



UPDATES IN MESOTHELIOMA

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Medical Director, UPenn Mesothelioma Program**

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Endorsed by



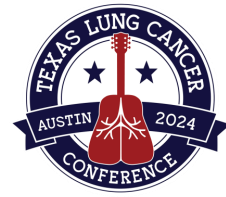
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2023: Mesothelioma as seen through Taylor Swift



LA Times, Aug 2023, Quotes <https://tinyurl.com/yp422s3w>

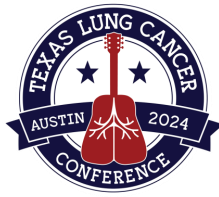
2024...



Leonard Bernstein (August 25, 1918 – October 14, 1990)
Died of a heart attack secondary to mesothelioma



Bradley Cooper as Leonard Bernstein
Maestro



Independent UK, <https://tinyurl.com/3hya3j36>

Pleural Mesothelioma

- Role of surgery
- Updates on immunotherapy trials
- Emerging targets

Bernstein or Bradley Cooper?



Bernstein



Bradley Cooper

Photo Credit: Netflix X post on December 27, 2023

The World Beyond MARS2

'Once one dismisses
The rest of all possible worlds
One finds that this is
The best of all possible worlds!
-Candide by Leonard Bernstein and Richard Wilbur

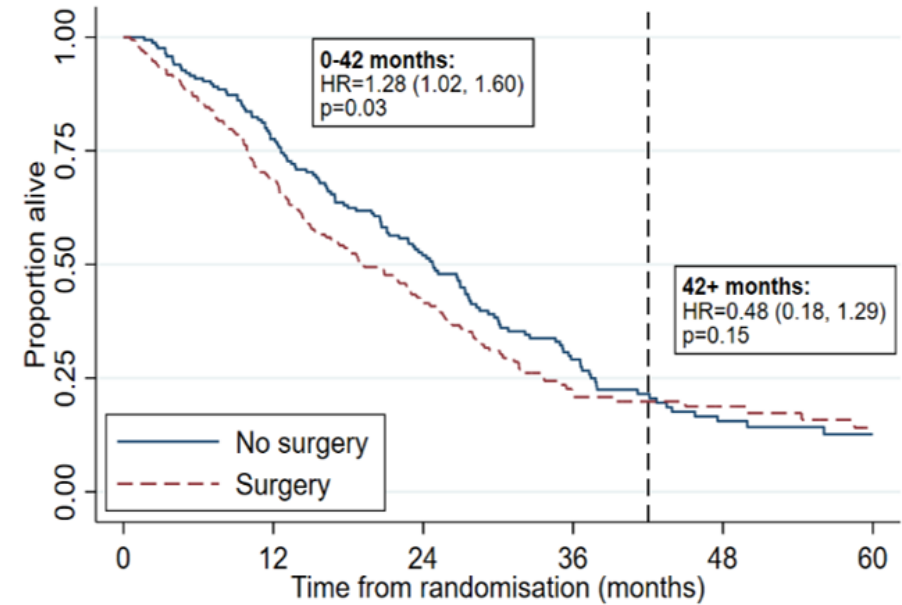
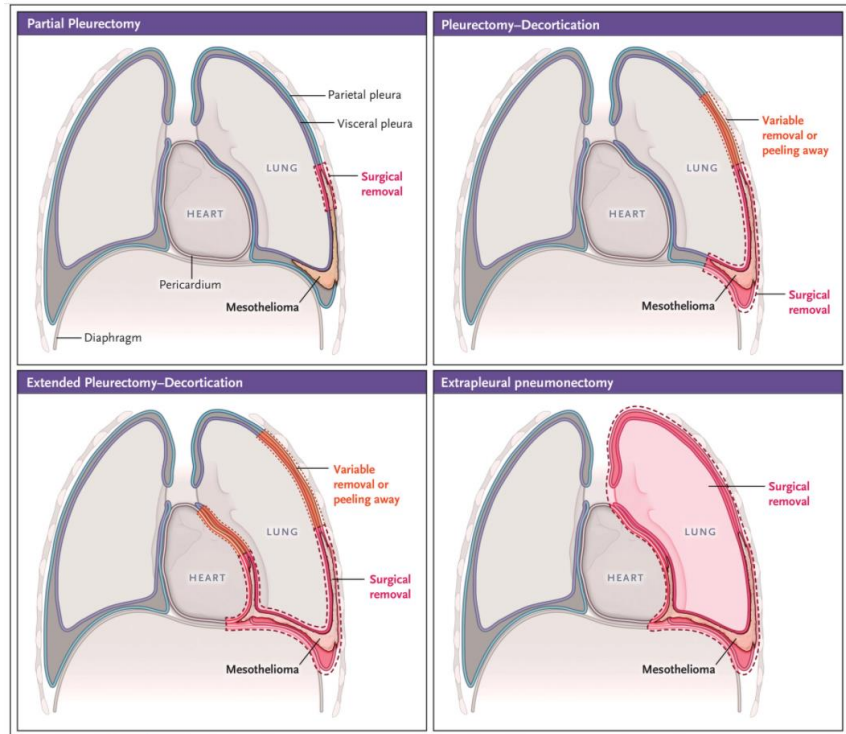


Before MARS2

After MARS2

Is this patient's disease surgically resectable?

