2024 World Conference on Lung Cancer

SEPTEMBER 7-10, 2024 | SAN DIEGO, CA USA

Mesothelioma and Thymoma – Limited and Advanced Stage

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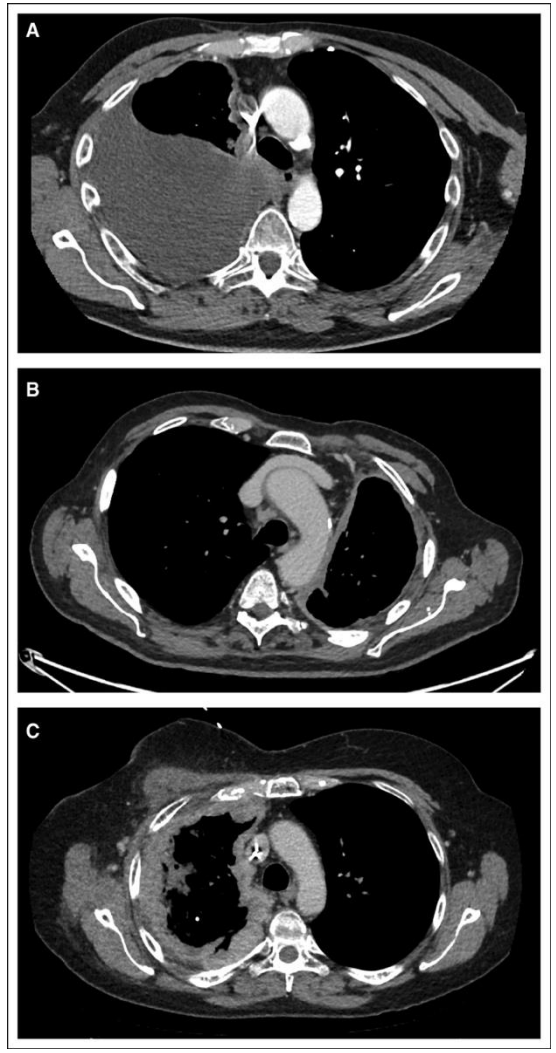
Assistant Professor
UC Davis Health

10/5/2024

Mesothelioma

- Rare cancer affecting approximately 40,000 people worldwide
- Most commonly linked to asbestos exposure, but over 10% have an inherited predisposition, including *BAP1* loss
- Role of surgery is controversial and immunotherapy has revolutionized management based on CheckMate 743



Nowak et al. *JCO Onc. Prac.* 2021

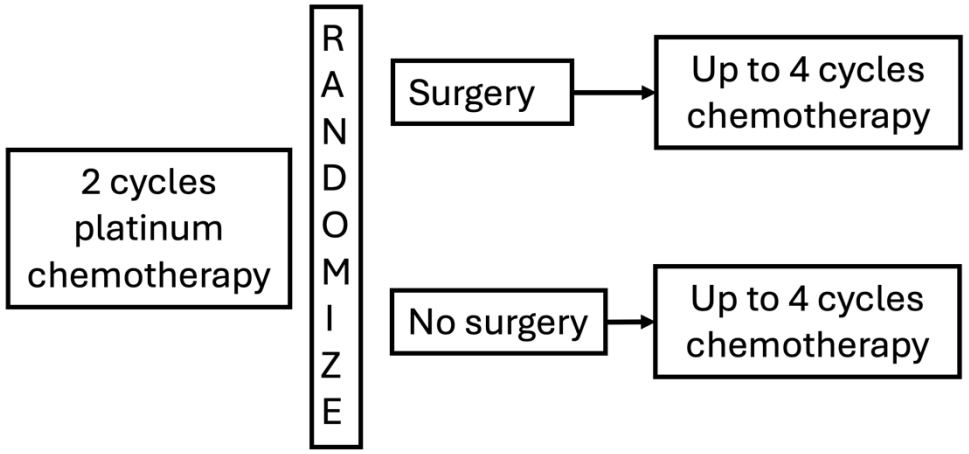
Perioperative Chemoimmunotherapy for Mesothelioma

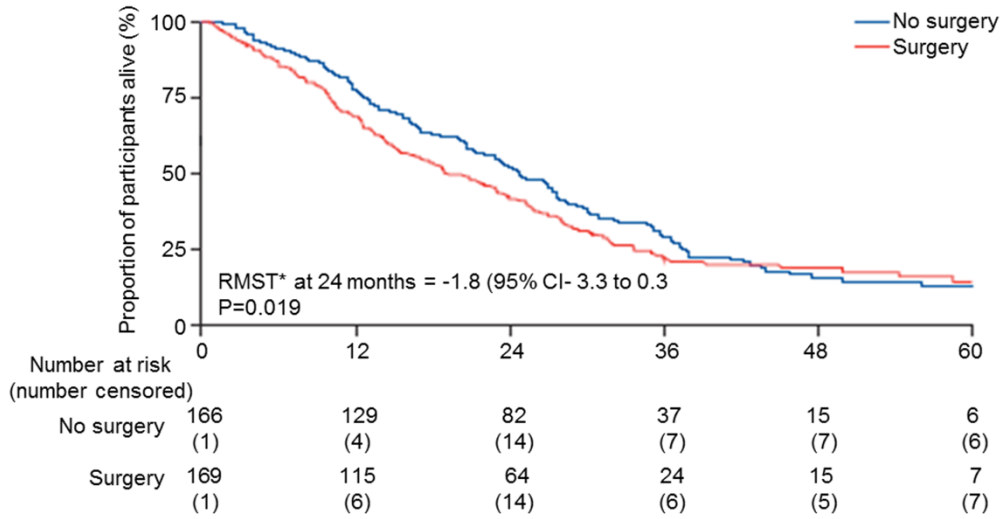
Michael Offin, MD

Memorial Sloan Kettering Cancer Center

USA

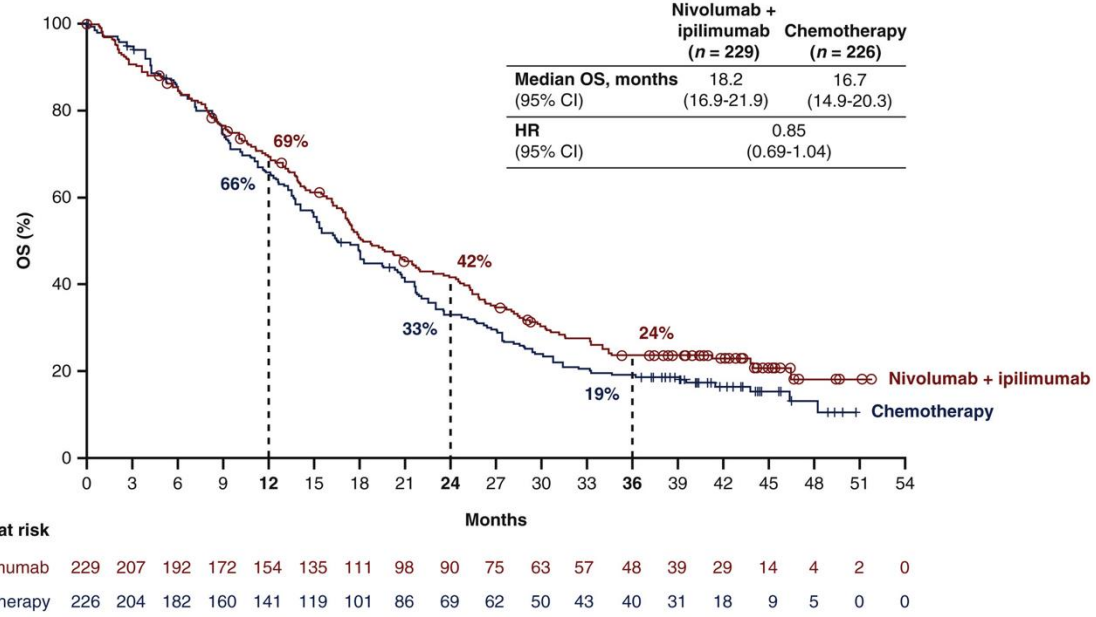
MARS2 randomized patients to pleurectomy decortication and noted inferior OS with surgery





Lim E, *et al,* Lancet Resp 2024.

