

THYMUSCARCINOMEN HOE AANPAKKEN?

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MALIGNE TUMOREN IN HET VOORSTE MEDIASTINUM

- Bij volwassenen vaak thymoma of thymuscarcinoma
- Lymfoom
- Germinoom
- Midline carcinoom

PRESENTATIE

- Incidentele bevinding
- Lokale symptomen: pijn, hoest, dyspnee, stridor, hemoptoë, dysfagie, dysfonie, vena cava superiorsyndroom
- Systemische symptomen:
 - Anorexie
 - Gewichtsverlies
 - Koorts
 - nachtzweten
- Paraneoplastische symptomen

PARANEOPLASTISCH

- Neuromusculair:
 - Myasthenia gravis (15% heeft thymoma)
- Immunologisch:
 - T-cell dysfunctie
- Hematologisch:
 - Pure red cell aplasie
 - Thrombopenie
- Endocrien:
 - Cushing
 - Hypercalcemie
- Mucocutaan:
 - Lichen planus



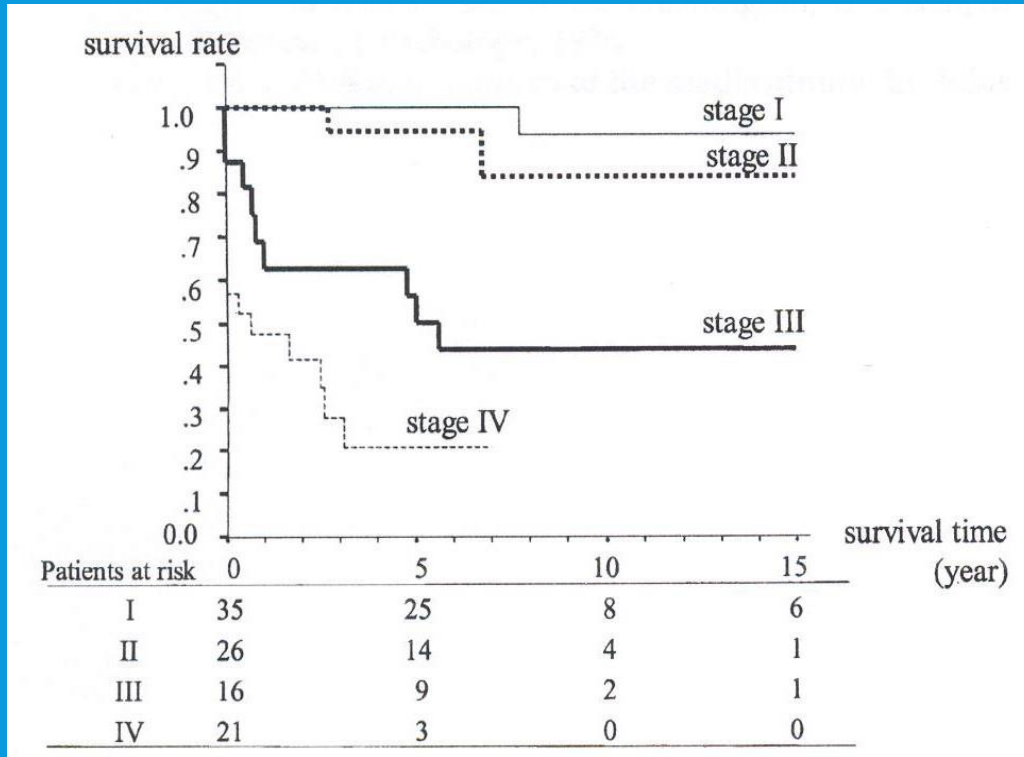
PATHOLOGIE

- Thymoma (A, AB, B1, B2, B3): 85-90%; omkapseld of lokaal invasief
- Thymuscarcinoma (C): 5-10%; lokaal invasief, hematogene spreiding
- Neuro-endocriene tumor (NET) en neuro-endocrien thymuscarcinoma: 5%
- Thymolipoma
- Adenocarcinoma

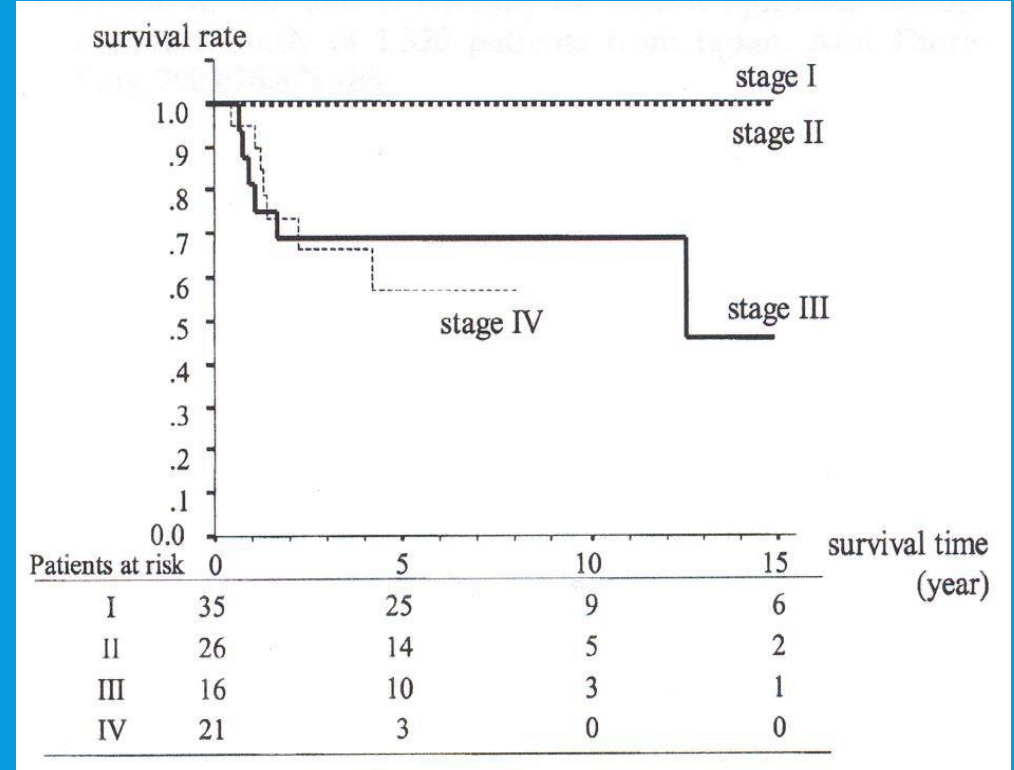
MASAOKA

- Stadium I: volledig omkapseld
- Stadium II
 - A: Invasie in het kapsel
 - B: Invasie in het vetweefsel of de pleura
- Stadium III: invasie in naburige organen (de long, de n. phrenicus, de vaten)
- Stadium IV
 - A: Pleurale of pericardiale spreiding (droplet metastasen)
 - B: Lymfogene of hematogene spreiding

