University of California
San Francisco

Mesothelioma and Thymoma

Best of IASLC World Conference on Lung Cancer 2022

Matthew Gubens, MD, MS
Associate Professor
Medical Director, Thoracic Medical Oncology

November 12, 2022

Disclosures

- Consulting
  - AstraZeneca, BMS, Cardinal Health, Genentech/Roche, Genzyme, Guardant, iTeos, Sanofi, Surface
- Research Funding (to institution)
  - Amgen, Celgene, JNJ, Merck, Novartis, OncoMed, Trizell

- I will discussing non-FDA approved treatment/ indications during my presentation today (research findings)

Phase III Study of Pemetrexed in Combination With Cisplatin Versus Cisplatin Alone in Patients With Malignant Pleural Mesothelioma

By Nicholas J. Vogelzang, James J. Rusthoven, James Symanowski, Claude Denham, E. Ka[illegible] Ulrich Gatzemeier, Michael Boyer, Salih Emri, Christian Manegold, Clet Niyiki[illegible]

Purpose: **Patients with malignant pleural mesothelioma [illegible] a rapidly progressing malignancy with a median su[illegible] time of 6 to 9 months, have previously respond[illegible] chemotherapy. We conducted a phase III [illegible] whether treatment with pemetrexed [illegible] survival time superior to that [illegible]ne.**

Patients and Metho[illegible] **patients who were not eli[illegible] were randomly assigned to receiv[illegible] mg/m^2 and cisplatin 75 mg/m^2 on day [illegible] 75 mg/m^2 on day 1. Both regimens were give[illegible] avenously every 21 days.**

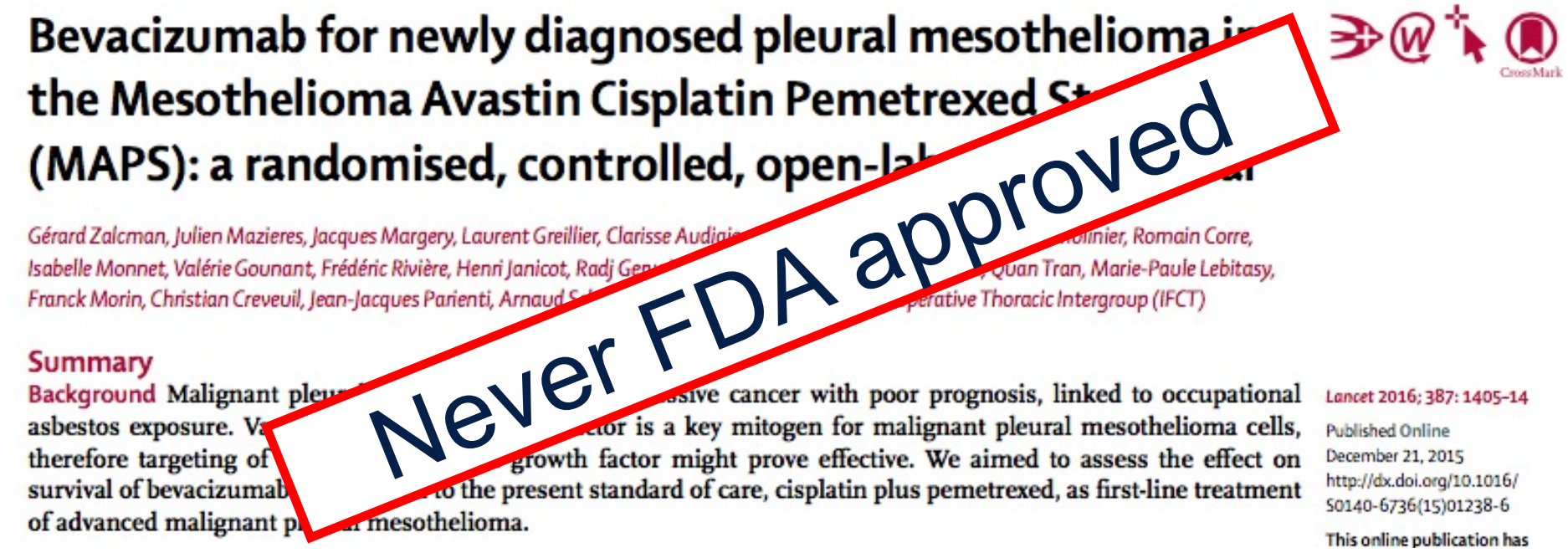
Results: **A total of 456 patients were assigned: 226 received pemetrexed and cisplatin, 222 received cisplatin alone, and eight never received therapy. Median survival time in the pemetrexed/cisplatin arm was 12.1 months versus 9.3 months in the control arm (P = .020, two-sided log-rank test). The hazard ratio for death of patients in the pemetrexed/[illegible]e in the control arm was 0.77. Me[illegible]ession was significantly longer in the pem[illegible]platin arm: 5.7 months versus 3.9 months (P = [illegible] Response rates were 41.3% in the pemetrexed/cispla[illegible]n arm versus 16.7% in the control arm (P < .0001). After 117 patients had enrolled, folic acid and vitamin B_{12} were added to reduce toxicity, resulting in a significant reduction in toxicities in the pemetrexed/cisplatin arm.**

Conclusion: **Treatment with pemetrexed plus cisplatin and vitamin supplementation resulted in superior survival time, time to progression, and response rates compared with treatment with cisplatin alone in patients with malignant pleural mesothelioma. Addition of folic acid and vitamin B_{12} significantly reduced toxicity without adversely affecting survival time.**

J Clin Oncol 21:2636-2644.