B

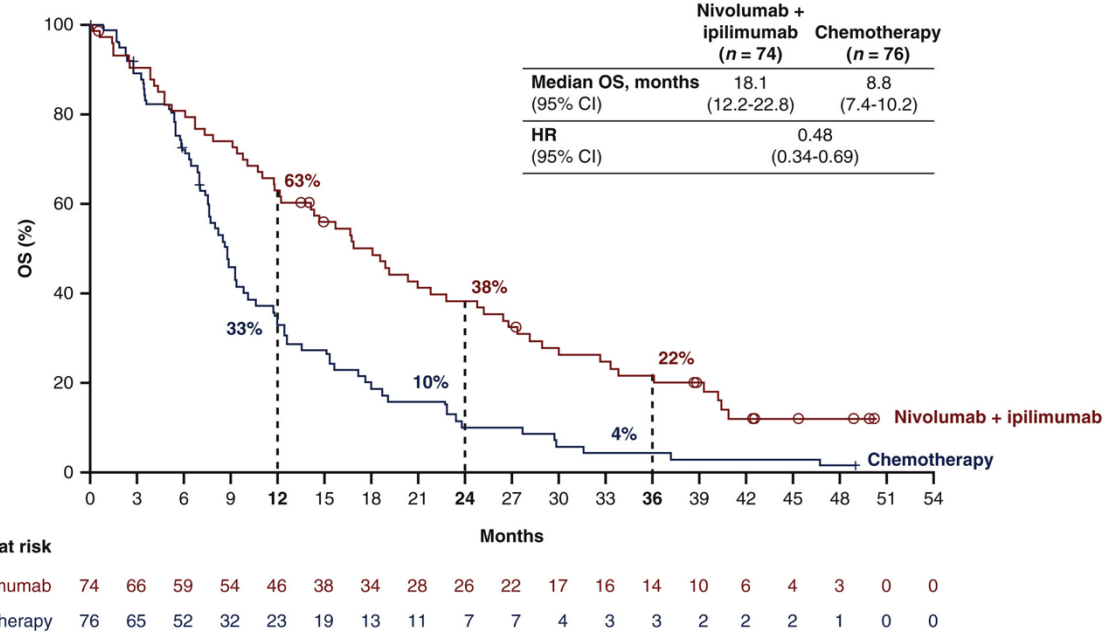


	Nivolumab + ipilimumab (*n* = 229)	Chemotherapy (*n* = 226)
Median OS, months (95% CI)	18.2 (16.9-21.9)	16.7 (14.9-20.3)
HR (95% CI)	0.85 (0.69-1.04)	

No. at risk																			
Nivolumab + ipilimumab	229	207	192	172	154	135	111	98	90	75	63	57	48	39	29	14	4	2	0
Chemotherapy	226	204	182	160	141	119	101	86	69	62	50	43	40	31	18	9	5	0	0

Epithelioid

C



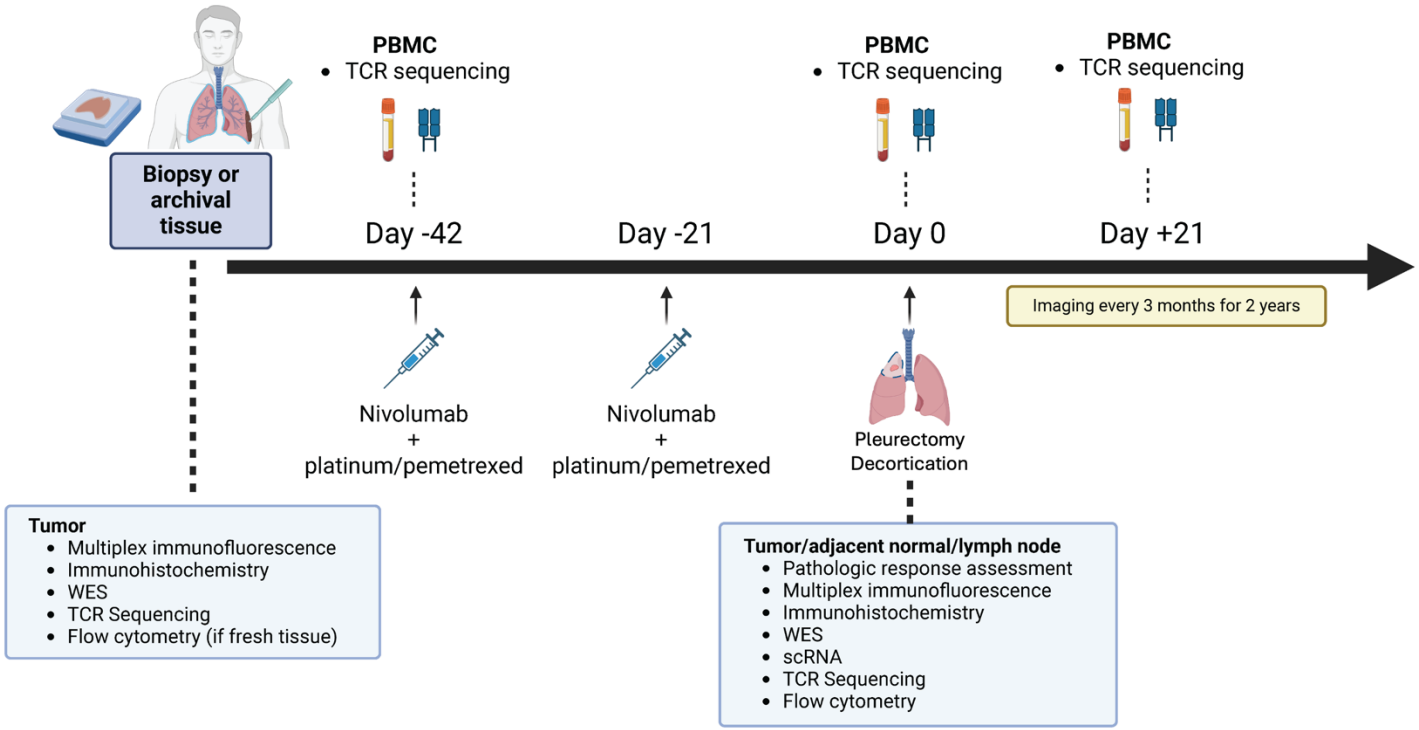
	Nivolumab + ipilimumab (*n* = 74)	Chemotherapy (*n* = 76)
Median OS, months (95% CI)	18.1 (12.2-22.8)	8.8 (7.4-10.2)
HR (95% CI)	0.48 (0.34-0.69)	

No. at risk																			
Nivolumab + ipilimumab	74	66	59	54	46	38	34	28	26	22	17	16	14	10	6	4	3	0	0
Chemotherapy	76	65	52	32	23	19	13	11	7	7	4	3	3	2	2	2	1	0	0

Non-epithelioid

Peters et al. *Annals of Onc.* 2022

Prospective trial of neoadjuvant platinum/pemetrexed + nivolumab (NCT04162015)



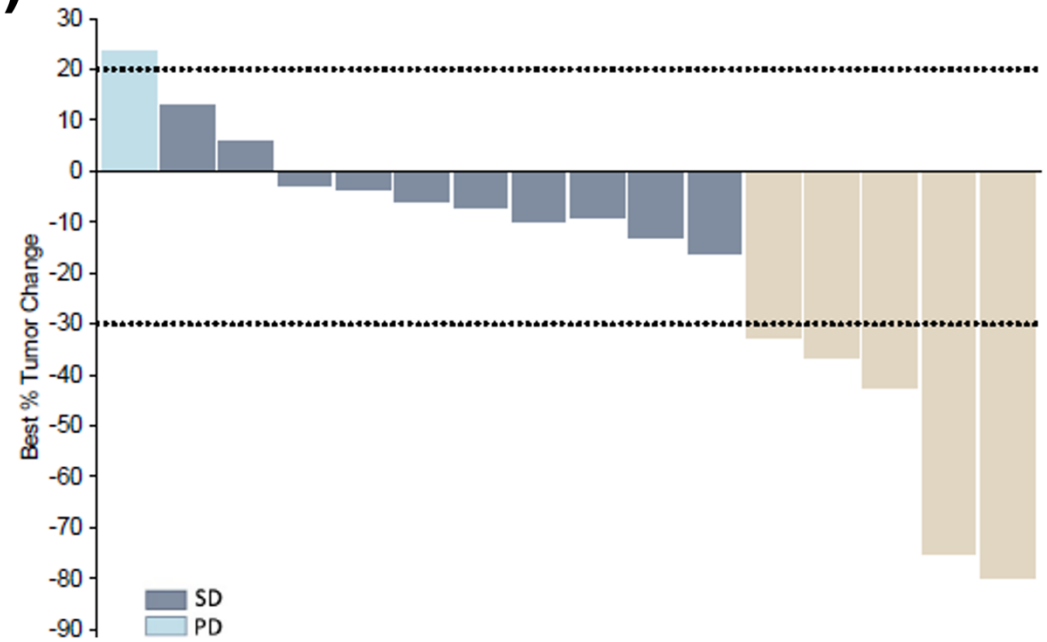
Key Inclusion Criteria:
- Operable/Resectable
- KPS ≥ 70%
- Platinum/pemetrexed/ ICI naïve

Primary Objective:
- Attempted P/D within 30 days of the planned surgery date

Secondary Objective:
- Safety
- Overall survival (OS) from treatment start
- Progression free survival (PFS)

