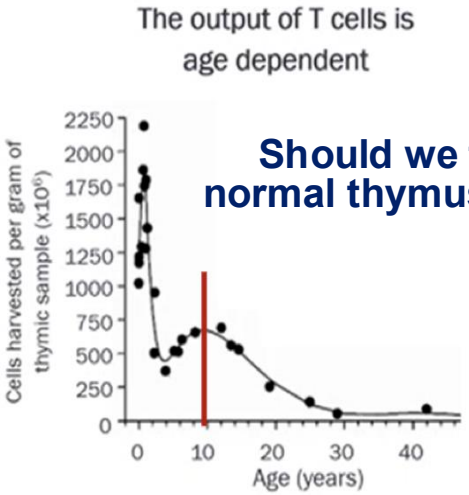
Adjuvant Data

1. Adj chemotherapy improved PFS and OS (HR = 0.14, *P* = 0.027)
2. Adj radiotherapy Improved mPFS (HR = 0.17,*P* = 0.024), but not in OS *P* = 0.071).

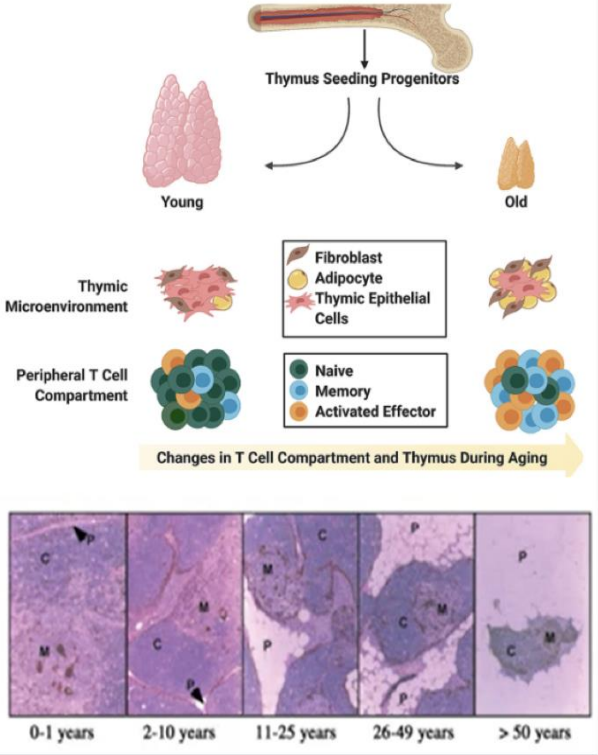
Joshua Ross et al., Nat Communication, 2025, WCLC 2025