Decreased survival in patients who underwent surgery



Number at risk		0	12	24	36	48	60
No surgery	166	128	82	37	15	6	
Surgery	169	115	64	24	15	7	

Janes, NEJM, 2021; Lim, WCLC 2023

What changed after MARS2?



Well...maybe we just need to be better about patient selection

What about immunotherapy?

Surgery for mesothelioma should not be performed



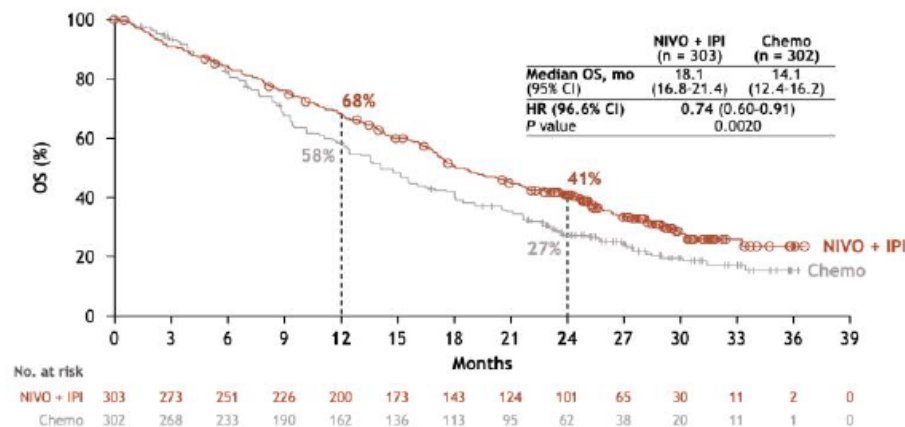
Dr. Ibiayi Dagogo-Jack and medical oncologists everywhere

<https://tinyurl.com/3v4nnavm>

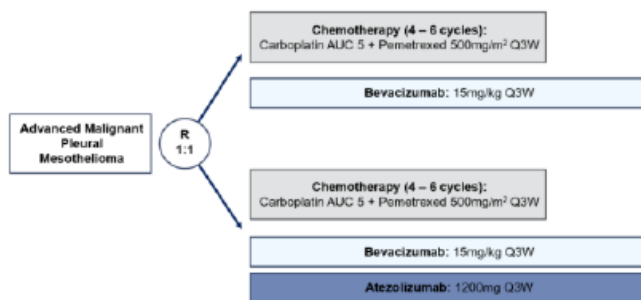
Immunotherapy as first-line therapy



CM 743: 1L
Nivolumab + Ipilimumab
vs Chemo

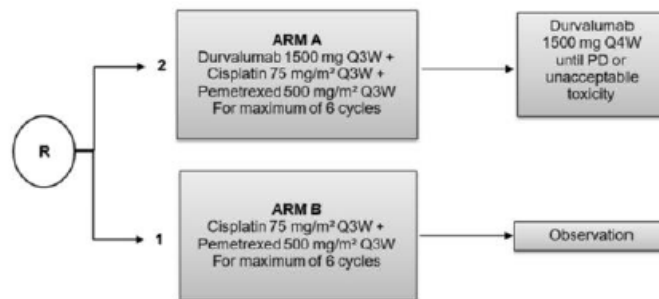


BEAT-meso: 1L
Carboplatin/Pemetrexed/Bevacizumab
+/- Atezolizumab



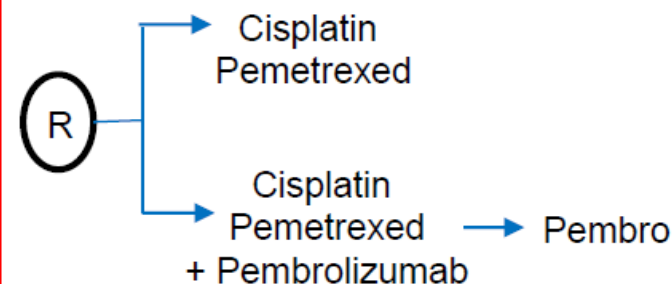
Accrual Complete. Awaiting Data.

