The evolving role of thoracic surgeons in the era of immunotherapy

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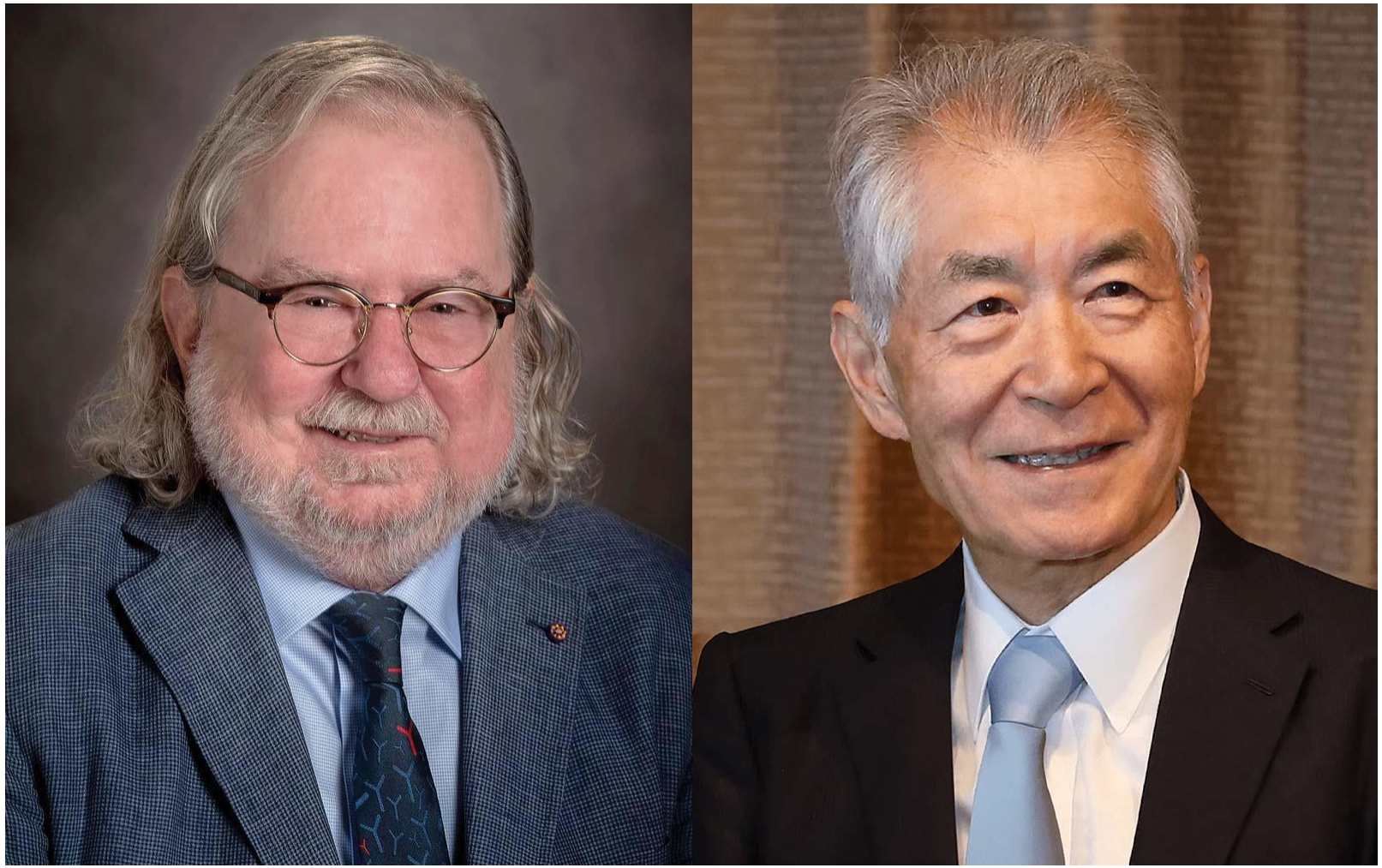
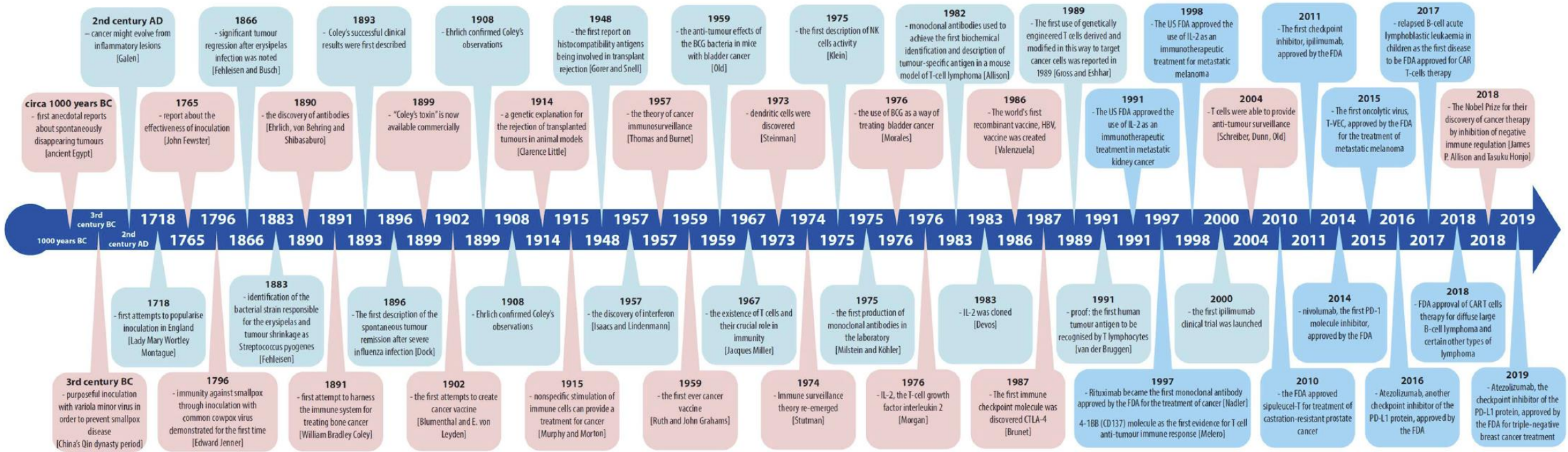
2018 Nobel Prize in Physiology or Medicine