Thymus size and function decrease with aging

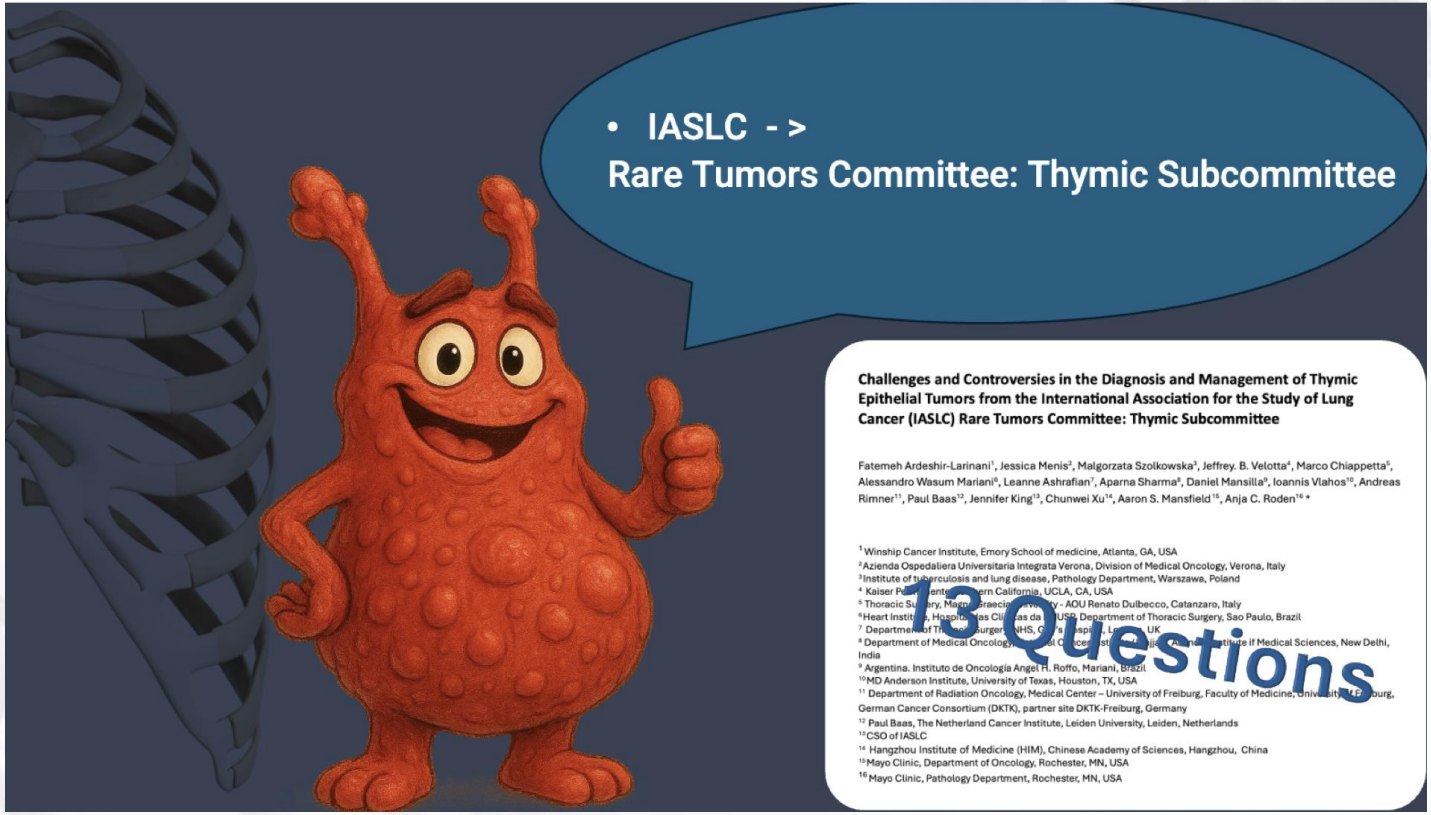
- Thymus cell numbers decrease significantly after puberty.
- In adults>50yr, less than 5%-10% is functional.



Should we try to save the normal thymus tissue in TETs?



Thymectomy vs Thymomectomy?



Mariani, WCLC, 2025
Ardeshir et al., unpublished manuscript- Under review

FULL LENGTH ARTICLE · Volume 101, P22-27, November 2016 · Download Full Issue

Limited thymectomy as a potential alternative treatment option for early-stage thymoma: A multi-institutional propensity-matched study

Kyoung Shik Narm, MD [a] · Chang Young Lee [a] · Young Woo Do, MD [a] · ... · Seung-Il Park, MD, PhD [d] · Kyung Young Chung, MD [a] · the Korea Association for Research on the Thymus ... Show more

ORIGINAL ARTICLE · Volume 8, Issue 7, P952-958, July 2013 · Open Archive · Download Full Issue

Is Thymectomy Necessary in Nonmyasthenic Patients with Early Thymoma?

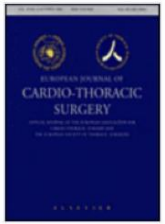
Yen-Chiang Tseng, MD * · Chih-Cheng Hsieh, MD * · Hsin-Yi Huang, MS † · ... · Biing-Shiun Huang, MD, PhD * · Min-Hsiung Huang, MD * · Han-Shui Hsu, MD, PhD *†‡ ... Show more

JOURNAL ARTICLE

Unilateral thoracoscopic subtotal thymectomy for the treatment of stage I and II thymoma FREE

Makoto Odaka ✉, Tadashi Akiba, Mitsuo Yabe, Miyako Hiramatsu, Hideki Matsudaira, Jun Hirano, Toshiaki Morikawa

European Journal of Cardio-Thoracic Surgery, Volume 37, Issue 4, April 2010, Pages 824–826, https://doi.org/10.1016/j.ejcts.2009.10.003