DREAM3R: 1L
Carboplatin/Pemetrexed
+/- Durvalumab



Closed Early

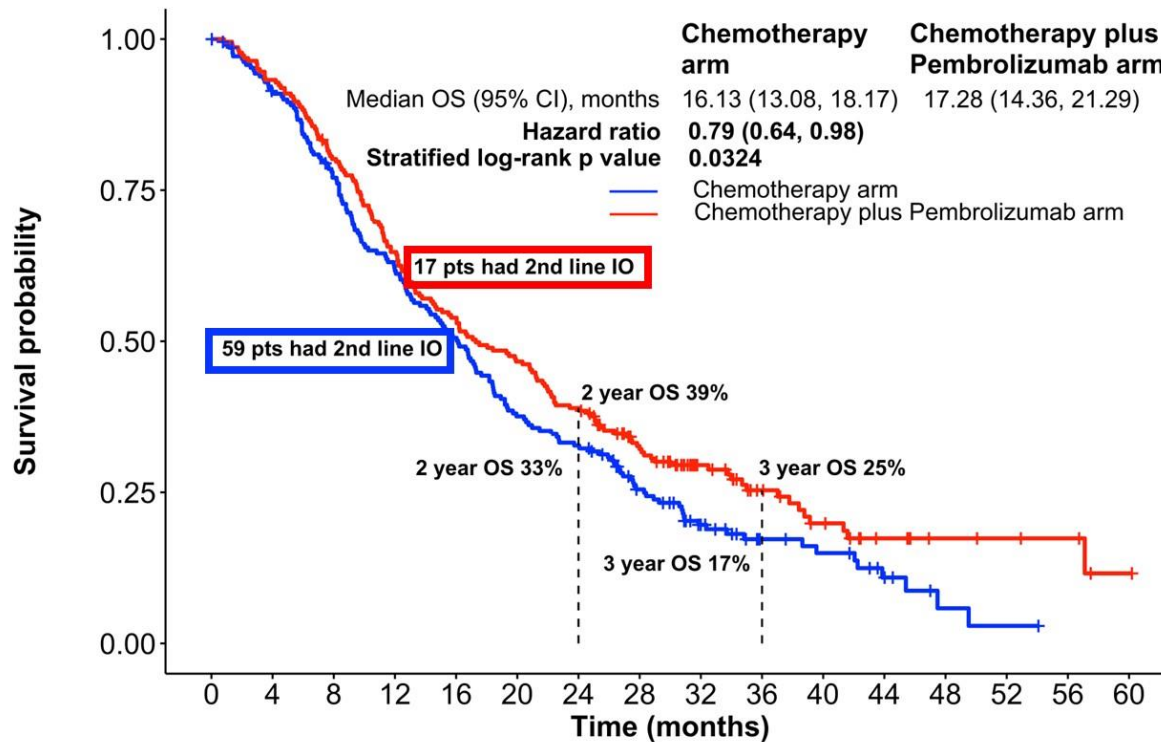
IND.227: 1L
Cisplatin/Pemetrexed
+/- Pembrolizumab



Presented ASCO 2023

IND 227: Chemotherapy +/- Pembrolizumab

Overall survival



Improved median OS for Chemotherapy + Pembrolizumab arm

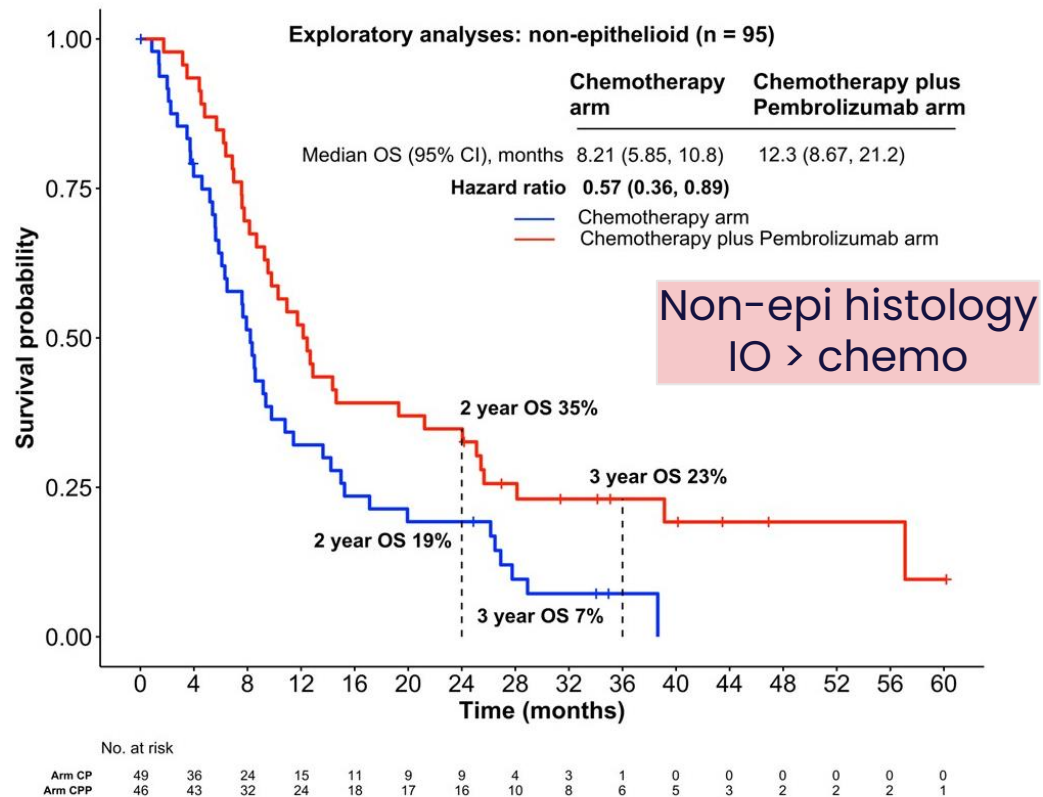
Patients enrolled Jan 2017-Sept 2020
Median follow up 16.16 months
All pts discontinued all study drugs

	No. at risk															
	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60
Arm CP	218	190	160	128	105	78	68	46	29	16	13	7	2	1	0	0
Arm CPP	222	207	177	143	119	103	86	62	39	25	17	10	6	5	4	1