Offin M., *et* al, ASCO, 2024

Best overall response to neoadjuvant chemo/nivolumab by modified (m)RECIST (NCT04162015)



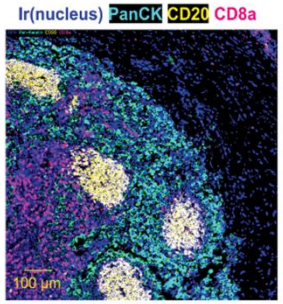
*3 patients were not evaluable

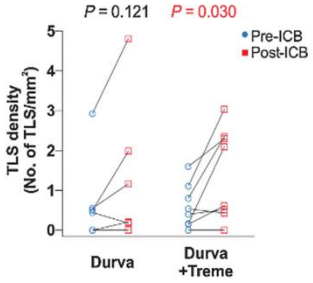
Unconfirmed PR: (31%) 5/16

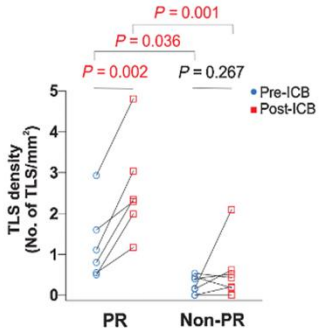
Offin M., *et* al, ASCO, 2024

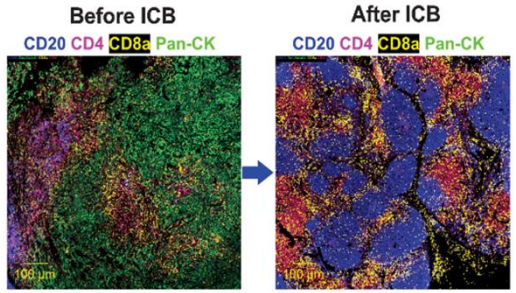
Tertiary Lymphoid Structures (TLS) potentially correlate with clinical outcomes

NCT02592551

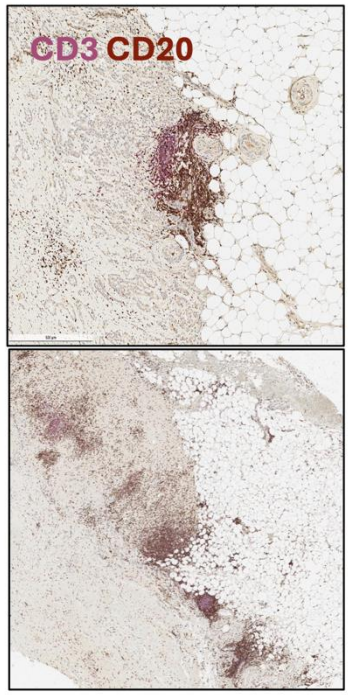


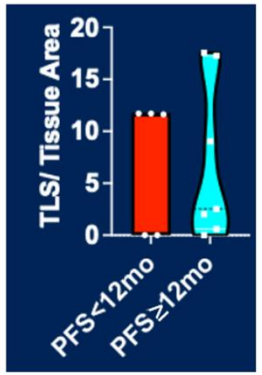






NCT04162015





Lee HS., *et* al, Clin Cancer Res, 2023; Offin M., *et* al, ASCO, 2024

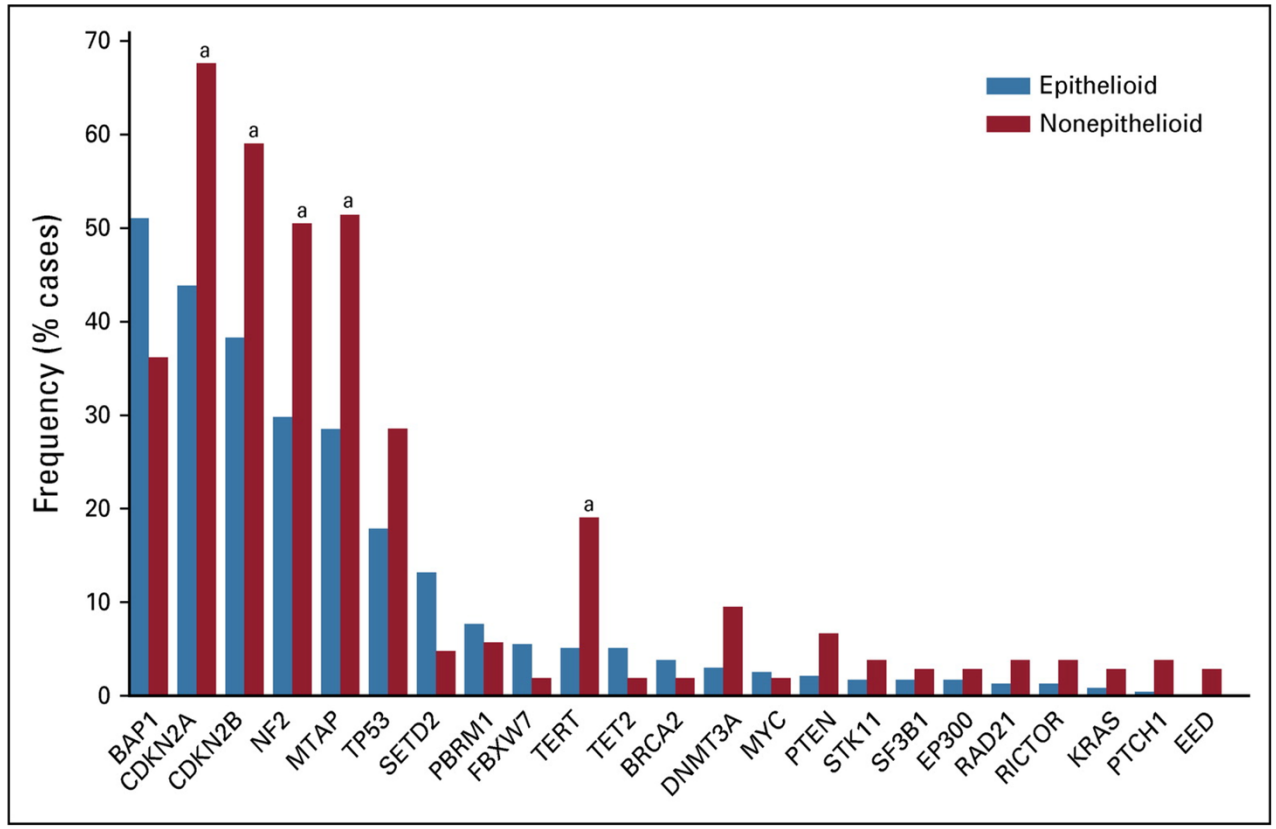
Mesothelioma: Molecular Landscape and Histological Terrain

Ibiayi Dagogo-Jack, MD

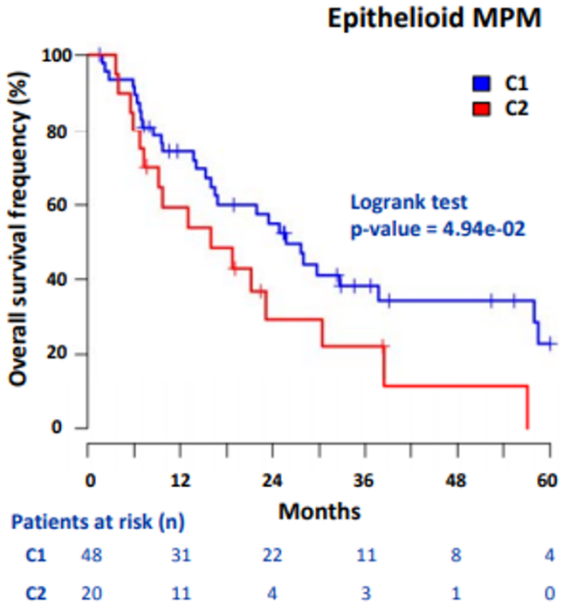
Massachusetts General Hospital

USA

Alterations in Epithelioid vs Non-Epithelioid



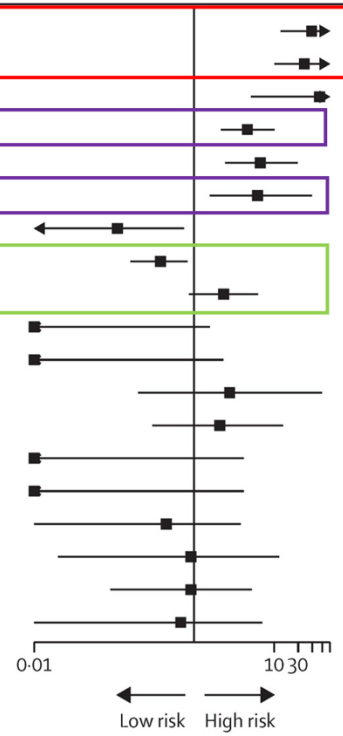
C2= EMT Gene Expression



Dagogo-Jack JCO Precision Oncology 2022, de Reynies Clinical Cancer Research 2014

