BEOORDELING CHIRURGISCHE PREPARATEN NA NEOADJUVANTE IMMUUNTHERAPIE

Jan von der Thüsen

Erasmus MC

DISCLOSURES

(Potentiële) Belangenverstrengeling	
Voor bijeenkomst mogelijk relevante relaties met bedrijven	
Sponsoring of onderzoeksgeld	Astra Zeneca Bristol-Myers Squibb Roche Diagnostics
Honorarium of andere (financiële) vergoeding	Astra Zeneca Bristol-Myers Squibb Eli Lilly MSD Pfizer Roche

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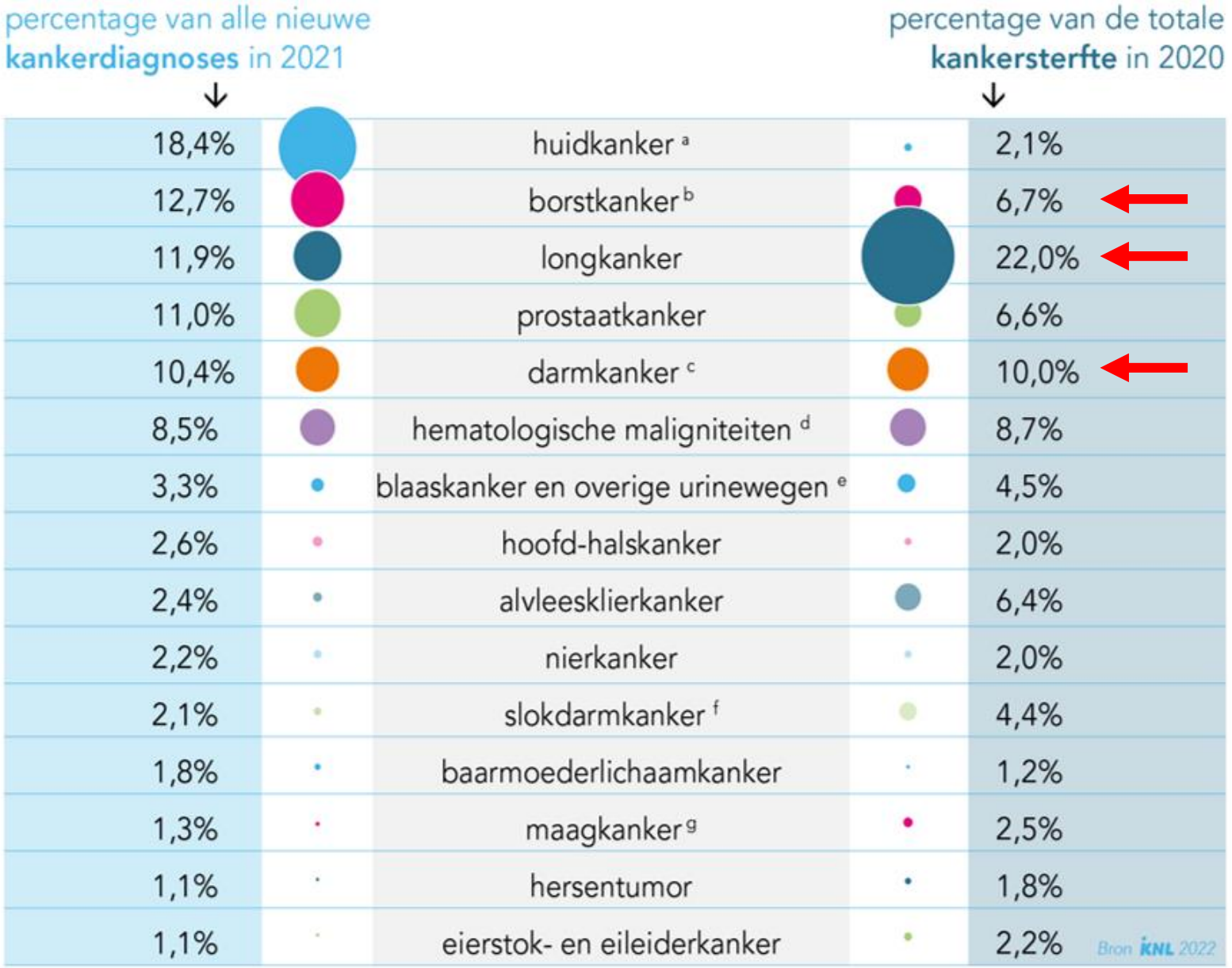

[a] exclusief basaalcelcarcinoom
[b] invasief mammacarcinoom
[c] dikke- en endeldarmkanker
[d] leukemie, lymfklierkanker, multipel myeloom en andere vormen van beenmergkanker
[e] nierbekkenkanker, urineleiderkanker, niet-spierinvasieve blaaskanker, spierinvasieve blaaskanker, urachuskanker, kanker van de urinewegen overig,
[f] exclusief cardiakanker,
[g] inclusief cardia

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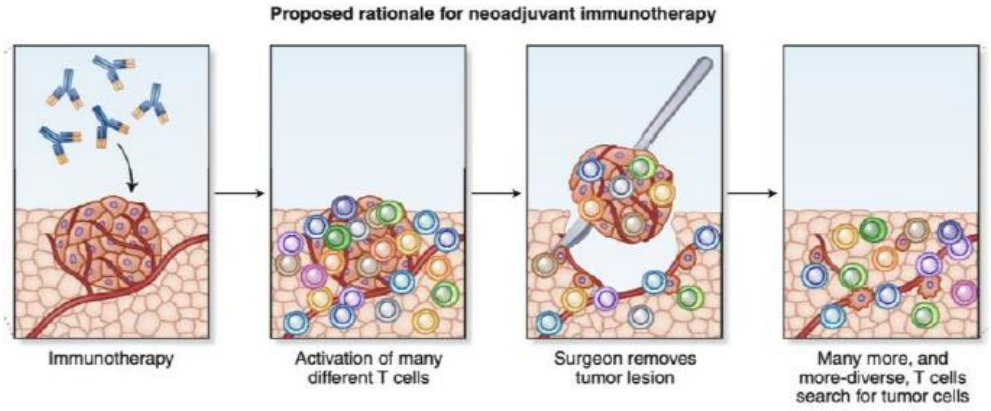
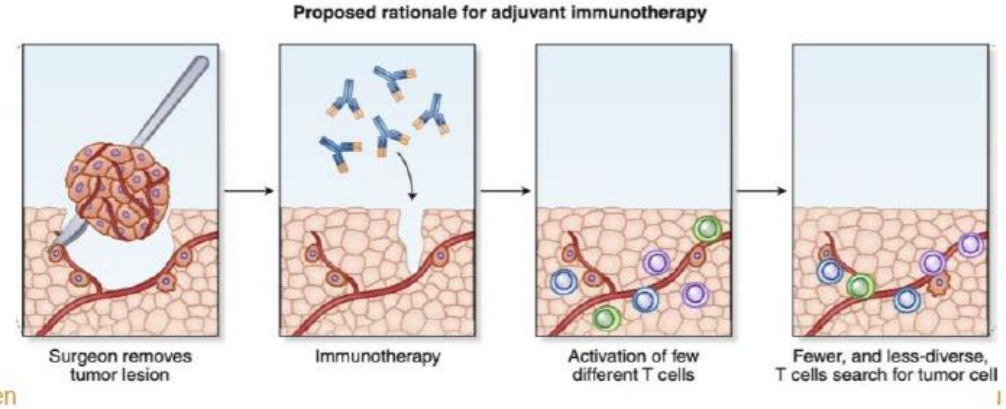
NEOADJUVANTE VS. ADJUVANTE IO

Chalabi, 2022 ESMO

Neoadjuvant
Improve surgical and survival outcomes
Treat micrometastases
Antigenicity (tumor in situ)
Organ-sparing treatment
Identify biomarkers

Adjuvant
Accurate staging
Patient perspective: “remove the tumor asap”
Diagnostics using the whole tumor specimen instead of biopsy





Conten

Adapted from: Versluis et al, Nat Med 2020 ; Rozeman et. Al, Nat med 2021

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BEOORDELING VAN RESECTIES NA NEO-ADJUVANTE THERAPIE

- Mamma carcinoom
- Colorectaal carcinoom
- Niet-kleincellig longcarcinoom

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NEOADJUVANTE IO BORSTKANKER

- Triple-negatieve borstkanker heeft een relatief slechte overleving
- Neoadjuvante chemotherapie is de huidige standard of care
- Toch blijft een verhoogd risico van recidief en mortaliteit bestaan

NEOADJUVANTE IO BORSTKANKER

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pembrolizumab for Early Triple-Negative Breast Cancer

P. Schmid, J. Cortes, L. Pusztai, H. McArthur, S. Kümmel, J. Bergh, C. Denkert, Y.H. Park, R. Hui, N. Harbeck, M. Takahashi, T. Foukakis, P.A. Fasching, F. Cardoso, M. Untch, L. Jia, V. Karantza, J. Zhao, G. Aktan, R. Dent, and J. O'Shaughnessy, for the KEYNOTE-522 Investigators*

Schmid et al. N Engl J Med. 2020 Feb 27;382(9):810-821.

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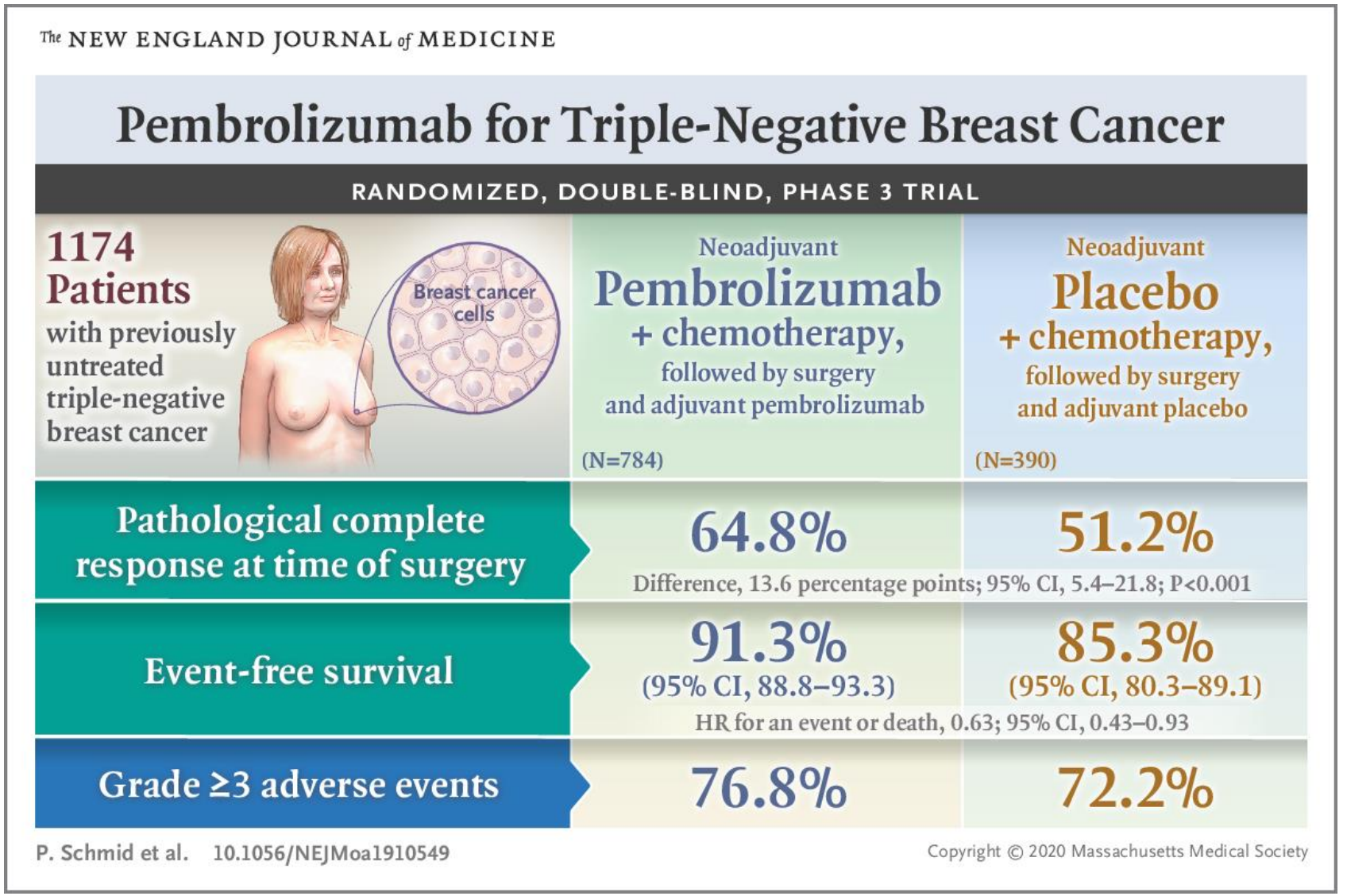
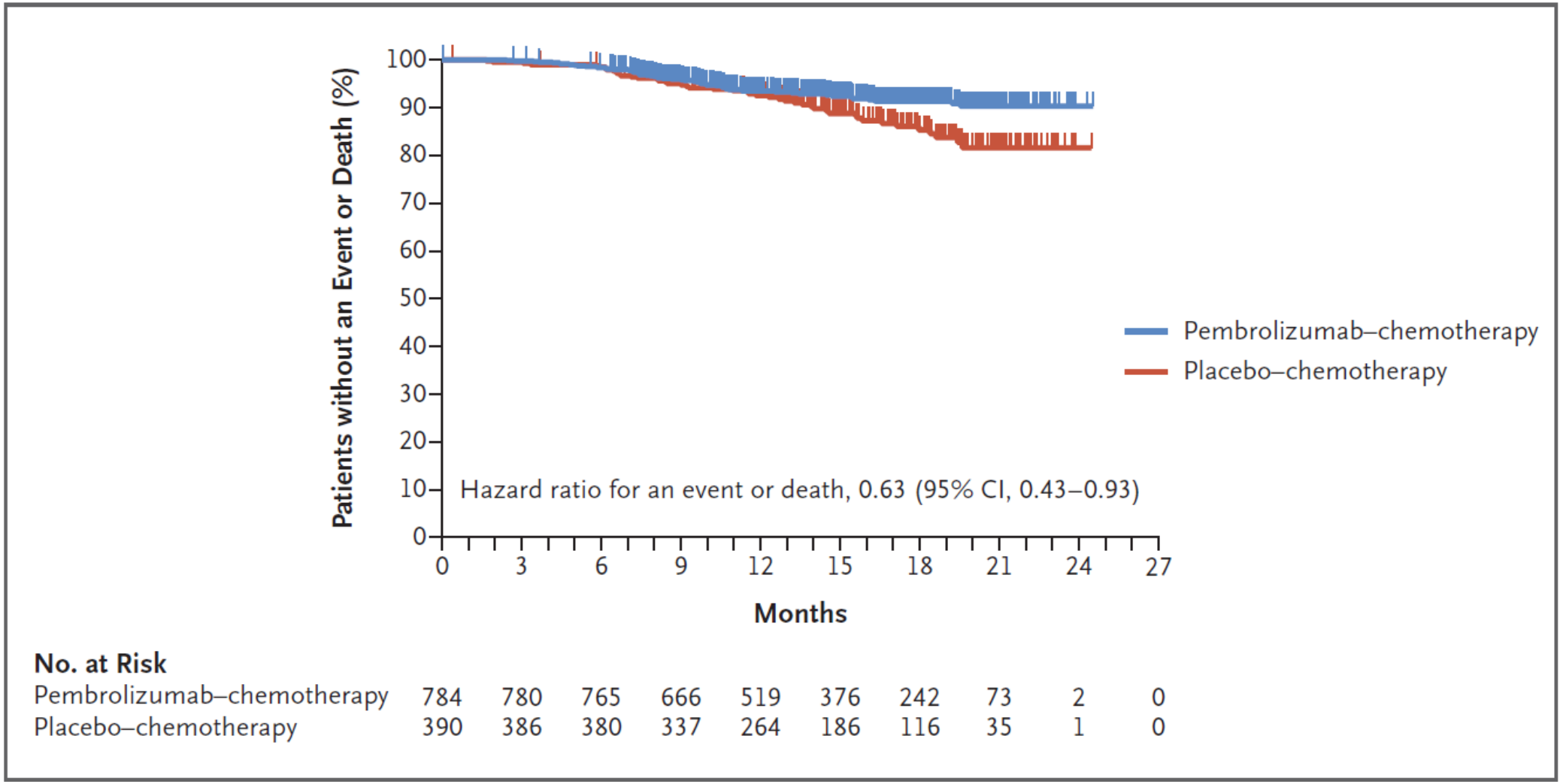
NEOADJUVANTE IO BORSTKANKER



Schmid et al. N Engl J Med. 2020 Feb 27;382(9):810-821.

NEOADJUVANTE IO BORSTKANKER



Schmid et al. N Engl J Med. 2020 Feb 27;382(9):810-821.

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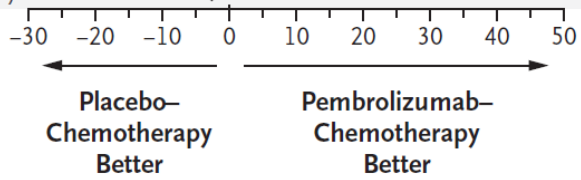
Subgroup	Pembrolizumab–Chemotherapy	Placebo–Chemotherapy	Difference in Pathological Complete Response (95% CI)
	no. of patients with response/no. of patients (%)		*percentage points*
Overall	260/401 (64.8)	103/201 (51.2)	13.6 (5.4 to 21.8)
Nodal status			
Positive	136/210 (64.8)	45/102 (44.1)	20.6 (8.9 to 31.9)
Negative	124/191 (64.9)	58/99 (58.6)	6.3 (–5.3 to 18.2)
Tumor size			
T1 to T2	207/295 (70.2)	84/149 (56.4)	13.8 (4.3 to 23.3)
T3 to T4	53/106 (50.0)	19/52 (36.5)	13.5 (–3.1 to 28.8)
Carboplatin schedule			
Every 3 wk	105/165 (63.6)	47/84 (56.0)	7.7 (–5.0 to 20.6)
Weekly	154/231 (66.7)	56/116 (48.3)	18.4 (7.4 to 29.1)
PD-L1 status			
Positive	230/334 (68.9)	90/164 (54.9)	14.2 (5.3 to 23.1)
Negative	29/64 (45.3)	10/33 (30.3)	18.3 (–3.3 to 36.8)
Age			
<65 yr	235/355 (66.2)	95/176 (54.0)	12.2 (3.4 to 21.0)
≥65 yr	25/46 (54.3)	8/25 (32.0)	22.3 (–2.1 to 43.5)
ECOG performance-status score			
0	215/328 (65.5)	85/173 (49.1)	16.4 (7.3 to 25.4)
1	45/73 (61.6)	18/28 (64.3)	–2.6 (–22.1 to 18.9)



Schmid et al. N Engl J Med. 2020 Feb 27;382(9):810-821.