DFS



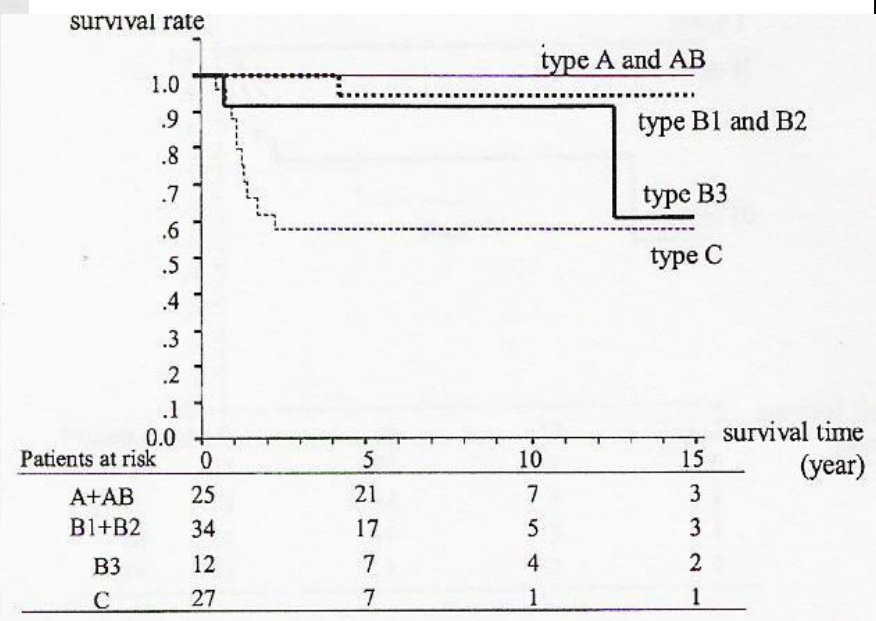
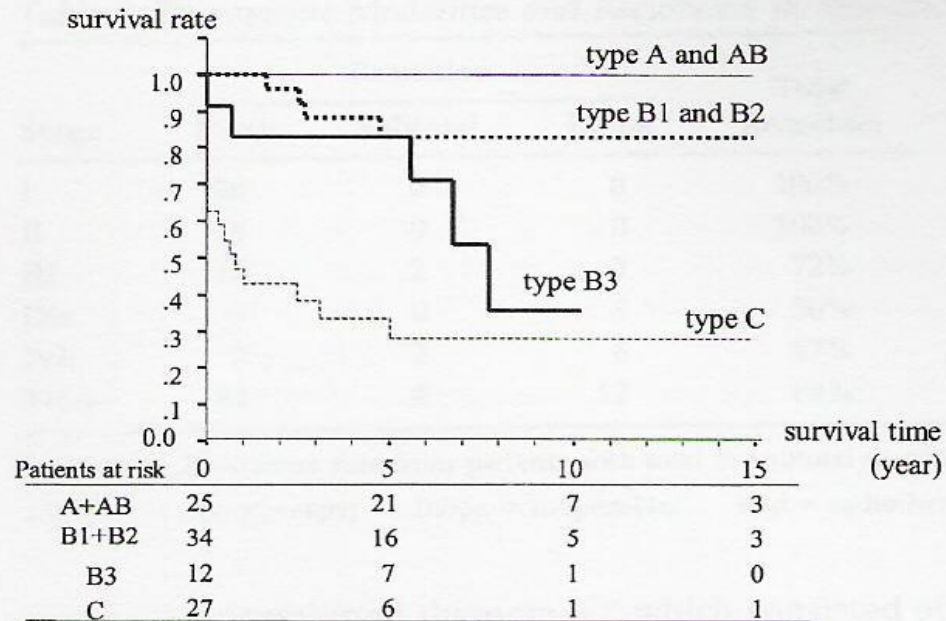
OS



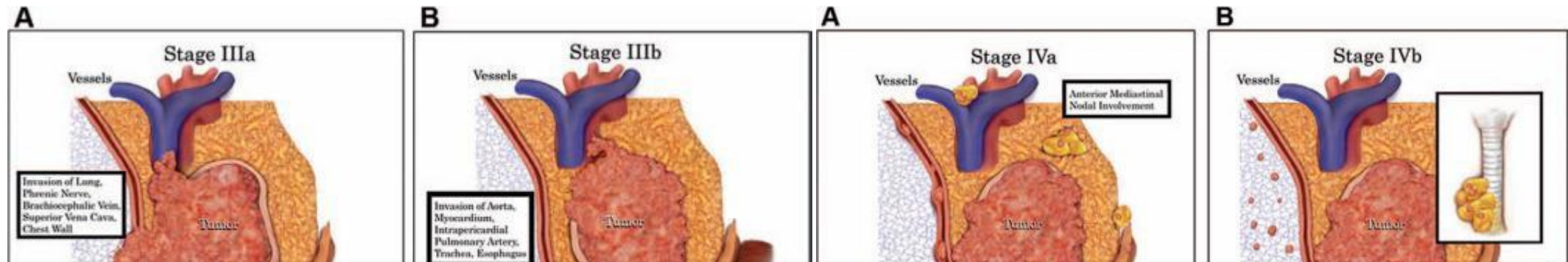
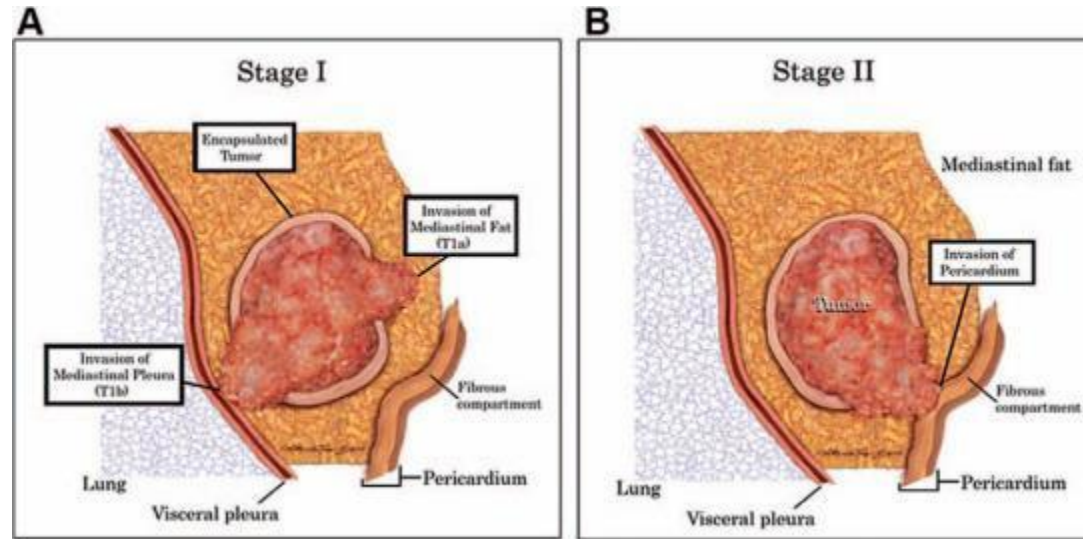
DFS

OS

WHO classification

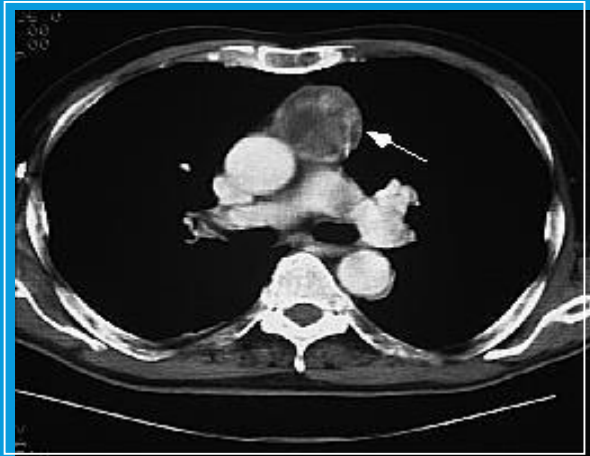


TNM 8th Edition



Multimodale therapie

IN DE PRAKTIJK:



Indicatie voor resectie:

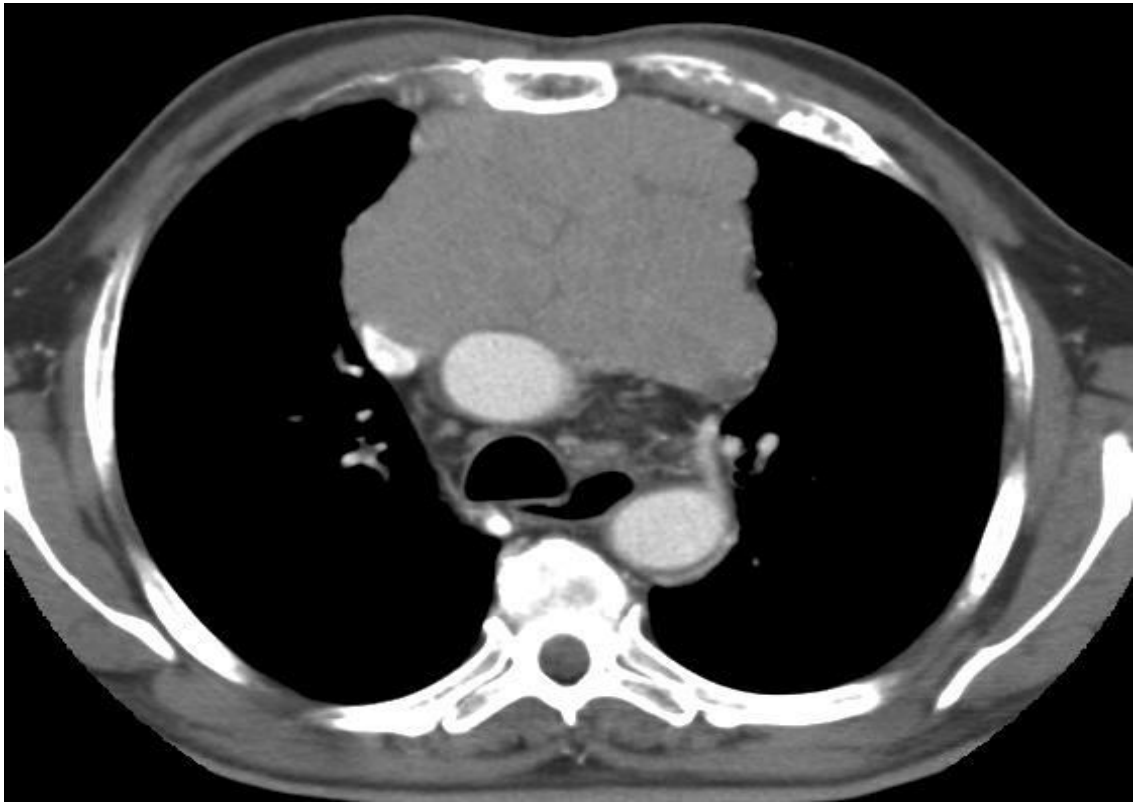
- Solitair
- Niet invasief
- Geen kiemcelmerkers
- Volledig resecabel



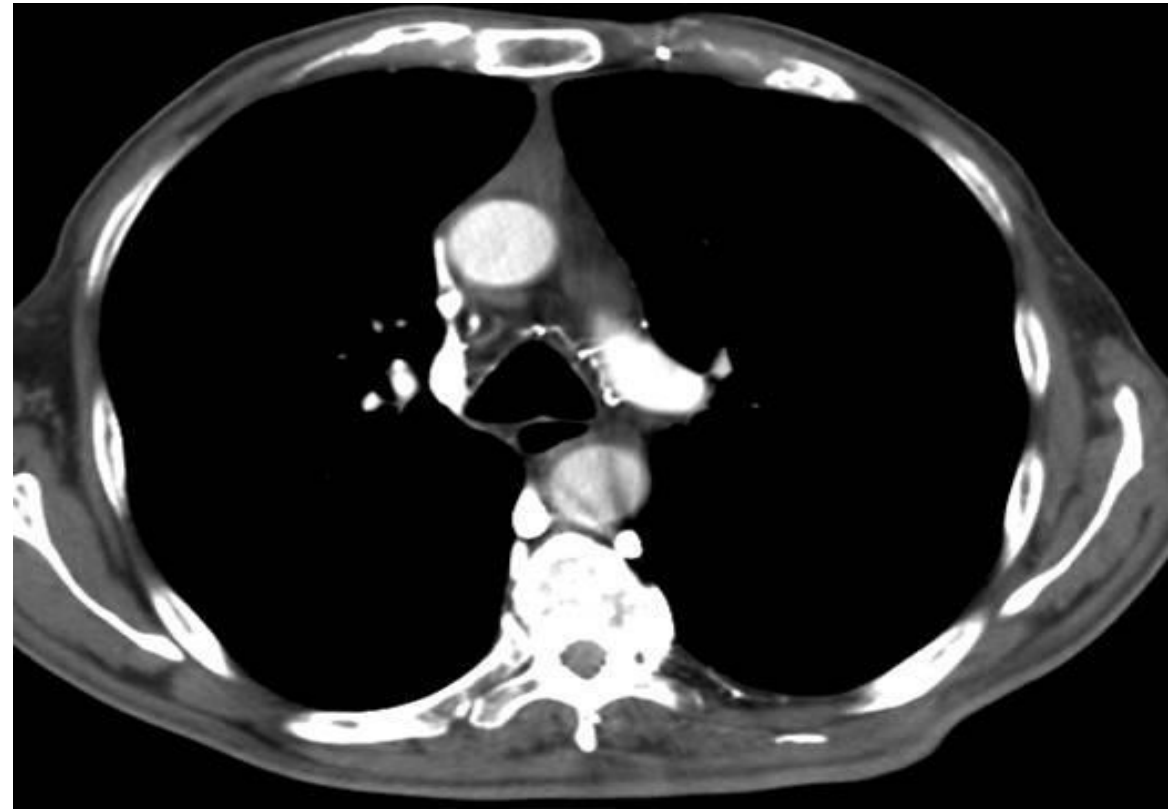
Indicatie voor biopsie en
inductie

- Niet goed primair resecabel
- Nood aan weefseldiagnose

Inductiechemotherapie



Pre



Post

Baseline



Na 3 cycli



GEEN RCT...



		n	ORR	CR	OS (maanden)
CAP 500-50-50	thymoma	29	50%	10%	38
CAP 500-60-90	thymoma, <i>induction</i>	22	77%	14%	
ADOC 50-40-0,6-700	thymoma, <i>retrospective</i>	37	92%	43%	15
Cbcda taxol (6auc-225)	thymoma	21	43%	14%	NR
Cbcda taxol (6auc-225)	thymuscarcinoma	23	22%	0%	20
Cddp vp16 (60-360)	thymoma	16	56%	31%	52
VIP (75-5000-80)	both	28	32%	0%	32
Pembrolizumab	thymuscarcinoma	40	23%	0%	>24
Pembrolizumab	both	33	21%	0%	NR
Sunitinib	both	41	17%	0%	
Lenvatinib	thymuscarcinoma	42	38%	0%	

RESPONS (PLATINUM)