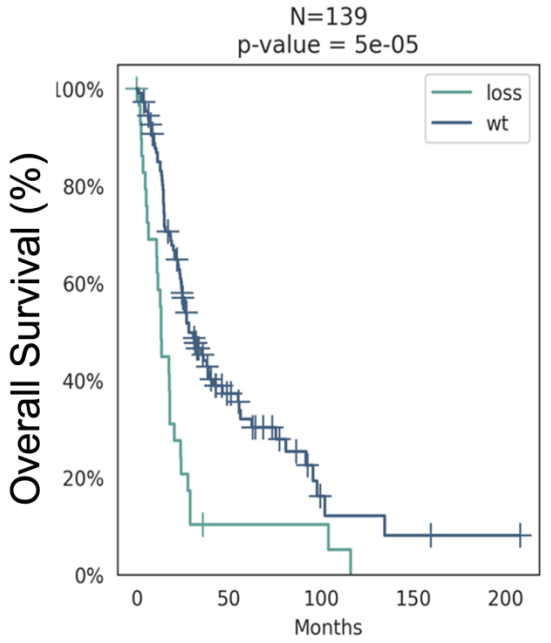
Impact of Molecular Alterations on Prognosis

	Total (n=194)	Low risk (n=142)	High risk (n=52)	OR (95% CI)	p value
CDKN2B deletion	54 (28%)	14	40	29·54 (12·12–78·20)	$3·99\times10^{-19}$
CDKN2A deletion	57 (29%)	17	40	23·87 (10·08–60·81)	$1·32\times10^{-17}$
TERT	12 (6%)	1	11	37·05 (5·12–1624·76)	$2·09\times10^{-6}$
NF2	46 (24%)	22	24	4·63 (2·16–10·08)	$3·66\times10^{-5}$
TP53	23 (12%)	8	15	6·70 (2·45–19·77)	$4·18\times10^{-5}$
LATS2	12 (6%)	4	8	6·20 (1·57–29·52)	0·0034
SETD2	22 (11%)	21	1	0·11 (0·00–0·75)	0·0099
BAP1	70 (36%)	59	11	0·38 (0·16–0·83)	0·011
BAP1 deletion	23 (12%)	13	10	2·35 (0·86–6·30)	0·077
PBRM1	8 (4%)	8	0	0·00 (0·00–1·57)	0·11
FBXW7	6 (3%)	6	0	0·00 (0·00–2·31)	0·20
PTEN	4 (2%)	2	2	2·78 (0·20–39·35)	0·29
LATS1	7 (4%)	4	3	2·10 (0·30–12·91)	0·39
CDKN2A	4 (2%)	4	0	0·00 (0·00–4·15)	0·58
ABL1	4 (2%)	4	0	0·00 (0·00–4·15)	0·58
CREBBP	7 (4%)	6	1	0·45 (0·01–3·82)	0·68
PIK3CA	4 (2%)	3	1	0·91 (0·02–11·62)	1
BAP1 fusion	8 (4%)	6	2	0·91 (0·09–5·29)	1
WT1 amplification	5 (3%)	4	1	0·68 (0·01–7·06)	1



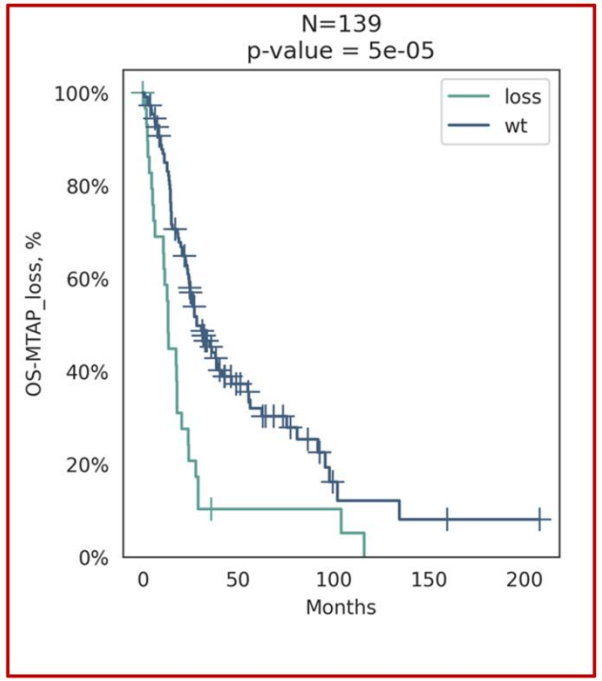
Zauderer Lancet Digital Health 2021

MTAP Status (TCGA + NCI)

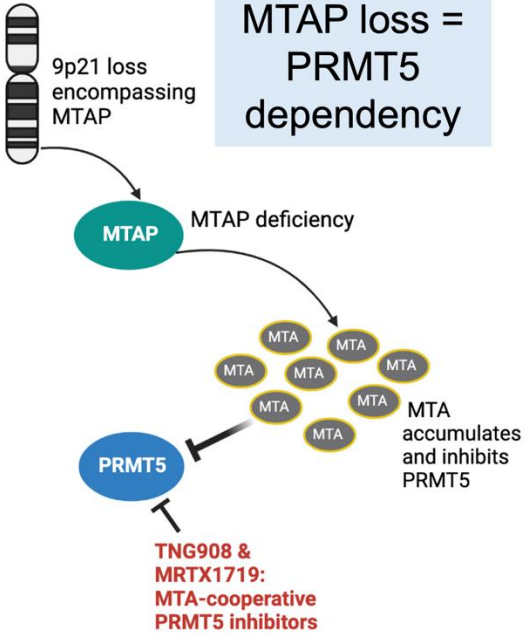


Exploiting Meso Therapeutic Vulnerabilities

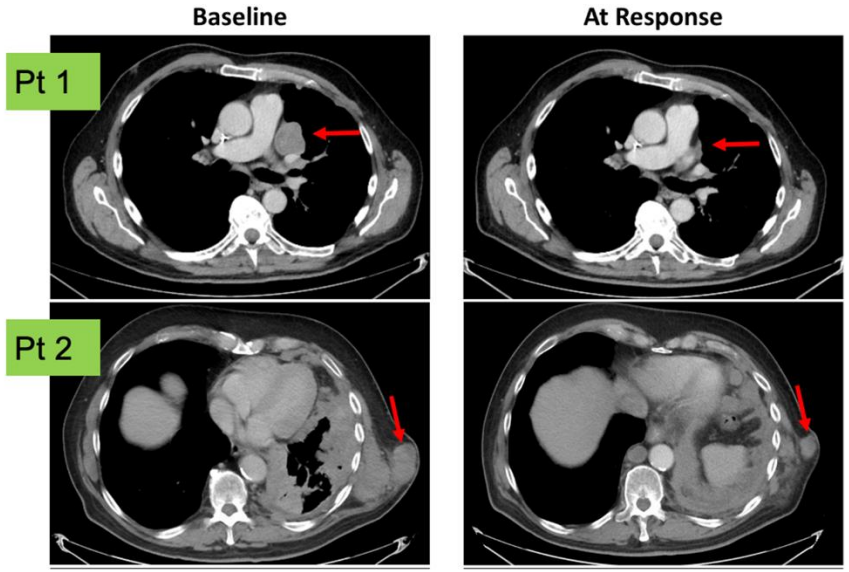
Impact of MTAP loss on Survival



MTAP loss = PRMT5 dependency



Clinical responses to MRTX1719



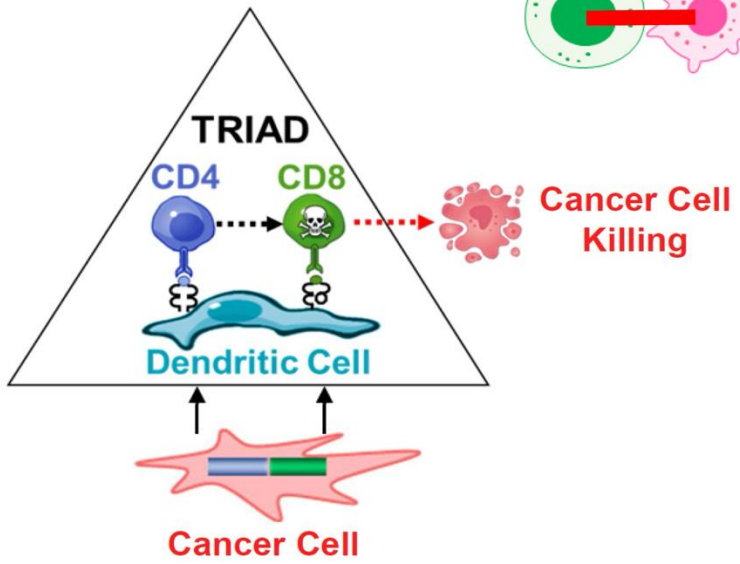
Engstrom Cancer Discovery 2023

Advances in Mesothelioma Immunology

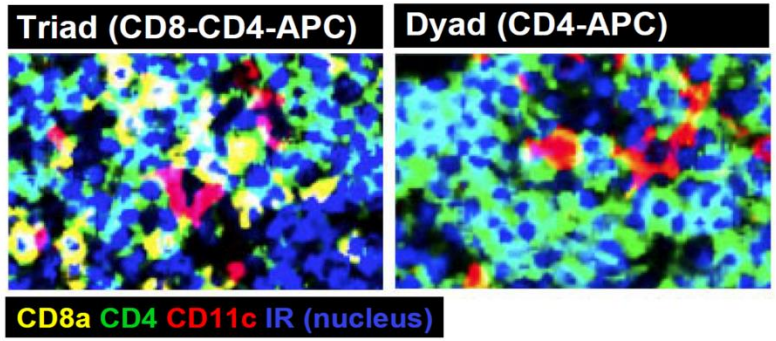
Hyun-Sung Lee, M.D., Ph.D.