Then 2004-2016…

2016: MAPS trial



Bevacizumab for newly diagnosed pleural mesothelioma i
the Mesothelioma Avastin Cisplatin Pemetrexed St
(MAPS): a randomised, controlled, open-lab

Gérard Zalcman, Julien Mazieres, Jacques Margery, Laurent Greillier, Clarisse Audigie
Isabelle Monnet, Valérie Gounant, Frédéric Rivière, Henri Janicot, Radj Ger
Franck Morin, Christian Creveuil, Jean-Jacques Parienti, Arnaud S

olinier, Romain Corre,
Quan Tran, Marie-Paule Lebitasy,
perative Thoracic Intergroup (IFCT)

Never FDA approved

Summary

Background Malignant pleu ssive cancer with poor prognosis, linked to occupational asbestos exposure. Va ctor is a key mitogen for malignant pleural mesothelioma cells, therefore targeting of growth factor might prove effective. We aimed to assess the effect on survival of bevacizumab to the present standard of care, cisplatin plus pemetrexed, as first-line treatment of advanced malignant pl mesothelioma.

Lancet 2016; 387: 1405–14
Published Online
December 21, 2015
http://dx.doi.org/10.1016/
S0140-6736(15)01238-6

OS benefit: 18.8 vs 16.1 mo, HR 0.77, p=0.0167

UCSF

2016-2021: Not quite a desert

- Immunotherapy
  - Salvage PD-(L)1 inhibition
    - KEYNOTE-028, pembro in PD-L1+: PR 20%
    - Nivo-Meso, nivo in PD-L1 unselected: PR 15%
    - JAVELIN meso cohort, avelumab in PD-L1 unselected: PR 9.4%
  - Salvage CTLA4 inhibition
    - DETERMINE, tremelimumab (DETERMINE): RP2b study negative
  - Salvage combination
    - MAPS-2, nivo+ipi: PR 24%
    - INITIATE,nivo+ipi: PR 27%
    - NIBIT-Meso, durva+treme PR 28%

2020 WCLC in "Singapore"

First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate [illegible]): a multicentre, randomised, open-label

Paul Baas, Arnaud Scherpereel, Anna K Nowak, Nobukazu Fujimoto, [illegible]ield, Sanjay Popat, Thierry Jahan, Scott Antonia, Youssef Oulkhouir, Yolanda Bautista, Robin [illegible]ossi, Dariusz Kowalski, Jerónimo Rodríguez-Cid, Praveen Aanur, Abderrahi[illegible]aicman

FDA approved 10/2/20

Summary

Background Appr[illegible]alignant pleural mesothelioma (MPM) have been limited to chemotherapy [illegible] survival benefit with poor outcomes. Nivolumab plus ipilimumab has shown clinical [illegible]ur types, including first-line non-small-cell lung cancer. We hypothesised that this regimen wo[illegible]verall survival in MPM.

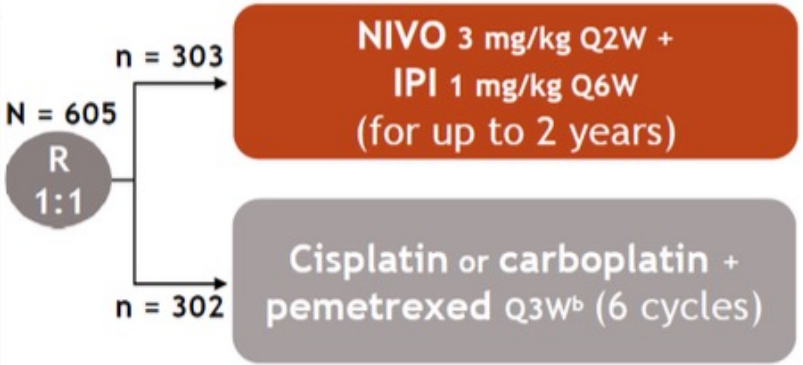
Lancet 2021; 397: 375–86
Published Online January 21, 2021
https://doi.org/10.1016/S0140-6736(20)32714-8

UCSF

CheckMate 743: Nivolumab + ipilimumab

Key Eligibility Criteria
- Unresectable pleural mesothelioma
- No prior systemic therapy
- ECOG performance status 0-1

Stratified by:
histology (epithelioid vs non-epithelioid) and gender



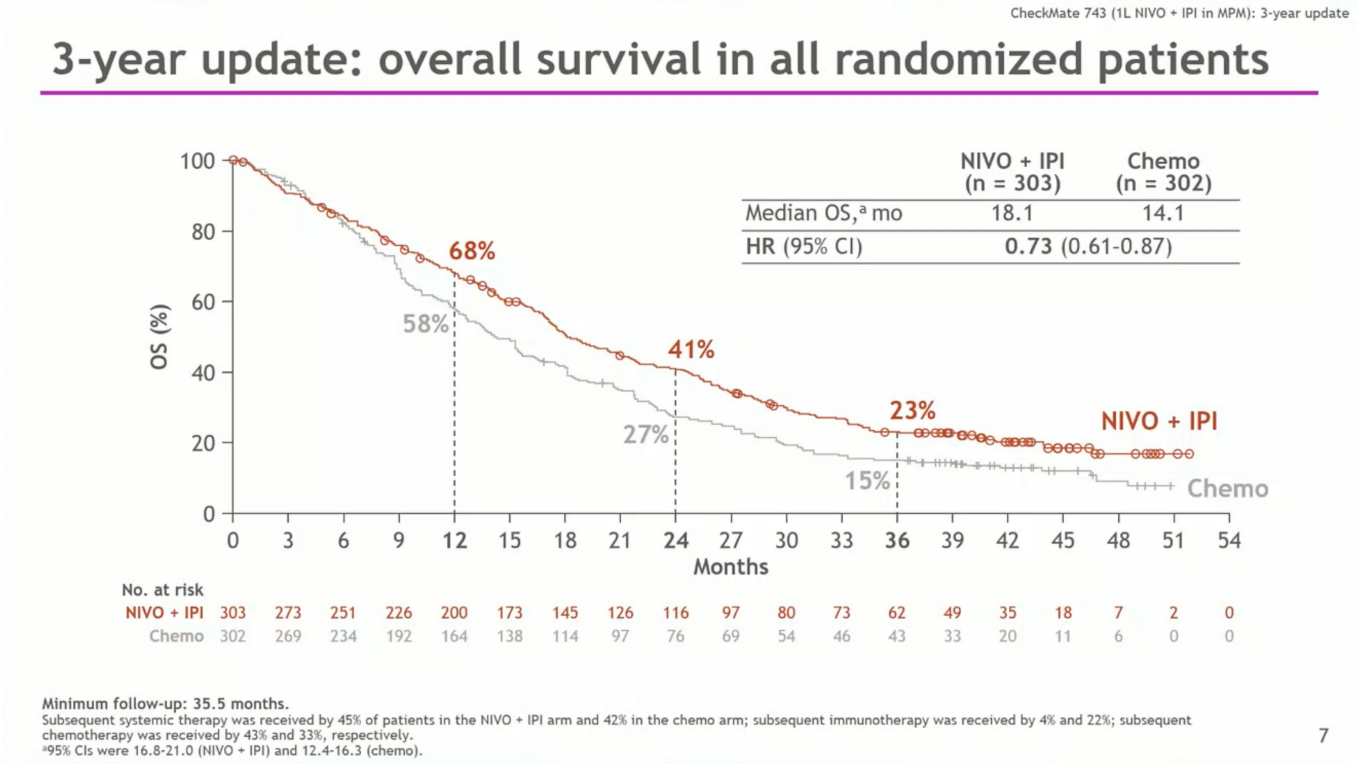
Until disease progression, unacceptable toxicity *or* for 2 years for immunotherapy arm