James P. Allison
CTLA-4

Tasuku Honjo
PD-1

Evolution of Immunotherapy



Dobosz et al. Frontiers in Immunology 2019

Table 1 Classification of Immunotherapy for Cancer with examples of specific agents

Immunomodulators	Targeted antibodies	Adoptive cell therapy	Cancer vaccines	Oncolytic viruses
Immune checkpoint inhibitors (ICIs) Ipilimumab, nivolumab, pembrolizumab	**Unconjugated monoclonal antibodies** Rituximab, pertuzumab, cetuximab, bevacizumab	**Chimeric antigen receptor (CAR) T cell therapy** Axicabtagene ciloleucel, lisocabtagene maraleucel	**Therapeutic** BCG, sipuleucel-T	Talimogene laherparepvec (T-VEC)
Cytokines GM-CSF, interferon alfa, aldesleukin	**Antibody–drug conjugates (ADCs)** Belantamab mafodotin-blmf, brentuximab vedotin	**Tumor-infiltrating lymphocyte (TIL) therapy**	**Personalized neoantigen**	
Toll-like Receptor (TLR) Agonists & Adjuvants Imiquimod, poly ICLC	**Bispecific antibodies, including Bispecific T-cell engagers (BiTEs)** Amivantamab, blinatumomab	**Engineered T cell receptor (TCR) therapy**	**Preventive** HPV and HBV vaccines	
Other Pexidartinib		**Natural killer (NK) cell therapy**		

Granulocyte–macrophage colony-stimulating factor (*GM-CSF*), polyriboinosinic-polyribocytidylic acid (*poly-ICLC*), human papillomavirus (*HPV*), hepatitis B virus (*HBV*), Bacillus Calmette-Guerin (*BCG*)