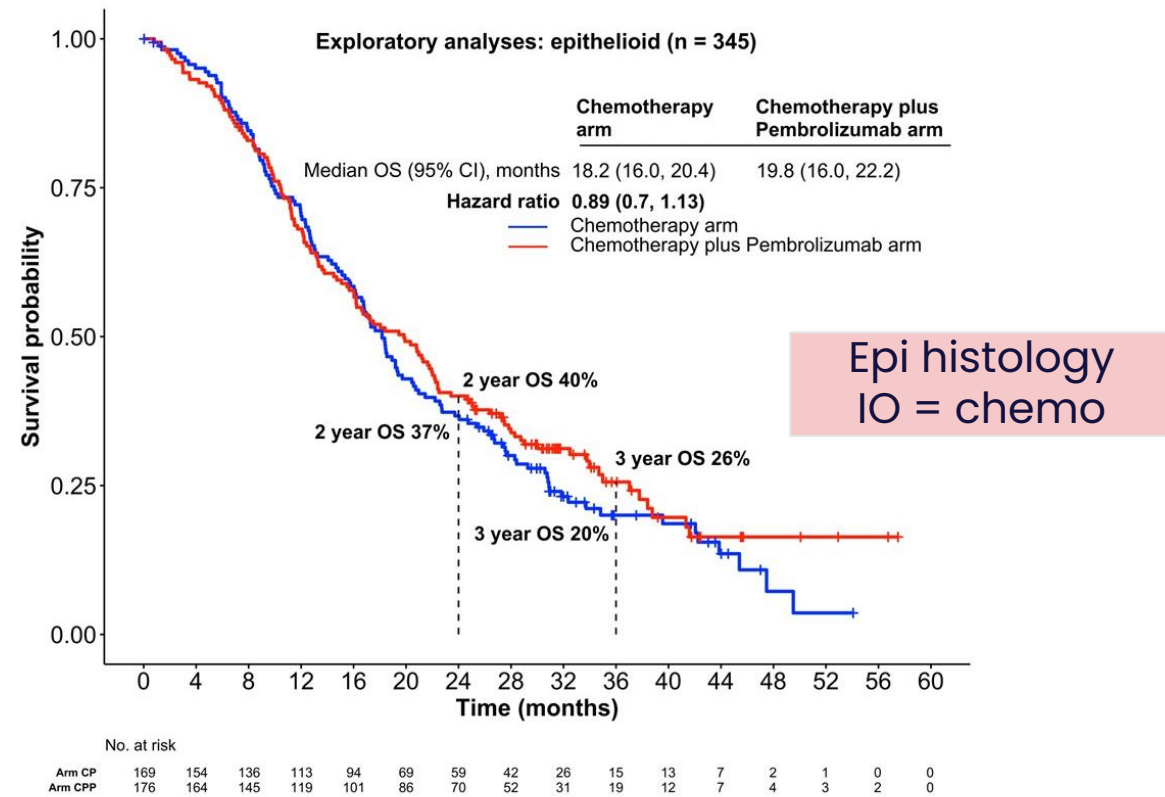
QS Chu, ASCO 2023; Chu et al, Lancet, 2023

OS Result Driven by Non-Epithelioid Population

Non-Epithelioid



Epithelioid



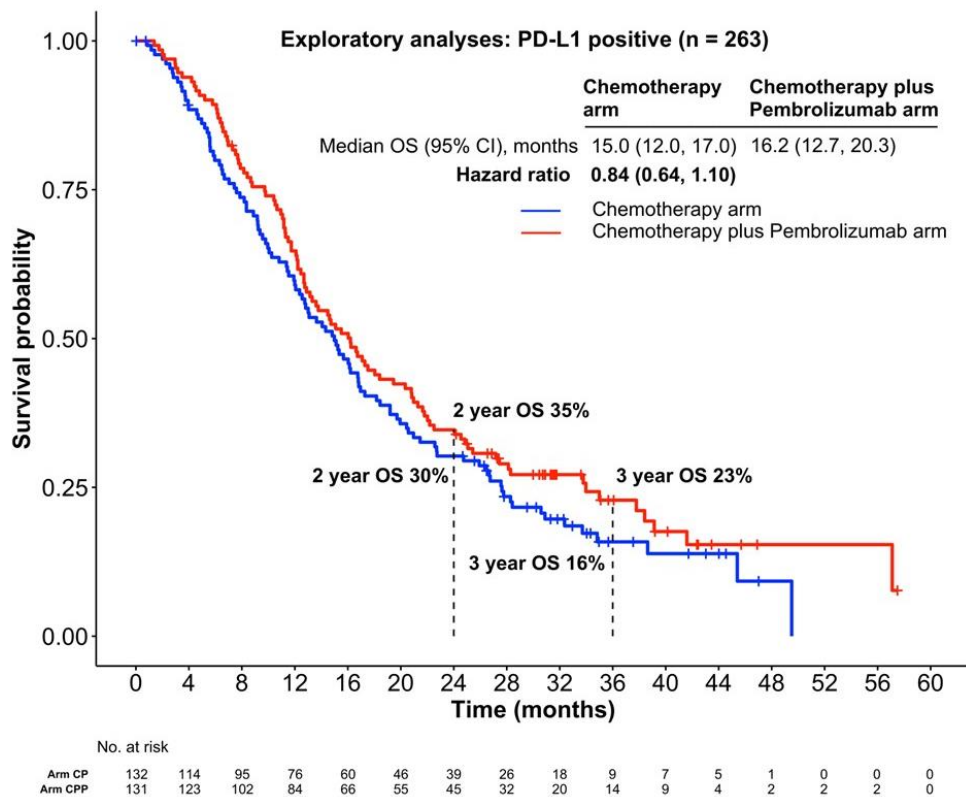
QS Chu, ASCO 2023; Chu et al, Lancet, 2023