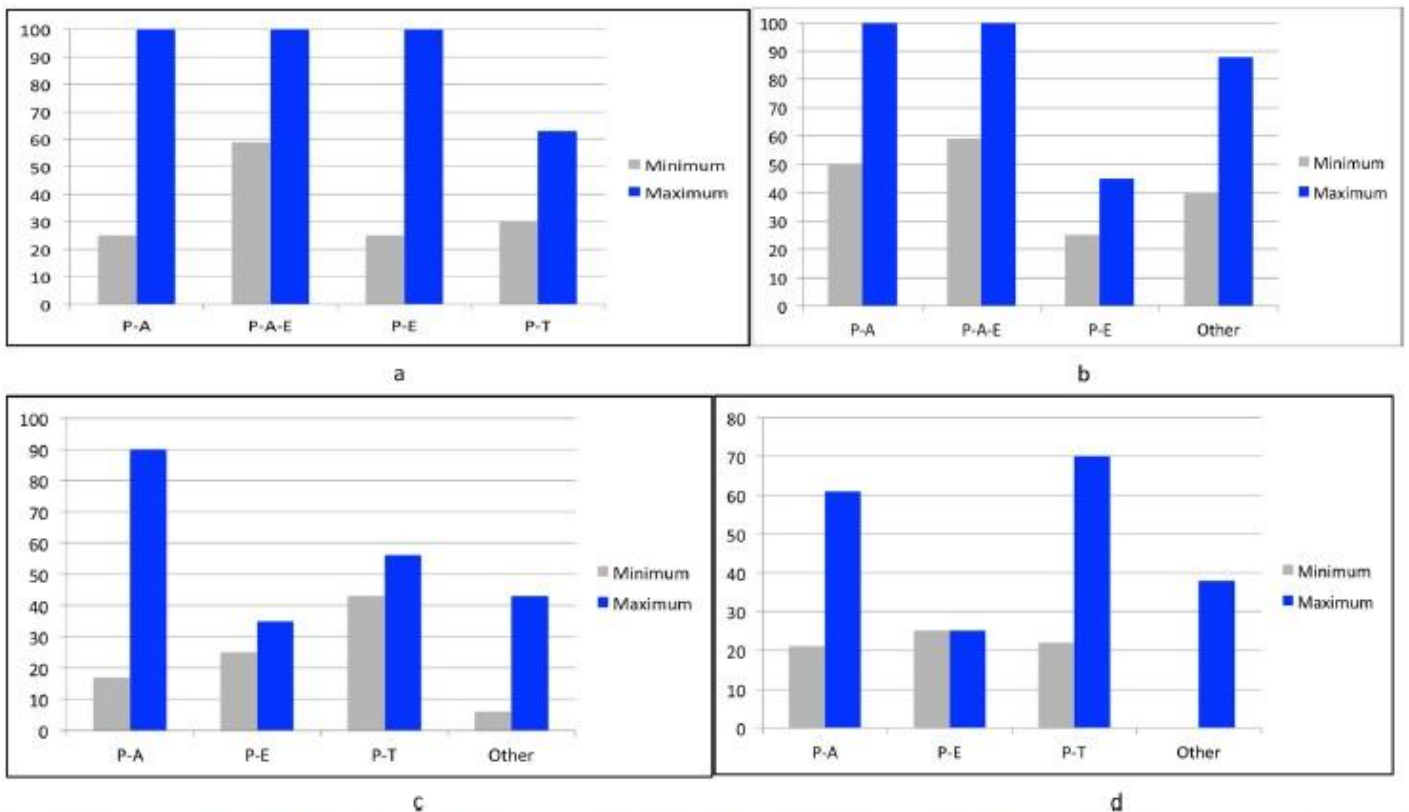


Fig. 1. (a) Response rates of platinum-based regimens. (b) Response rates of 1st line therapy. (c) Response rates in thymoma. (d) response rates in thymic carcinoma.

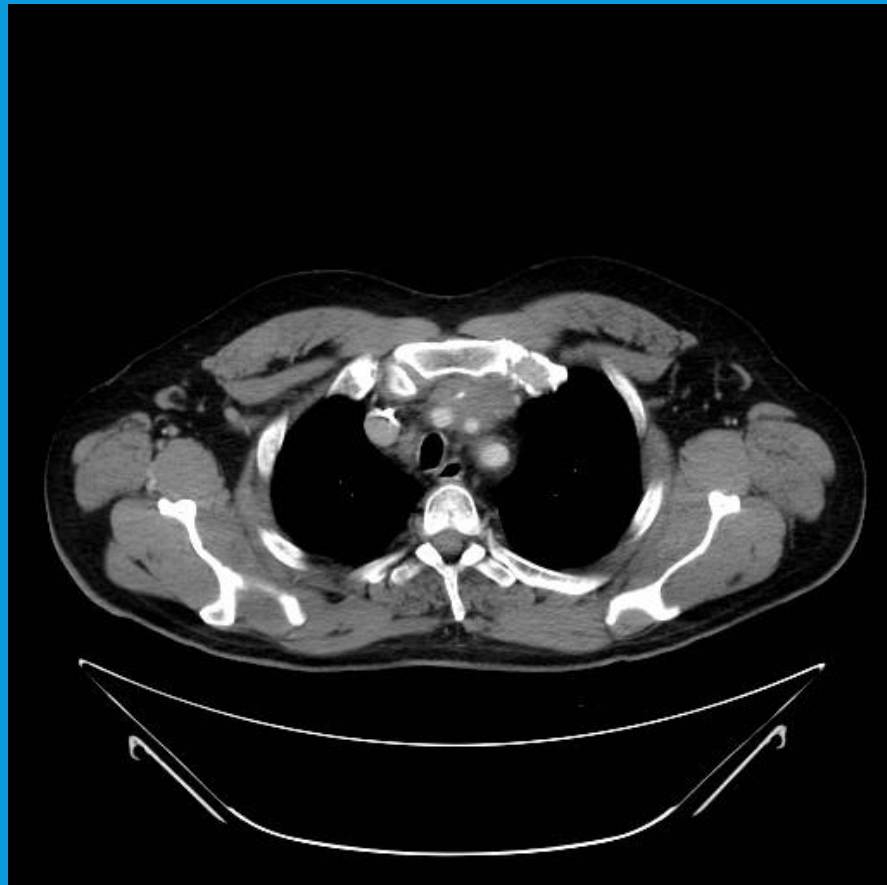
SAMENGEVAT



- Cisplatin-gebaseerde schema's lijken meest actief
- Partner compounds anthracycline of etoposide lijken evenwaardig
- Response rates boven 50%, zowel primair als bij hervat
- Zelfde schema's bij thymuscarcinomen als bij thymomen

Berghmans et al., Lung Cancer, 2018
Wei et al., Cochrane Database Syst Rev, 2013

NIET RESECABEL



INOPERABEL OF TWEEDE LIJN



- Chemotherapie: zelfde schema's
- Checkpoint inhibitoren
 - Pembrolizumab
 - Nivolumab
- Tyrosine kinase inhibitoren
- Octreotide

OCTREOTIDE



UZ
LEUVEN

KU LEUVEN

LKI
KANKERINSTITUUT



Table 5

Summary of targeted therapies and octreotide.