Ackerman et al. Current Oncology Reports 2022

The NEW ENGLAND JOURNAL of MEDICINE

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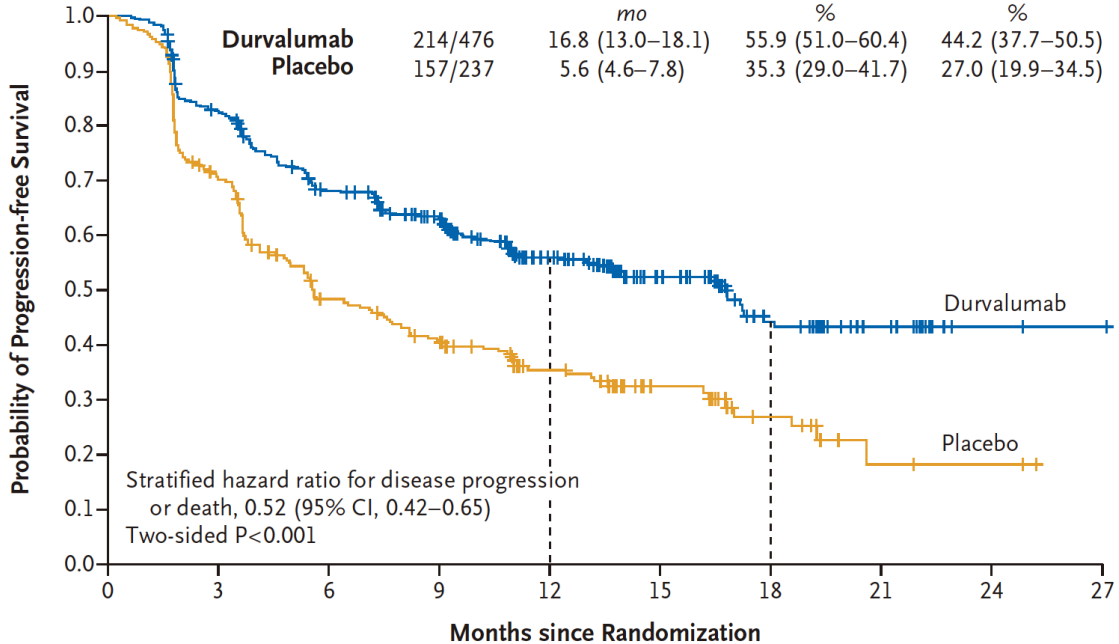
Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer

S.J. Antonia, A. Villegas, D. Daniel, D. Vicente, S. Murakami, R. Hui, T. Yokoi, A. Chiappori, K.H. Lee, M. de Wit, B.C. Cho, M. Bourhaba, X. Quantin, T. Tokito, T. Mekhail, D. Planchard, Y.-C. Kim, C.S. Karapetis, S. Hiret, G. Ostoros, K. Kubota, J.E. Gray, L. Paz-Ares, J. de Castro Carpeño, C. Wadsworth, G. Melillo, H. Jiang, Y. Huang, P.A. Dennis, and M. Özgüroğlu, for the PACIFIC Investigators*

	No. of Events/ Total No. of Patients	Median PFS (95% CI)	12-Mo PFS (95% CI)	18-Mo PFS (95% CI)
		mo	%	%
Durvalumab	214/476	16.8 (13.0–18.1)	55.9 (51.0–60.4)	44.2 (37.7–50.5)
Placebo	157/237	5.6 (4.6–7.8)	35.3 (29.0–41.7)	27.0 (19.9–34.5)



No. at Risk										
Durvalumab	476	377	301	264	159	86	44	21	4	1
Placebo	237	163	106	87	52	28	15	4	3	0

Editorial

Conducted by EDWIN H. ELLISON, M.D.

Cancer immunology and the surgeon

DONALD L. MORTON, M.D.
BETHESDA, MD.
From the Tumor Immunology Section, Surgery Branch, National Cancer Institute of the National Institutes of Health

Since it has been difficult or impossible to cause regression of established tumors in animals by immunologic means, it is unlikely that immunotherapy *alone* will ever play the major role in the treatment of cancer.