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NEOADJUVANTE IO BORSTKANKER

Neoadjuvant atezolizumab in combination with sequential nab-paclitaxel and anthracycline-based chemotherapy versus placebo and chemotherapy in patients with early-stage triple-negative breast cancer (IMpassion031): a randomised, double-blind, phase 3 trial

Elizabeth A Mittendorf, Hong Zhang, Carlos H Barrios, Shigehira Saji, Kyung Hae Jung, Roberto Hegg, Andreas Koehler, Joohyuk Sohn, Hiroji Iwata, Melinda L Telli, Cristiano Ferrario, Kevin Punie, Frédérique Penault-Llorca, Shilpen Patel, Anh Nguyen Duc, Mario Liste-Hermoso, Vidya Maiya, Luciana Molinero, Stephen Y Chui, Nadia Harbeck

Mittendorf, et al. Lancet 2020; 396: 1090–100.

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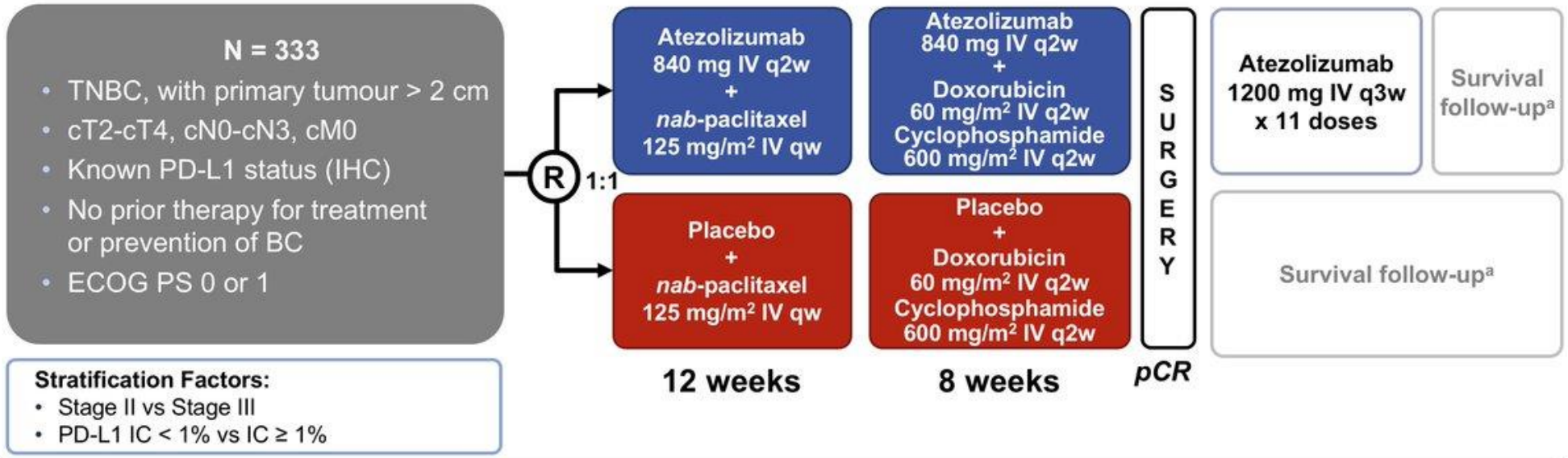
NEOADJUVANTE IO BORSTKANKER

VIRTUAL 2020 ESMO congress

IMpassion031:
Phase III atezolizumab neoadjuvant study in eTNBC[1,2]

A randomised, multicentre, international, double-blind, placebo-controlled trial



Co-primary endpoint: pCR (ypT0/is ypN0) in ITT and PD-L1+ (IC ≥ 1%) subpopulation

Secondary endpoints: EFS, DFS, and OS in ITT and in PD-L1+ subpopulation, safety, PROs

[a]Post-surgical management of patients was at the discretion of the treating investigator and based on local practice guidelines.
EFS, event-free survival, DFS, disease-free survival; PD-L1 IC, PD-L1–expressing tumor infiltrating immune cells as percentage of tumor area using the VENTANA SP142 assay; PRO, patient-reported outcome.

1. Mittendorf E, et al. SABCS 2017 [abstract 17-OT2-07-03]. 2. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/study/NCT03197935. Accessed 11 August 2020.

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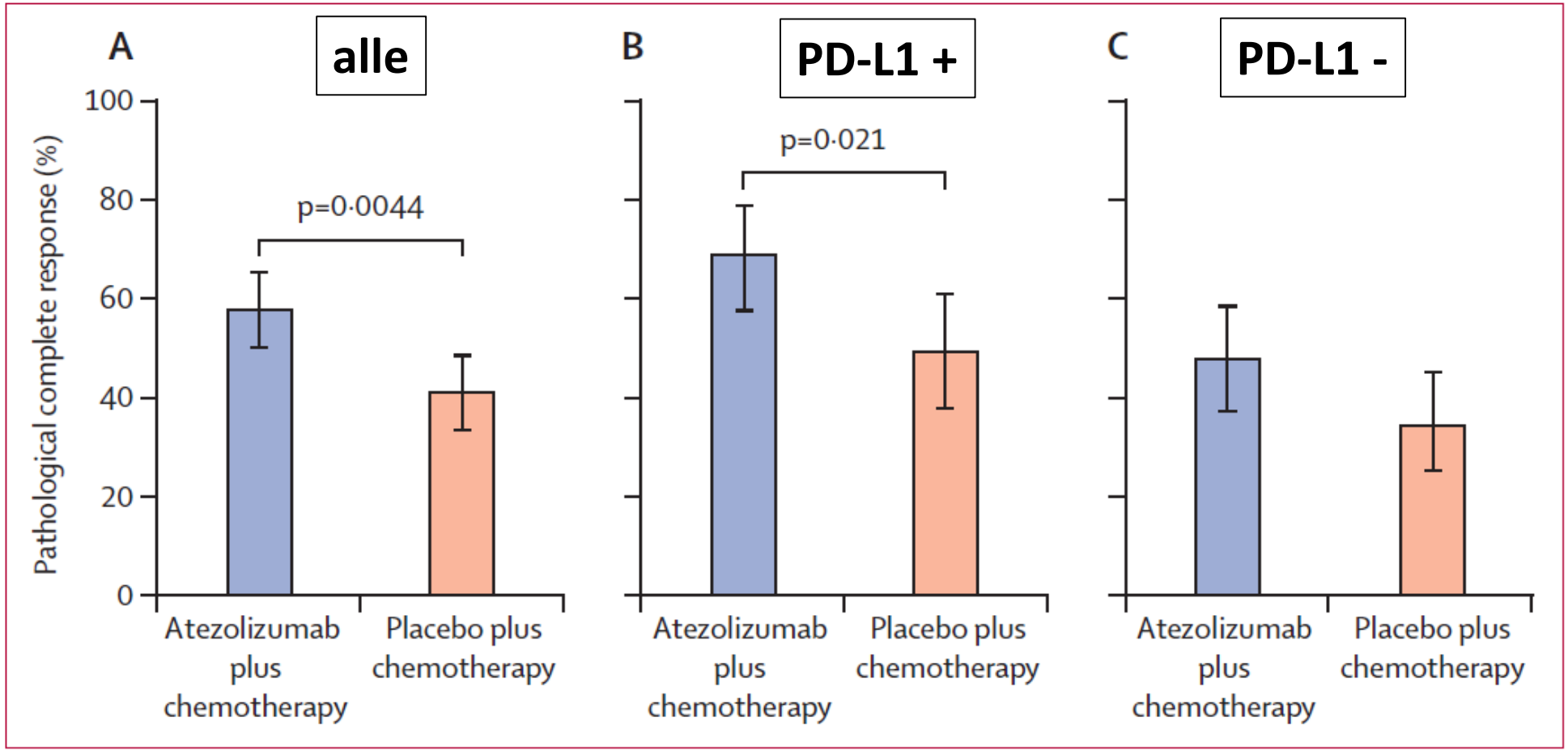
NEOADJUVANTE IO BORSTKANKER



Mittendorf, et al. Lancet 2020; 396: 1090–100.

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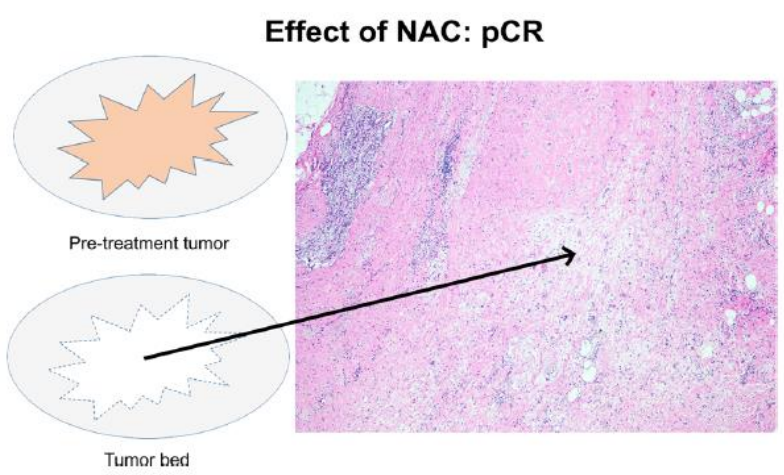
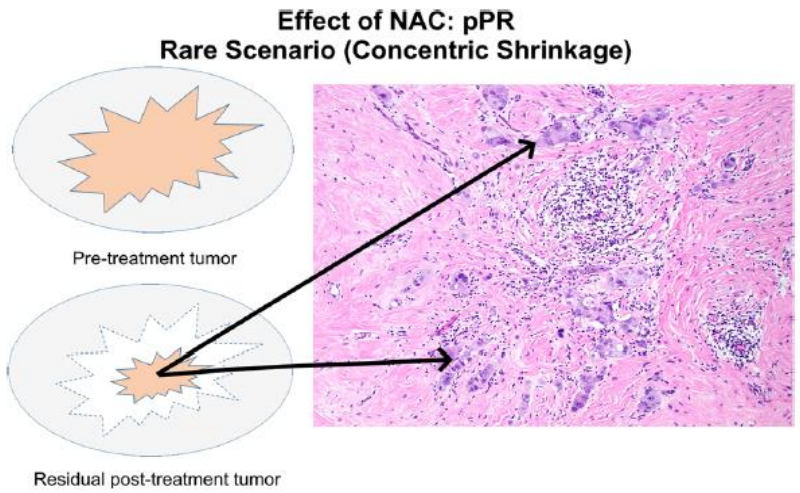
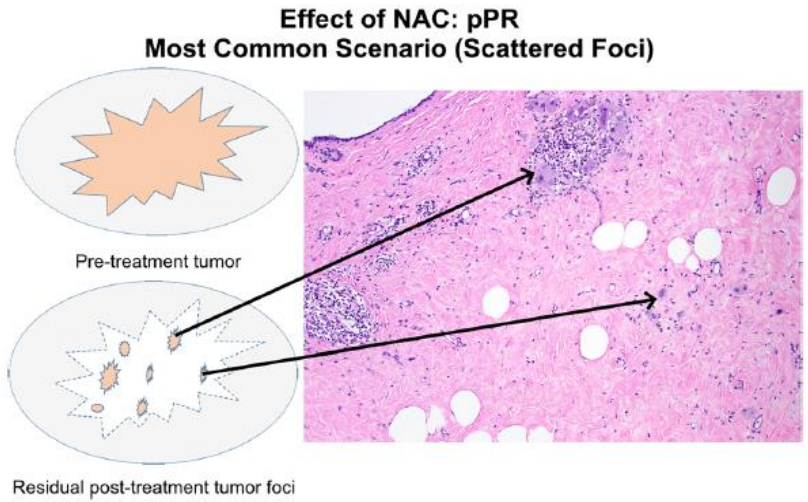
RESPONS PATRONENEN NA NAT







See and Siziopikou. Pathology - Research and Practice 230 (2022) 153753

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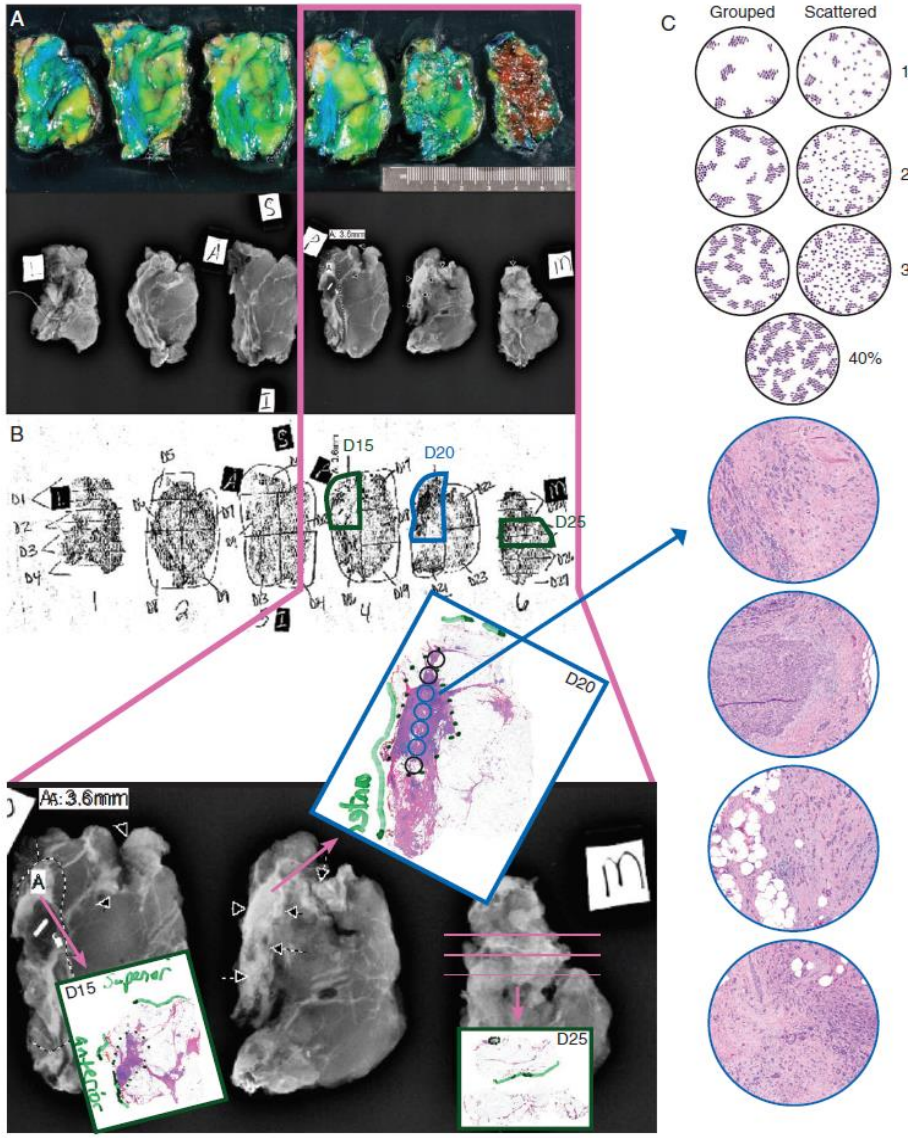
BEOORDELING MAMMA PREPARAAT NA NAT



Bossuyt et al. Annals of Oncology 26: 1280–1291, 2015

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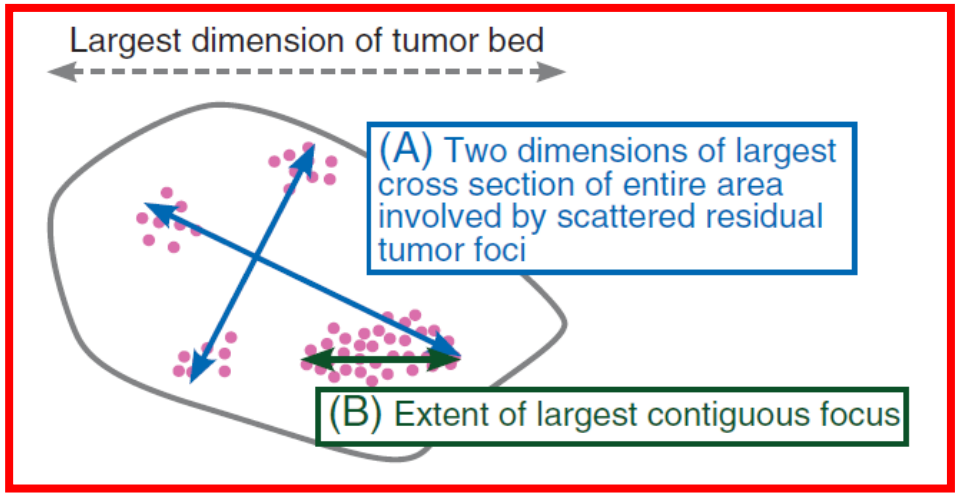
BEOORDELING MAMMA PREPARAAT NA NAT

Table 2. Elements not always routinely included in the adjuvant setting but recommended in the pathology report of the post-NAST specimen[a]

Report the elements as for any other type of specimen, plus the following:		Comment
1. Size	(A) Two dimensions of largest cross section of entire area involved by (possibly scattered) residual invasive tumor foci (=largest distance between invasive tumor cell foci) and (B) Extent of largest contiguous focus of invasive carcinoma as recommended by AJCC 7th edition [23]	In the opinion of the working group, the largest dimension in (A) (longest blue arrow), together with tumor cellularity, is likely a better indicator of response than measurement (B) [19, 24]. The report should clearly state how the size was determined and which dimension was used for staging, especially in cases with scattered residual disease, where there is possible interobserver variability due to differences in guidelines regarding how size should be measured. (A) is needed to calculate the Residual Cancer Burden (RCB) score.



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2.	Cellularity	– Qualitative statement – Largest cross section of residual tumor bed represented in blocks: … (e.g. 'G through F') – Compare with pretreatment cellularity if available (Miller–Payne or Pinder Systems)	Assessment of average cancer cellularity across the largest cross section of the residual tumor bed (that contains residual cancer) is needed to calculate the Residual Cancer Burden (RCB) score.
3.	Tumor bed	– Identified or not – Presence of tumor bed at margin	
4.	Lymph node metastasis	– Size of largest metastasis	The largest distance between tumor cell foci including intervening areas of fibrosis. Size of largest metastasis is needed to calculate the Residual Cancer Burden (RCB) score.
5.	Treatment effect	– Presence of treatment effect in the breast – Number of lymph nodes with possible treatment effect	

[a]This table discusses only those elements specific to NAST that may not be routinely included in pathology reports for non-NAST specimens. A complete list of elements recommended in the pathology report of the post-NAST specimen can be found in our pathology-focused paper [14]. Information about size, cellularity, and lymph node metastasis is required for quantification of residual disease.