Primary Endpoint
- OS

Secondary Endpoints
- ORR, DCR, and PFS by BICR
- PD-L1[c] expression as a predictive biomarker

UCSF

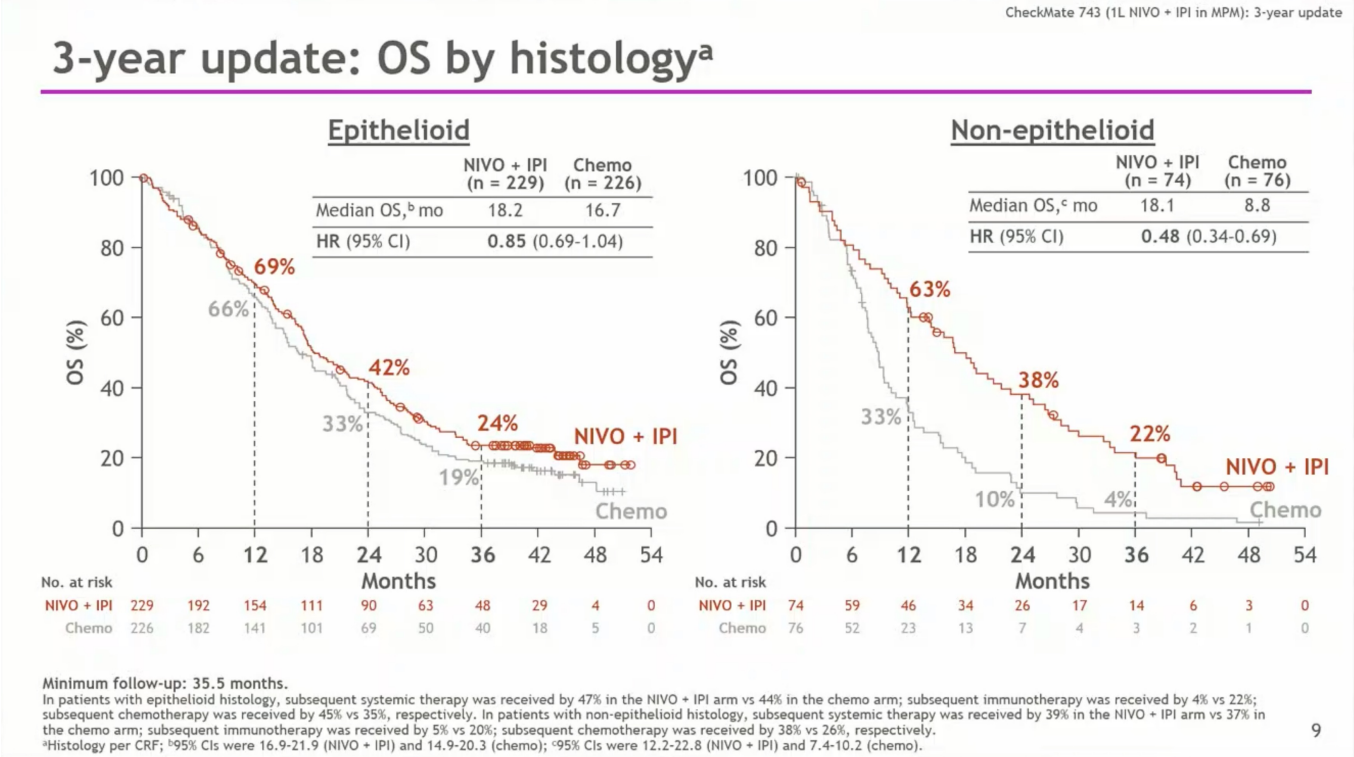
CheckMate 743: Nivolumab + ipilimumab– 3 year update