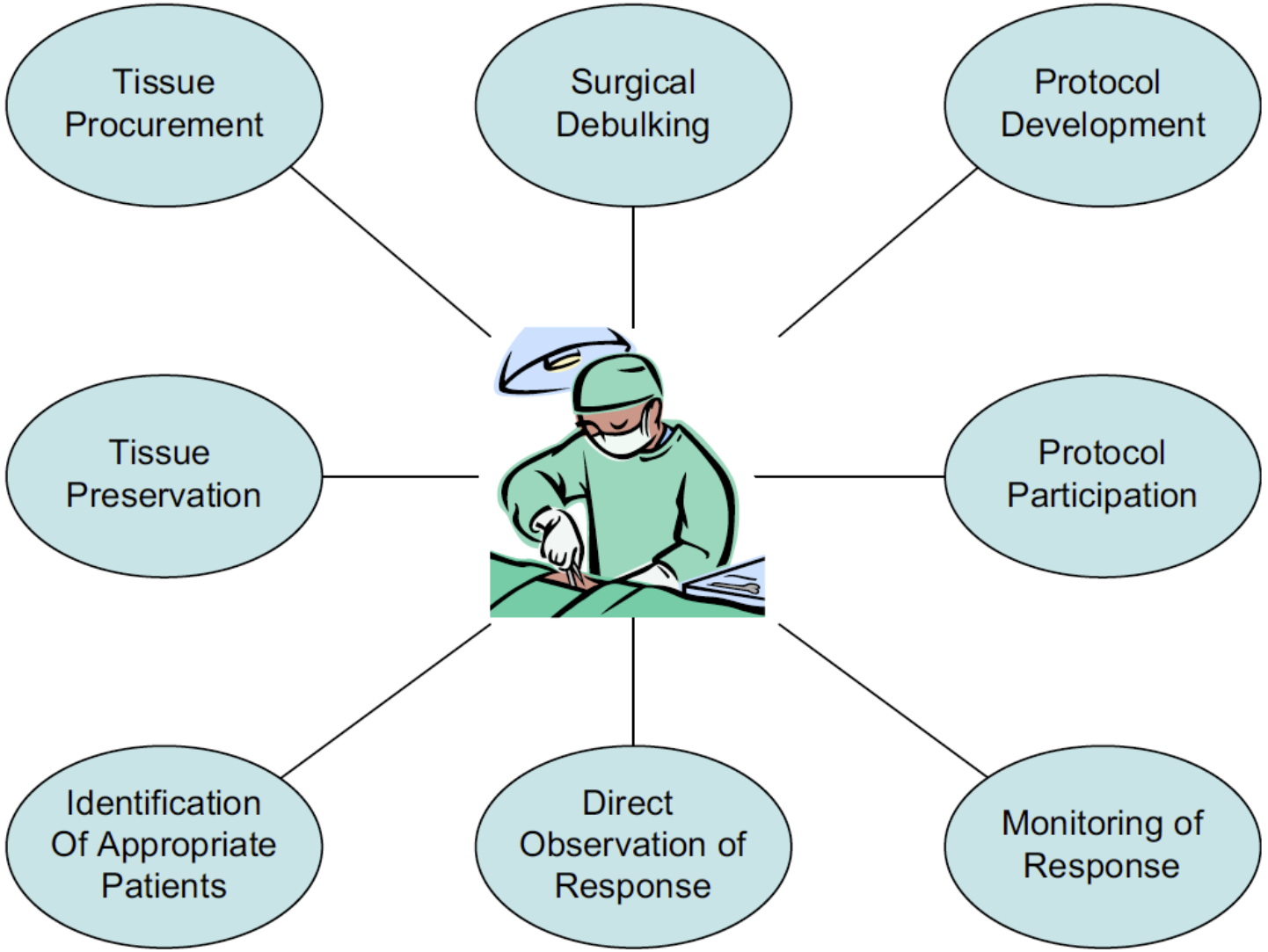
For these reasons, the surgeon is ideally suited to utilize immunotherapy as a therapeutic tool and should welcome its development. One of the major obstacles to the clinical development of immunotherapy is the paucity of clinicians with adequate training in cancer immunology. Therefore, surgeons with a serious interest in cancer are invited to consider a period of special training in this rapidly advancing area of cancer research.

Morton. Surgery 1970

Immunotherapy is a local adjunct to definitive surgery

- Patients who have only small foci of cancer cells remaining after surgical removal of the bulk of tumor are those most likely to benefit f rom immunotherapy.
- The cancer patient's immunological competence is greatest in the stage of localized cancer and progressively declines with advancing disease.
- Immunotherapy would be expected to compliment rather than to interfere with other currently available methods of managing cancer recurrences following surgery, such as irradiation and chemotherapy.