Bossuyt et al. Annals of Oncology 26: 1280–1291, 2015

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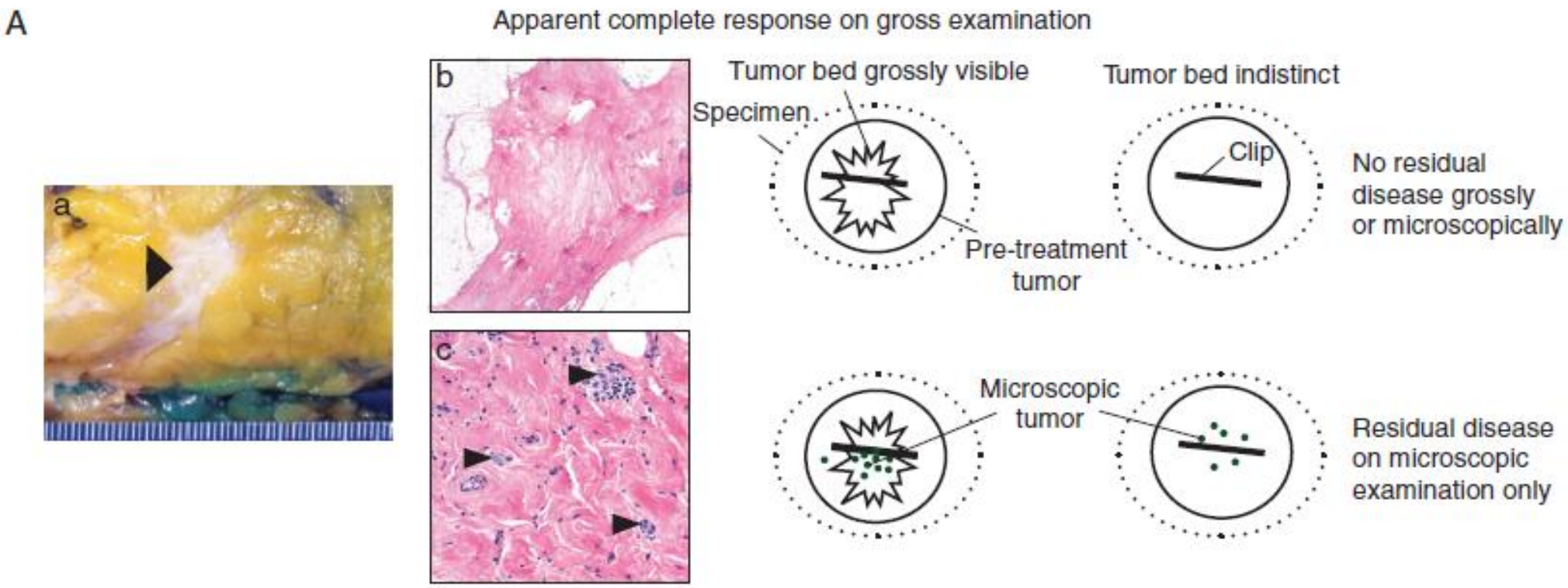

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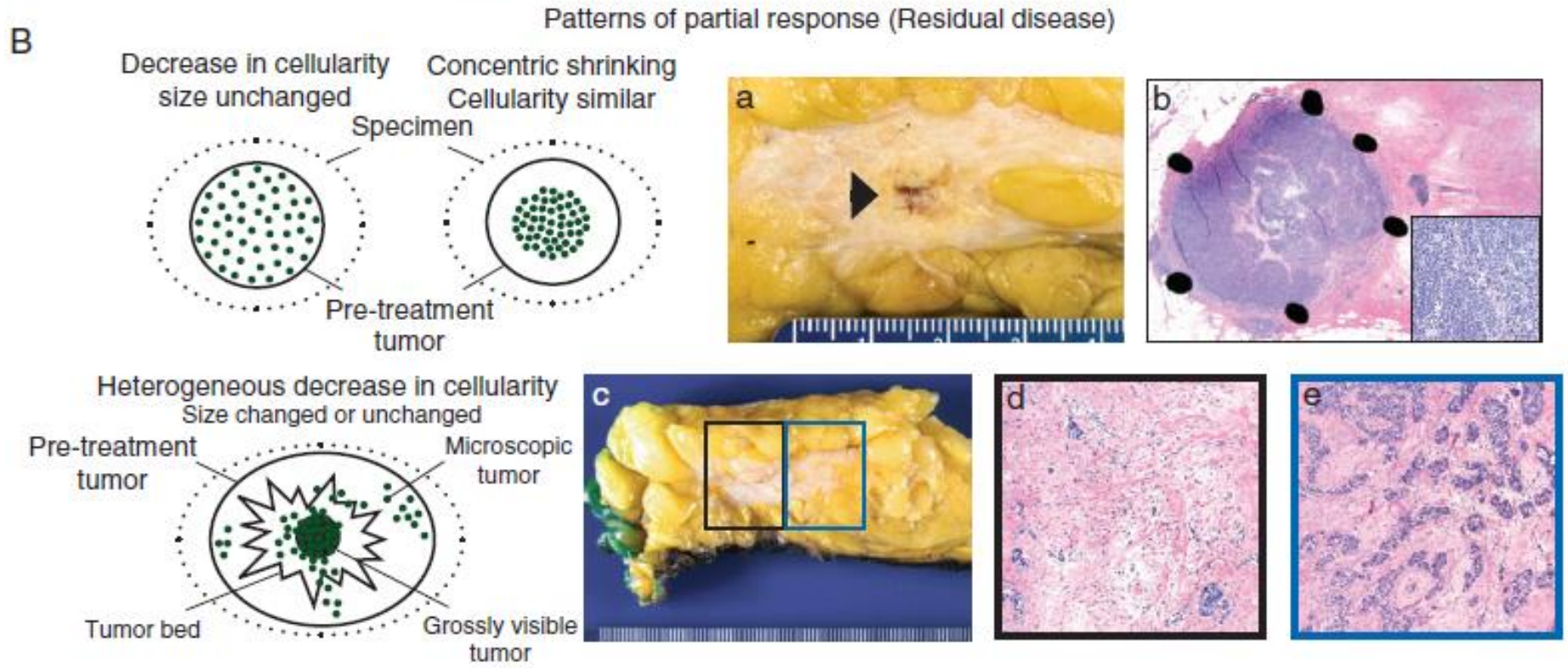

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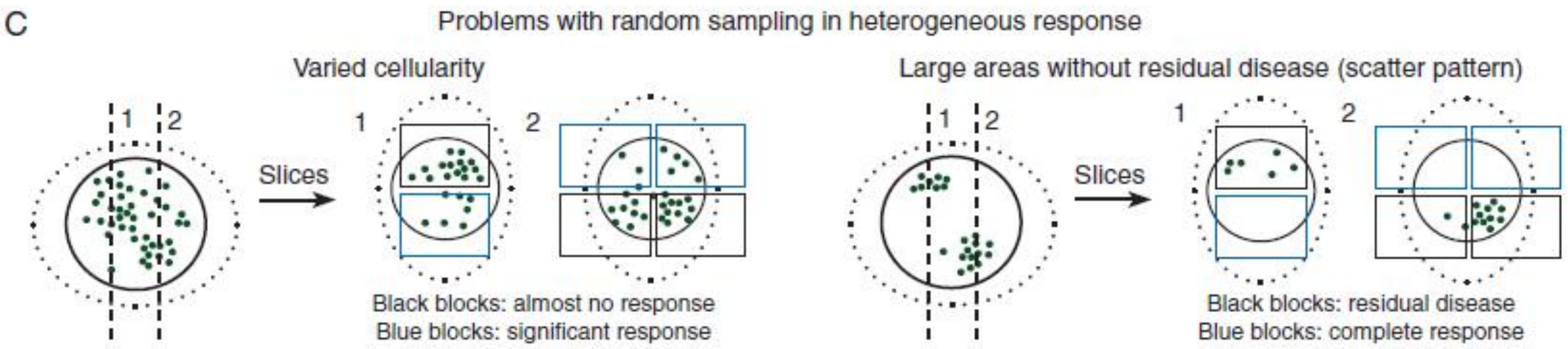

Bossuyt et al. Annals of Oncology 26: 1280–1291, 2015

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BEOORDELING MAMMA PREPARAAT NA NAT

Table 3. Requirements for accurate and reliable histologic assessment of pathologic complete response (pCR)

Assessment of pathologic complete response (pCR)

pCR = No residual invasive carcinoma in the breast and in all sampled lymph nodes (ypT0/is ypN0 or ypT0 ypN0) [1, 5]

Requires adequate sampling of the correct area of the breast:
- Correlate area to sample with clinical and imaging findings (pretreatment tumor size and location)
- Identify clip, if present/tumor bed
- Document the (largest) cross section(s) of pretreatment area of involvement with a map of the tissue blocks. (For initially large tumors, 5 representative blocks per 1–2 cm of pretreatment size with maximum of ~25 blocks should be sufficient.)[a]

Immunohistochemistry is not routinely required but may be helpful.

All surgically removed lymph nodes must be entirely submitted for histologic evaluation, sectioned at 2-mm intervals. (Additional levels and immunohistochemistry are not routinely required.)

Occasionally controversial elements:

	pCR	NOT pCR	Insufficient evidence	Comment
Ductal carcinoma *in situ* (DCIS)	x	x		pCR definitions vary [1, 3, 60]; adding pT0 or pTis clarifies the pCR definition
Lobular carcinoma *in situ*	x			
Lymphovascular invasion (LVI)		x	x	Very rarely a problem for designation as pCR or not because significant LVI-only residual disease without residual disease in the lymph nodes is extremely rare.
Micro- and macrometastasis in lymph node(s) (pN1mic and above)		x		Residual disease in the lymph nodes confers a worse prognosis irrespective of the presence of disease in the breast [7, 35–41].
Isolated tumor cells in lymph node(s) (pN0i+)		x		The significance of micrometastases and isolated tumor cells is different in the neoadjuvant setting than in the adjuvant setting [43].

[a]The FDA has recommended a minimum of one block per cm of pretreatment tumor size or at least 10 blocks in total, whichever is greater [5].

Bossuyt et al. Annals of Oncology 26: 1280–1291, 2015

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BEOORDELING MAMMA PREPARAAT NA NAT

Table 1
Classification systems for evaluation of pathologic response to NAC.

Author, year	Definition of pCR	Is presence of DCIS only ok for pCR?	Requirement for pre/post comparison
Sinn et al., 1994	Breast and LNs	No	Yes
Sataloff et al., 1995	Breast and LNs	Yes	Yes
Chevallier et al., 1995	Breast and LNs	No	No
NSABP B-18, 2001	Breast only	Yes	No
Miller-Payne et al., 2003	Breast only	Yes	Yes
Pinder et al., 2007	Breast and LNs	Yes	Yes
Residual Cancer Burden (RCB), 2007	Breast and LNs	Yes	No
RDBN, 2008	Breast and LNs	Yes	No
AJCC ypTNM, 2017	Breast and LNs	Yes	No

See and Siziopikou. Pathology - Research and Practice 230 (2022) 153753

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BEOORDELING VAN RESECTIES NA NEO-ADJUVANTE THERAPIE

- Mamma carcinoom
- Colorectaal carcinoom
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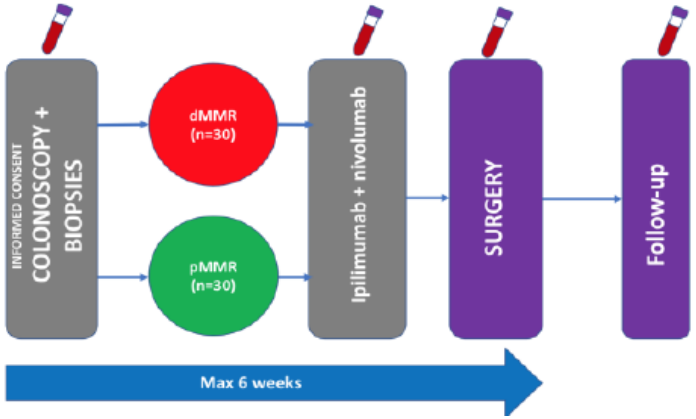
NICHE-2 TRIAL

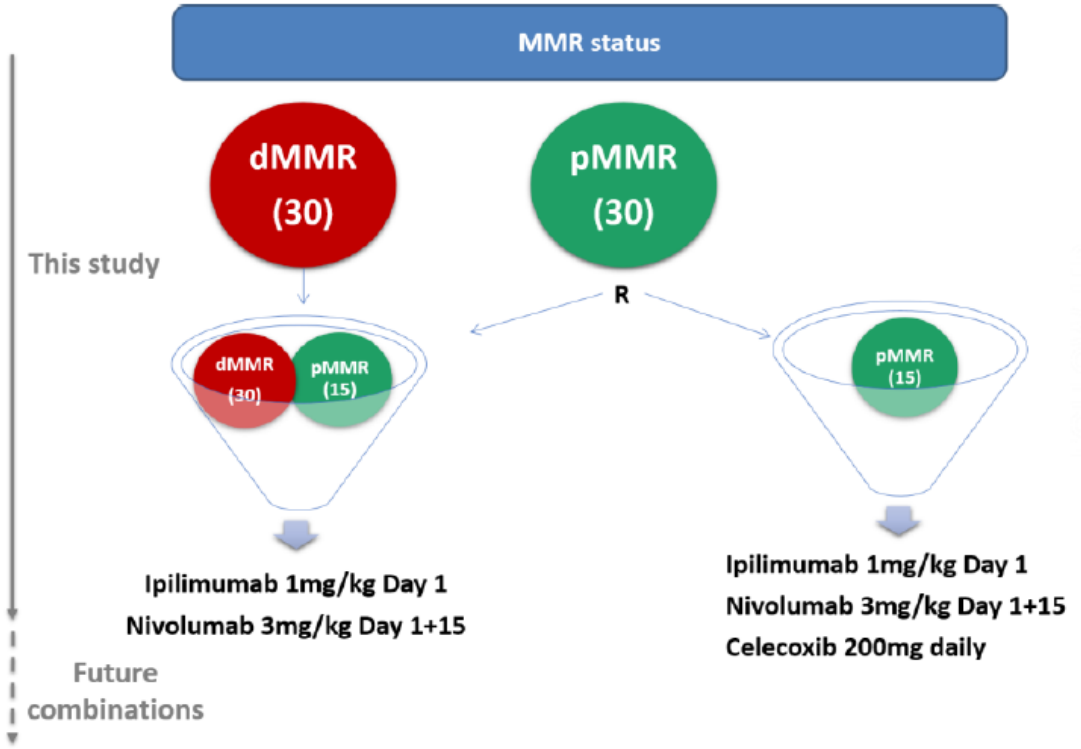
Chalabi. 2022 ESMO

Neoadjuvant nivolumab (2x) + ipilimumab (1x) in patients with non-metastatic colon adenocarcinoma

primarily resectable disease (minor extension of the procedure is acceptable to achieve free margins, e.g. small bowel segment, abdominal wall)

no previous treatment with chemotherapy





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NICHE-2 TRIAL

Chalabi, 2022 ESMO

Pathologic response according to subtype

	dMMR *n*= 32	pMMR *n*= 31
Yes (≤50% VTR)	**100%**	**29%**
Major (≤10% VTR)	**31 (97%)**	**7 (23%)**
Complete (0% VTR)	**22 (69%)**	**4 (13%)**
Partial (≤50% VTR)	1 (3%)	2 (6%)
No (>50% VTR)	0 (0%)	22 (71%)

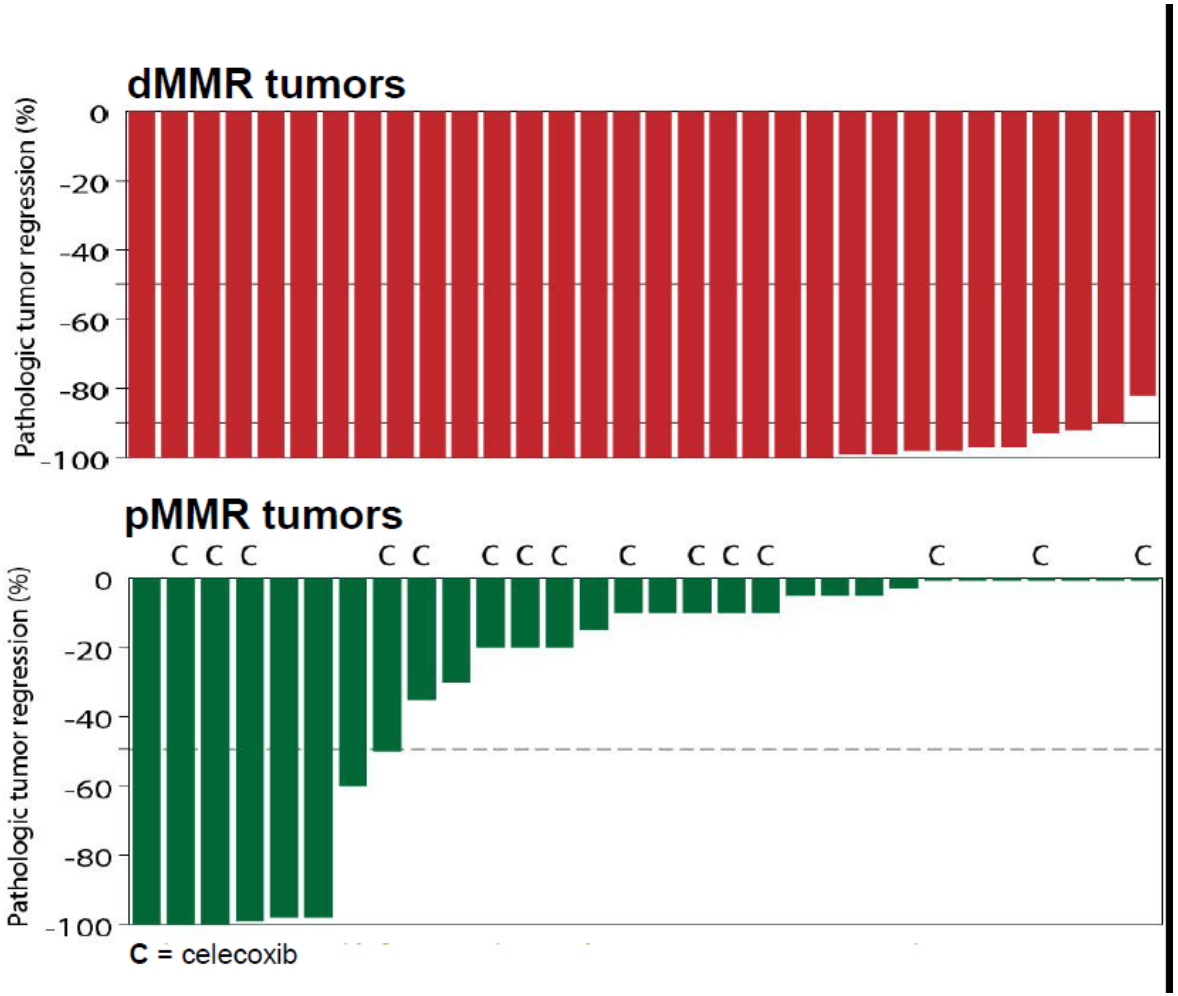
*1 patient has not undergone surgery, now 1 year after treatment completion and no longer evidence of intraluminal or radiological disease, incl neg biopsies