Reference	N	Drugs	Thymoma/TC	M/F	PS 0-1 (%)	ORR (%)	Survival	Therapeutic line	CT part of multimodal treatment
Giaccone 2009 [61]	7	Imatinib	2/5	6/1	43	0	MST 4m	> 1	NO
Palmieri 2012 [62]	15	Imatinib	12/3	10/5	100	0	NR	> 1	YES
Rajan 2014 [23]	49	Cixutumumab	37/12	26/23	84	10	MST 16.2m 5-year 0%	> 1	NO
Thomas 2015 [24]	40	Sunitinib	16/24	22/18	90	32	NR	> 1	NO
Remon 2016 [25]	28	Sunitinib	8/20	19/9	89	22	MST 15.4 m	> 1	NO
Gubens 2015 [63]	21	Saracatinib	12/9	11/10	NR	0	MST 23.1 m	> 1	NO
Zucali 2018 [26]	50	Everolimus	32/18	28/22	100	12	MST 25.7 m 1-year 72%	> 1	NO
Palmieri 2002 [27]	16	Octreotide + PDN	13/3	8/8	NR	38	MST 15 m	> 1	NO
Loehrer 2004 [28]	38	Octreotide +/- PDN	32/6	19/19	100	32	1 and 2-years 87% and 76%	> 1	NO
Kirzinger 2016 [64]	17	Octreotide + PDN	15/2	4/13	94	88	NR	1	NO

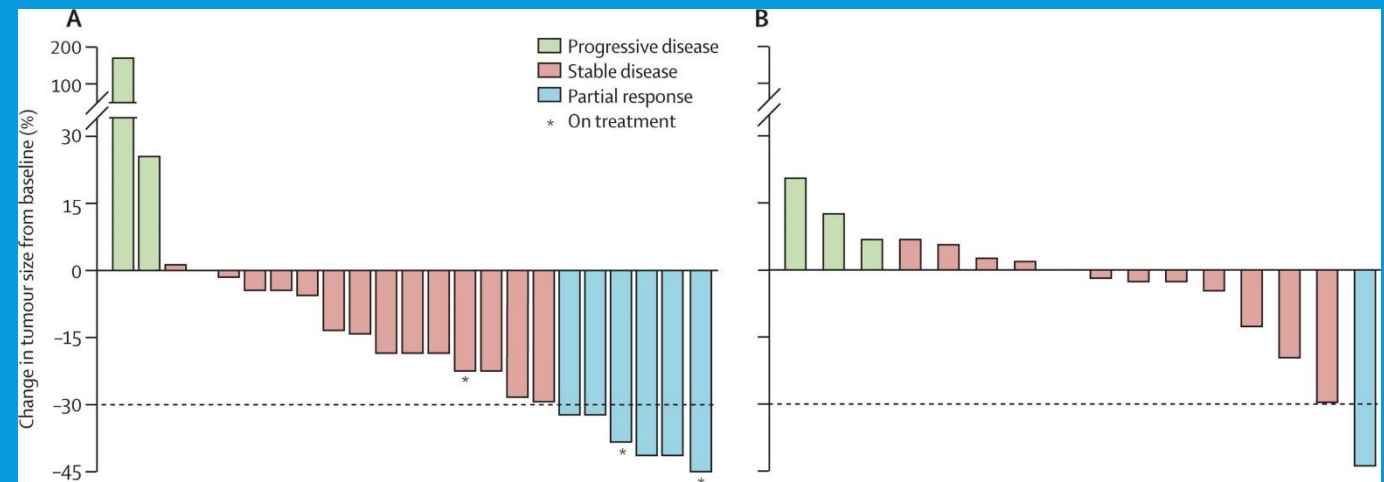
N = number of patients; TC = thymic carcinoma; ORR = overall response rate; M/F = male/female; PS = performance status; NR = not reported; MST = median survival time; PDN = prednisone; CT = chemotherapy.

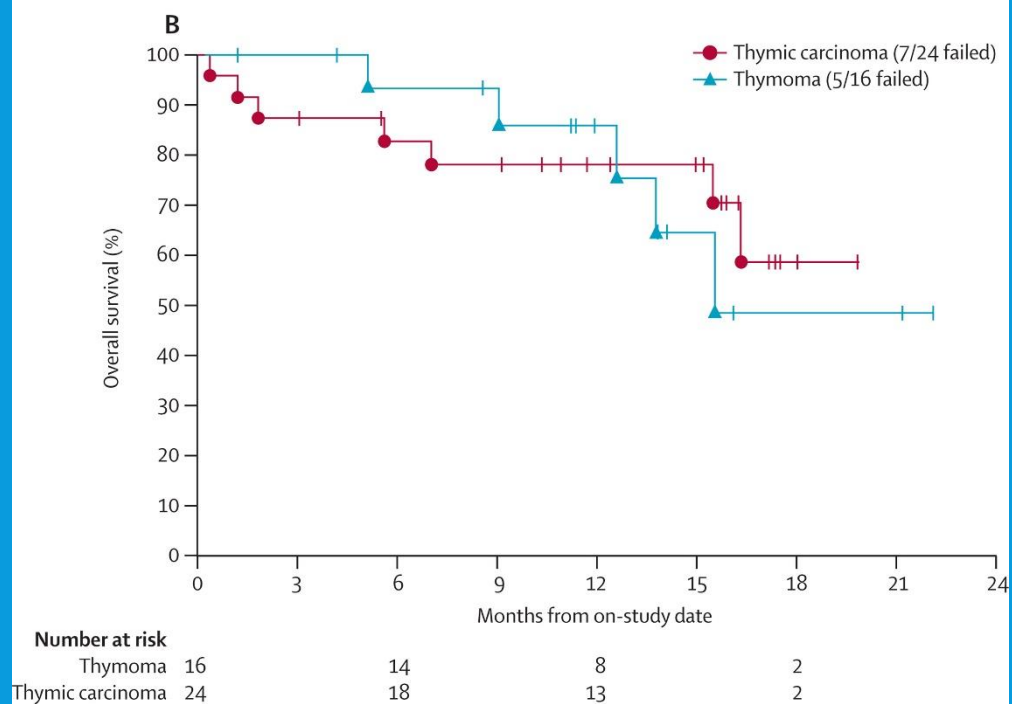
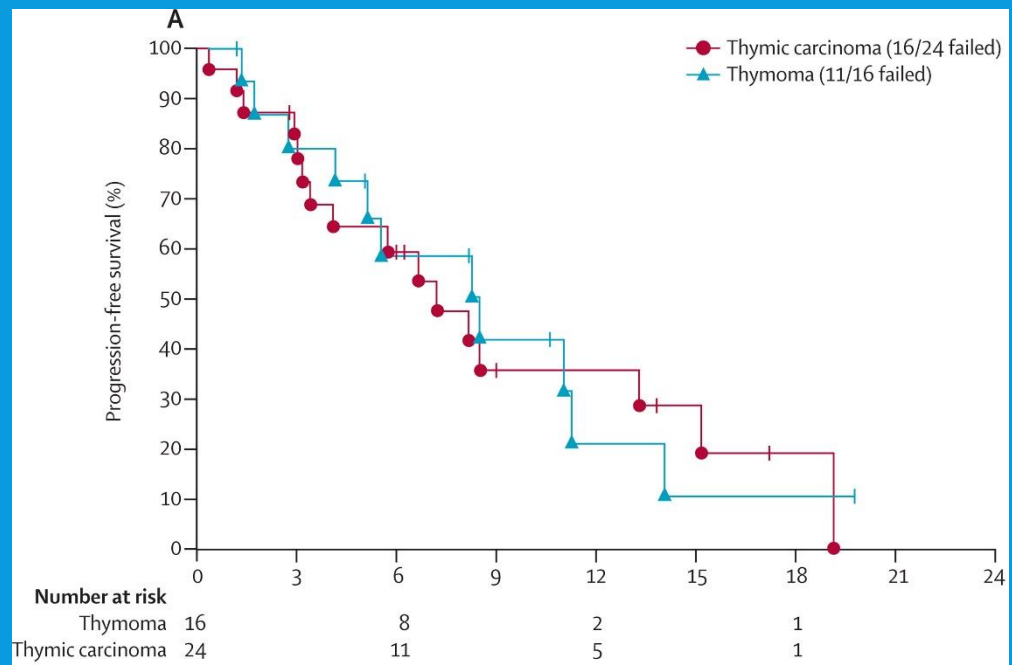
SUNITINIB