Morton. Surgery 1970



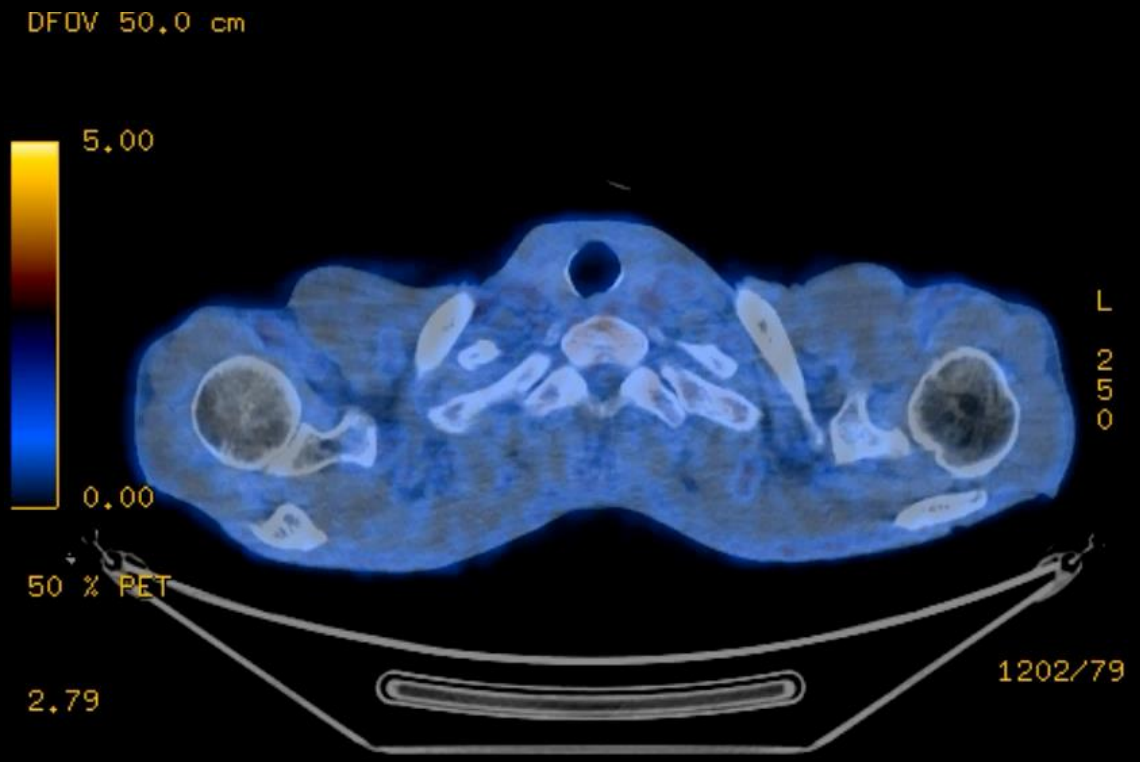
Sticca et al. Surg Oncol Clin N Am 2007

Surgeon as an investigator

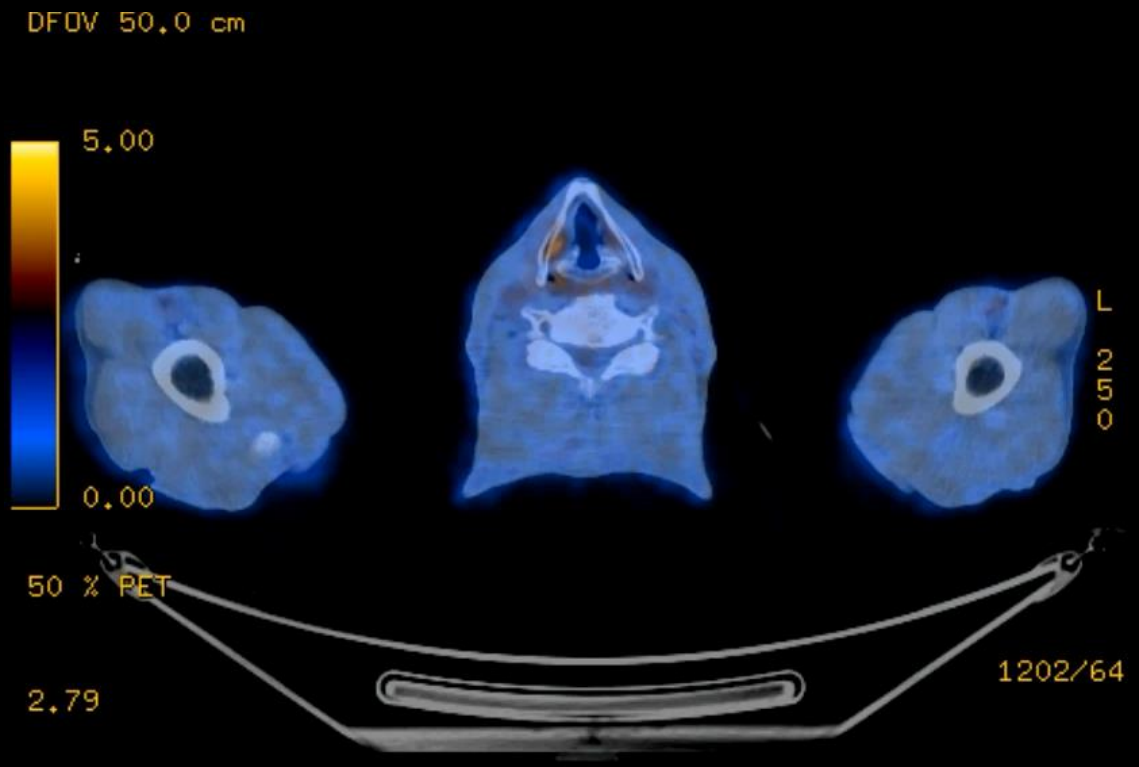
- Protocol awareness
  - First oncologic specialist to diagnose disease and develop the relationship with patients
  - Encourage and promote the clinical trials for patients