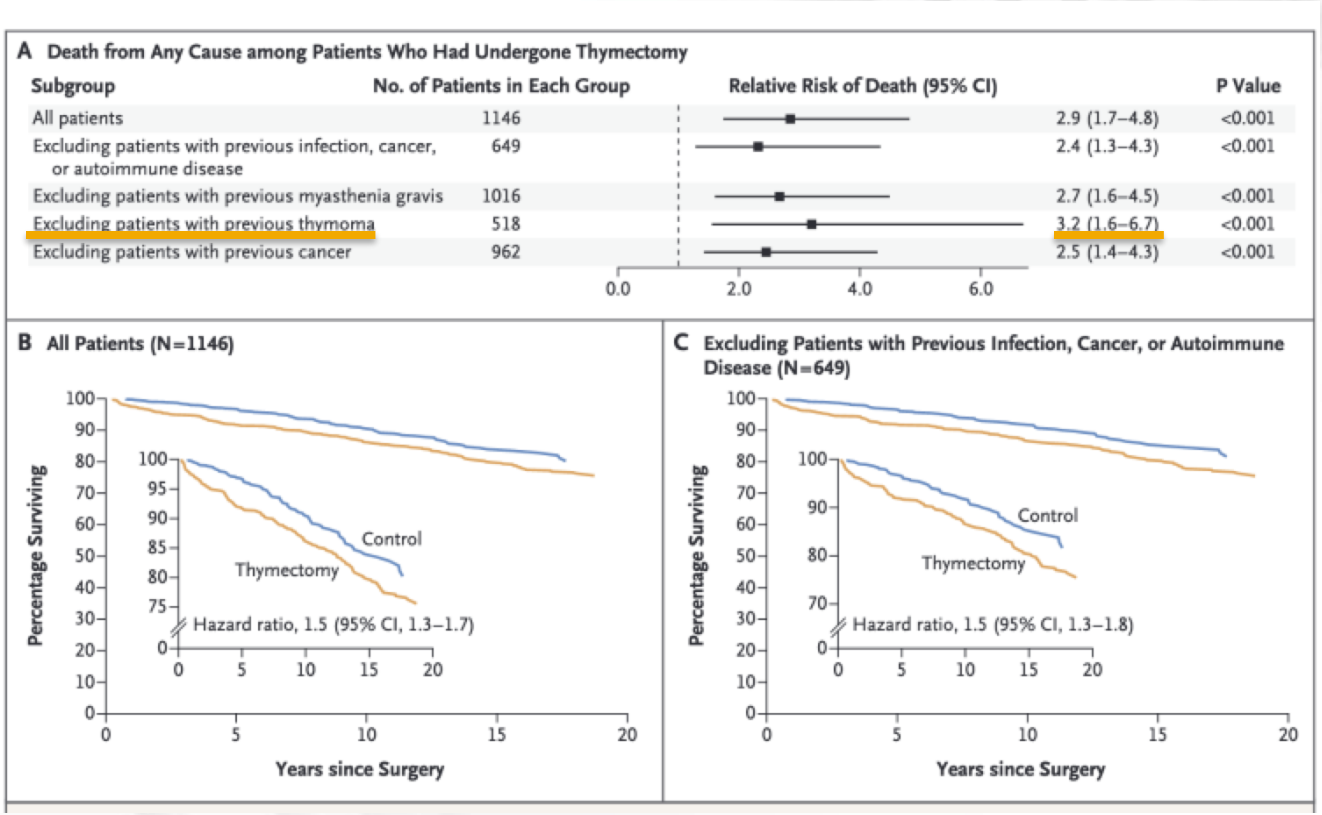


Thymomectomy is associated with lower complication rates:

- Less blood loss
- Shorter operative time
- Reduced hospital stay

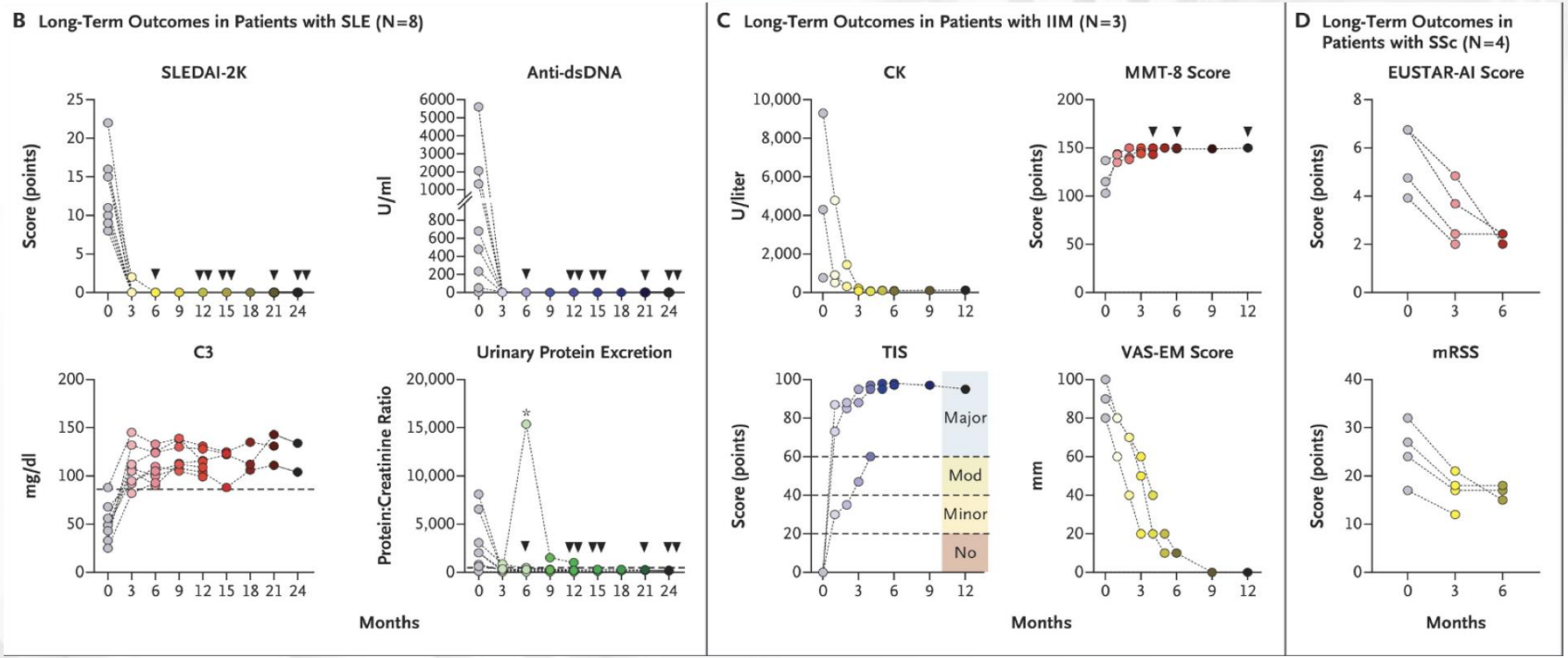
Mariani, WCLC, 2025

Health Consequence of Thymus Removal in Adults



Kooshesh, NEJM 2023

T-reg CAR-T cells treat auto-immunity



Müller et al., NEJM, 2024

MMT-8, Muscular test, IIM, idiopathic inflammatory myositis, EUSTAR-AI, European Scleroderma Trials and Research Group Activity Index

2025 ASCO ANNUAL MEETING

ETOP·IBCSG PARTNERS FOUNDATION

EORTC

Efficacy and safety of nivolumab plus ipilimumab for patients with pre-treated type B3 thymoma and thymic carcinoma: Results from the EORTC-ETOP NIVOTHYM phase II trial

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Study design

NIVOTHYM is an international multicenter phase II, 2-cohort, single-arm trial evaluating the use of nivolumab +/- ipilimumab in patients with advanced/relapsed thymic tumors.

Advanced/relapsed thymic tumor

Type B3 thymoma or thymic carcinoma

No more than one line of platinum-based chemotherapy

No autoimmune disorder

Cohort 1:

Nivolumab
(240 mg IV Q2 weeks)

n=55

Previously published

Cohort 2:
Nivolumab
(240 mg IV Q2 weeks)
+ Ipilimumab
(1 mg/kg IV Q6 weeks)
n=56

Imaging at week 8 and then every 6 weeks

Primary endpoint : PFS rate at 6 months per BICR (RECIST 1.1)

H0: PFSR-6 ≤ 40%
H1: PFSR-6 = 60%

Alpha = 0.1 (one-sided)
Power = 94%

Secondary endpoints: PFSR-6 per local investigator, PFS, Response, OS, Safety

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Treatment exposure

	Cohort 2 (n=56) n (%)
Treatment status	
Ongoing	6 (11)
Stopped	50 (89)
Disease progression	36 (72)
Treatment-related adverse events (TRAEs)	11 (22)
Completion	2 (4)
Patient decision	1 (2)
Nivolumab	
Median number of cycles (range)	6.5 (1.0-49.0)
Median treatment duration in weeks (range)	14.1 (2.1-108.9)
Ipilimumab	
Median number of cycles (range)	2.0 (1.0-17.0)
Median treatment duration in weeks(range)	16.1 (6.0-108.7)
Patients with at least one modification	44 (79)
Patients with at least one cycle on hold	28 (40)
Patients with at least one cycle delayed	18 (32)
Patients with at least one cycle anticipated	2 (4)