PD-L1 Level Does Not Predict Benefit From IO

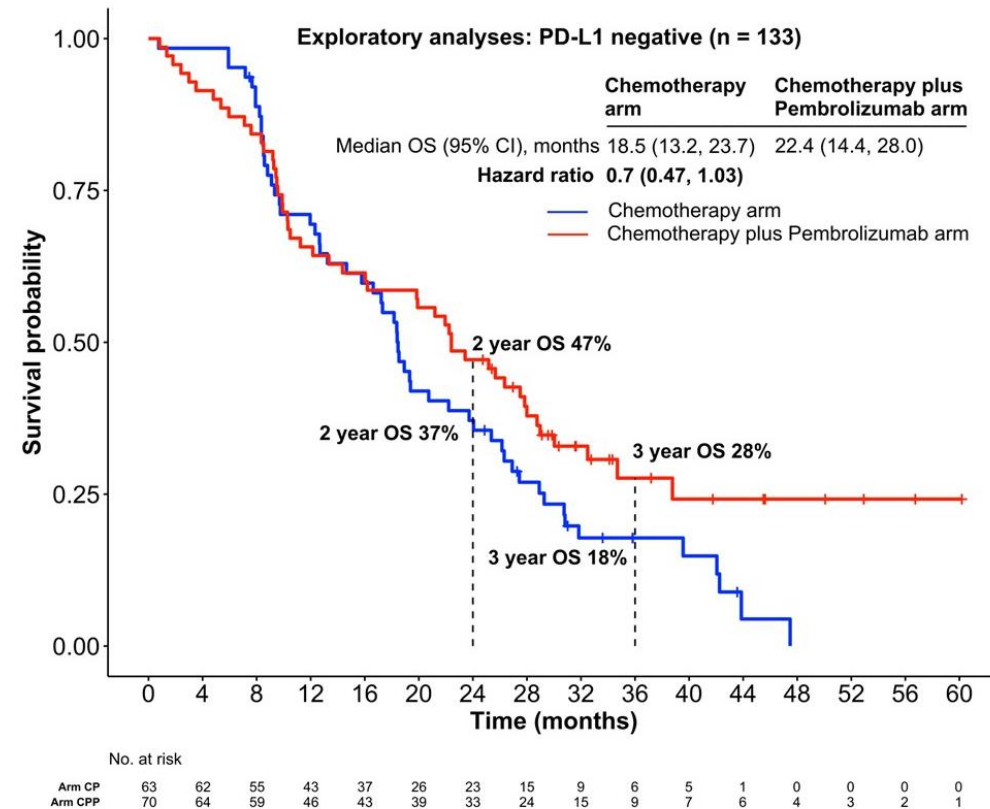


'When you're a Jet,
You're the top cat in town,
You're the gold-medal kid
With the heavyweight crown!
-West Side Story