- Trial involvement
  - Protocol development
  - Procurement and handling of specimen
  - Monitoring the results

Phase II clinical trial
Neoadjuvant pembrolizumab, docetaxel, cisplatin + surgery + adjuvant pembrolizumab



Initial diagnosis



After neoadjuvant therapy

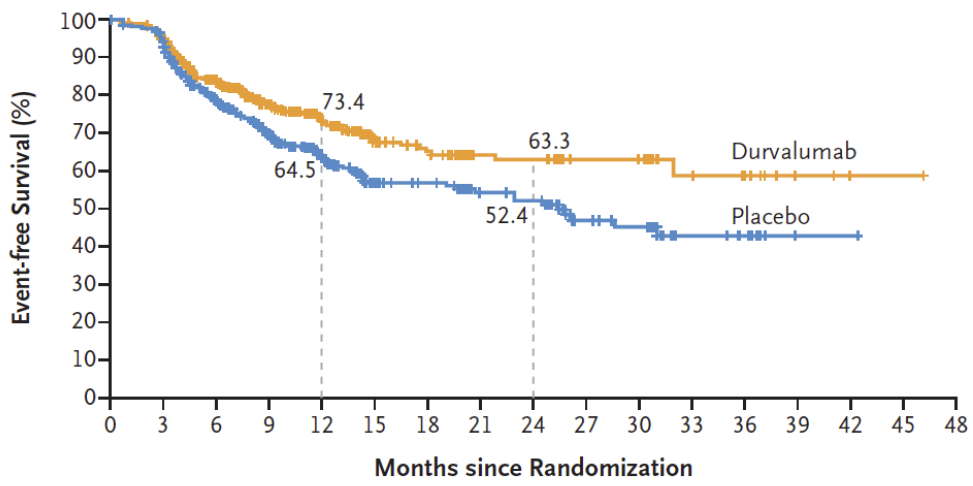
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Perioperative Durvalumab for Resectable Non–Small-Cell Lung Cancer

J.V. Heymach, D. Harpole, T. Mitsudomi, J.M. Taube, G. Galffy, M. Hochmair, T. Winder, R. Zukov, G. Garbaos, S. Gao, H. Kuroda, G. Ostoros, T.V. Tran, J. You, K.-Y. Lee, L. Antonuzzo, Z. Papai-Szekely, H. Akamatsu, B. Biswas, A. Spira, J. Crawford, H.T. Le, M. Aperghis, G.J. Doherty, H. Mann, T.M. Fouad, and M. Reck, for the AEGEAN Investigators*

A Event-free Survival



	No. of Events/ No. of Patients	Median Event-free Survival (95%CI)
		mo
Durvalumab	98/366 (26.8)	NR (31.9–NR)
Placebo	138/374 (36.9)	25.9 (18.9–NR)

Stratified hazard ratio for disease progression, recurrence, or death, 0.68 (95% CI, 0.53–0.88)
P=0.004 by stratified log-rank test