Peters et al. ESMO 2021

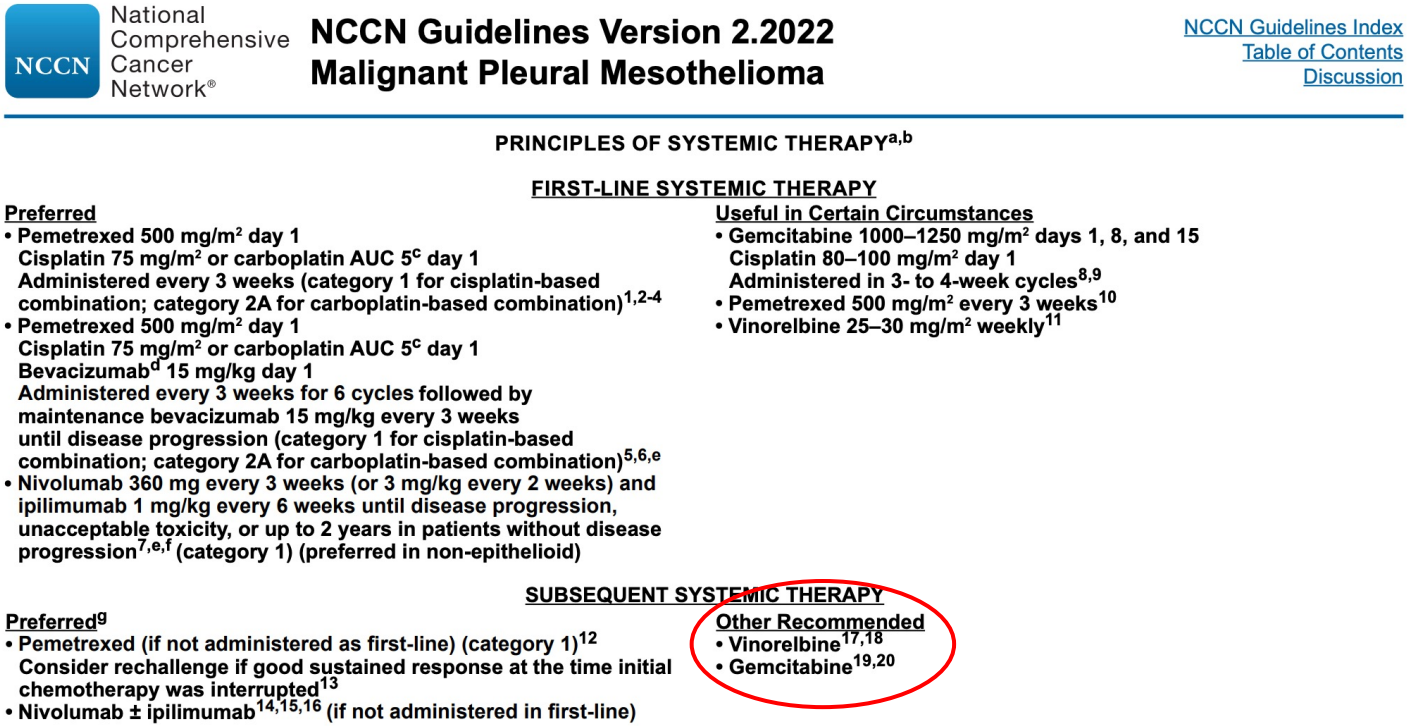
UCSF

CheckMate 743: Nivolumab + ipilimumab– 3 year update



 Peters et al. ESMO 2021

What about 2nd and 3rd line?



National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2022
Malignant Pleural Mesothelioma

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF SYSTEMIC THERAPY[a,b]

FIRST-LINE SYSTEMIC THERAPY

Preferred

- Pemetrexed 500 mg/m² day 1
  Cisplatin 75 mg/m² or carboplatin AUC 5[c] day 1
  Administered every 3 weeks (category 1 for cisplatin-based combination; category 2A for carboplatin-based combination)[1,2-4]
- Pemetrexed 500 mg/m² day 1
  Cisplatin 75 mg/m² or carboplatin AUC 5[c] day 1
  Bevacizumab[d] 15 mg/kg day 1
  Administered every 3 weeks for 6 cycles followed by maintenance bevacizumab 15 mg/kg every 3 weeks until disease progression (category 1 for cisplatin-based combination; category 2A for carboplatin-based combination)[5,6,e]
- Nivolumab 360 mg every 3 weeks (or 3 mg/kg every 2 weeks) and ipilimumab 1 mg/kg every 6 weeks until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression[7,e,f] (category 1) (preferred in non-epithelioid)

Useful in Certain Circumstances

- Gemcitabine 1000–1250 mg/m² days 1, 8, and 15
  Cisplatin 80–100 mg/m² day 1
  Administered in 3- to 4-week cycles[8,9]
- Pemetrexed 500 mg/m² every 3 weeks[10]
- Vinorelbine 25–30 mg/m² weekly[11]

SUBSEQUENT SYSTEMIC THERAPY

Preferred[g]

- Pemetrexed (if not administered as first-line) (category 1)[12]
  Consider rechallenge if good sustained response at the time initial chemotherapy was interrupted[13]
- Nivolumab ± ipilimumab[14,15,16] (if not administered in first-line)

Other Recommended

- Vinorelbine[17,18]
- Gemcitabine[19,20]