PD-L1 Positive



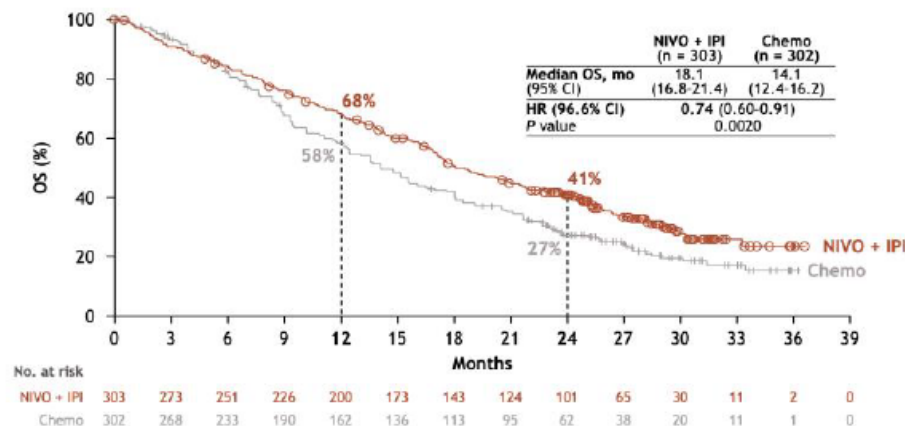
PD-L1 Negative



QS Chu, ASCO 2023; Chu et al, Lancet, 2023

Immunotherapy as first-line therapy

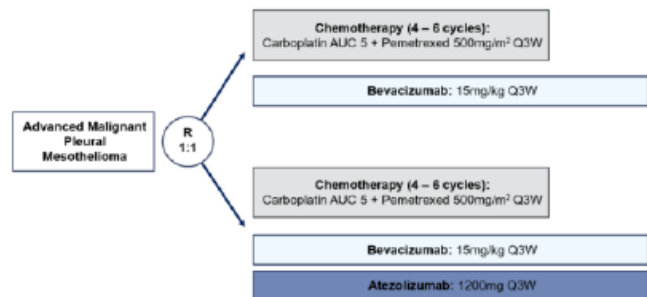
CM 743: 1L
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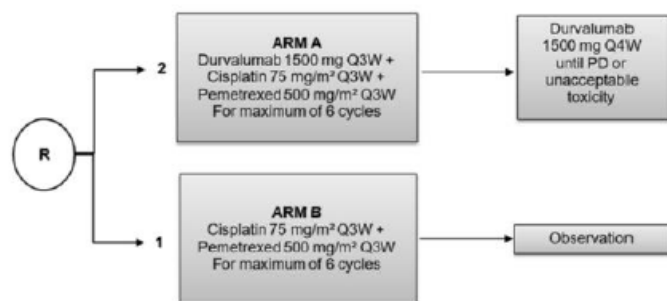
Ipi/Nivo : SOC in non-epi

Ipi/Nivo = Chemo in Epi

BEAT-meso: 1L
Carboplatin/Pemetrexed/Bevacizumab
+/- Atezolizumab

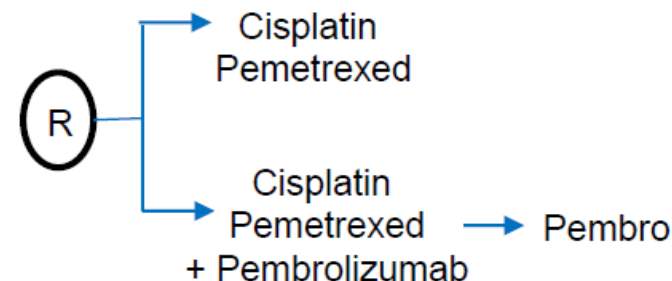


DREAM3R: 1L
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Closed Early. Awaiting Data.

IND.227: 1L
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Potentially a treatment option

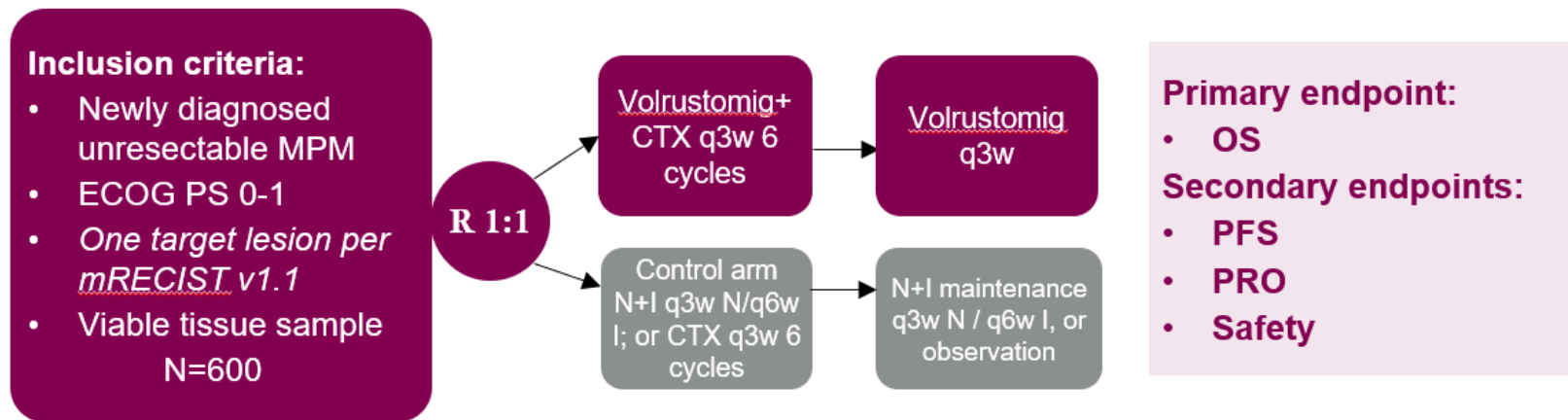
Is there synergy between IO and anti-VEGF?

Baas, Lancet Oncol, 2021

Novel Dual Immunotherapy + Chemotherapy?

eVOLVE Meso Study design

An open-label phase III, randomized trial of Volrustomig + Chemotherapy vs active control of physician's choice of Chemotherapy or N+I in patients with untreated unresectable MPM

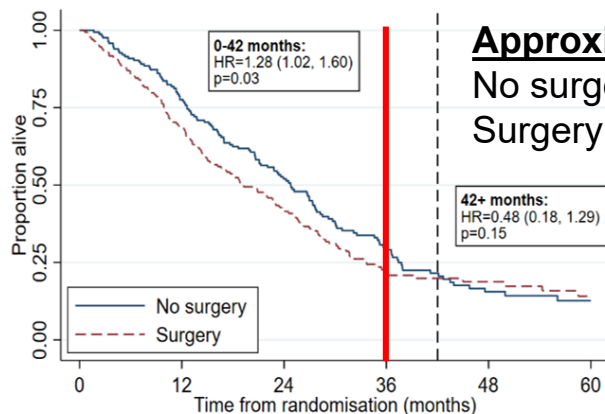


- Stratification factors:**
- Epithelioid or non-epithelioid
 - Sex: M vs F
 - Region

- Volrustomig: 750mg, q3w, up to 2 yrs
- CTX: cisplatin 75mg/m² or carboplatin AUC 5 in combination with Pemetrexed 500mg/m², q3w, up to 6 cycles
- N 360mg q3w + I 1mg/kg q6w, up to 2 yrs

How do we think about mesothelioma surgery in the era of immunotherapy?