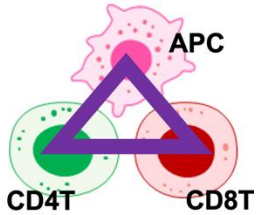
Systems Onco-Immunology Laboratory
David J. Sugarbaker Division of Thoracic Surgery
Michael E. DeBakey Department of Surgery
Baylor College of Medicine, Houston TX, USA

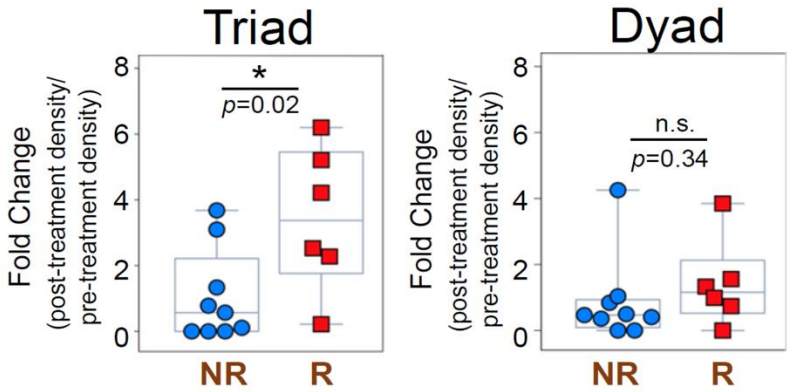
Triad (CD4+CD8+DC): Co-localization of immune cells



Cancer Cell Killing



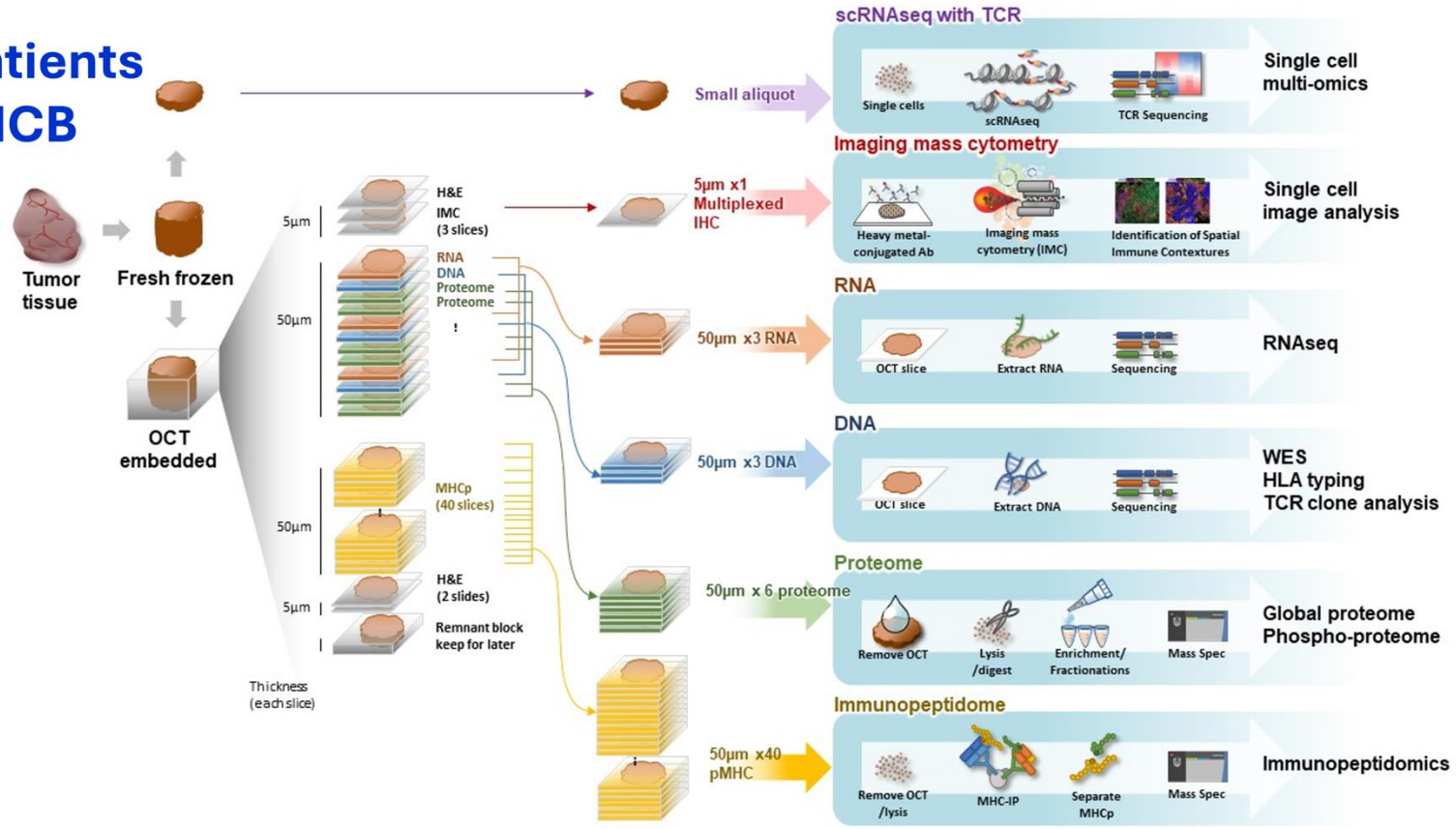




Intratumoral immune triads are required for immunotherapy-mediated elimination of solid tumors: Espinosa-Carrasco,..., Burt, Lee, Schietinger. Cancer Cell 2024

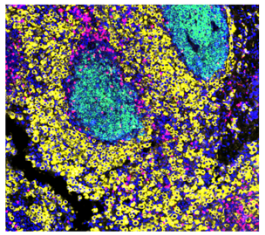
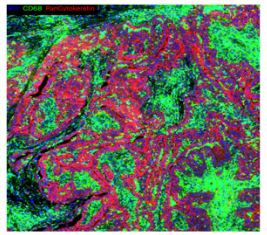
MPM Immunoproteogenomics

54 MPM patients
Receiving ICB



Unpublished

Determinants of response/resistance to ICB for MPM

Immune Checkpoint Treatment	Favorable	Unfavorable
Intrinsic	BAP1 mutation Tumor PD-L1 (+) Non-epithelioid	9p21.3 loss Tumor PD-L1(-) Epithelioid
Extrinsic	TLS, Triads, NK-like T 	CAF, TAMs 
Immunogenetics	HLA-A*02:01	HLA-A*03:01/24:02
pMHC-I Cluster	1	2 or 3
Liquid biomarker	Low SMRP	High SMRP