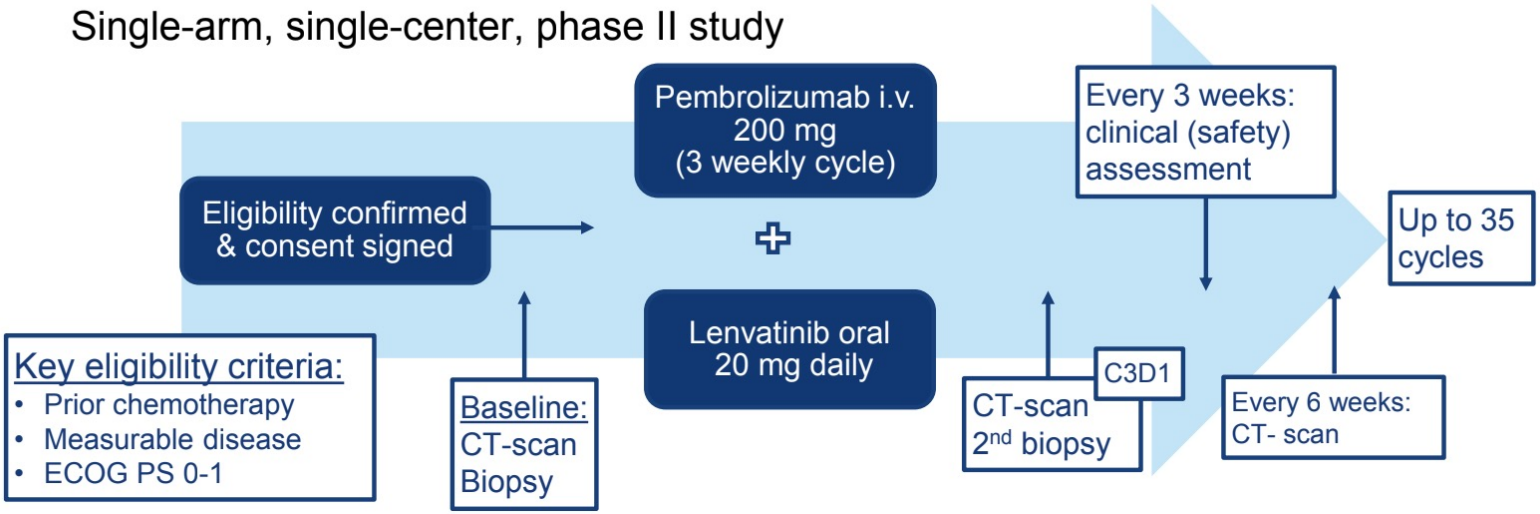
UCSF

Pembrolizumab + Lenvatinib 2/3L

Pembrolizumab + Lenvatinib 2/3L

Trial design

Single-arm, single-center, phase II study



Primary endpoint: ORR by PI
Secondary: ORR by central review, PFS, OS, tox

Plan n=38 pts
Target ORR 22→40%

Douma et al. WCLC 2022

UCSF

Pembrolizumab + Lenvatinib 2/3L

	All patients (n=38)
Sex (male), n(%)	33 (86.8)
Median age (range), years	70.5 (36-83)
ECOG PS 0, n(%)	19 (50)
Histology, n(%)	
Epithelioid	34 (89.5)
Non-epithelioid	2 (5.3)
Mixed	2 (5.3)
PD-L1 status, n(%)	
Positive (≥1%)	18 (47.4)
Negative (<1%)	17 (44.7)
Not available	3 (7.9)

Accrual March 2021 – Feb. 2022

ORR

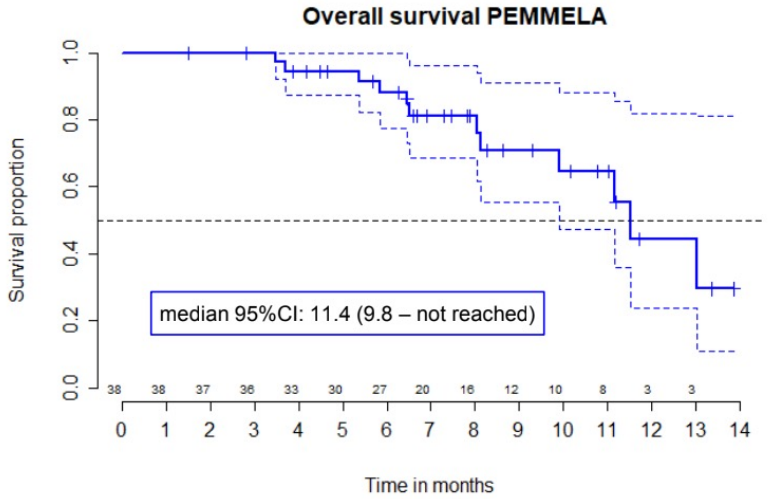
	Local investigator	Independent central reviewer (2nd endpoint)
	PEM+LEN (N=38)	PEM+LEN (N=38)
Objective response (95% CI) -%	58 (41-74)	42 (26-59)
Best overall response – n(%)		
CR	0	0
PR	22 (58)	16 (42)
SD	16 (42)	22 (58)
PD	0	0
Objective response (only confirmed) (95% CI) -%	40 (24-57)	37 (22-54)

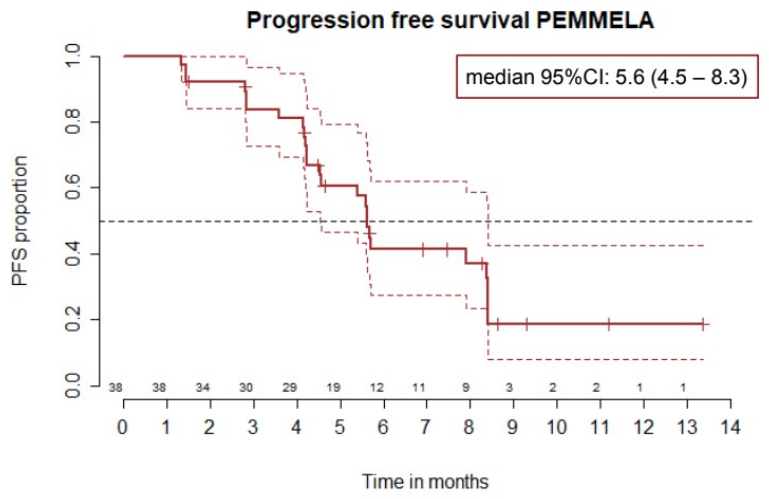
At evaluation, 13 patients still on treatment

UCSF

Pembrolizumab + Lenvatinib 2/3L

OS & PFS (preliminary results)





Douma et al. WCLC 2022

Pembrolizumab + Lenvatinib 2/3L

Safety summary – treatment related

	Grade 1-2 (n=38)	Grade 3 (n=38)	Grade 4 (n=38)
Fatigue	21	0	0
Hoarseness	21	0	0
Anorexia	13	3	0
Diarrhea	13	2	0
Hypertension	5	8	0
ALAT/ASAT increased	5	2	0
Stroke	0	2	0
Myositis	0	0	2

SAE's: 13 in 10 patients

Lenvatinib: 29 out of 38 patients (76%) required ≥ 1 dose reduction/ permanent discontinuation

Pembrolizumab: 3 out of 38 (8%) patients permanent discontinuation.