- Single arm fase 2, 2 centre
- Voorbehandeld met chemotherapie
- Eindpunt response rate

Thymuscarcinoma (25)

Thymoma (16)

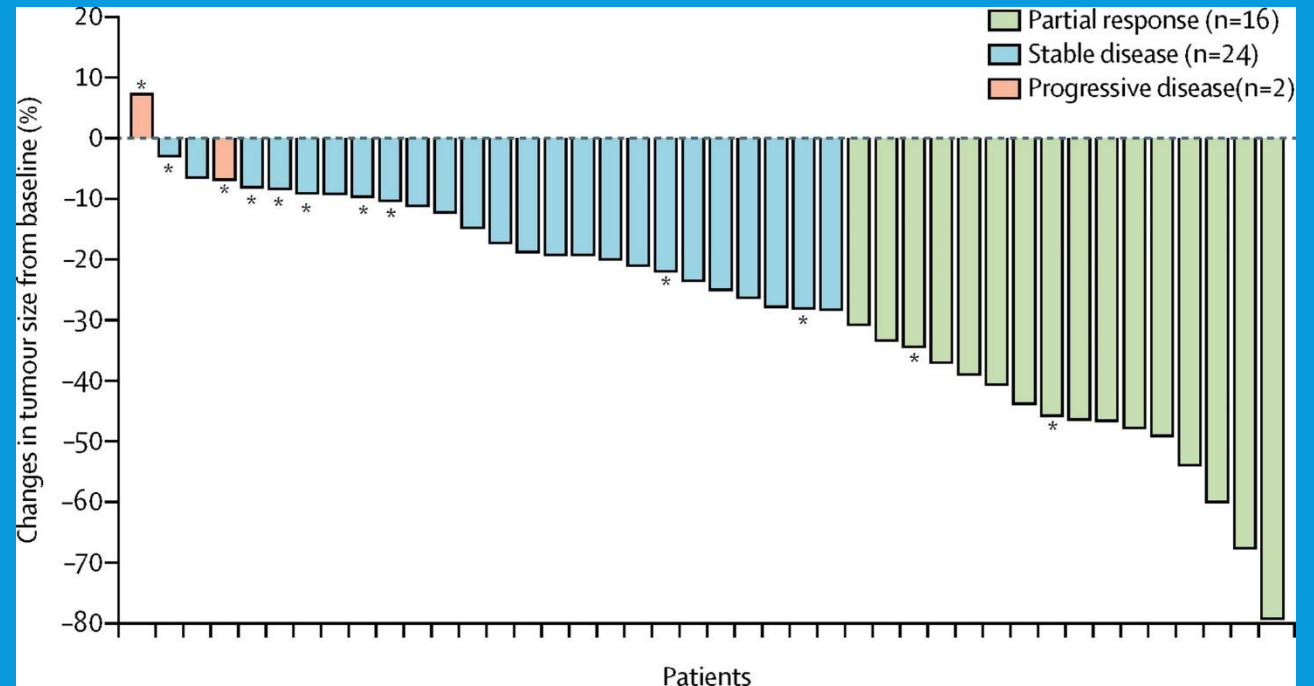


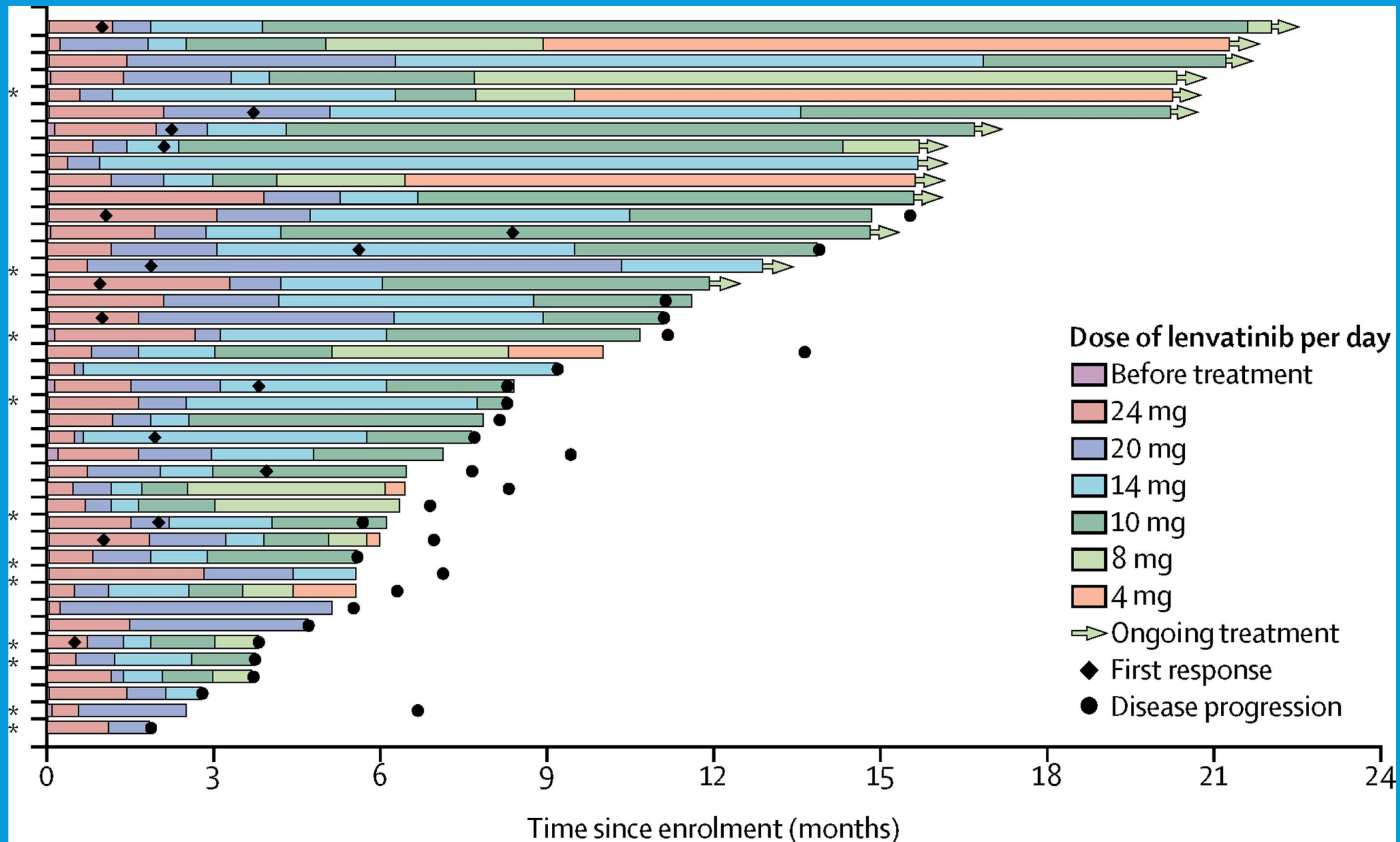


Thomas A., et al., Lancet Oncol, 2015

LENVATINIB

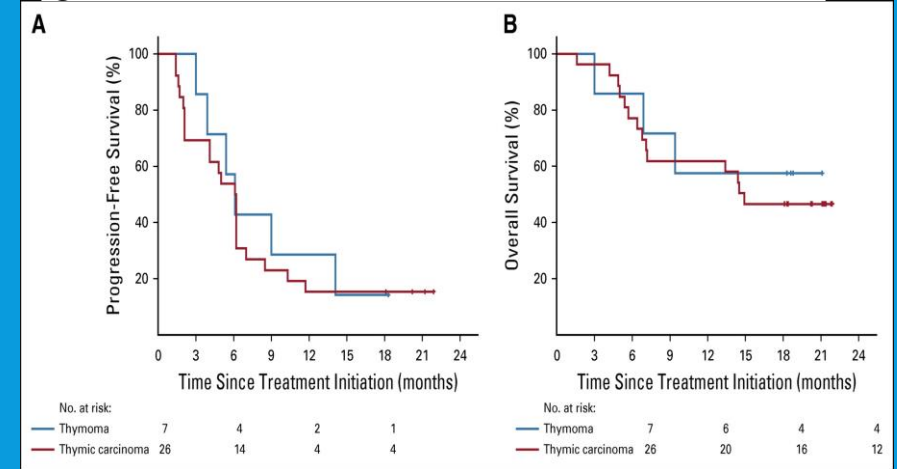
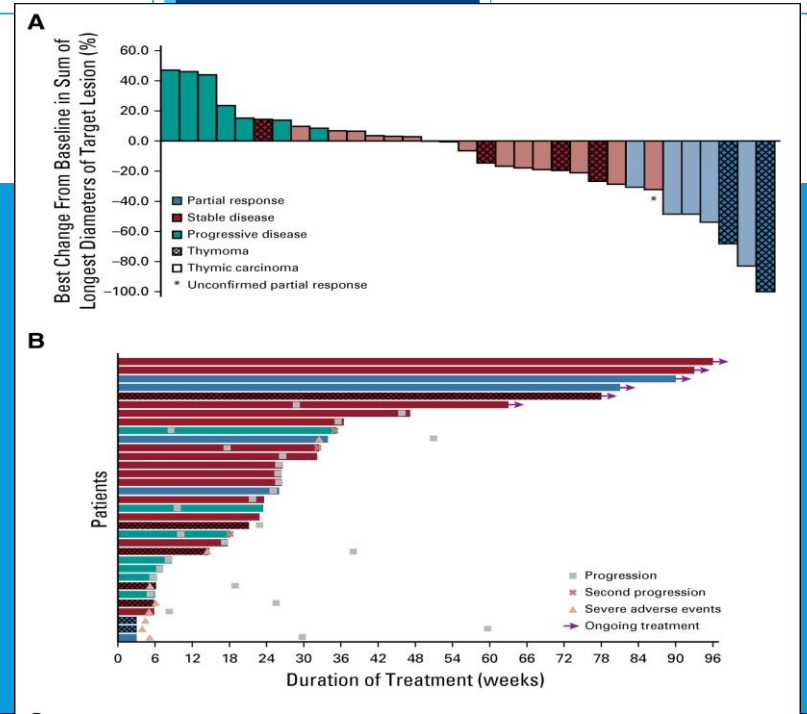
- Single arm fase II studie, multi center
- Voorbehandeld met chemotherapie