VTR= viable tumor rest; MPR = major pathologic response; pCR = pathologic complete response; PR= partial response

PARIS 2022 ESMO congress

Dr. M. Chalabi

Verschoor et. al, ASCO 2022



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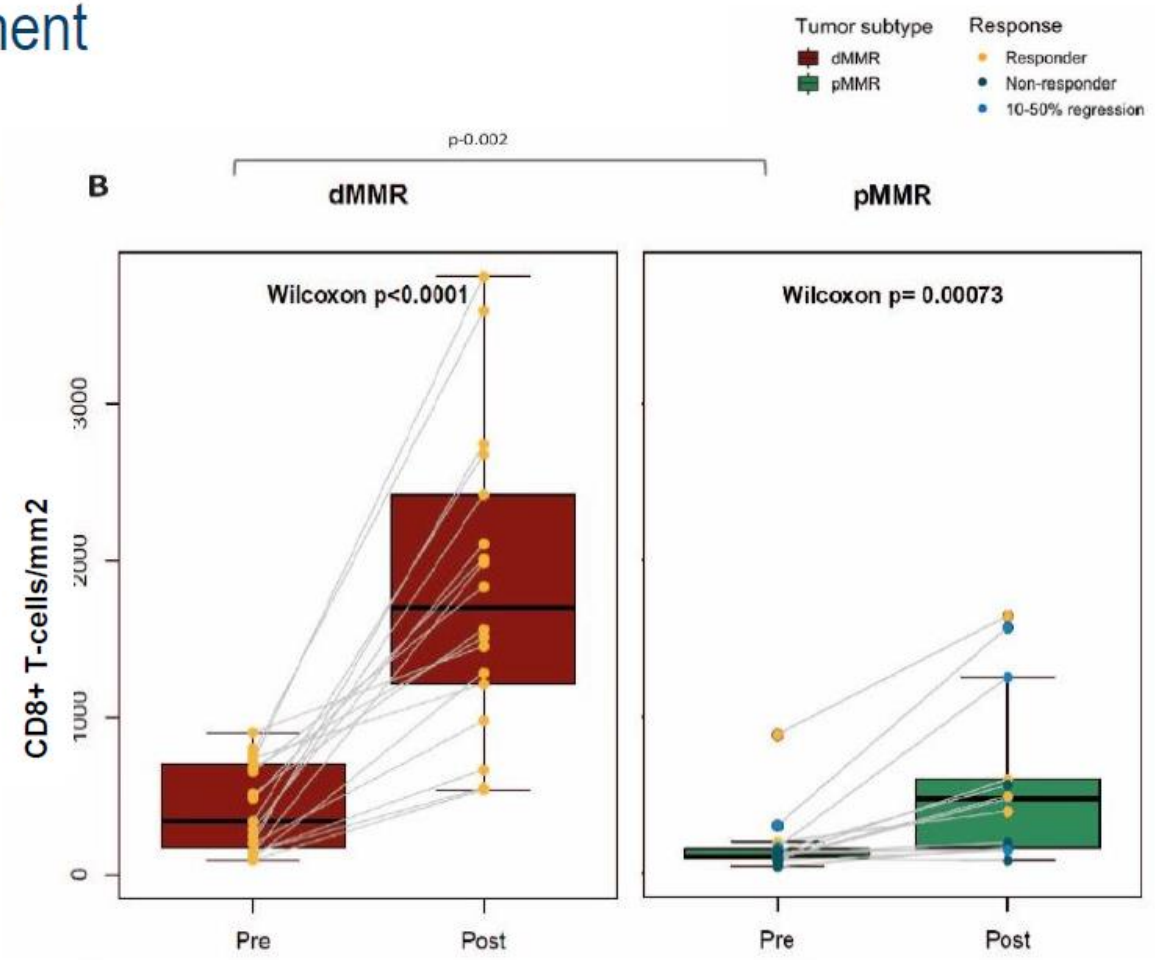
NICHE-2 TRIAL

Chalabi, 2022 ESMO

Changes in paired biopsies pre-/post-treatment

- Baseline CD8+ T-cells higher in dMMR tumors
  - Sign increase in dMMR + pMMR tumors

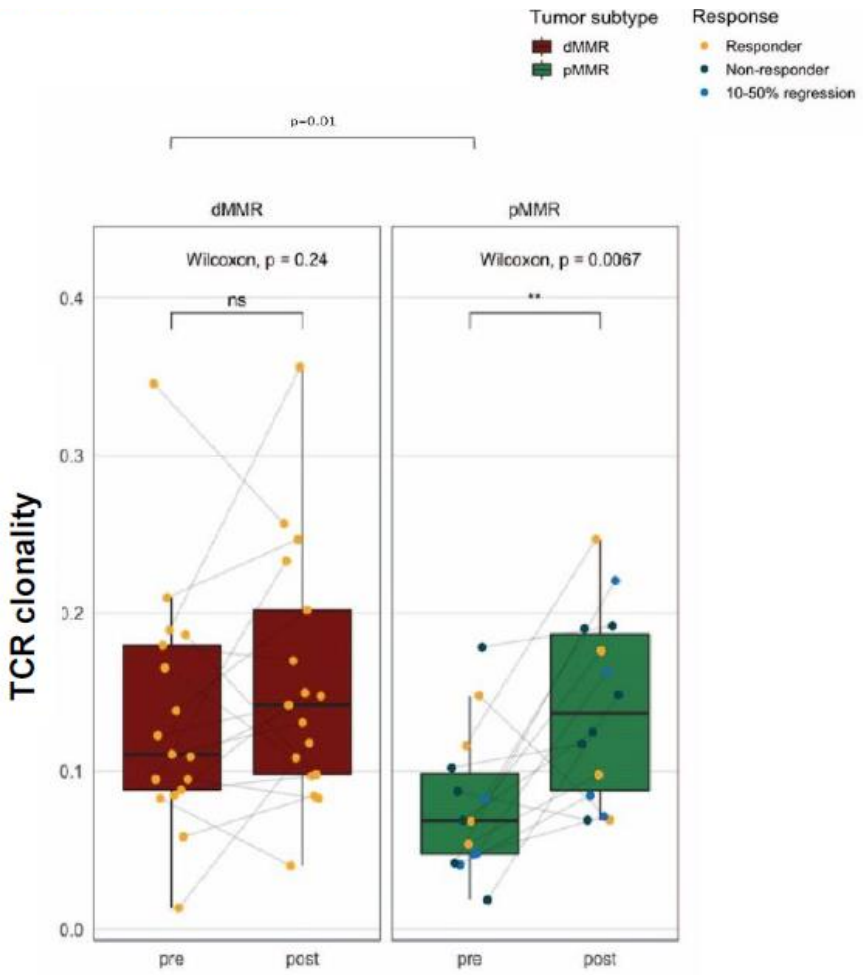


NICHE-2 TRIAL

Chalabi, 2022 ESMO

Changes in paired biopsies pre-/post-treatment

- Baseline CD8+ T-cells higher in dMMR tumors
  - Sign increase in dMMR + pMMR tumors
- TCR clonality higher in dMMR tumors at baseline
  - Sign increase only in pMMR tumors post-treatment

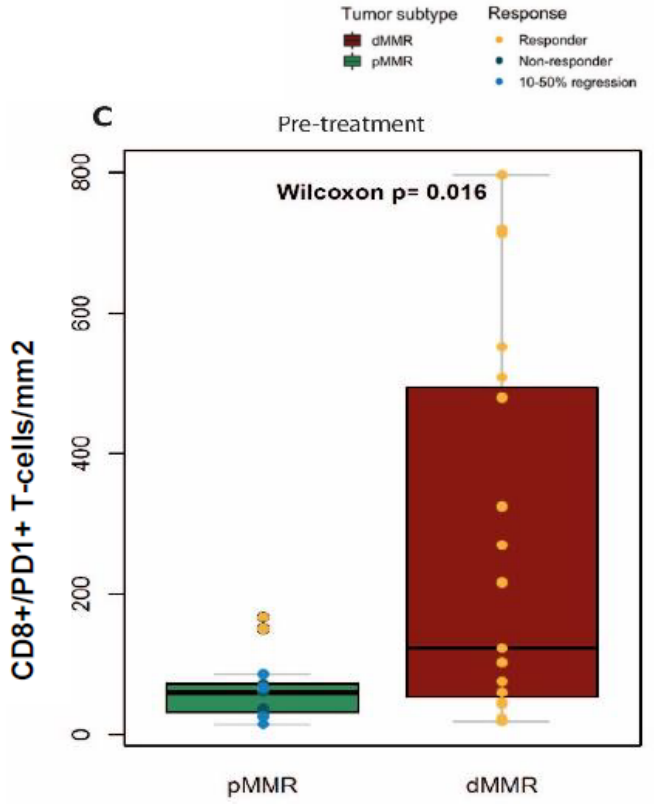


NICHE-2 TRIAL

Chalabi, 2022 ESMO

Changes in paired biopsies pre-/post-treatment

- Baseline CD8+ T-cells higher in dMMR tumors
  - Sign increase in dMMR + pMMR tumors
- TCR clonality higher in dMMR tumors at baseline
  - Sign increase only in pMMR tumors post-treatment
- CD8+/PD1+ T-cells sign. Higher in dMMR tumors at baseline

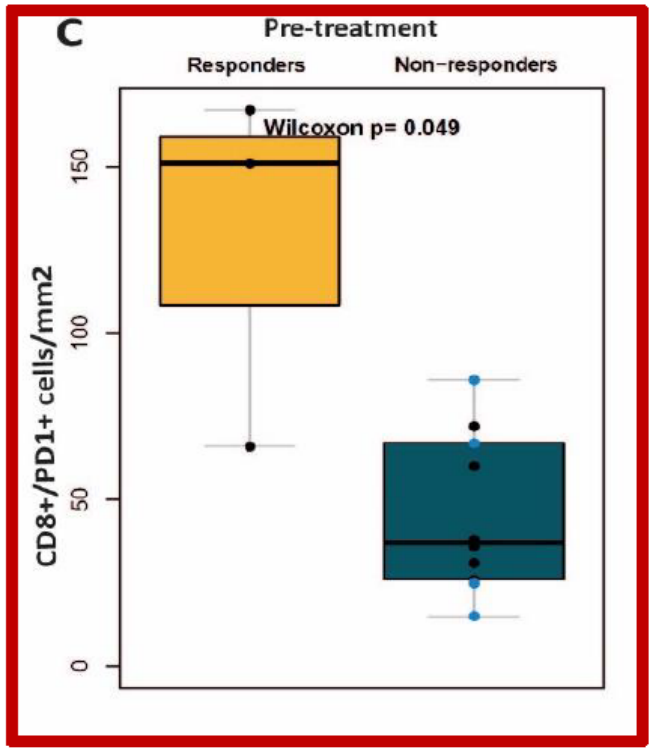


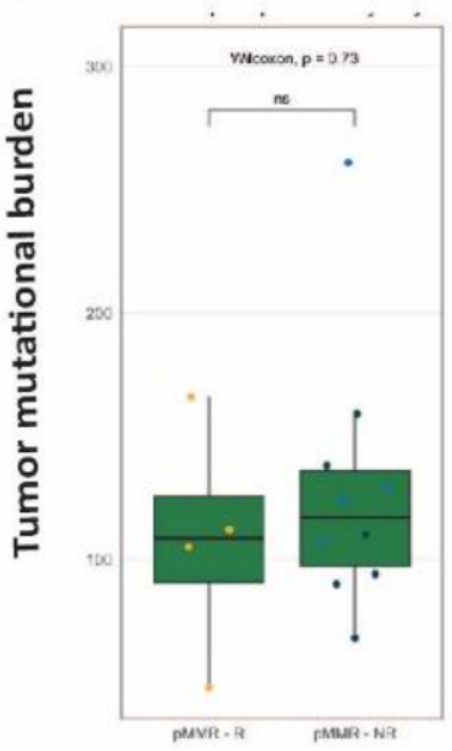
NICHE-2 TRIAL

Chalabi, 2022 ESMO

Predictors of response in pMMR tumors?

- Despite small cohort (*n*=15): CD8+/PD1+ T-cells seem predictive of response in pMMR tumors
- Validation for complete cohort ongoing
- TMB not predictive in this cohort





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NEOADJUVANTE IO IN RECTUMCA.

ORIGINAL ARTICLE

PD-1 Blockade in Mismatch Repair–Deficient, Locally Advanced Rectal Cancer

A. Cercek, M. Lumish, J. Sinopoli, J. Weiss, J. Shia, M. Lamendola-Essel, I.H. El Dika, N. Segal, M. Shcherba, R. Sugarman, Z. Stadler, R. Yaeger, J.J. Smith, B. Rousseau, G. Argiles, M. Patel, A. Desai, L.B. Saltz, M. Widmar, K. Iyer, J. Zhang, N. Gianino, C. Crane, P.B. Romesser, E.P. Pappou, P. Paty, J. Garcia-Aguilar, M. Gonen, M. Gollub, M.R. Weiser, K.A. Schalper, and L.A. Diaz, Jr.

Phase 2

Cercek et al. N Engl J Med. 2022 Jun 23;386(25):2363-2376.

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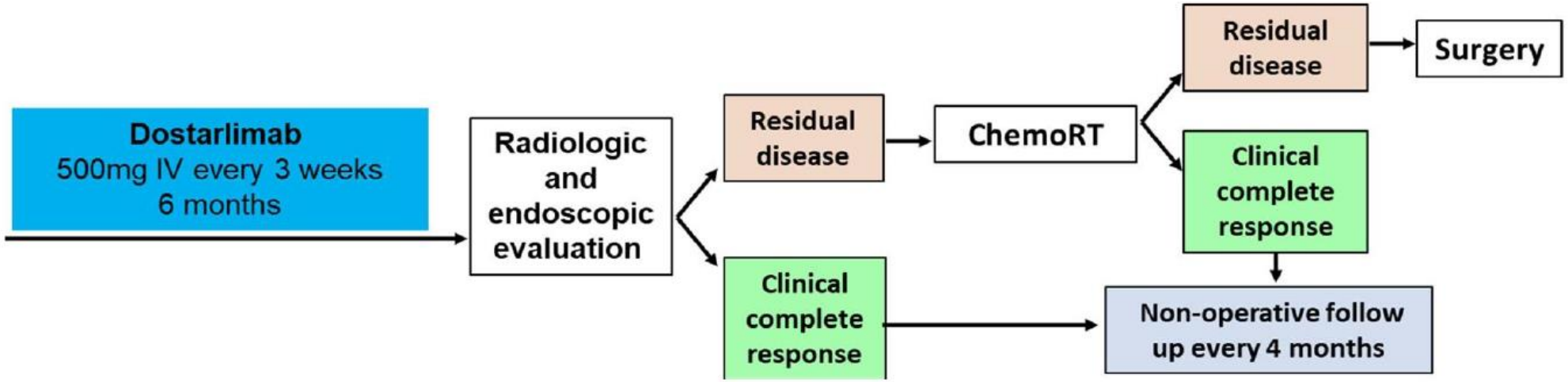
NEOADJUVANTE IO IN RECTUMCA.

Cercek, 2022 ASCO

Study design



Patient population: stage 2 and 3 dMMR rectal cancer

Primary objectives:
- overall response rate
- pathologic or clinical complete response rate

NEOADJUVANTE IO IN RECTUMCA.

Cercek, 2022 ASCO

Individual responses to PD-1 blockade with dostarlimab

Patients who completed 6-months of dostarlimab

ID	Age	Stage T	Stage N	FU (months)	Digital rectal exam response	Endoscopic best response	Rectal MRI best response	Overall response 100%
1	38	T4	N+	23.8	CR	CR	CR	cCR
2	30	T3	N+	20.5	CR	CR	CR	cCR
3	61	T1/2	N+	20.6	CR	CR	CR	cCR
4	28	T4	N+	20.5	CR	CR	CR	cCR
5	53	T1/2	N+	9.1	CR	CR	CR	cCR
6	77	T1/2	N+	11.0	CR	CR	CR	cCR
7	77	T1/2	N+	8.7	CR	CR	CR	cCR
8	55	T3	N+	5.0	CR	CR	CR	cCR
9	68	T3	N+	4.9	CR	CR	CR	cCR
10	78	T3	N-	1.7	CR	CR	CR	cCR
11	55	T3	N+	4.7	CR	CR	CR	cCR
12	27	T3	N+	4.4	CR	CR	CR	cCR
13	26	T3	N+	0.8	CR	CR	CR	cCR
14	43	T3	N+	0.7	CR	CR	CR	cCR

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NEOADJUVANTE IO IN DMMR CRC

Chalabi, 2022 ESMO

	Patient population	Treatment duration	No. of patients	Response rates
Verschoor et. al, 2022 (NICHE)				
Nivolumab + ipilimumab	Colon cancer Stage I-III	4 weeks	32	100% pathologic responses[1]
Cercek et. al, 2022				
Dostarlimab	Rectal cancer Stage II-III	6 months	12	100% clinical responses[2]
Overman et. al, 2021				
Pembrolizumab	Colorectal cancer Unresectable or high-risk	6 months – 1 year	31	74% radiologic responses[3]

[1]Pathologic responses include major pathologic response (97%), pathologic complete response (70%) and partial response (3%). [2]Clinical responses consisted of clinical complete responses (100%). [3]Radiologic responses include complete responses (26%) and partial responses (48%) according to RECIST 1.1.