MARS2



Approximate 3yr OS

No surgery: 30%

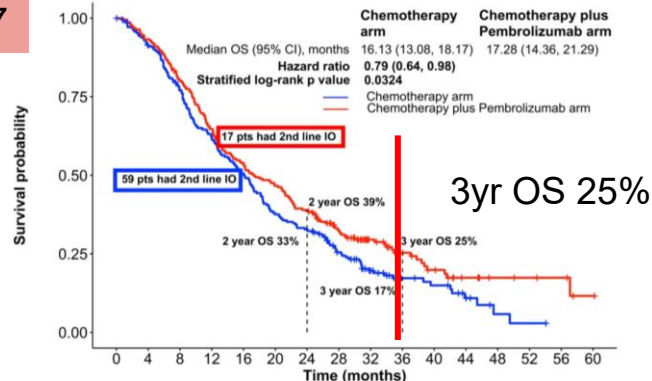
Surgery: 22%

Number at risk	0	12	24	36	48	60
No surgery	166	128	82	37	15	6
Surgery	169	115	64	24	15	7

- MARS2 trial enrolled surgical patients, which will have a lower disease burden and better prognosis than patients enrolled to 1L systemic therapy trials
- However, 3 yr OS rates are not that different...
- BUT...the majority of our LONG-term survivors have received surgery.



IND.227



Summary

Surgery can provide long-term survival for some

Immunotherapy can provide long-term survival for some

Medians don't capture the hope of that long-term survival (or the potential risks patients are willing to take)



Bernstein or Bradley Cooper?



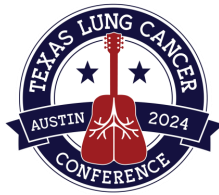


<https://tinyurl.com/6e6duc64>
<https://tinyurl.com/23tambds>

Bernstein

Bradley Cooper

New Approaches in Pleural Mesothelioma



Inhaled Asbestos Fibers

LUNG

HEART

20-to-50-year latency period

Mesothelioma tumor

Considerations and Targets for Future Therapy

Phenotypic Histologic Subtypes	Current and Future Systemic Approaches	Genomic or Epigenomic Landscape	
Epithelioid (50–60% of cases)	Chemotherapy Antibody-drug conjugates Immune checkpoint inhibition (PD-1 or PD-L1 inhibition) Ferroptosis inducers Cellular therapy (CAR-T cells targeting mesothelin) Angiogenesis inhibition	Mutation	Therapeutic Targets
Biphasic (30–40% of cases)		BAP1	EZH2; PARP
Sarcomatoid (10% of cases)		CDKN2A	p16
		NF2	FAK; YAP-TEAD; mTOR and PI3K
		ASS1	Arginine

TONY

Could be . . .
 Who knows? . . .
 There's something due any day—
 I will know right away,
 Soon as it shows.
 It may come cannonballing down
 through the sky,
 Gleam in its eye,
 Bright as a rose.
 Who knows?