- Eindpunt = response rate
- N = 42





PEMBROLIZUMAB

- Single arm fase II, single center
- Voorbehandeld met chemotherapie
- Eindpunt = response rate
- Thymuscarcinoma n = 26; Thymoma n = 7
- Graad >2 AI nevenwerkingen bij 4/26 en 5/7(!)



Cho et al., J Clin Oncol 2019

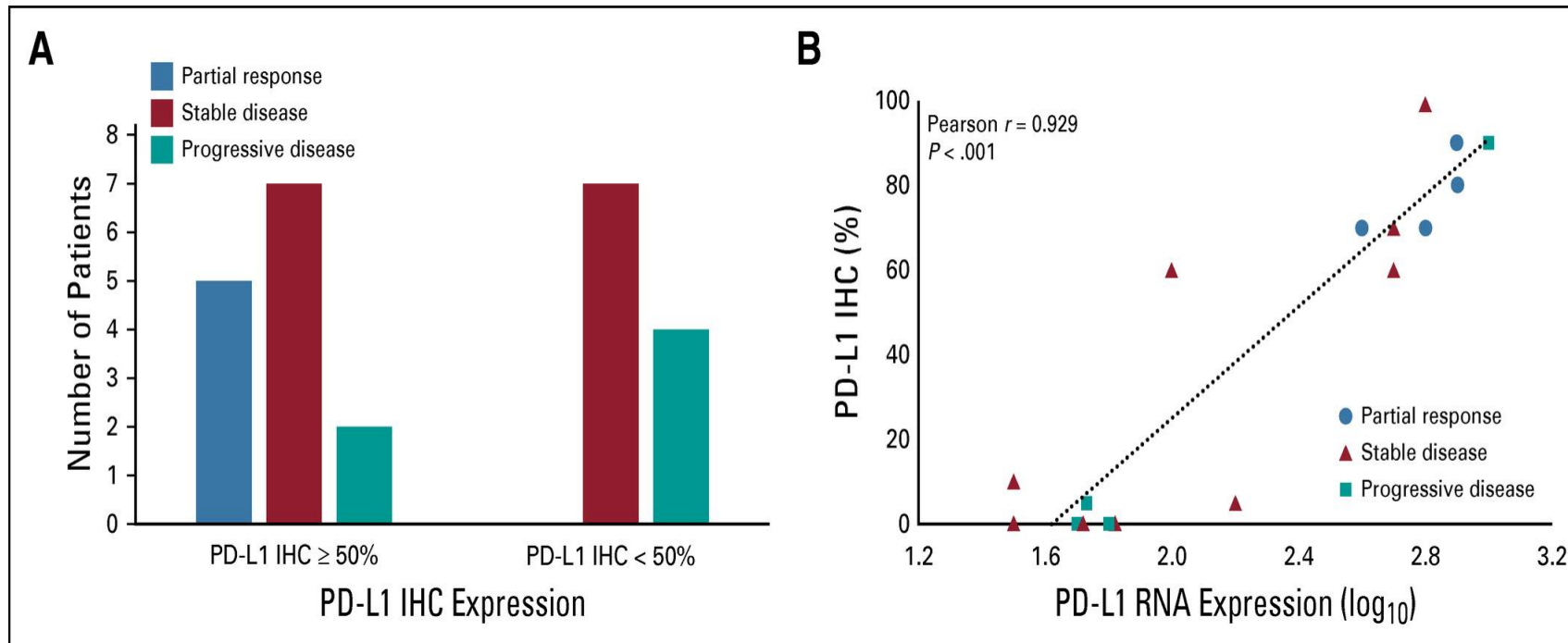
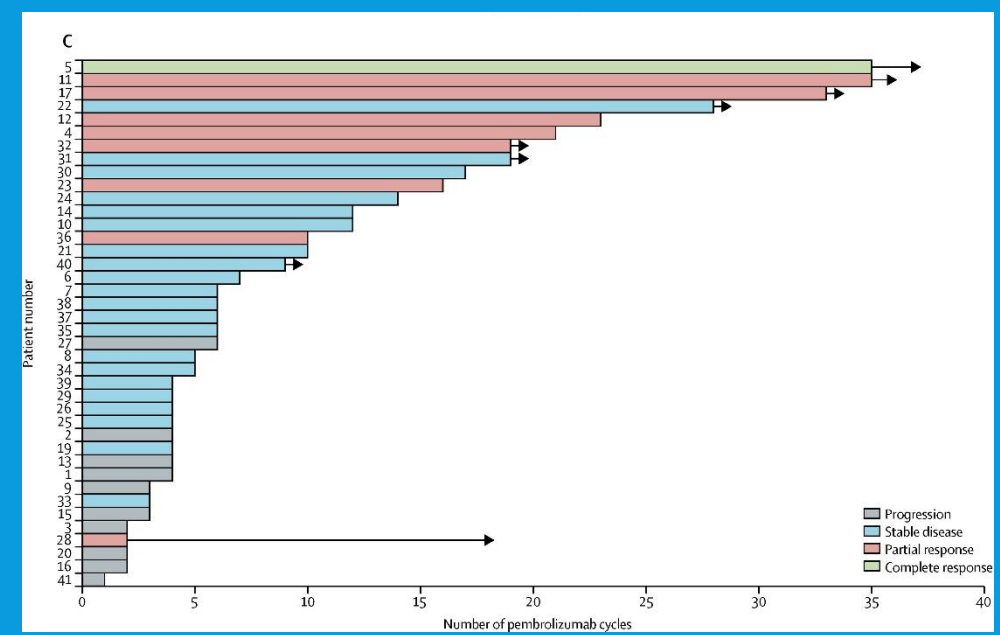
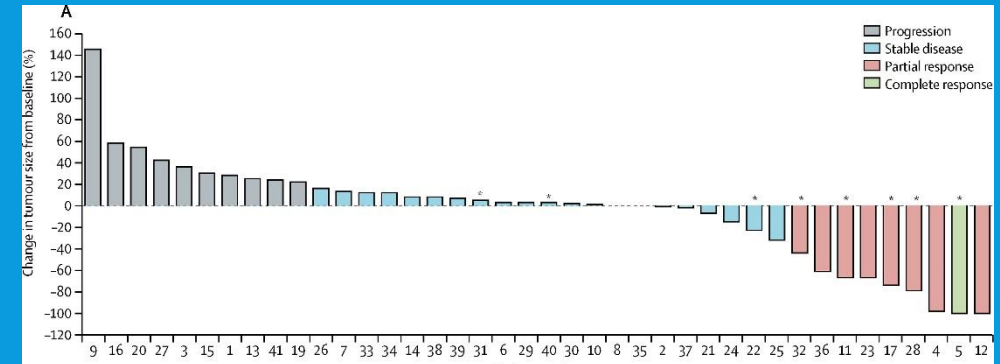