Douma et al. WCLC 2022

Pembrolizumab + Lenvatinib 2/3L: Authors conclusion

Conclusion

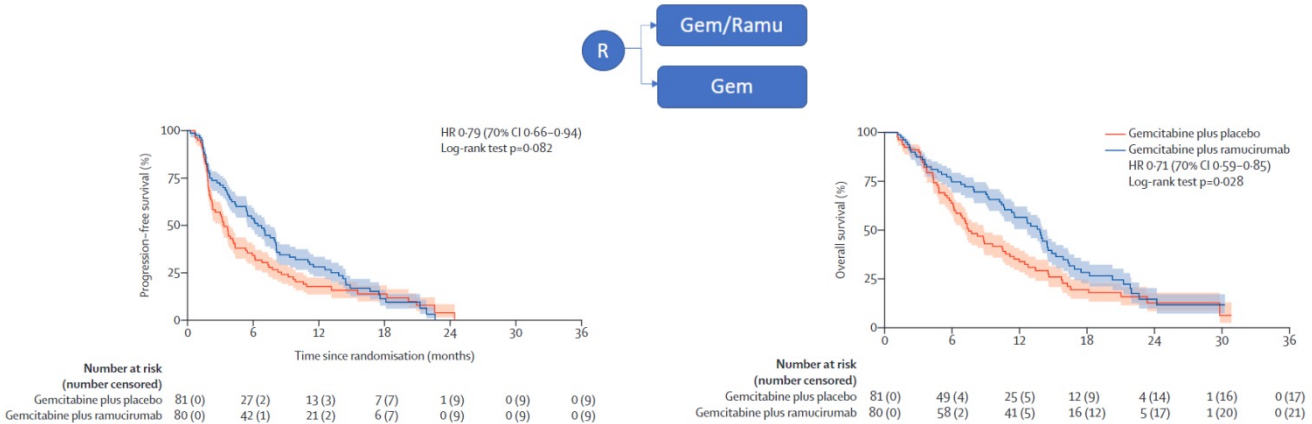
- The primary endpoint (ORR) was met with 58%
  - Highest ORR in MPM in second line treatment
- Promising clinical activity of pembrolizumab plus lenvatinib
- Remarkable but manageable toxicity
  - Dose reductions in 76%

UCSF

Pembrolizumab + Lenvatinib 2/3L

- Activity with anti-angiogenesis (as with MAPS, but here with IO instead of chemo)

Gemcitabine/Ramucirumab (VEGFR2) confers longer progression-free and overall survival



Pinto et al, Lancet Oncology 2021

Pembrolizumab + Lenvatinib 2/3L

- Activity with anti-angiogenesis (as with MAPS, but here with IO instead of chemo)
- What of patients previously exposed to IO?
  - Consider LungMAP S1800A, pembro/ramucirumab, success with prior-treated
- What of sarcomatoid? n=2 (and biphasic n=2)
- BEAT-MESO trial accruing: cisplatin, pemetrexed, bevacizumab +/- atezolizumab, n=400

Future WCLC?

- Chemoimmunotherapy
  - DREAM3R phase 3: Cis/pemetrexed +/- durva
  - ETOP 13-18 BEAT Meso: Carbo/pemetrexed/bev +/- atezo
  - CCTG IND227/IFCT1901: Platinum/pemetrexed +/- pembro

Future WCLC?

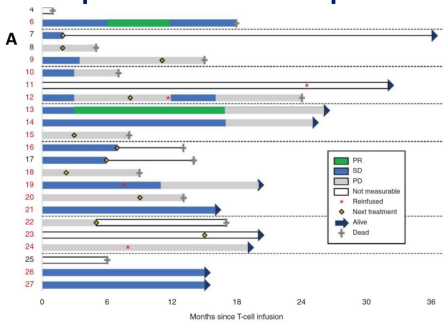
- Other immunotherapy
  - Cellular therapies…
    - Intra-pleural or systemic mesothelin and FAP-directed CARs

M28z Anti-mesothelin CAR-T: MSKCC

- **Anti-MSLN scFv, m912 fused to CD28 and CD3ζ signaling domain; retroviral transduction of T cells**
- **23 mesothelioma patients treated with Cytoxan lymphodepletion**
- **CAR-T cells infused into pleural cavity; 0.3 - 60M CAR-T cells/kg; No DLT**
- **CAR-T cells detectable in blood for > 6 months in 17% of patients**
- **No objective tumor response by mRECIST; median OS, 17.7 months**

Adusumilli et al., Cancer Discovery, 2021

Outcome of patients with mesothelioma who received pembrolizumab off protocol following M28z CAR T (n=18)



2 of 16 (12.5%) had PR after pembrolizumab
Median OS, 23.9 months

Ongoing study: Phase II study of fixed dose CAR-T ($6x10^7$/kg) with pembrolizumab 4 weeks after CAR-T administration

ClinicalTrials.gov: NCT02414269

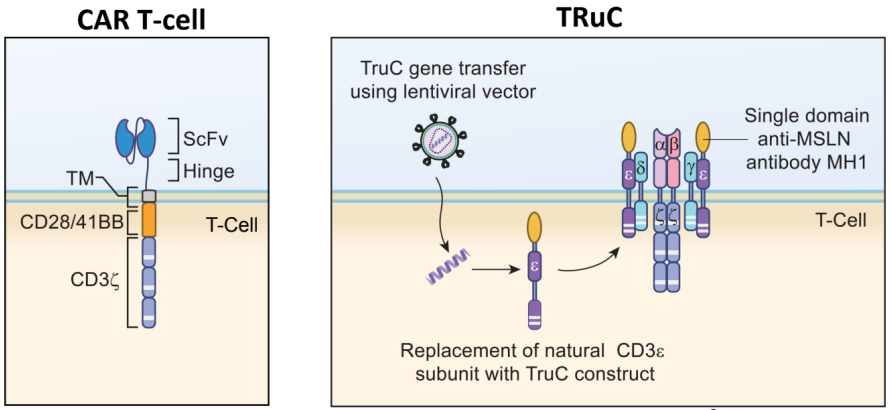
Adusumilli P et al., Cancer Discovery, 2021

UCSF

Future WCLC?

- Other immunotherapy
  - Cellular therapies…
    - Intra-pleural or systemic mesothelin and FAP-directed CARs
    - Anti-mesothelin T cell receptor fusion construct (TRuC)

TC-210 (gavo-cel): anti-mesothelin T cell receptor fusion construct (TRuC)



TCR² Therapeutics

UCSF

Future WCLC?