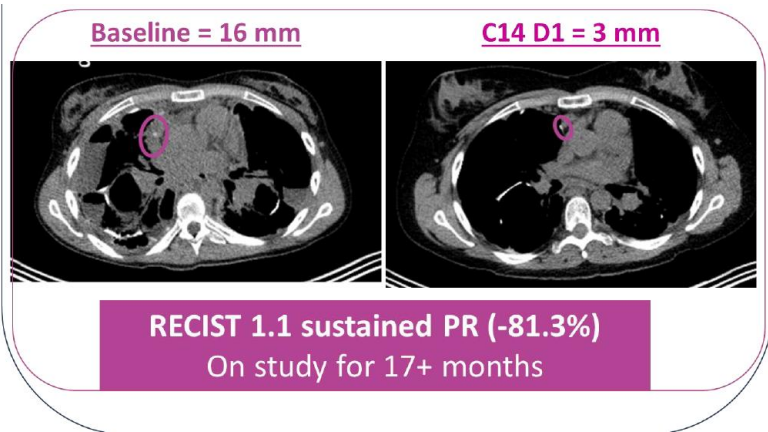
-*Something's Coming*, West Side Story

Sam Janes, Doraid Alrifai, Dean Fennel. NEJM, 2021

TEAD Inhibitors in Mesothelioma



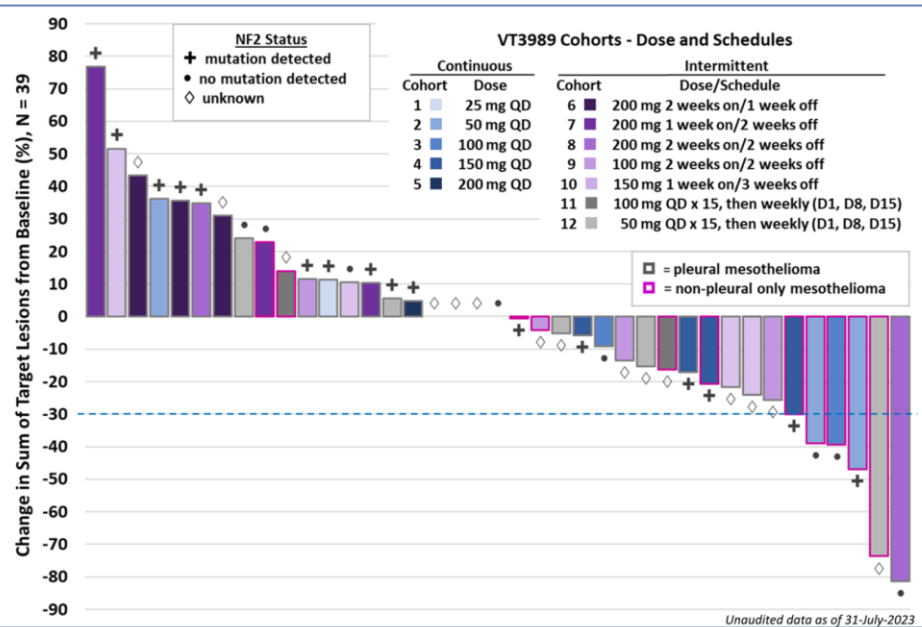
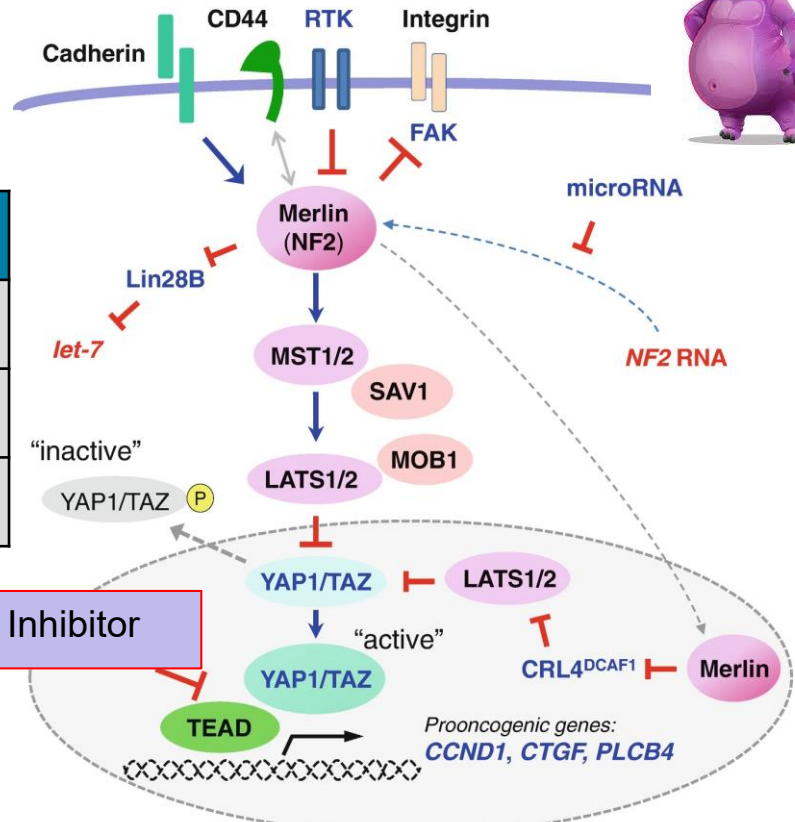
No NF2 mutation



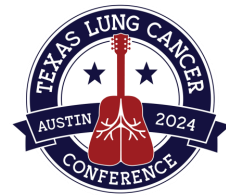
NCT05228015	IK0930; TEAD inhibitor	158 pts, solid tumors, NF2 loss
NCT04857372	IAG933; YAP/TEAD inhibitors	156 pts, solid tumors
NCT04665206	VT3989; TEAD inhibitor	80 pts, solid tumors, NF2 loss

Duration of Response

Group	>16 weeks	>24 weeks
All patients	48% (30/63)	33% (20/63)
Mesothelioma	46% (18/39)	28% (11/39)
Solid Tumors	50% (12/24)	38% (9/24)



Kwiatkowski WCLC 2023; Sekido, RDSDTDM, 2021; Sato, Int J Mol Sci, 2018; Yap AACR 2023



Pleural Mesothelioma Summary

- **Surgery for mesothelioma should only be considered at high volume centers and for select patients.**
- **Immunotherapy should be included in systemic therapy (1L or 2L) for patients with pleural mesothelioma.**
- **Clinical trials are now focusing on molecular subsets of mesothelioma. Molecular testing should be done to evaluate potential clinical trial approaches for patients.**



'To achieve great things,
two things are needed: a
plan and not quite
enough time.'

-Leonard Bernstein

Rolling Stone, <https://tinyurl.com/9bmsth5r>