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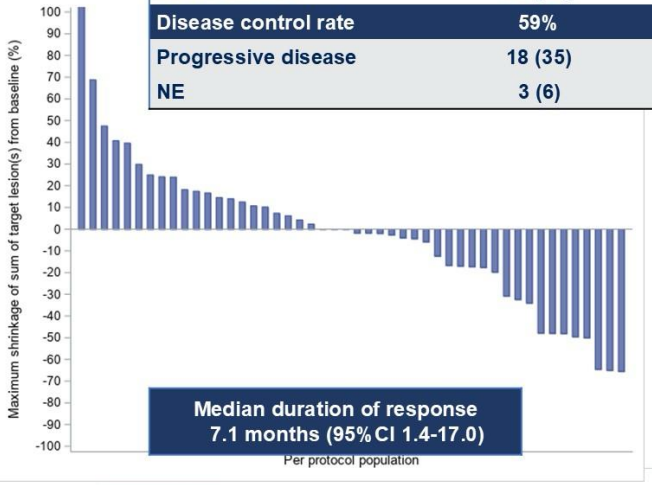
Secondary endpoints - per-protocol population

Objective response

	Nivolumab + Ipilimumab (n=51) n (%)
Partial response	8 (16)
Stable disease	22 (43)
Disease control rate	59%
Progressive disease	18 (35)
NE	3 (6)

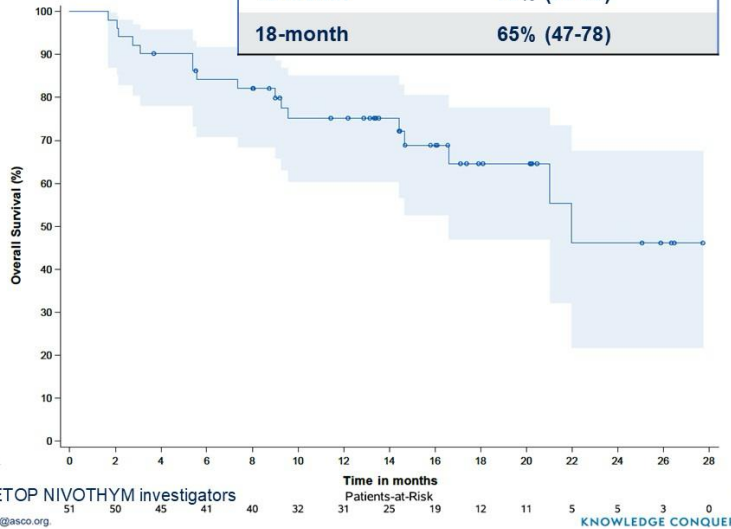


Median duration of response
7.1 months (95% CI 1.4-17.0)

Overall survival

Median OS: 22.0 (16.6-NE) months

Survival rates	% (95% CI)
6-month	84% (71-92)
12-month	75% (60-85)
18-month	65% (47-78)



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Safety

	Cohort 2 (n=56) n (%)
Maximal grade of adverse events	
1-2	29 (52)
3-4	27 (48)
Grade ≥3 Treatment-Related Adverse Events	16 (29)
Myocarditis	2 (4)
Colitis	4 (8)
Infusion-related reaction/allergy	2 (4)
Skin rash	2 (4)
Other: heart failure, immune-related hepatitis, arthritis, myositis, hypophysitis, Gougerot-Sjögren syndrome, pharyngitis, fatigue, fever, infusion-related reaction	1 patient each
Death related to Treatment-Related Adverse Events	0 (0)

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Conclusions

- Nivolumab plus ipilimumab has modest activity in pretreated advanced/metastatic type B3 thymomas and thymic carcinomas, with DCR at 59% but median PFS of only 3.1 months; primary endpoint of NIVOTHYM was not met.
- As compared to the NIVOTHYM nivolumab monotherapy cohort, reporting DCR of 67% and median PFS of 6.2 months, **the addition of ipilimumab is not improving outcomes, while safety was similar.**
- Recently reported trials evaluated various combinations of immunotherapy, antiangiogenic agents, and chemotherapy in frontline or late line for advanced/metastatic thymic tumors[1,2].
- The optimal sequencing strategy and combination regime is unclear.
- **NIVOTHYM demonstrates the major role of pan-European academic groups to conduct multicenter collaborative research and trials.**