- Other immunotherapy
  - Cellular therapies…
    - Intra-pleural or systemic mesothelin and FAP-directed CARs
    - Anti-mesothelin T cell receptor fusion construct (TRuC)

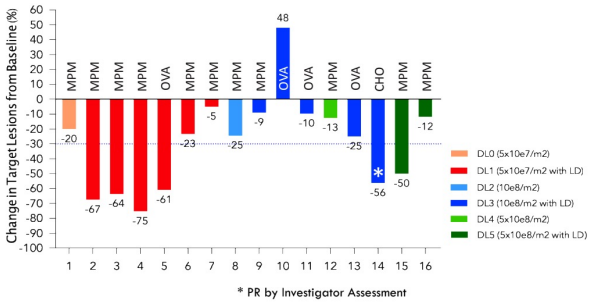
Gavo-cel: Phase I study

- **Single intravenous infusion ± lymphodepletion with cytoxan/fludarabine**
- **17 patients treated (12 mesothelioma, 4 ovarian, 1 cholangiocarcinoma)**
- **Median number of prior treatments 5 (range 1-9)**
- **DLT at 5x10^8 cells/m^2 with lymphodepletion (grade ≥3 CRS in all 3 pts.)**
- **RP2D 1x10^8 cells/m^2 with lymphodepletion**
- **Lymphodepletion was associated with greater persistence of gavo-cel**

ClinicalTrials.gov: NCT 03907852

Data cut-off date: June 30th, 2021

Tumor Response (n=16 patients)



	Overall	LD Group
DCR	81%	77%
ORR (independent)	25%	31%
ORR (investigator)	31%	38%

DCR = PR or SD lasting at least 3 months

MPM: malignant pleural/peritoneal mesothelioma; OVA: ovarian cancer; CHO: cholangiocarcinoma; DL: dose level; LD: lymphodepletion; DCR: disease control rate; ORR: overall response rate

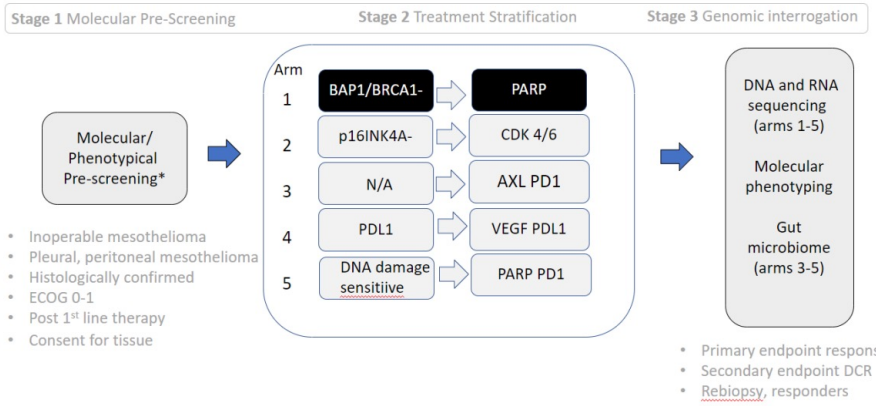
Future WCLC?

- Targeted therapy

IASLC 2022 World Conference on Lung Cancer
AUGUST 6-9, 2022 | VIENNA, AUSTRIA

Mesothelioma Stratified Therapy (MiST) study design

Trials.gov ID NCT03654833



Dean A. Fennell, University of Leicester & University Hospitals of Leicester NHS Trust, UK

UCSF

Thymoma

- First line CAP (thymoma) or carboplatin/paclitaxel (thymic carcinoma)

NCCN Guidelines Version 2.2022
Thymomas and Thymic Carcinomas

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF SYSTEMIC THERAPY

SECOND-LINE SYSTEMIC THERAPY
(in alphabetical order)

THYMOMA
Other Recommended
- Etoposide[4,8,9]
- Everolimus[10]
- 5-FU and leucovorin[11]
- Gemcitabine ± capecitabine[12,13]
- Ifosfamide[14]
- Octreotide[b] (including LAR) +/- prednisone[15]
- Paclitaxel[16]
- Pemetrexed[17]

THYMIC CARCINOMA
Other Recommended
- Everolimus[10]
- 5-FU and leucovorin[11]
- Gemcitabine ± capecitabine[12,13]
- Lenvatinib[c,18]
- Paclitaxel[17]
- Pembrolizumab[d,19,20]
- Pemetrexed[16]
- Sunitinib[21]

Useful in Certain Circumstances
- Etoposide[4,8,9]
- Ifosfamide[14]

[b] Nuclear medicine scan to assess for octreotide-avid disease.
[c] There is a high risk for side effects and frequent dose reductions may be needed.
[d] Pembrolizumab is not recommended for patients with thymoma. In patients with thymic carcinoma, there is concern for a higher rate of immune-related adverse events than seen in most other malignancies treated with PD-1/PD-L1 inhibitor therapy. For example, grade 3–4 myocarditis has been reported in 5%–9% of patients receiving pembrolizumab.

References THYM-C 3 of 3

Thymoma

- Proto: Phase II sunitinib in B3 thymoma or thymic carcinoma 2L+

Sunitinib for Thymoma and Thymic carcinoma

	Thymic carcinoma (n=23)		Thymoma (n=16)	
	Patients (%)	95% CI	Patients (%)	95% CI
Objective response*	6 (26%)	10·2–48·4†	1 (6%)	0·2–30·2
Stable disease	15 (65%)	42·7–83·6	12 (75%)	47·6–92·7
Progressive disease	2 (9%)	1·1–28·0	3 (19%)	4·1–45·7
Disease control	21 (91%)	72·0–98·9	13 (81%)	54·4–96·0