Targeting TROP-2 in Diffuse Pleural Mesotheliomas

Michael Offin, MD

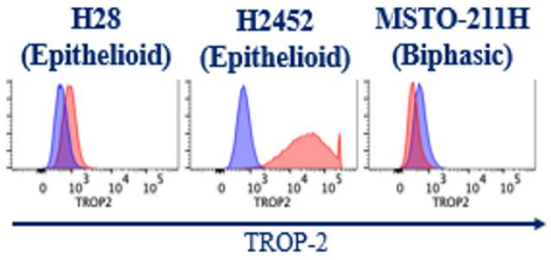
Memorial Sloan Kettering Cancer Center

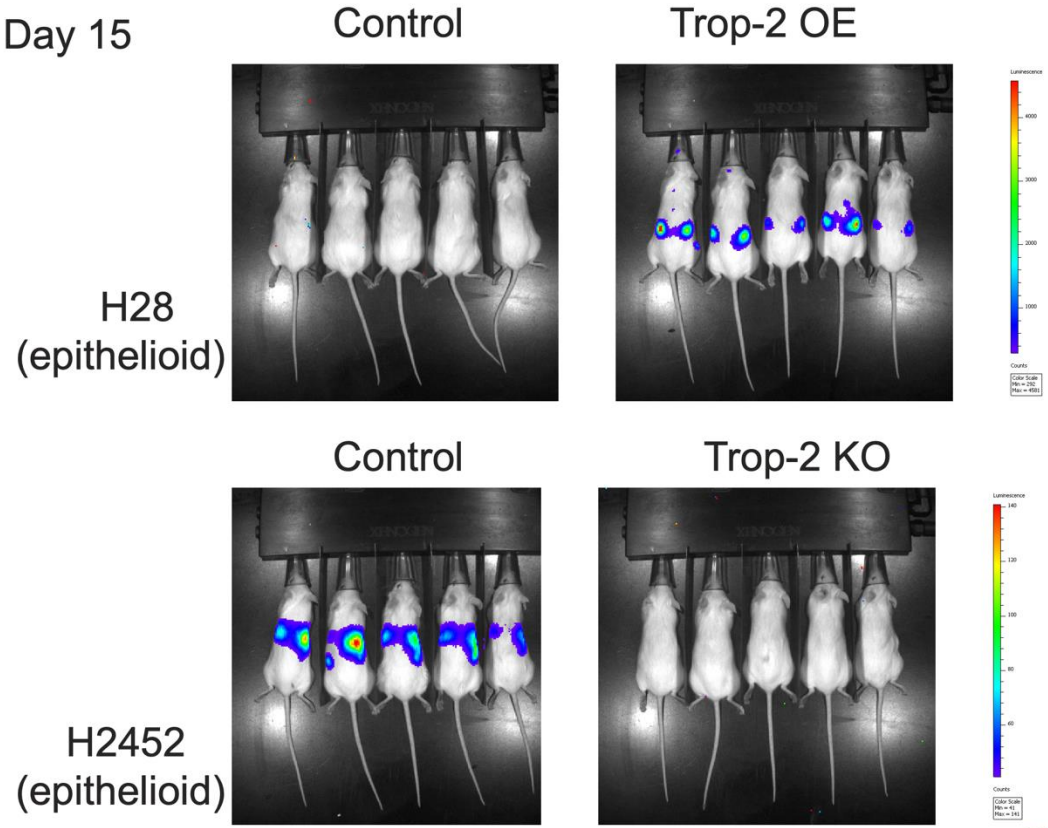
United States

TROP-2 expressing cell lines lead to increased in vivo metastatic potential

Intracardiac injection:

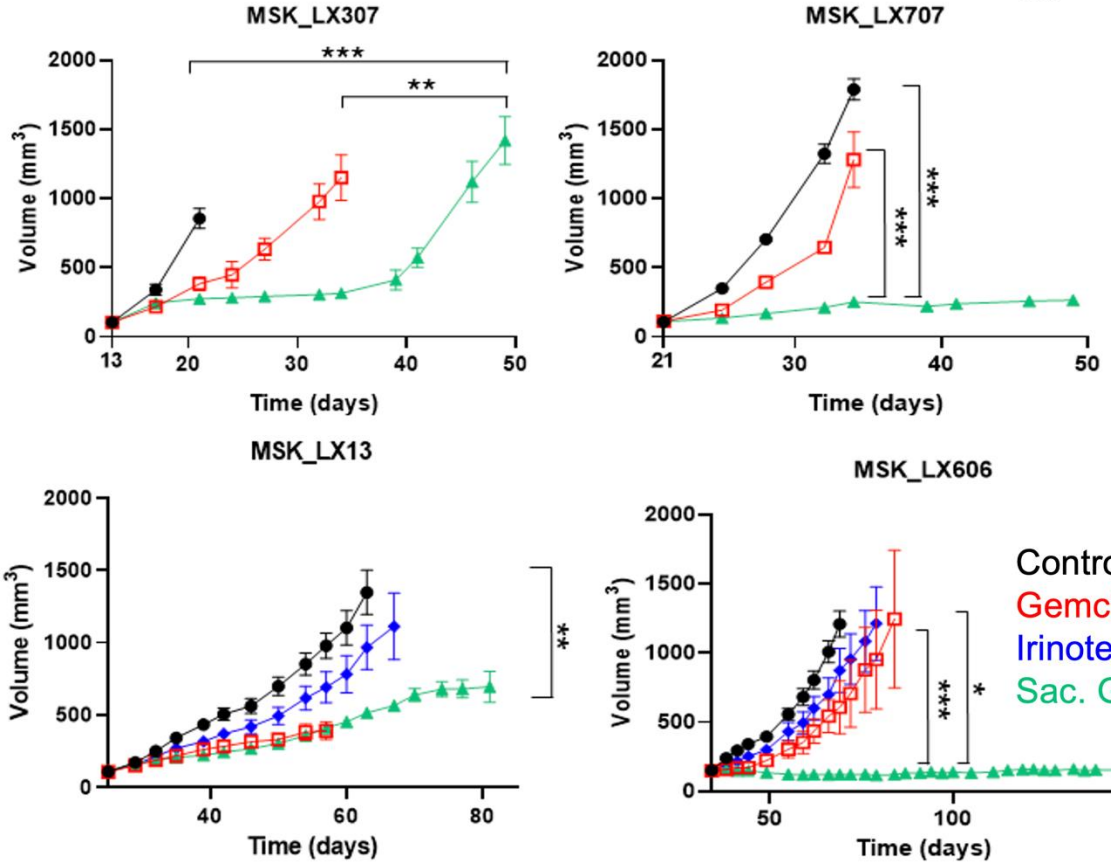
- TROP-2 expressing and induced cell lines lead to increased metastasis
- TROP-2 low and knockout cell lines lead to decreased metastatic potential