[1] Mimori T, et al. ESMO ASIA 2024 ;[2] Proto C, et al. Ann Oncol 2024;35:817

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Ongoing studies in TETs

Trial	Setting	Regimen	Until Progression?	Key Outcomes
CAVEATT	Post-platinum	Avelumab + Axitinib	Yes	ORR 34%, DCR 90%
RELEVENT	1st-line (unresectable)	Ramucirumab + Carboplatin/Paclitaxel	Induction + maintenance	Ongoing trial with PFS endpoint
S1701	1st-line (unresectable)	Ramucirumab + Carboplatin/Paclitaxel	Yes	Ongoing trial with PFS
PECATI	Post-platinum	Pembrolizumab + Lenvatinib	Yes, up to 35 cycles	5-mo PFS 88%, median PFS 14.9mo
NIVOTHYM	Post-platinum	Nivolumab ± Ipilimumab	Yes	PFS, ORR, DCR under evaluation

Summary

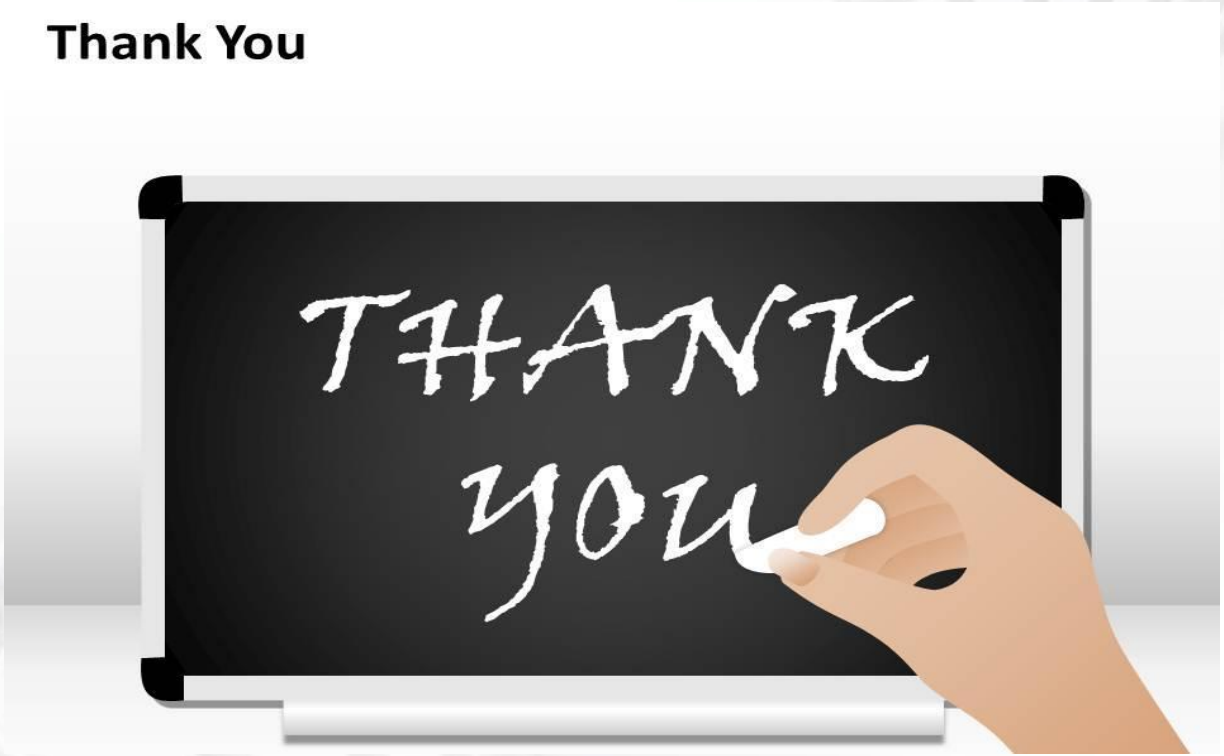
- **Immunotherapy and VEGF inh are potential next approval for TETs, first line setting**
- **Dual IO** is preferred for **non-surgical MPM in both histology**, with a **mOS of ~18 months**
- In patients with **high disease burden**, **chemo + IO (IND227)** may yield better responses: **ORR ~60%** vs **~40%** with chemo ± IO alone.
- **Non-epithelioid subtypes** respond **poorly to chemotherapy**, but **immunotherapy** has significantly improved outcomes and QOL.
- **Emerging therapies** under investigation include:

  BiTEs (Bispecific T-cell Engagers)

  CAR-T cell therapy

  ADCs (Antibody–Drug Conjugates)

Thank You



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