A. Thomas Lancet Oncol 2015

Thymoma

- Proto: Phase II sunitinib in B3 thymoma or thymic carcinoma 2L+

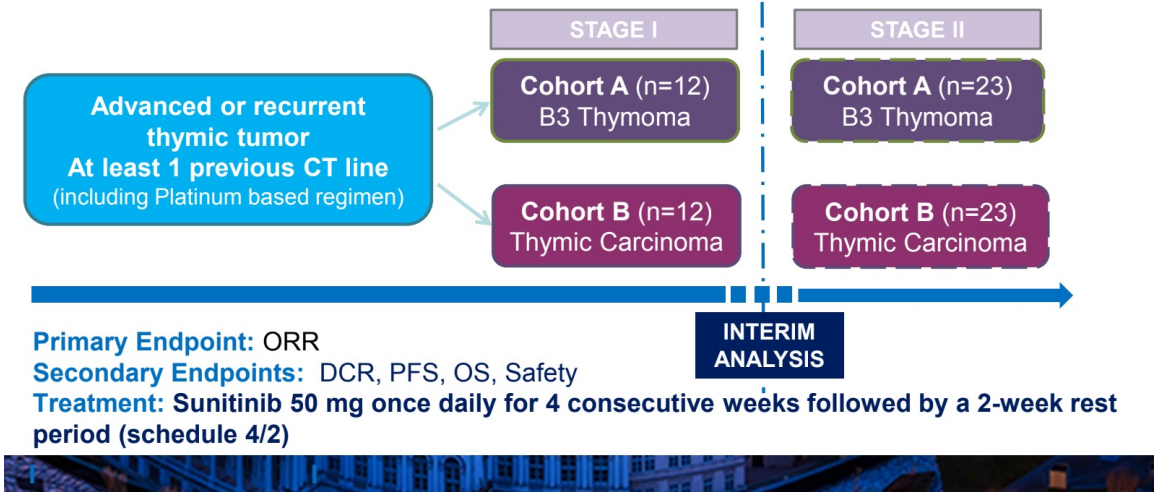
Sunitinib for Thymoma and Thymic carcinoma

	Thymic carcinoma (n=23)		Thymoma (n=16)	
	Patients (%)	95% CI	Patients (%)	95% CI
Objective response*	6 (26%)	10·2–48·4†	1 (6%)	0·2–30·2
Stable disease	15 (65%)	42·7–83·6	12 (75%)	47·6–92·7
Progressive disease	2 (9%)	1·1–28·0	3 (19%)	4·1–45·7
Disease control	21 (91%)	72·0–98·9	13 (81%)	54·4–96·0

A. Thomas Lancet Oncol 2015

IASLC 2022 World Conference on Lung Cancer
AUGUST 6-9, 2022 | VIENNA, AUSTRIA

Study design



Primary Endpoint: ORR
Secondary Endpoints: DCR, PFS, OS, Safety
Treatment: **Sunitinib 50 mg once daily for 4 consecutive weeks followed by a 2-week rest period (schedule 4/2)**

Proto et al. WCLC 2022

Thymoma

- Proto: Phase II sunitinib in B3 thymoma or thymic carcinoma 2L+

Sunitinib for Thymoma and Thymic carcinoma

	Thymic carcinoma (n=23)		Thymoma (n=16)	
	Patients (%)	95% CI	Patients (%)	95% CI
Objective response*	6 (26%)	10·2–48·4†	1 (6%)	0·2–30·2
Stable disease	15 (65%)	42·7–83·6	12 (75%)	47·6–92·7
Progressive disease	2 (9%)	1·1–28·0	3 (19%)	4·1–45·7
Disease control	21 (91%)	72·0–98·9	13 (81%)	54·4–96·0

A. Thomas Lancet Oncol 2015

Results

	INTERIM ANALYSIS	EFFICACY ANALYSIS	ITT ANALYSIS
	Cohort A n=12	Cohort B n=23	Cohort B n=31
Best Response – n (%)			
CR	0 (0.0)	1 (4.3)	1 (3.6)
PR	0 (0.0)	4 (17.4)	5 (17.9)
SD	11 (91.7)	15 (65.2)	19 (67.9)
PD	1 (8.3)	3 (13.0)	3 (10.7)
Not evaluated (*)	0	0	3
ORR - n (%) [95% CI]	0 (0.0) [0.0 - 26.5]	5 (21.7) [7.5 – 43.7]	6 (21.4) [8.3 - 41.0]
DCR - n (%) [95% CI]	11 (91.7) [61.5 - 99.8]	20 (87.0) [66.4 – 97.2]	25 (89.3) [71.8 - 97.7]

Legend: Cohort A: B3 Thymoma, Cohort B: Thymic Carcinoma; ITT: Intention To Treat; n: Number of subjects; CI: Confidence Interval;(*) Patients who did not receive at least one radiological evaluation after study entry; ORR: Objective response rate; DCR: disease control rate

B3 thymoma
mPFS 7.7m
mOS 47.9m

Thymic ca
mPFS 8.8m
mOS 27.8m

Confirms signal for sunitinib in thymic carcinoma, less clear for B3 thymoma

Thymoma

- CD47 as target?
  - CD47 when expressed on tumor board sends “don’t eat me” signal to macrophages
  - Anti-CD47 monoclonal abs have been successful in heme malignancies
  - In a basket trial of 28 pts, best response was in a thymoma pt with high CD47 exp
- Sun et al from Stanford:
  - Thymic epithelial tissue microarray in 64 thymomas, 3 thymic carcinomas, 14 thymic controls
  - Thymic tumors had higher CD47 expression than nl tissue by 14 fold, mean H-score 75vs 4.6, p=0.003
  - Anti-CD47 may be a promising approach

Sun et al. WCLC 2022

Summary for mesothelioma and thymoma

- CheckMate 743 has established nivolumab+ipilimumab as a meso 1st line standard of care
  - Clear advantage for sarcomatoid
  - Likely comparable to chemo for epithelioid
  - PD-L1 not an effective predictive biomarker, but inflammation score might be
- Immunotherapy at *least* in 2nd line warranted
  - CONFIRM phase 3 trial: Nivo > placebo
  - But I'd still try for nivolumab+ipilimumab!
- Pembro/Lenvatinib promising in a phase 2, though in IO-inexperienced
- Cellular therapies to come, and updates in phase 3 chemo+IO combos
- Thymoma… alas no practice changers this year
  - Sunitinib with benefit at least in thymic carcinoma 2L+
  - CD47 might be a good thymoma target
  - Be mindful of immunotherapy adverse in thymic carcinoma (and don't use in thymoma off-trial)

ENROLL IN TRIALS!

Parnassus Heights

SFVA

UCSF

University of California
San Francisco

Mission Bay

Mt. Zion