Fig 2. Association between programmed cell death ligand 1 (PD-L1) immunostaining or PD-L1 mRNA expression and best response in patients with available tumor samples for analysis. (A) All of five responders had \geq 50% PD-L1 immunohistochemistry (IHC) proportion score. (B) Correlation between PD-L1 IHC proportion score and PD-L1 mRNA expression on the basis of best response.

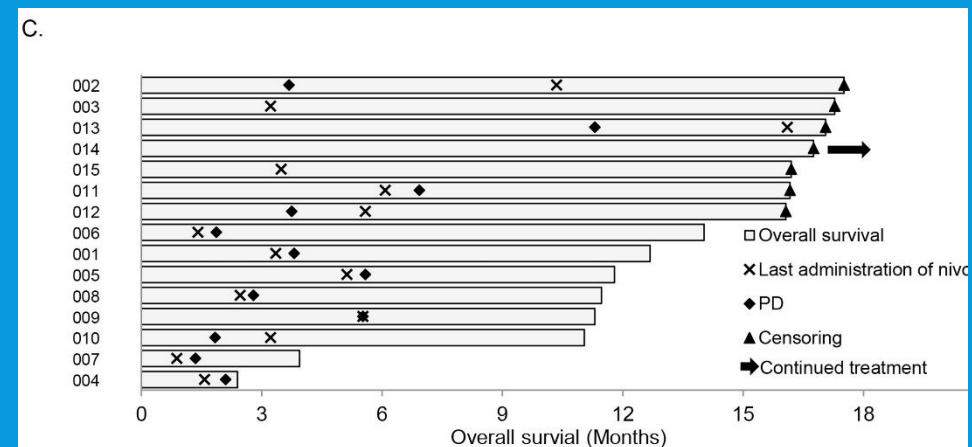
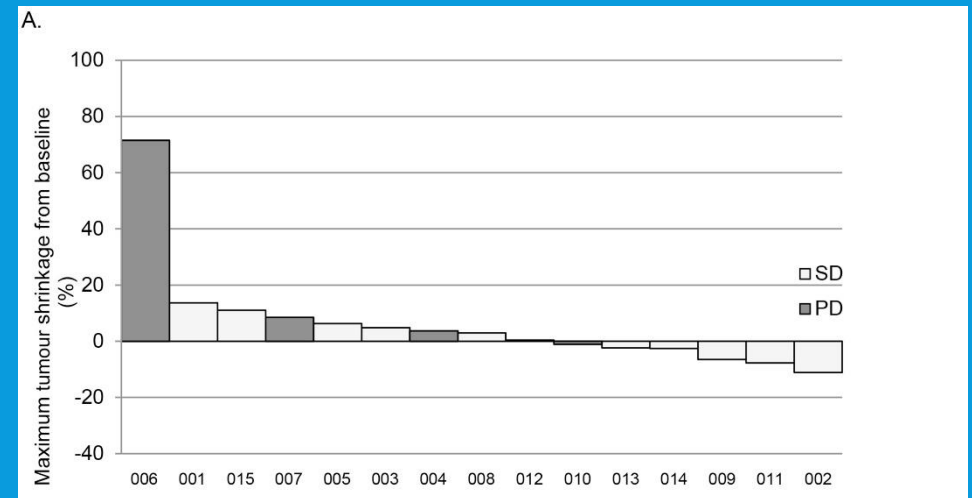
PEMBROLIZUMAB

- Single arm single center fase 2
- Voorbehandeld met chemotherapie
- Eindpunt = response rate
- Thymuscarcinoma, n = 41
- 6/41 AI SAE



NIVOLUMAB

- Single arm multicentre fase II
- Voorbehandeld met chemotherapie
- Thymuscarcinoma, n = 15
- Eindpunt = response rate: 0%
- 1/15 AI grade 3 AE



NIVOLUMAB

- EORTC Nivothym studie
- Voorbehandeld met chemotherapie
- N = 55 (45 thymuscarcinoma)
- Response rate 35% (39%)
- PFS 6: 50% (35%)
- OS 21,3 maanden
- 9 iAE graad 3

GEMCITABINE + CAPECITABINE

- Single arm multicentre fase II
- Voorbehandeld met chemotherapie
- 22 thymomas, 8 thymuscarcinomas (12 en 3 in preliminair report)
- 12 responsen (40%; 33% in TC)
- PFS 11 maanden
- OS₂₄ = 67%

PEMETREXED

- Single arm fase II
- Voorbehandeld met chemotherapie
- Eindpunt = PFS
- N = 27: Thymoma en Thymuscarcinoma (16/11)
- PFS 11 maanden (T) en 3 maanden (TC)

CONCLUSIE

- Bij nood aan inductie: platinum-gebaseerde chemotherapie
 - CAP
 - VIP of CE
- In palliatief stadium (keuze afhankelijk van ziektegeschiedenis, evolutiesnelheid, comorbiditeit):
 - Tweede lijn chemotherapie
 - Gemcitabine capecitabine
 - Paclitaxel
 - Octreotide bij positieve dotatate (vooral bij thymoma)
 - Tyrosinekinaseremmers off label
 - Immun Checkpoint inhibitie (niet beschikbaar)