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CRC NEOADJUVANT RESECTIE SPECIMEN

Table 1 Schemes for tumor regression grading in rectal adenocarcinomas after neoadjuvant therapy

Tumor regression grading scheme (references)	*Score*	*Criteria*
Mandard[23]	1	Complete regression; fibrosis without detectable tumor
	2	Fibrosis with rare, scattered residual cancer cells
	3	Fibrosis and tumor cells with a predominance of fibrosis
	4	Fibrosis and tumor cells with a predominance of tumor cells
	5	No changes of regression
Dworak[26]	0	No regression
	1	Dominant tumor mass with obvious fibrosis and/or vasculopathy
	2	Dominantly fibrotic changes with few tumor cells or groups (easy to find)
	3	Very few tumor cells in fibrotic tissue with or without mucous substance
	4	No tumor cells, only fibrotic mass (total regression)
Becker[24,25]	1	No residual carcinoma
	2	1–10% residual carcinoma
	3	11–50% residual carcinoma
	4	>50% residual carcinoma
Rodel[27]	0	No regression
	2	1–25% residual carcinoma
	3	≥25–50% residual carcinoma
	4	Complete regression
Ryan[28]	1	Complete regression or only microscopic foci of adenocarcinoma remaining, with marked fibrosis
	2	Increased number of cancer cells but fibrosis still predominates
	3	Absence of regressive change or residual cancer out growing fibrosis
Modified rectal cancer regression grade[29]	1	No tumor cells or scattered foci of tumor occupying <5% of the overall area of abnormality
	2	Combination of viable tumor cells and fibrosis (5–50% of the overall area of abnormality)
	3	More than 50% of the area of abnormality comprises malignant epithelium
College of American Pathologists (modification of ref. 28)	0	No viable cancer cells (complete response)
	1	Single cells or rare groups of cancer cells (near complete response)
	2	Residual cancer with evident tumor regression, but more than single cells or rare groups of cancer cells (partial response)
	3	Extensive residual cancer with no evident tumor regression (poor or no response)

Pai and Pai. Modern Pathology (2018) 31, 4–23

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BEOORDELING VAN RESECTIES NA NEO-ADJUVANTE THERAPIE

- Mamma carcinoom
- Colorectaal carcinoom
- Niet-kleincellig longcarcinoom

CM816 TRIAL – CHEMO-IO

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 26, 2022 VOL. 386 NO. 21

Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer

P.M. Forde, J. Spicer, S. Lu, M. Provencio, T. Mitsudomi, M.M. Awad, E. Felip, S.R. Broderick, J.R. Brahmer, S.J. Swanson, K. Kerr, C. Wang, T.-E. Ciuleanu, G.B. Saylors, F. Tanaka, H. Ito, K.-N. Chen, M. Liberman, E.E. Vokes, J.M. Taube, C. Dorange, J. Cai, J. Fiore, A. Jarkowski, D. Balli, M. Sausen, D. Pandya, C.Y. Calvet, and N. Girard, for the CheckMate 816 Investigators*

Forde et al. N Engl J Med 2022;386:1973-85.

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CM816 TRIAL

CheckMate 816 study design[a,1]

Key eligibility criteria

- Newly diagnosed, resectable, stage IB (≥ 4 cm)-IIIA NSCLC (per TNM 7th edition)
- ECOG PS 0-1
- No known sensitizing *EGFR* mutations or *ALK* alterations

Stratified by stage (IB/II vs IIIA), PD-L1[b] (≥ 1% vs < 1%[c]), and sex

N = 358 R 1:1

- NIVO 360 mg Q3W + chemo[d] Q3W (3 cycles)
- Chemo[e] Q3W (3 cycles)

Radiologic restaging → Surgery (within 6 weeks post-treatment) → Optional adjuvant chemo ± RT → Follow-up

Primary endpoints	Key secondary endpoints	Key exploratory endpoints included
• pCR by BIPR	• MPR by BIPR	• ORR by BICR
• EFS by BICR	• OS	• Feasibility of surgery; peri- and post-operative surgery-related AEs
	• Time to death or distant metastases	

Database lock: September 16, 2020; minimum follow-up: 7.6 months for NIVO + chemo and chemo arms.

[a]NCT02998528; this study included an exploratory arm: NIVO 3 mg/kg Q2W (3 cycles) + ipilimumab 1 mg/kg (cycle 1 only). Data from this arm are not included in this presentation; [b]Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako); [c]Included patients with PD-L1 expression status not evaluable and indeterminate; [d]NSQ: pemetrexed + cisplatin or paclitaxel + carboplatin; SQ: gemcitabine + cisplatin or paclitaxel + carboplatin; [e]Vinorelbine + cisplatin, docetaxel + cisplatin, gemcitabine + cisplatin (SQ only), pemetrexed + cisplatin (NSQ only), or paclitaxel + carboplatin.

1. Forde PM, et al. Oral presentation at the AACR Annual Meeting; April 8-10, 2021; virtual. Abstract 5218.

Forde et al. N Engl J Med 2022;386:1973-85.

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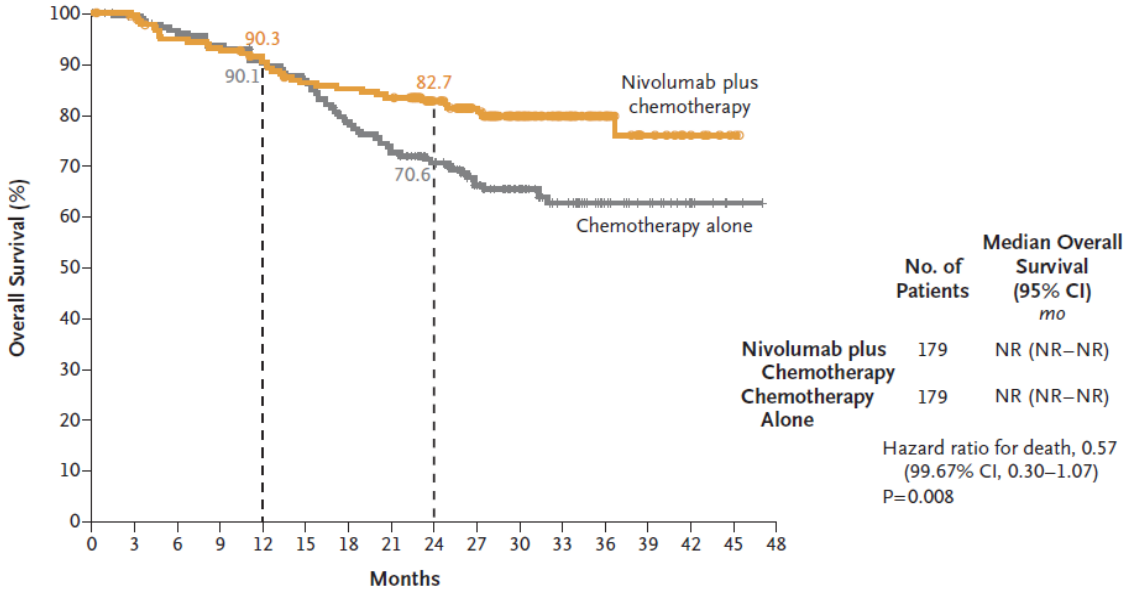
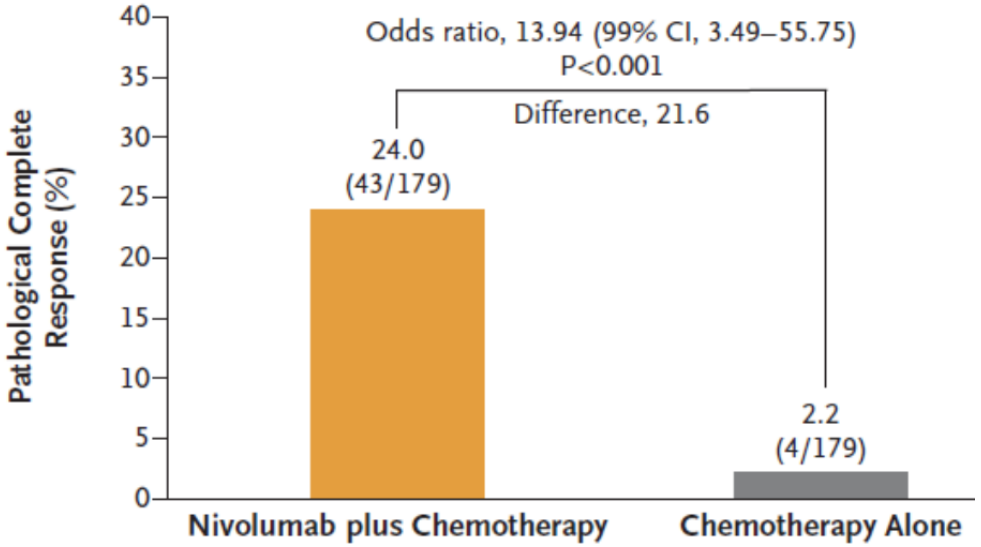
CM816 TRIAL



No. at Risk																	
Nivolumab plus chemotherapy	179	176	166	163	156	148	146	143	122	101	72	48	26	16	7	3	0
Chemotherapy alone	179	172	165	161	154	148	133	123	108	80	59	41	24	16	7	2	0

	No. of Patients	Median Overall Survival (95% CI) *mo*
Nivolumab plus Chemotherapy	179	NR (NR–NR)
Chemotherapy Alone	179	NR (NR–NR)

Hazard ratio for death, 0.57
(99.67% CI, 0.30–1.07)
P=0.008



Forde et al. N Engl J Med 2022;386:1973-85.

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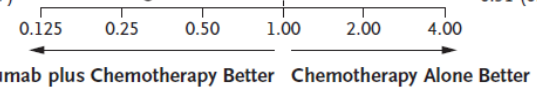
CM816 TRIAL

Subgroup	No. of Patients	Median Event-free Survival (95% CI)		Unstratified Hazard Ratio for Disease Progression, Disease Recurrence, or Death (95% CI)
		Nivolumab plus chemotherapy (N=179)	Chemotherapy alone (N=179)	
		mo		
Overall	358	31.6 (30.2–NR)	20.8 (14.0–26.7)	0.63 (0.45–0.87)
Age				
<65 yr	176	NR (31.6–NR)	20.8 (14.0–NR)	0.57 (0.35–0.93)
≥65 yr	182	30.2 (23.4–NR)	18.4 (10.6–31.8)	0.70 (0.45–1.08)
Sex				
Male	255	30.6 (20.0–NR)	16.9 (13.8–24.9)	0.68 (0.47–0.98)
Female	103	NR (30.5–NR)	31.8 (13.9–NR)	0.46 (0.22–0.96)
Geographic region				
North America	91	NR (25.1–NR)	NR (12.8–NR)	0.78 (0.38–1.62)
Europe	66	31.6 (13.4–NR)	21.1 (10.2–NR)	0.80 (0.36–1.77)
Asia	177	NR (30.2–NR)	16.5 (10.8–22.7)	0.45 (0.29–0.71)
ECOG performance-status score				
0	241	NR (30.2–NR)	22.7 (16.6–NR)	0.61 (0.41–0.91)
1	117	30.5 (14.6–NR)	14.0 (9.8–26.2)	0.71 (0.41–1.21)
Disease stage at baseline				
IB or II	127	NR (27.8–NR)	NR (16.8–NR)	0.87 (0.48–1.56)
Histologic type of tumor				
Squamous	182	30.6 (20.0–NR)	22.7 (11.5–NR)	0.77 (0.49–1.22)
Nonsquamous	176	NR (27.8–NR)	19.6 (13.8–26.2)	0.50 (0.32–0.79)
Current or former smoker	318	31.6 (30.2–NR)	22.4 (15.7–NR)	0.68 (0.48–0.96)
PD-L1 expression level				
<1%	155	25.1 (14.6–NR)	18.4 (13.9–26.2)	0.85 (0.54–1.32)
≥1%	178	NR (NR–NR)	21.1 (11.5–NR)	0.41 (0.24–0.70)
1–49%	98	NR (27.8–NR)	26.7 (11.5–NR)	0.58 (0.30–1.12)
≥50%	80	NR (NR–NR)	19.6 (8.2–NR)	0.24 (0.10–0.61)
<12.3 mutations/megabase	102	30.5 (19.4–NR)	26.7 (16.6–NR)	0.86 (0.47–1.57)
≥12.3 mutations/megabase	76	NR (14.8–NR)	22.4 (13.4–NR)	0.69 (0.33–1.46)
Type of platinum therapy				
Cisplatin	258	NR (25.1–NR)	20.9 (15.7–NR)	0.71 (0.49–1.03)
Carboplatin	72	NR (30.5–NR)	10.6 (7.6–26.7)	0.31 (0.14–0.67)



Forde et al. N Engl J Med 2022;386:1973-85.

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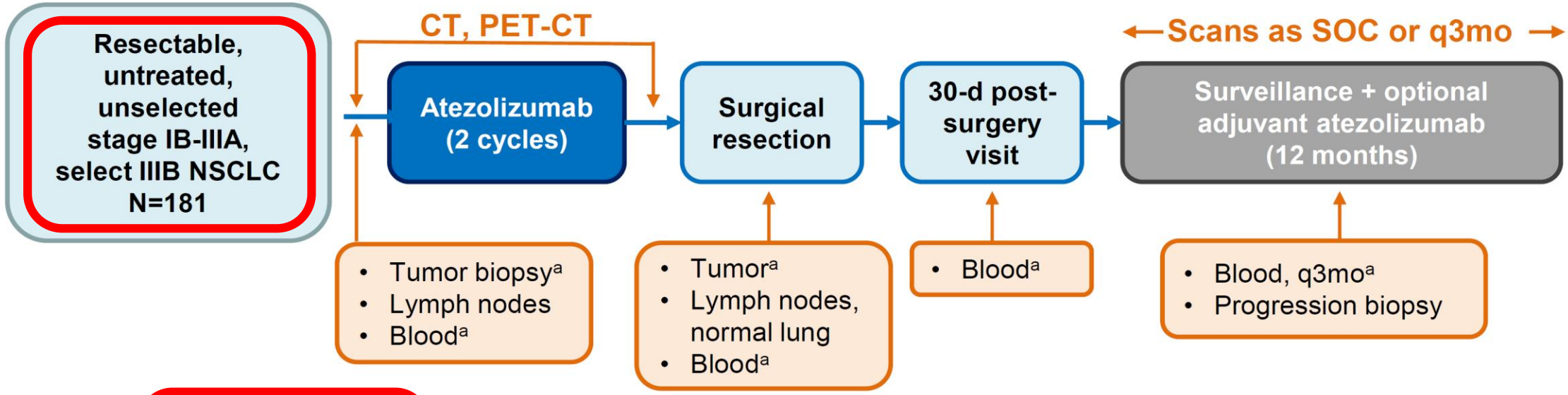
LCMC3 TRIAL – MONO-IO

WCLC 2021, Carbone



Primary endpoint:
- Major pathologic response (≤10% viable tumor cells)

Secondary endpoints:
- Pathologic response by PD-L1
- Radiographic response by
  - PD-L1, TMB, neoantigen, GEP

Exploratory endpoints:
- DFS, OS
- Biomarkers
  - ctDNA, TCRseq, flow cytometry, IF, IHC, NGS

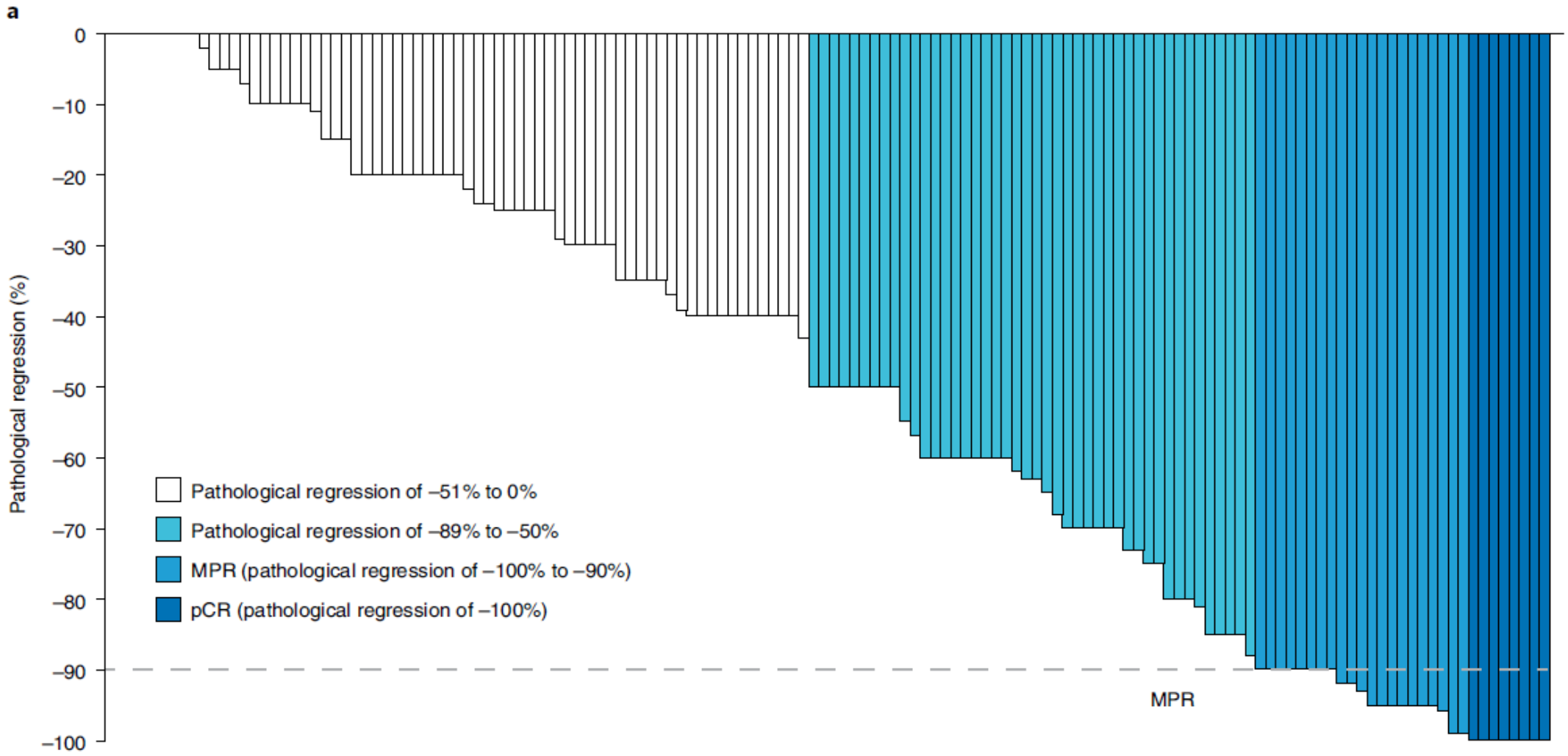
Safety
- AEs

NCT0292730
[a] Mandatory.
ctDNA, circulating tumor DNA; DFS, disease-free survival; GEP, gene expression profiling; IF, immunofluorescence; NGS, next-generation sequencing; PET-CT, positron emission tomography–computed tomography; q3mo, every 3 months; SOC, standard of care; TCRseq, T-cell receptor sequencing; TMB, tumor mutational burden.