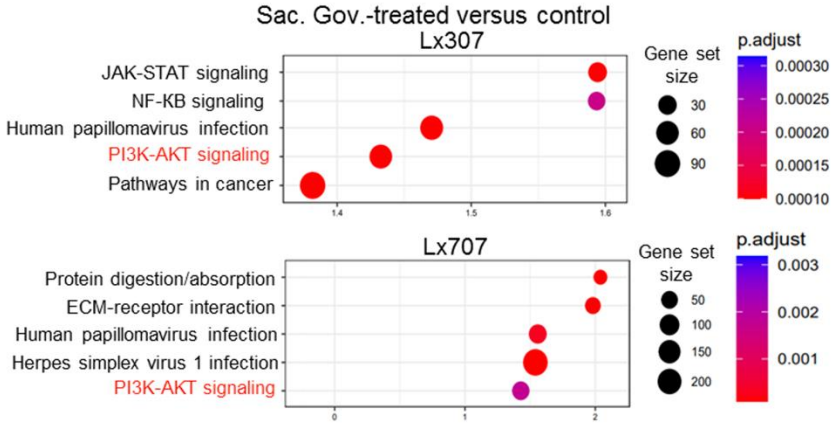


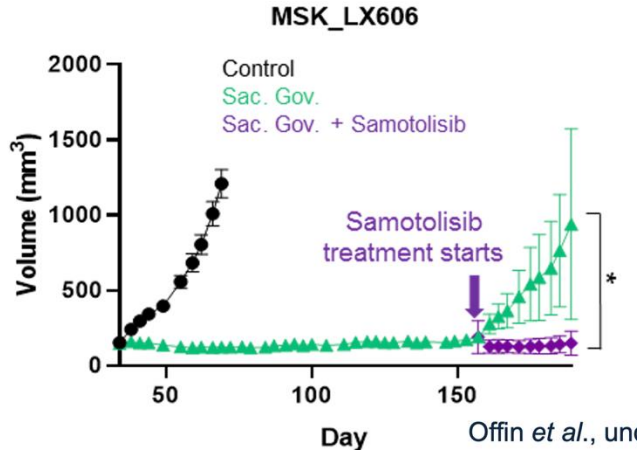


Offin *et al.*, under review

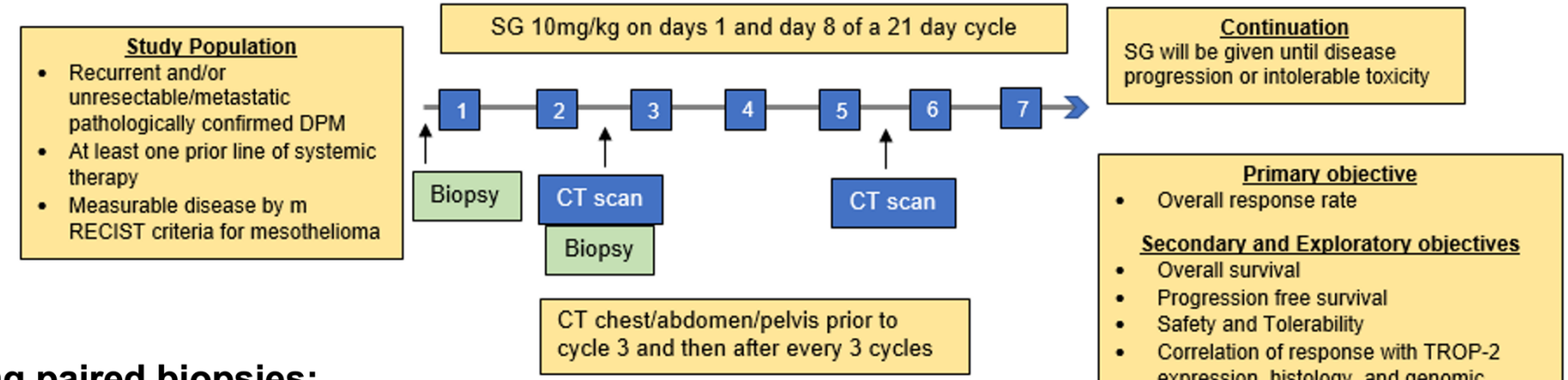
We demonstrated *in vivo* activity and a potential pathway of resistance with Sacituzumab govitecan in our PDX models







Offin *et al.*, under review



Leveraging paired biopsies:

A. Determine TROP-2 expression in biopsy samples
- identify a critical minimum threshold (if any) of expression for SG activity
- correlate expression with clinicopathologic features and pathway changes

B. Define the role of PI3K-AKT activation and mechanistic changes in DPM tumor samples treated with SG

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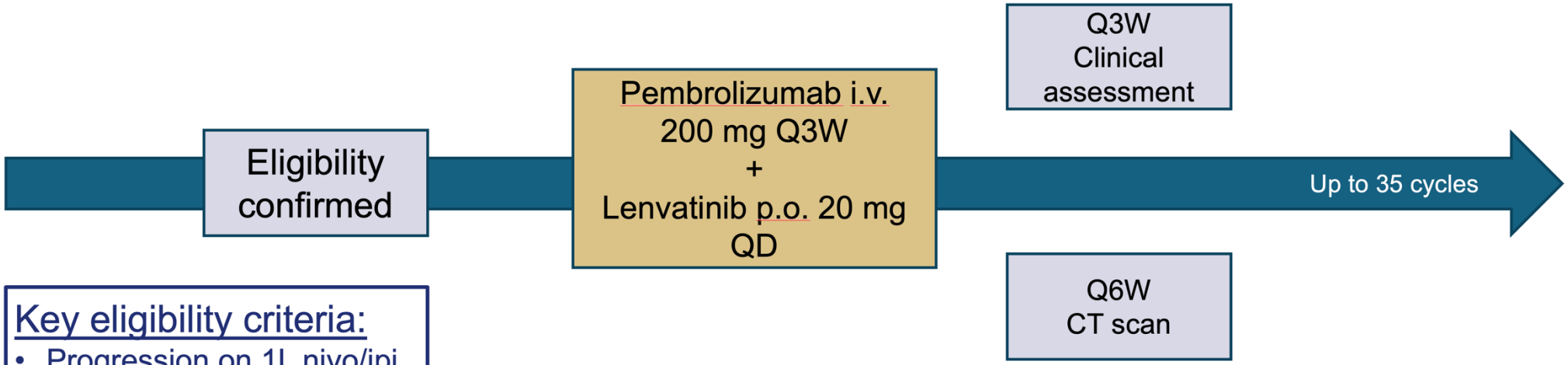
PEMbrolizumab Plus Lenvatinib In Second-Line Pleural MEsotheLiomA Patients: A Single Arm Phase II Study - PEMMELA (second cohort)

L.H. Douma, V. van der Noort,
F. Lalezari, J. de Vries, M. Vermeulen, B. Schilder,
I. Smesseim, P. Baas, J.A. Burgers, C.J. de Gooijer

Netherlands Cancer Institute
Department of Thoracic Oncology

Trial Design

Single-arm, single-center, phase II study

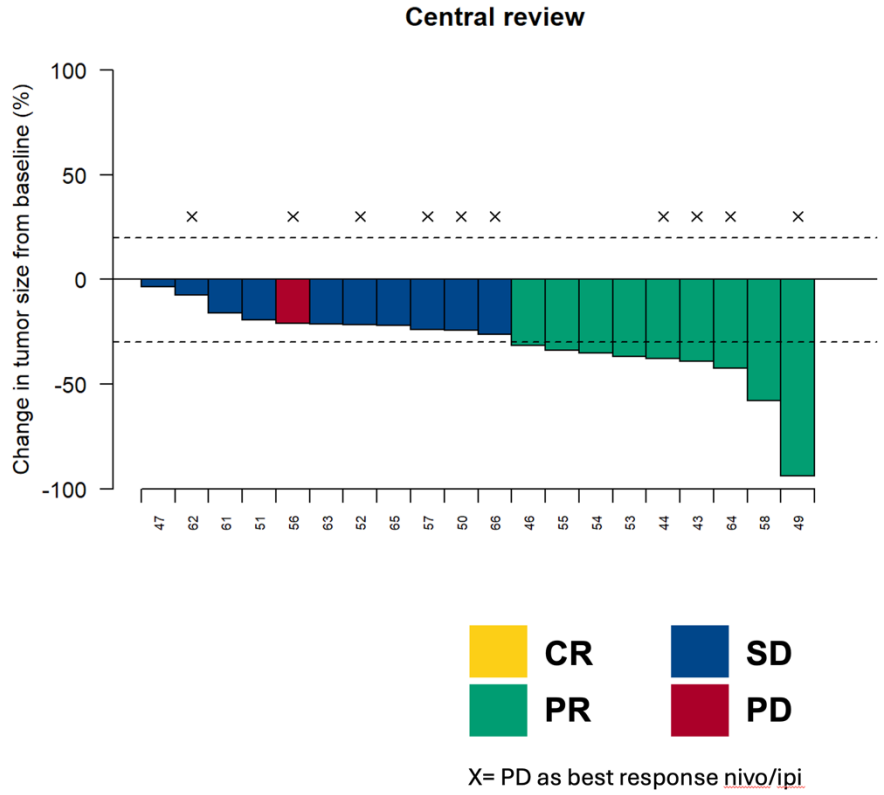


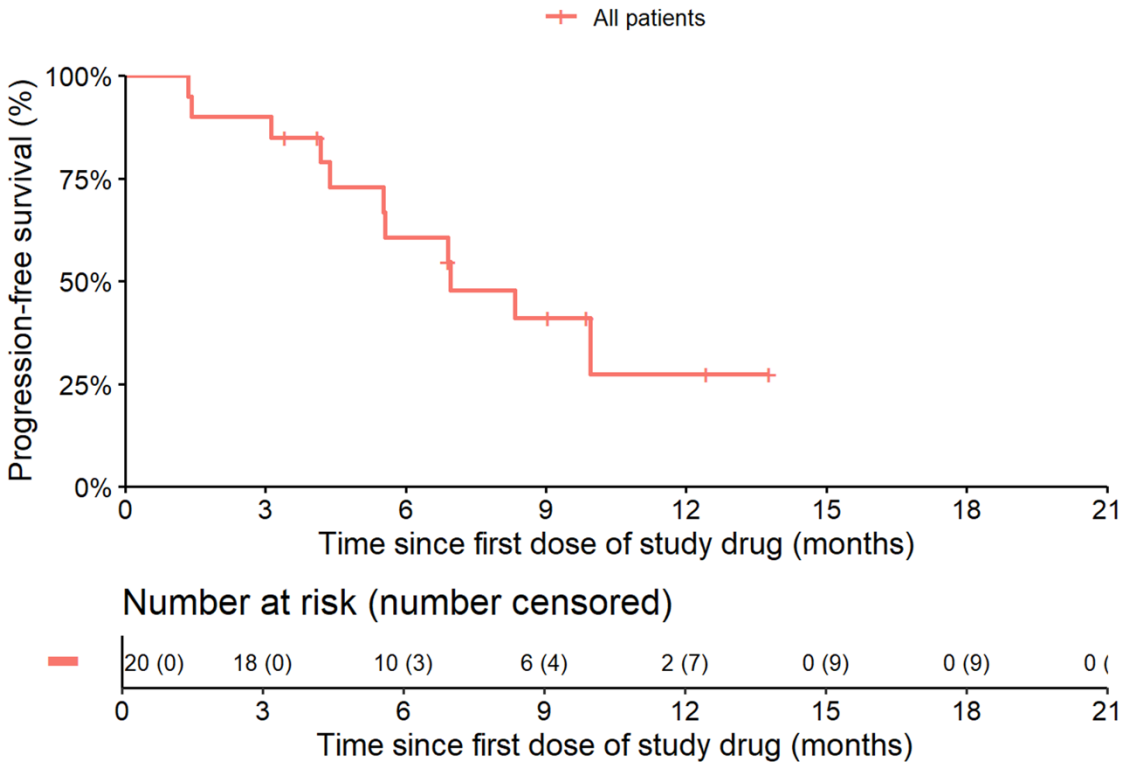
Key eligibility criteria:

- Progression on 1L nivo/ipi
- Measurable disease
- ECOG PS 0-1

Objective Response Rate

	Local investigator	Independent central reviewer (2nd endpoint)
	PEM+LEN (N=20)	PEM+LEN (N=20)
Objective response (95% CI) -%	60 (39-82)	45 (23-67)
Best overall response – n(%)		
CR	1 (5)	0 (0)
PR	11 (55)	9 (45)
SD	6 (30)	10 (50)
PD	2 (10)	1 (5)





mPFS 7.0 months (95% CI 5.5 – NA)

	Grade 1-2 n,(%)	Grade 3 n,(%)	Grade 4 n,(%)
Fatigue	14 (70)	1 (5)	0
Dysphonia	12 (60)	0	0
Anorexia	7 (35)	1 (5)	0
Diarrhea	9 (45)	0	0
Hypertension	4 (20)	5 (25)	0
Oral pain	7 (35)	0	0
Malaise	3 (15)	3 (15)	0
Proteinuria	4 (20)	0	0
Hyponatremia	0	0	1 (5)
Neutrophil count decreased	0	0	1 (5)
Respiratory failure	0	0	1 (5)

Thymoma

- Originates from epithelial cells of the thymus
- Symptoms such as chest pain, cough, phrenic nerve palsy can arise from mass effect
- Paraneoplastic syndromes including MG, PRCA, hypogammaglobulinemia, pancytopenia, and collagen vascular disease can occur with thymoma
- Treatment can involve surgery, radiation, and chemotherapy

Kumawat et al. *APJCC.* 2024

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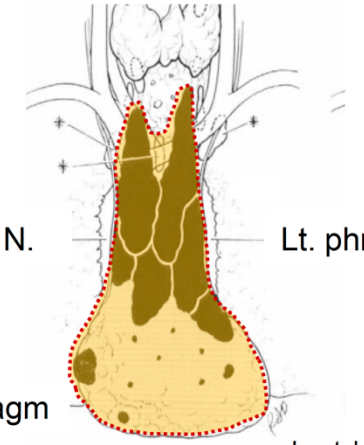
Validity of simple thymomectomy for clinical stage I thymoma without myasthenia gravis:a propensity score-matched analysis

Tomoyuki Hishida, Takahiro Suzuki, Seiji Omura, Yu Okubo, Kyohei Masai, Kaoru Kaseda, and Keisuke AsakuraDivision of Thoracic Surgery, Department of Surgery,Keio University School of Medicine, Tokyo, Japan

The modes of resection of thymomas

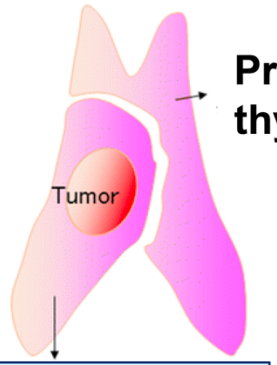
Total thymectomy (extended thymectomy, "Total")



Jaretzki, A. Neurology 1997.

Has been recommended as a standard mode of resection for all thymomas.[1]

Simple thymomectomy ("Simple")



Preserved healthy thymus

Resected thymus

Yano, M, et al. World J Surg 2017.

Has been widely introduced for early stage thymomas without myasthenia gravis (MG).[2,3]

Patients and methods

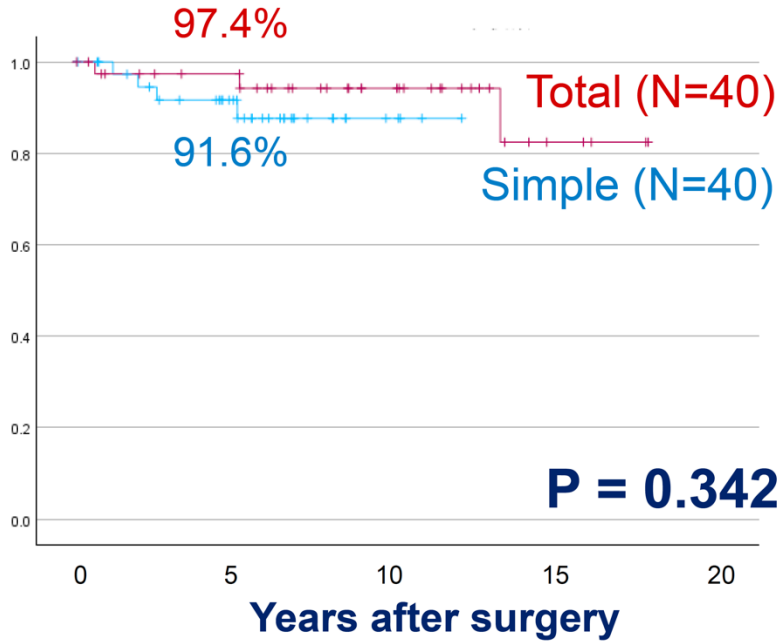
- A total of 119 consecutive patients who underwent surgery for clinical stage I thymoma without MG (cT1N0M0 in the 8th TNM) or a suspected lesion which was diagnosed with thymoma at final pathology between 2003 to 2018 at our institution.
- “Simple” or “Total” was determined by a multidisciplinary treatment board, but recent trend favored “Simple” using minimally invasive approaches if the tumor was <5 cm preoperatively.
- “Total” was performed according to extended thymectomy proposed by Masaoka et al.[1]
- We conducted a one-by-one propensity score-matched analysis to reduce potential selection biases between “Simple” and “Total”.

[1]Masaoka, A, et al. Ann Thorac Surg 1996;62:853-9.

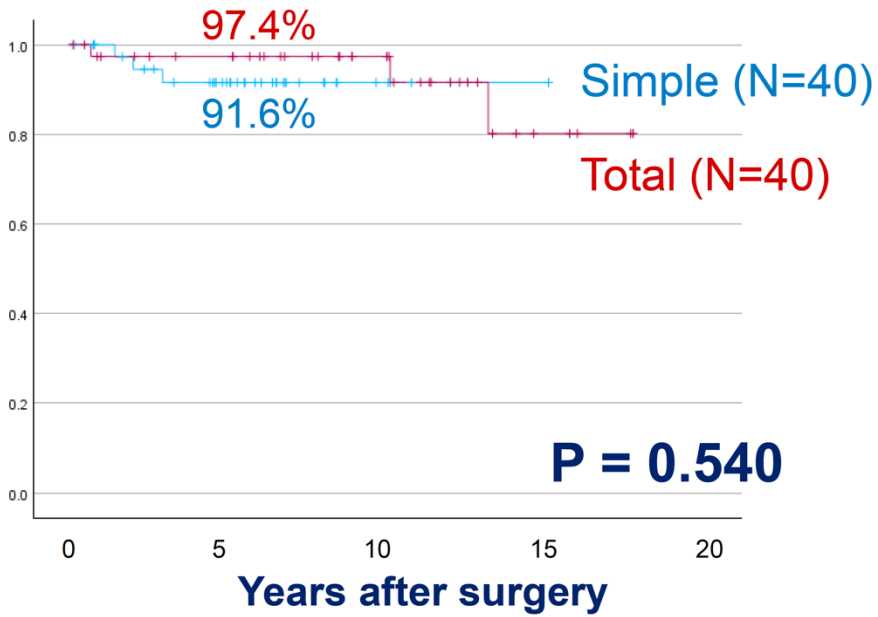
Survival outcomes (after PS matching)

- Matched with 4 preoperative factors (age, gender, preoperative size, anti-AchR antibody)
- Forty patients in each group were compared.

RFS



OS



Median follow-up period: 7.0 years (0.1-19.2)

Detailed long-term outcomes

	Simple thymomectomy (N = 50)	Total thymectomy (N = 69)
Thymoma recurrence	3 (6%) (Local: 2, lung: 1)	3 (4%) (Dissemination)
Preoperative size	All were ≥5 cm	All were ≥5 cm
Recurrence in ≥5 cm tumor	38% (3/8)	10% (3/29)
Death	3 (6%) (Thymoma: 2, gastric cancer: 1)	3 (4%) (Pneumonia: 2, unknown: 1)
Postoperative MG	0	3 (4%) (<1M, 3M, 1Y9M)
Postoperative autoimmune diseases other than MG	0	3 (4%) (Basedow disease: 2, SLE: 1)