Erasmus MC

CP-256904

LCMC3 TRIAL

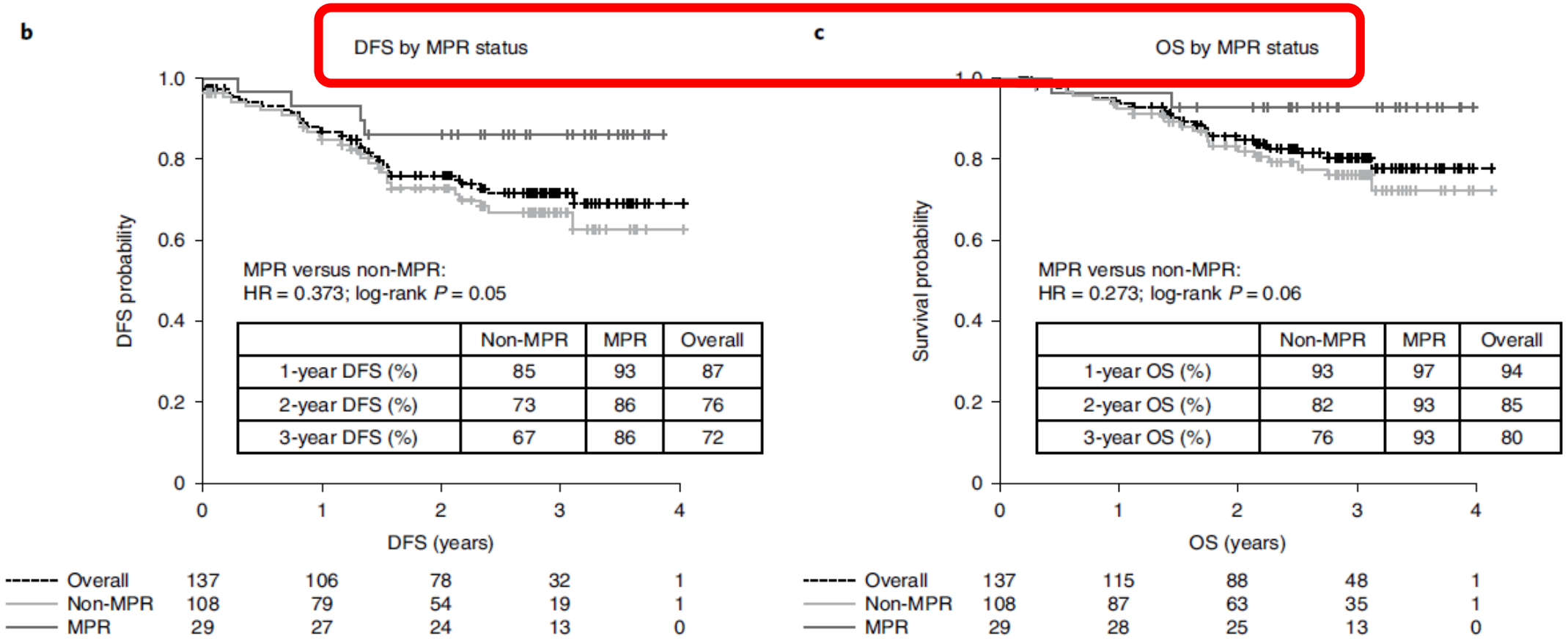


Chaft, et al. Nature Medicine; 2022:2155–2161.

Erasmus MC

CP-256904

LCMC3 TRIAL



	Non-MPR	MPR	Overall
1-year DFS (%)	85	93	87
2-year DFS (%)	73	86	76
3-year DFS (%)	67	86	72

	Non-MPR	MPR	Overall
1-year OS (%)	93	97	94
2-year OS (%)	82	93	85
3-year OS (%)	76	93	80

Fig. 2 | Clinical outcomes in patients who had surgical resection and whose tumors did not have known *EGFR* or *ALK* alterations. a, Pathological response ($n=143$). Pathological regression is defined as percentage viable tumor cells −100%. **b**, DFS by MPR status in patients with R0 resections ($n=137$). **c**, OS by MPR status in patients with R0 resections ($n=137$). HR, hazard ratio.

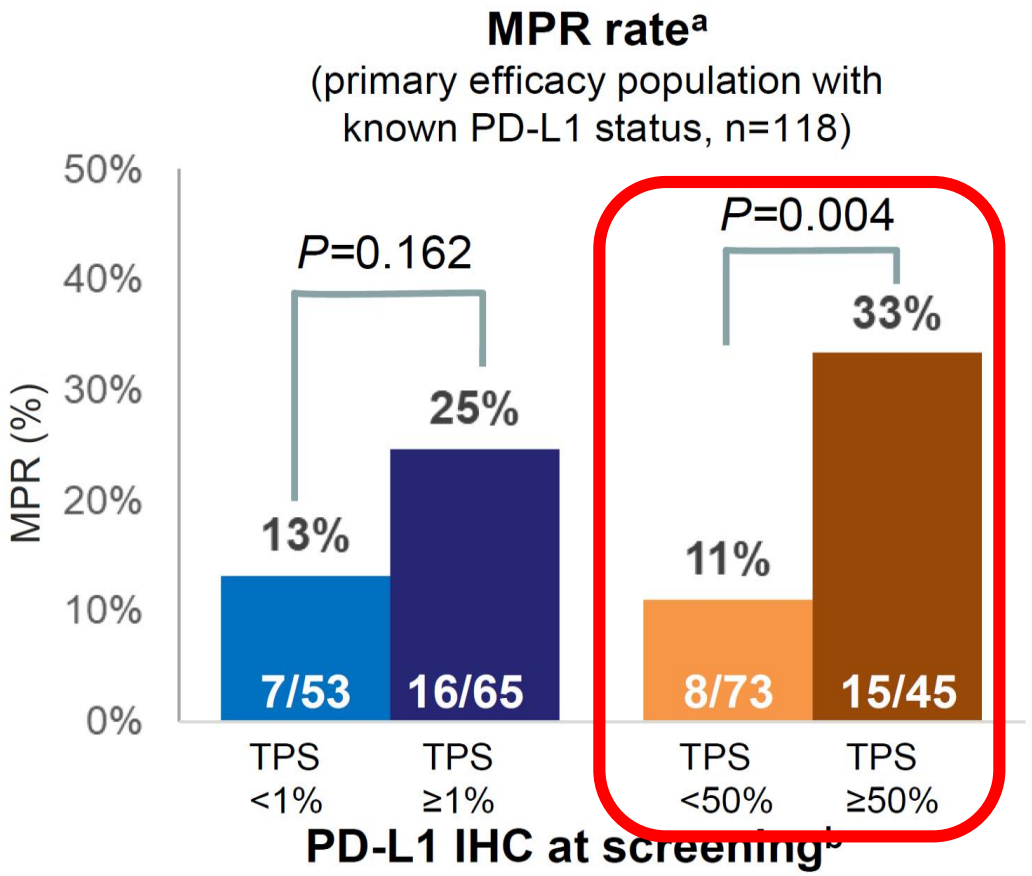
Chaft, et al. Nature Medicine; 2022:2155–2161.

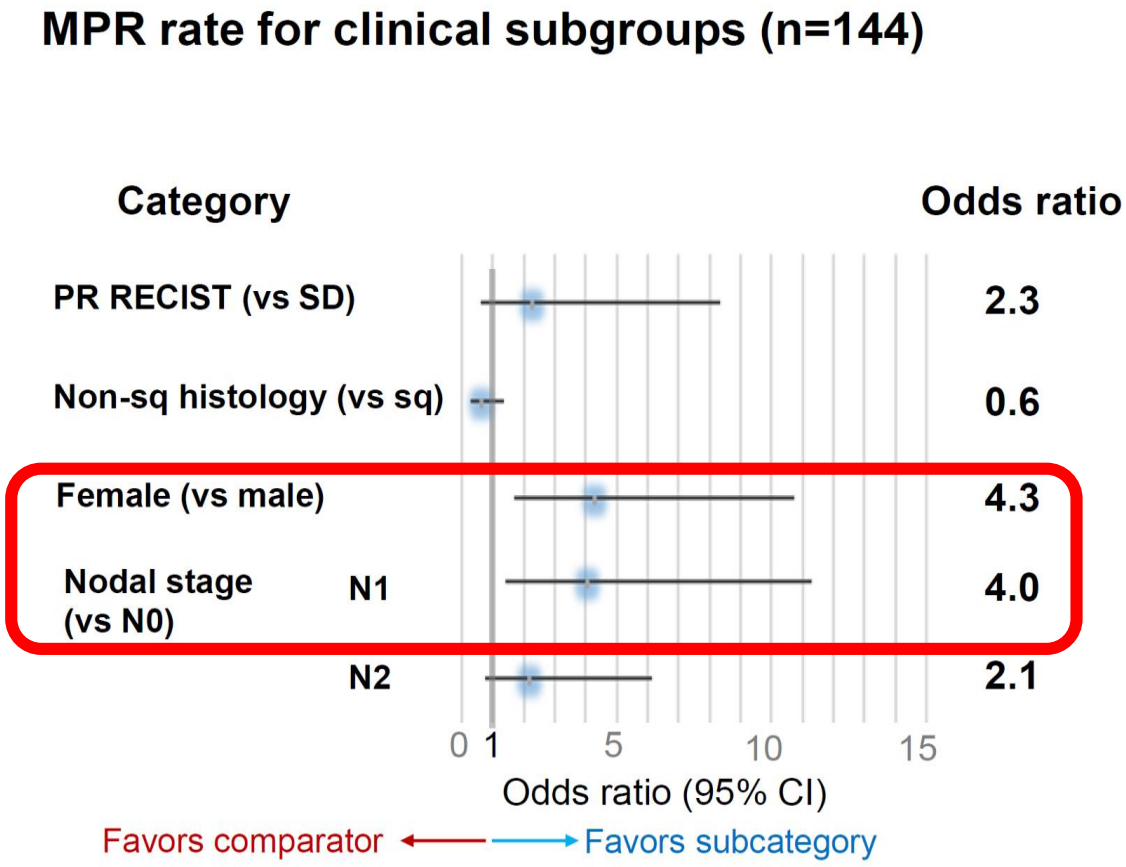
Erasmus MC

CP-256904

LCMC3 TRIAL

WCLC 2021, Carbone



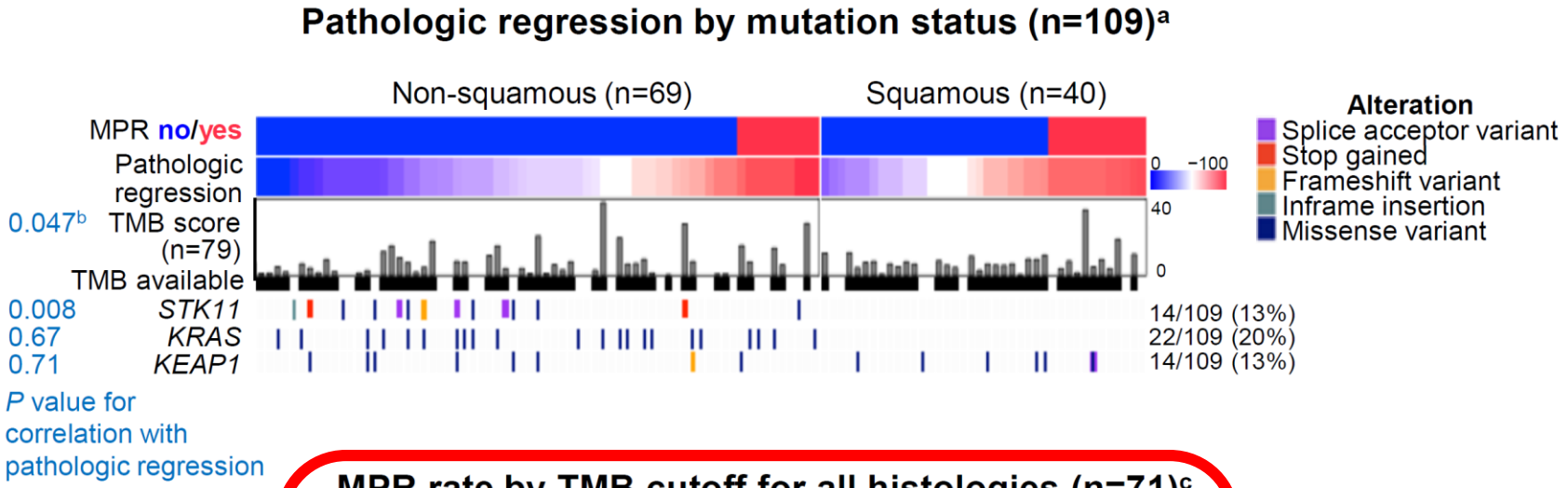


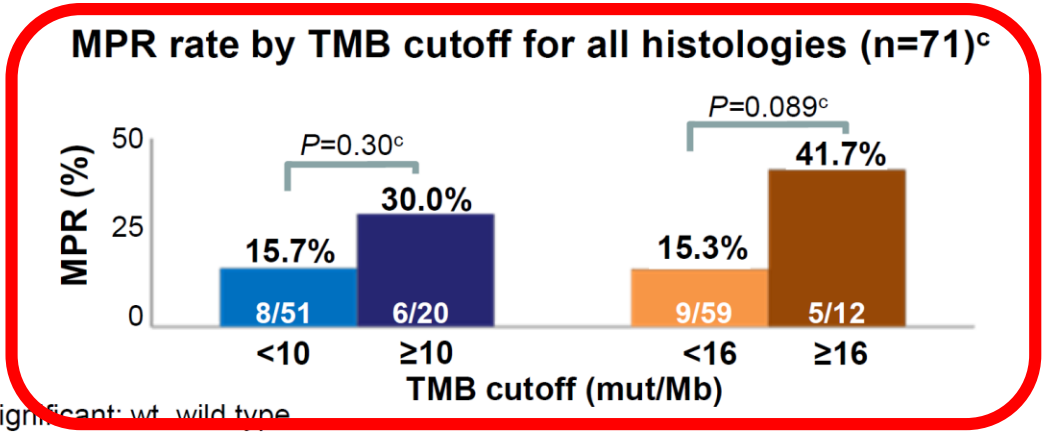
sq, squamous.

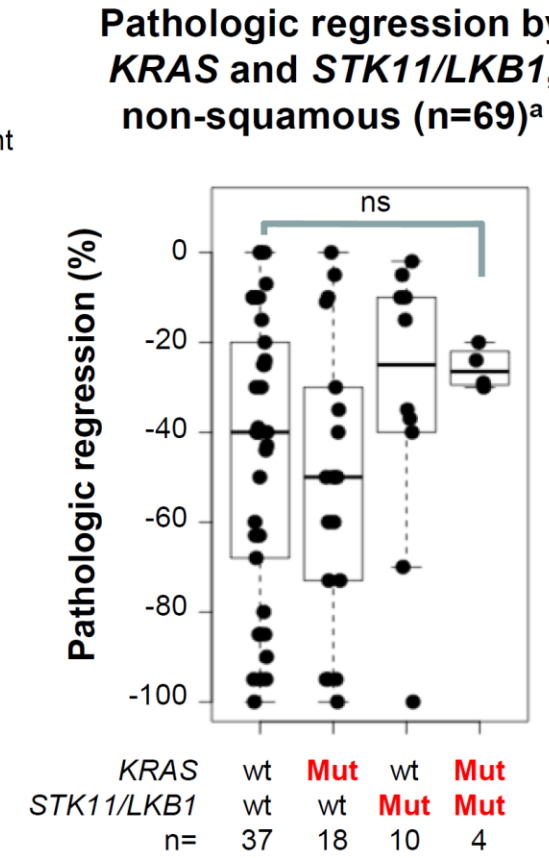
[a] Analysis population excluded of EGFR and ALK positive patients. [b] Local TPS score used if central score was not available.

LCMC3 TRIAL

WCLC 2021, Carbone





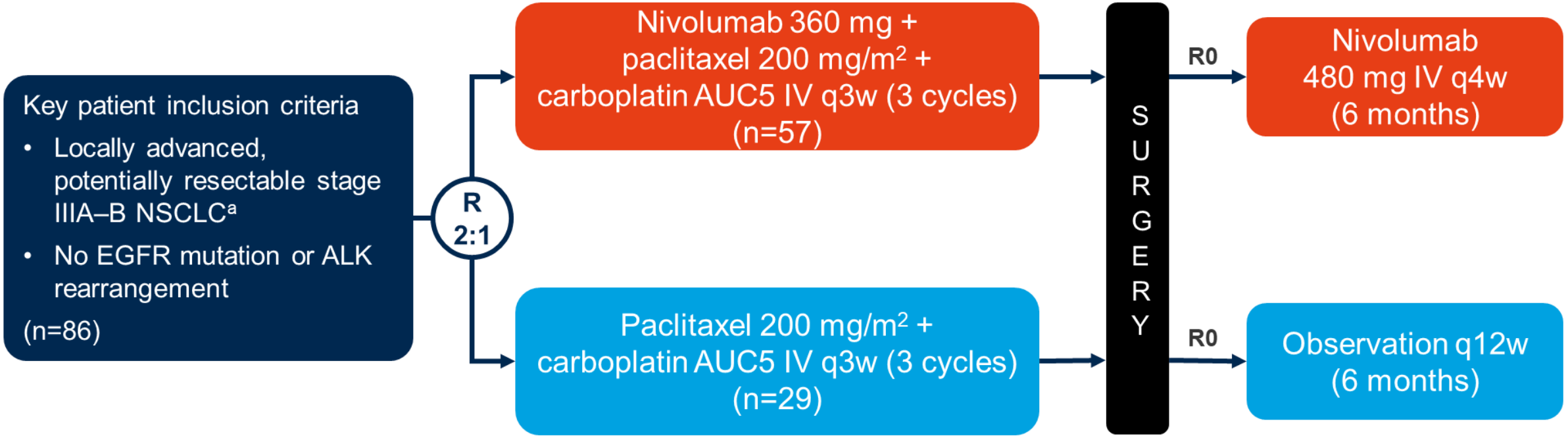


Mut, mutated; ns, not significant; wt, wild type

[a] Includes patients with pathologic regression assessment and with baseline and/or surgery whole exome sequencing, Wilcoxon. [b] Includes patients with pathologic regression assessment and TMB, Pearson. [c] MPR rate was calculated in the primary efficacy population with TMB results, χ^2; unadjusted *P* values.

NADIM TRIAL – CHEMO-IO

- **Study objective**
  - To evaluate the efficacy and safety of neoadjuvant nivolumab + chemotherapy in patients with resectable stage IIIA–B NSCLC in the NADIM II study



Primary endpoint

- pCR

Secondary endpoints

- MPR, surgical outcomes, OS, PFS, safety

[a]Per American Joint Committee on Cancer (AJCC) cancer staging manual, 8th edition

Provencio M, et al. J Thorac Oncol 2022;17(suppl):Abstr PL03.12

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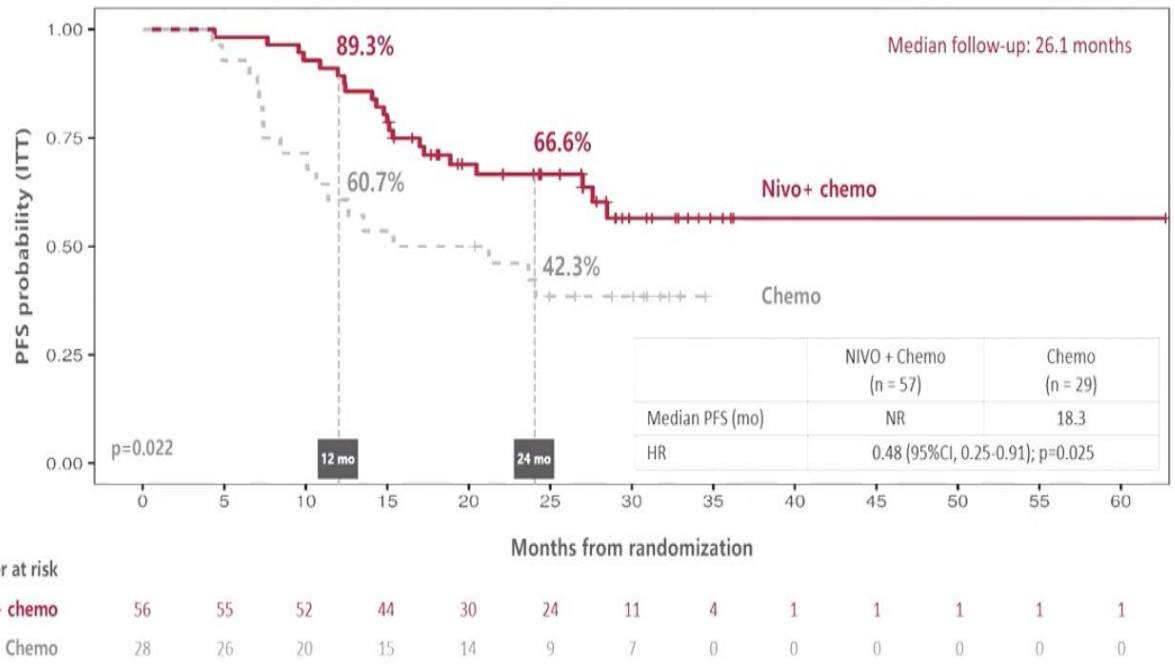
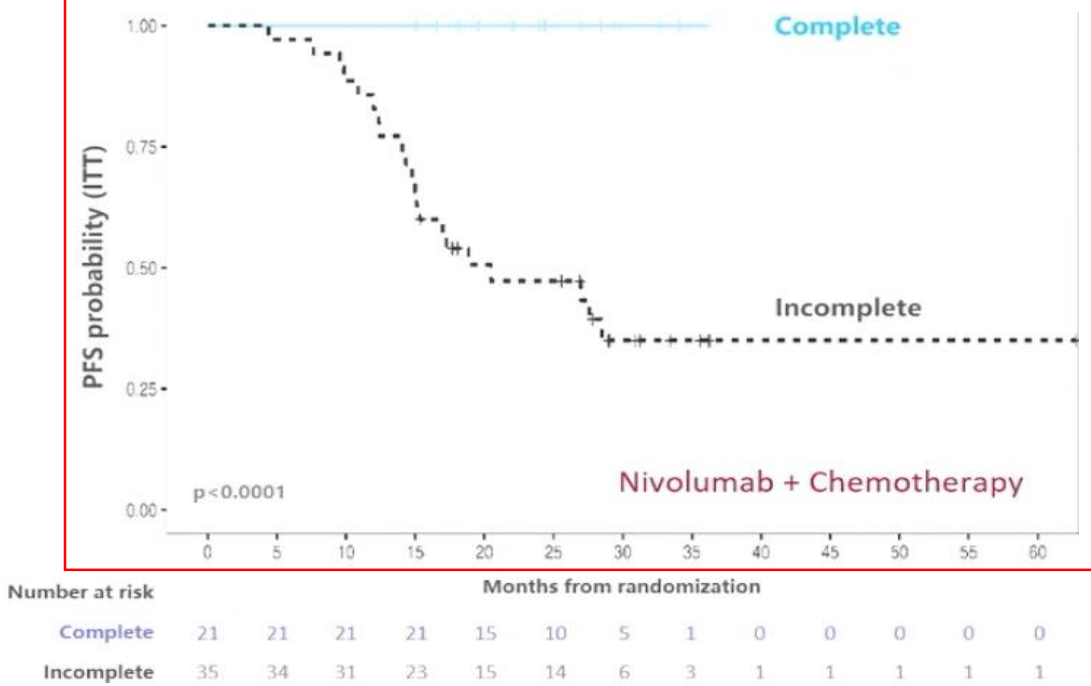
NADIM TRIAL

Provencio, 2022 WCLC

Progression free survival
(secondary endpoint)



Progression free survival
*(**Complete pathologisch respons vs. overige**)*



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NADIM TRIAL

TABLE 1. HR and Corresponding 95% CI According to Each Biomarker (TMB, PD-L1, and ctDNA levels at baseline)

Biomarker	No.	Deaths	Progressions	HR (PFS)[a]	95% CI[a]	*P*[a]	HR (OS)[a]	95% CI[a]	*P*[a]
Basal ctDNA < 1%	43	9	12	0.20	0.06 to 0.63	.006	0.07	0.01 to 0.39	.002
TMB ≥ 10 mut/Mb	29	6	6	1.67	0.41 to 6.83	.474	2.13	0.37 to 12.40	.399
PD-L1 ≥ 1%	28	5	8	0.64	0.17 to 2.40	.508	0.35	0.06 to 2.12	.252

Provencio et al. (2022). J Clin Oncol 40:2924-2933.

Erasmus MC

NADIM TRIAL

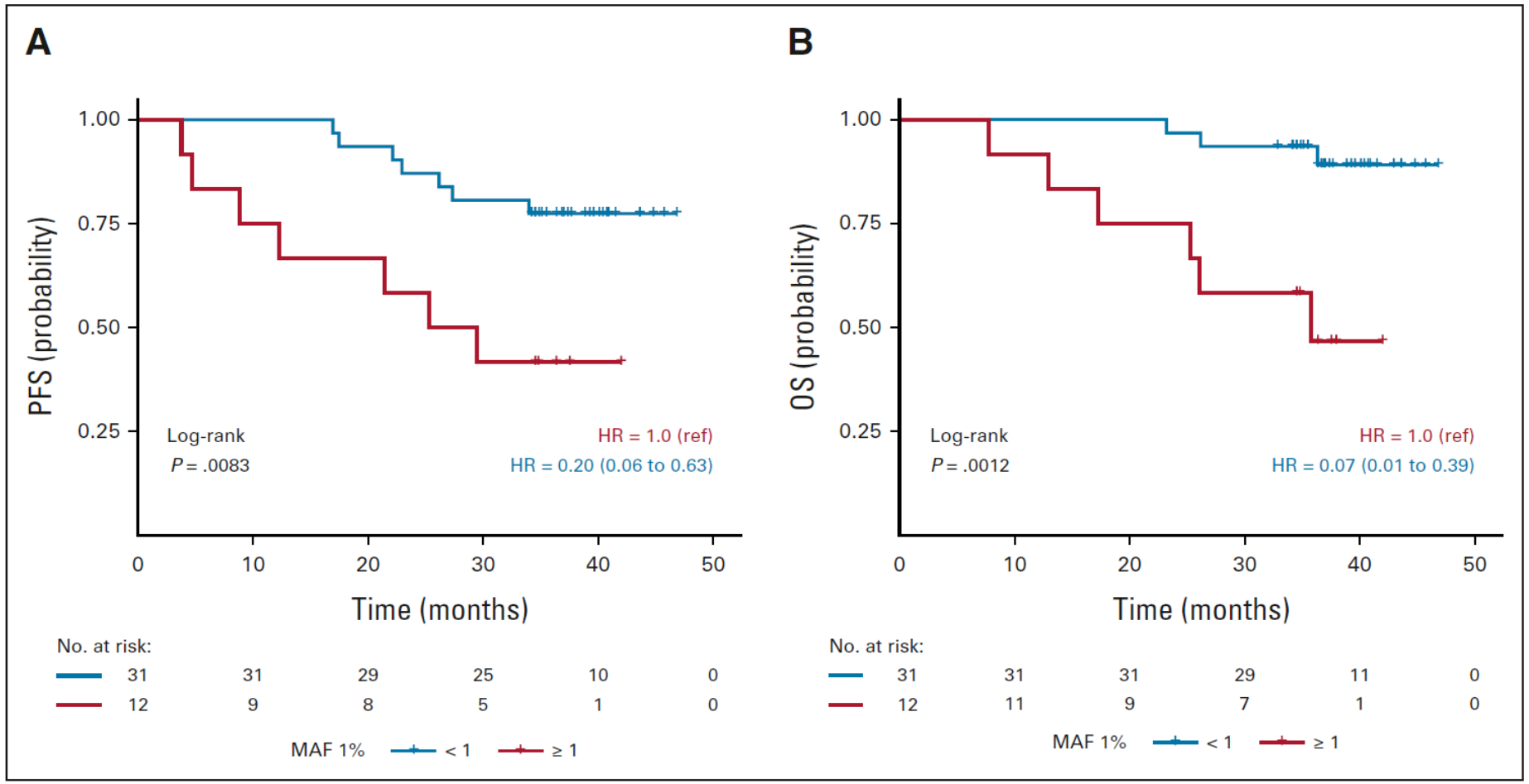


FIG 2. Kaplan-Meier curves for (A) PFS and (B) OS by ctDNA levels at baseline, using a cutoff of < 1% MAF. ctDNA, circulating tumor DNA; HR, hazard ratio; MAF, mutant allele fraction; OS, overall survival; PFS, progression-free survival; ref, reference category.

Provencio et al. (2022). J Clin Oncol 40:2924-2933.

Erasmus MC

BEOORDELING NSCLC RESECTIE NA NAT

Tumor regression cutoff and survival prediction

Non-responders

Grade Ⅰ: no or only minor,
mostly spontaneous tumor regression

Grade Ⅱ: morphological signs of
therapy-induced tumor regression

ⅡA : more than 10% vital tumor tissue

ⅡB : **less than 10%** vital tissue

Grade Ⅲ : complete tumour regression,
no evidence of vital tumor tissue.

Responders

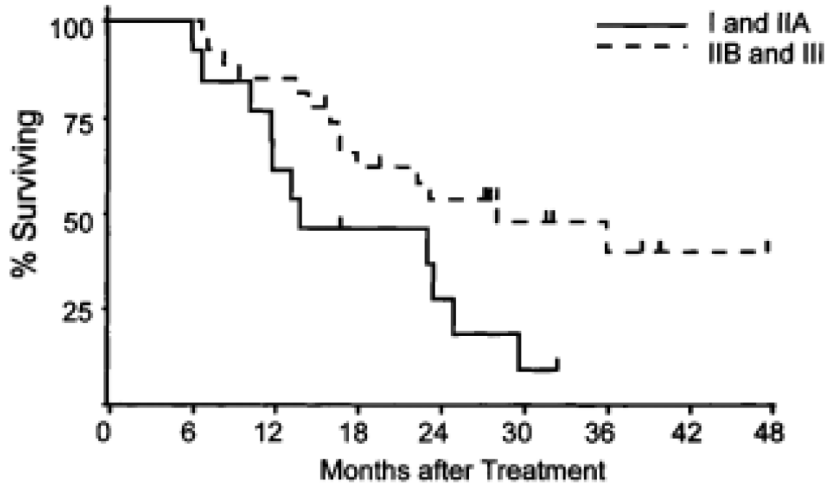


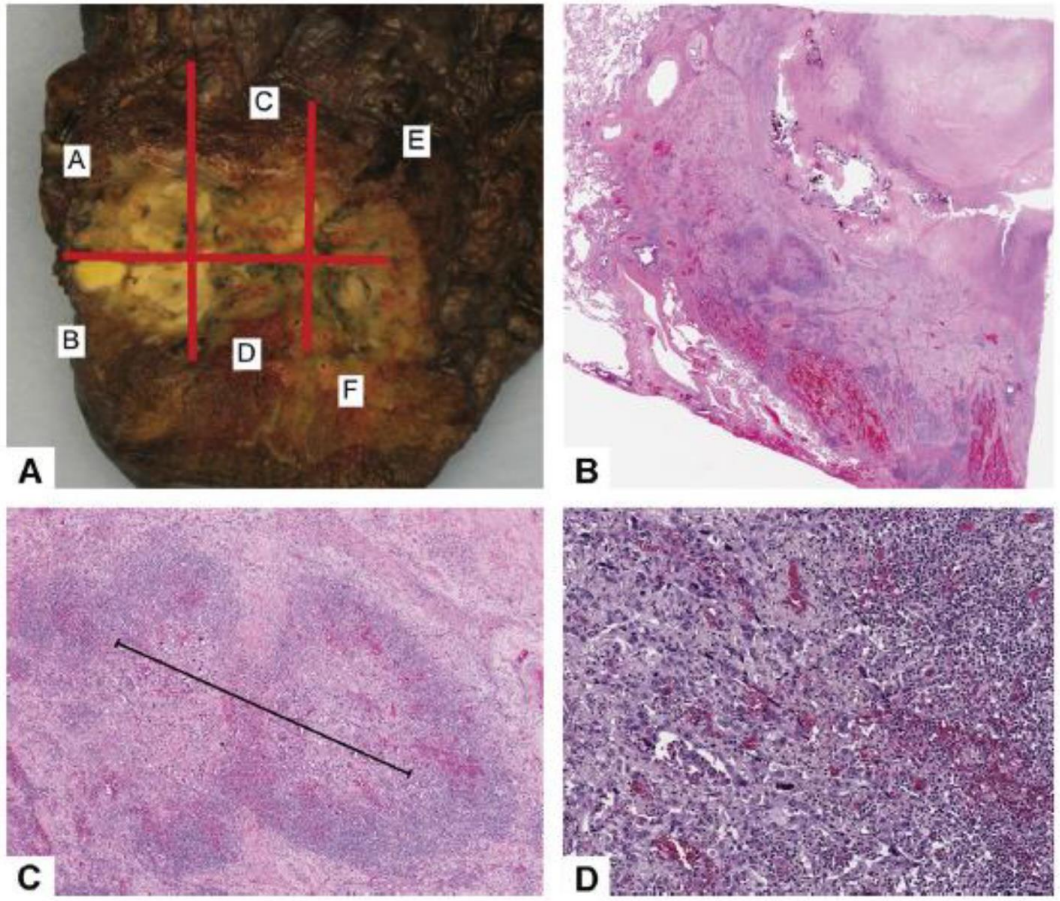
Fig. 4 Survival curves according to Kaplan and Meier for regression grades I and IIa ("non-responders") versus regression grades IIb and III ("responders") with a statistically significantly longer median survival period for patients with regression grade IIb or III (log-rank test. $P = 0.020$)

Junker K, et al. J Cancer Res Clin Oncol. 1997;123(9):469-77.

Erasmus MC

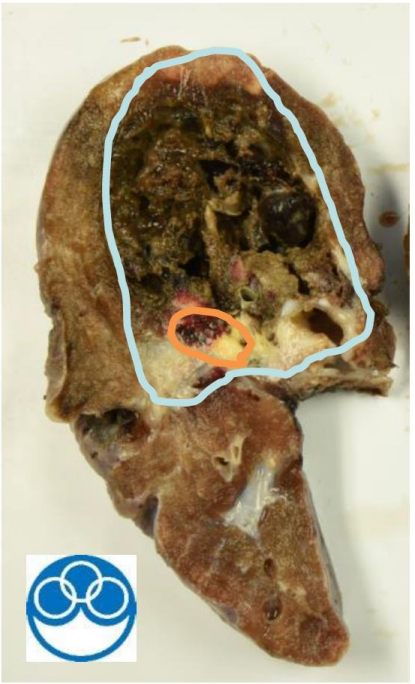
BEOORDELING NSCLC RESECTIE NA NAT

Major pathology response (MPR)



Defined as less than 10% residual viable tumor

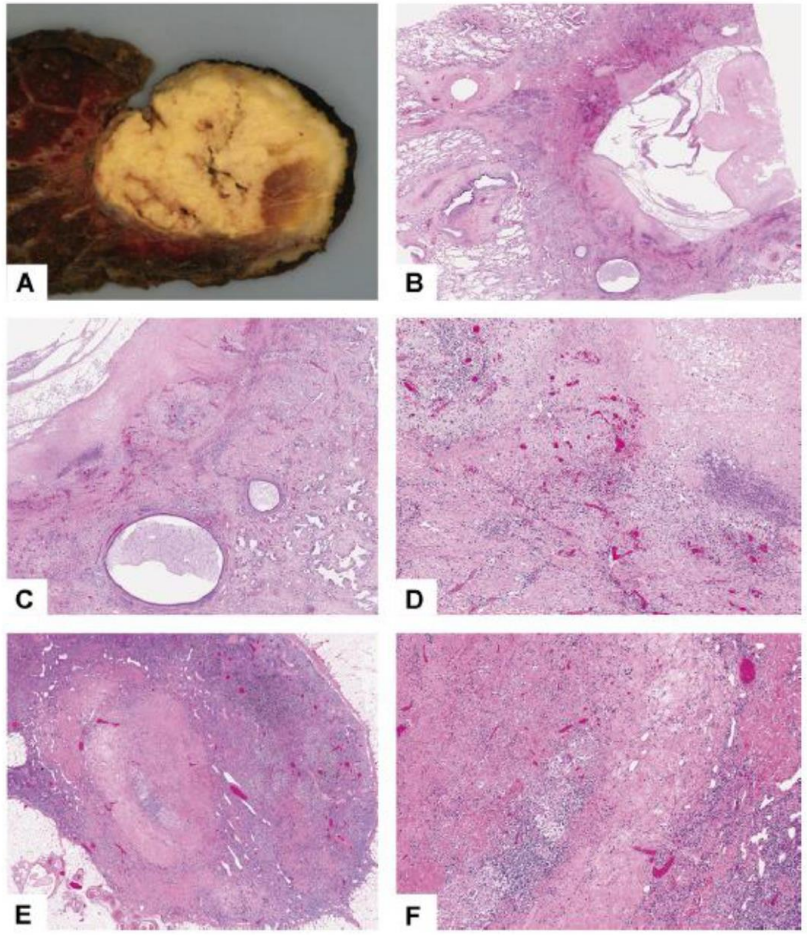
Residual viable adenocarcinoma, 2mm in size (less than 10%)
=MPR (+)



Travis WD, et al. J Thorac Oncol. 2020;15(5):709-40.

BEOORDELING NSCLC RESECTIE NA NAT

Pathological complete response (pCR)



Defined as complete loss of viable cancer (0%*)

* Some study include viable tumor less than 5% as pCR.

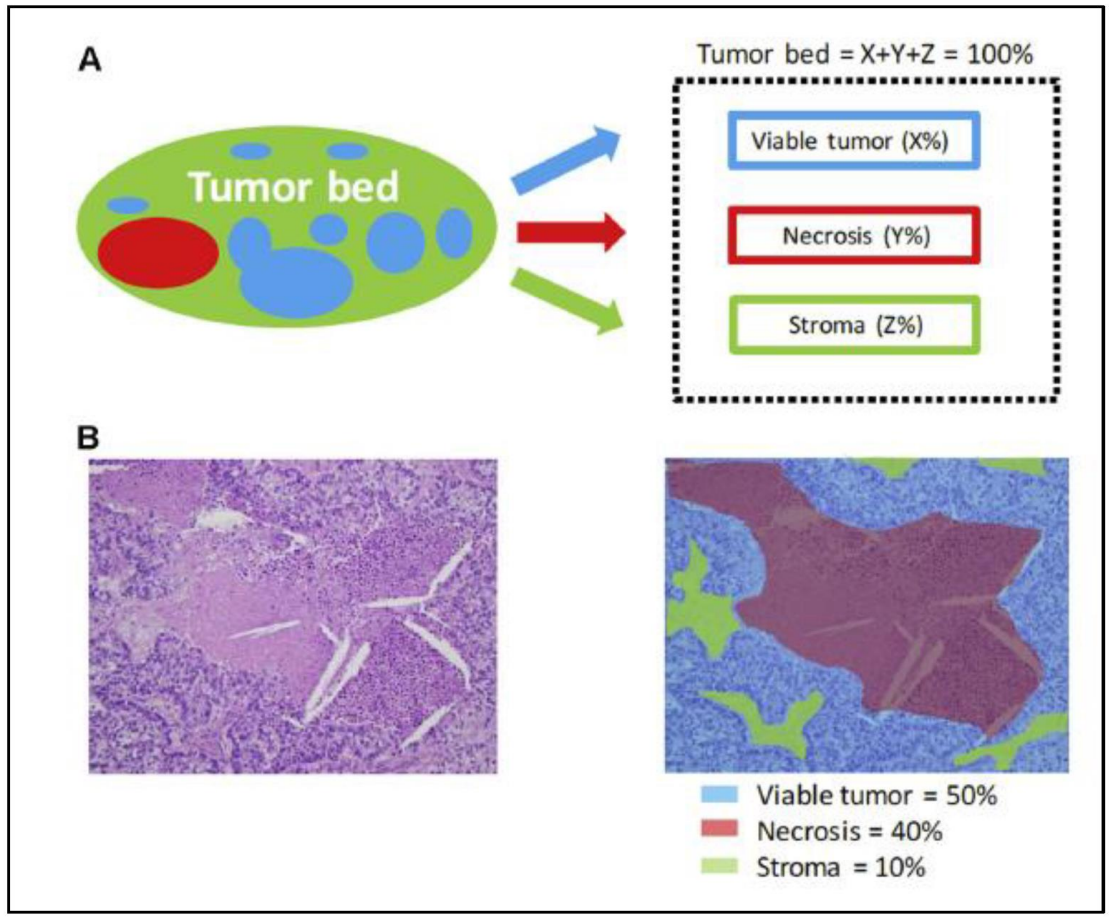
No viable tumor cells in the tumor bed (necrosis, fibrosis, inflammation)
= pCR(+)

Travis WD, et al. J Thorac Oncol. 2020;15(5):709-40.

Erasmus MC

BEOORDELING NSCLC RESECTIE NA NAT

How to determine the degree of pathologic response?



IASLC Recommendation
Residual tumor (%)
= viable tumor / tumor bed

The term “tumor bed ” refers to the area where the original pretreatment tumor was considered to be located.

Tumor bed
= 1) viable tumor + 2) necrosis + 3) stroma (including inflammation and fibrosis)

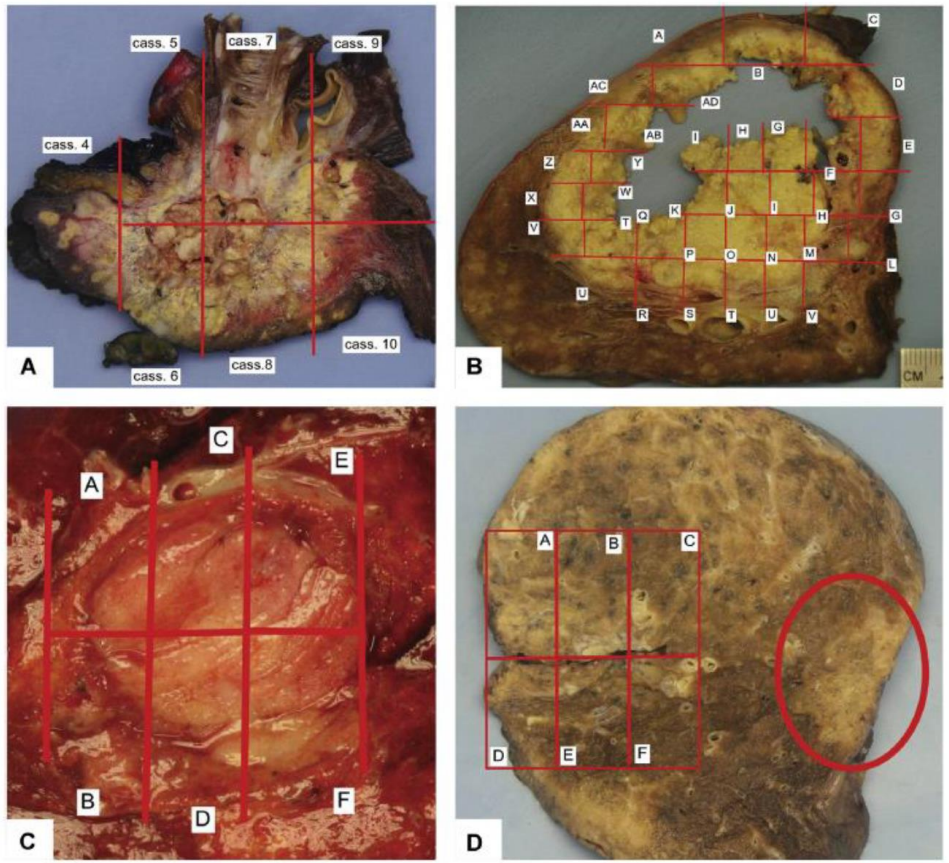
Note:
Tumor bed is not equal to the pre-existing tumor area.

Travis WD, et al. J Thorac Oncol. 2020;15(5):709-40.

Erasmus MC

BEOORDELING NSCLC RESECTIE NA NAT

How to sample the suitable area?



IASLC Recommendation

If the tumor is small (≤3 cm), it should be entirely sampled.

If the tumor is larger than 3 cm, an approximately 0.5 cm thick cross-section of tumor in its maximum dimension should be made.

Macroscopic photography is recommended (“mapping”).

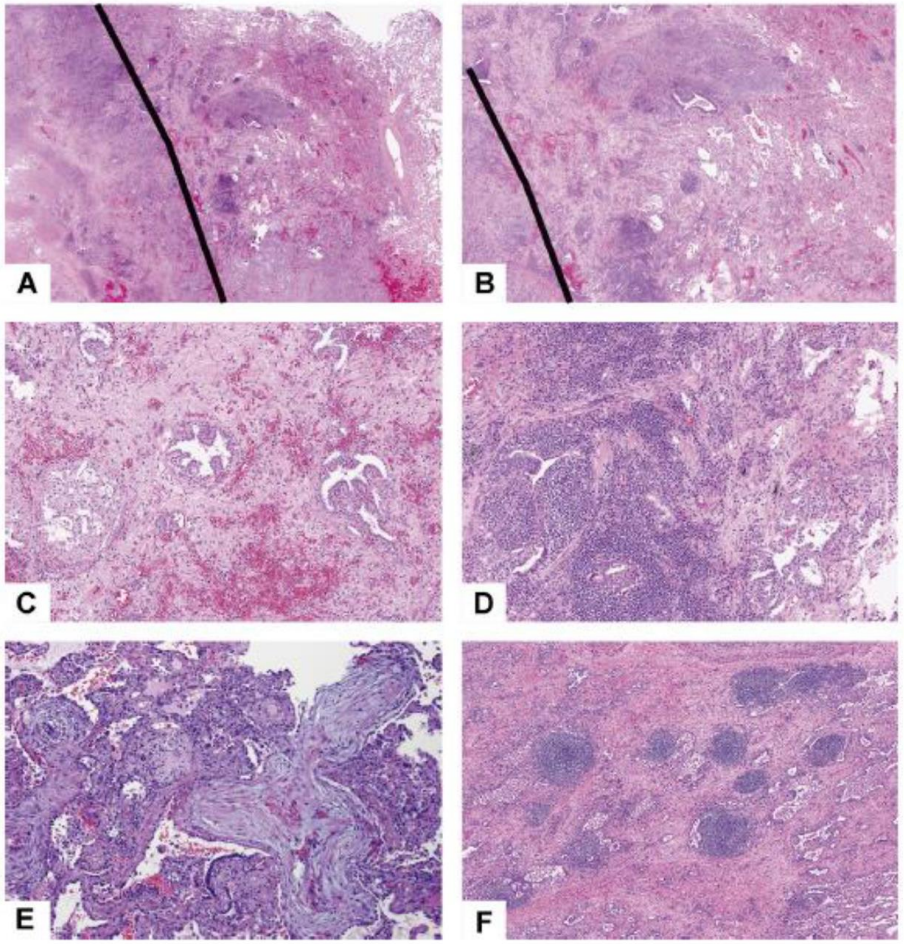
Peripheral sections of the tumor should include the border of the tumor with at least 1 cm of the surrounding non-neoplastic lung parenchyma.

Travis WD, et al. J Thorac Oncol. 2020;15(5):709-40.

Erasmus MC

BEOORDELING NSCLC RESECTIE NA NAT

How to assess the primary tumors?



IASLC Recommendation

Define the border of tumor bed from surrounding non-neoplastic lung
- exclude reactive changes (OP, IP, hemorrhage, inflammation etc.)
- correlate with the gross photo with mapping of histologic sections

Note:
Lepidic component should be excluded (but still controversial).

Travis WD, et al. J Thorac Oncol. 2020;15(5):709-40.

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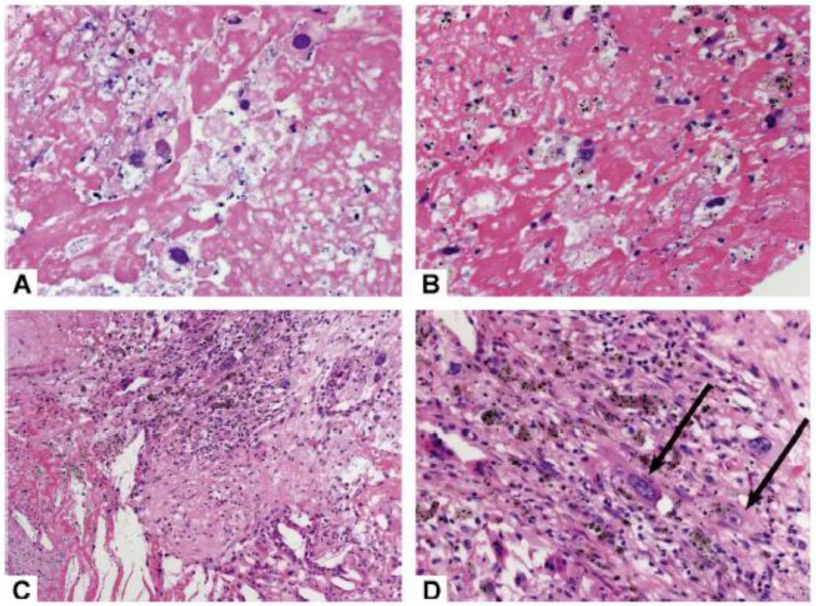
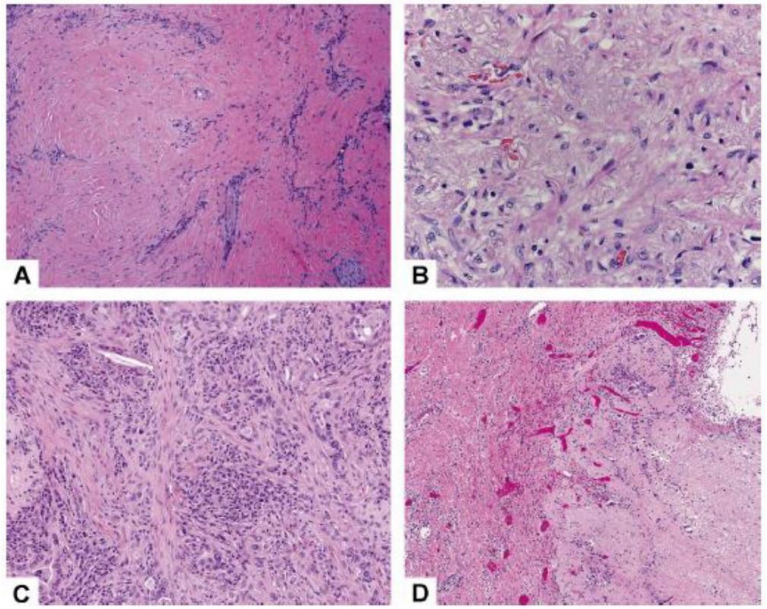
BEOORDELING NSCLC RESECTIE NA NAT

Difficult points of Pathologic Assessment

Necrosis vs viable tumor cell



Tumoral stroma vs reactive stroma



➡ affect the % of “viable cell” estimation / ➡ affect the tumor bed area estimation may include non-therapy-related area

→ **Need Consensus guideline, Training, Technology advance (Image analysis)**

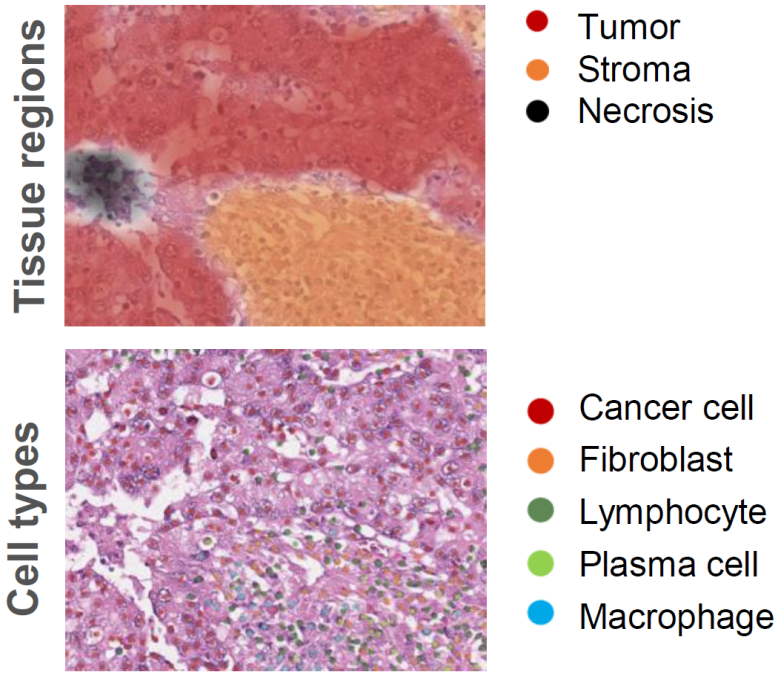
Travis WD, et al. J Thorac Oncol. 2020;15(5):709-40.

Erasmus MC

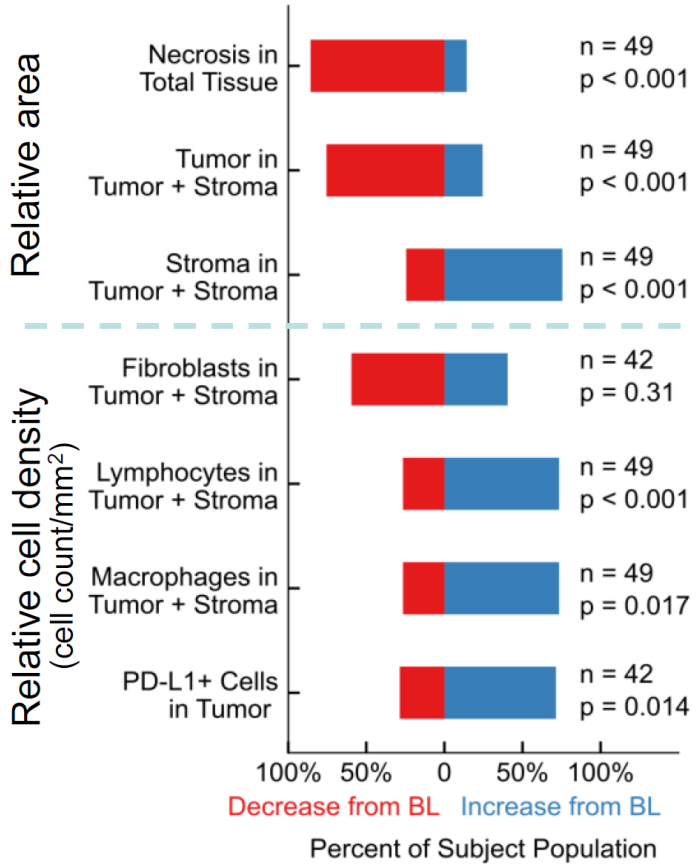
CLINICAL/BIOMARKER DATA FOR NEOADJUVANT ATEZOLIZUMAB IN RESECTABLE STAGE IB-IIIB NSCLC: PRIMARY ANALYSIS IN THE LCMC3 STUDY

WCLC 2021, Carbone

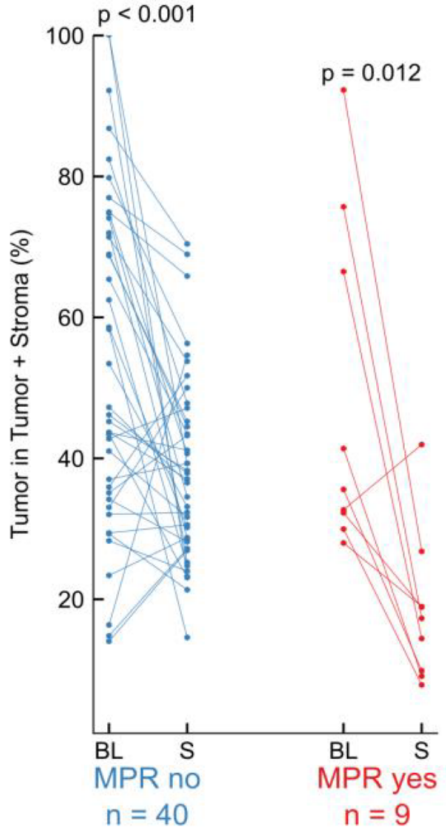
Machine learning models for H&E and PD-L1 images measure quantitative features for analysis:



Histologic changes measured in the TME[a]



Change in % relative tumor area by MPR[a]



P via uncorrected Wilcoxon signed-rank.

[a] Preliminary analysis of a subset of patients with available H&E and PD-L1 slides.

TAKE HOME

- Neoadjuvante immuuntherapie lijkt bijzonder effectief in het bereiken van complete pathologische respons in verschillende solide tumoren
- pCR is gecorreleerd met betere PFS en OS
- Beoordeling van preparaten na neoadjuvante IO heeft gelijkenis, maar er zijn ook duidelijke verschillen
- Studie naar de exacte effecten op weefselniveau nu mogelijk
- cfDNA analyse is mogelijk goede toevoeging => wellicht ook voor vermijden van resectie in de toekomst?

Dank voor uw aandacht!