No. at Risk

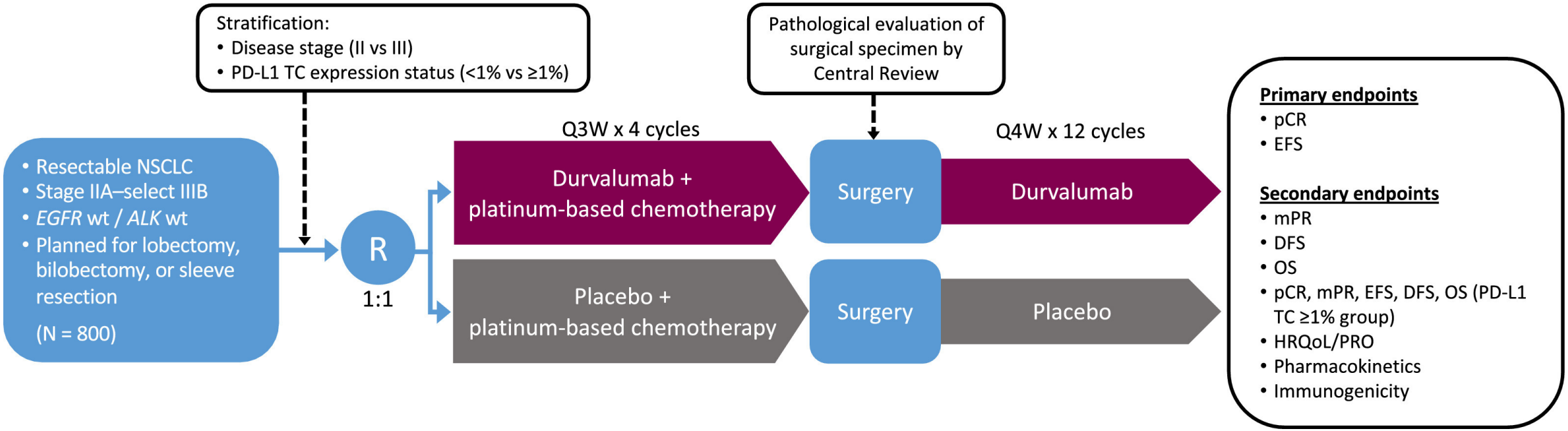
Durvalumab	366	336	271	194	140	90	78	50	49	31	30	14	11	3	1	1	0
Placebo	374	339	257	184	136	82	74	53	50	30	25	16	13	1	1	0	0

Heymach et al. NEJM 2023

Indication
Case selection

Timing of surgery
Type of surgery

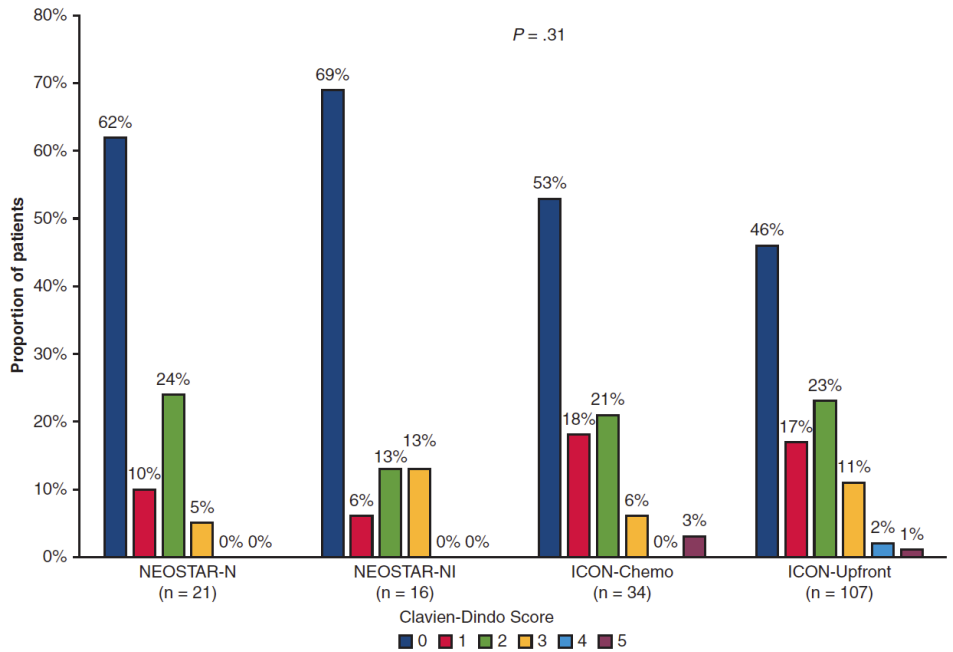
Complication profile
Surgical outcomes

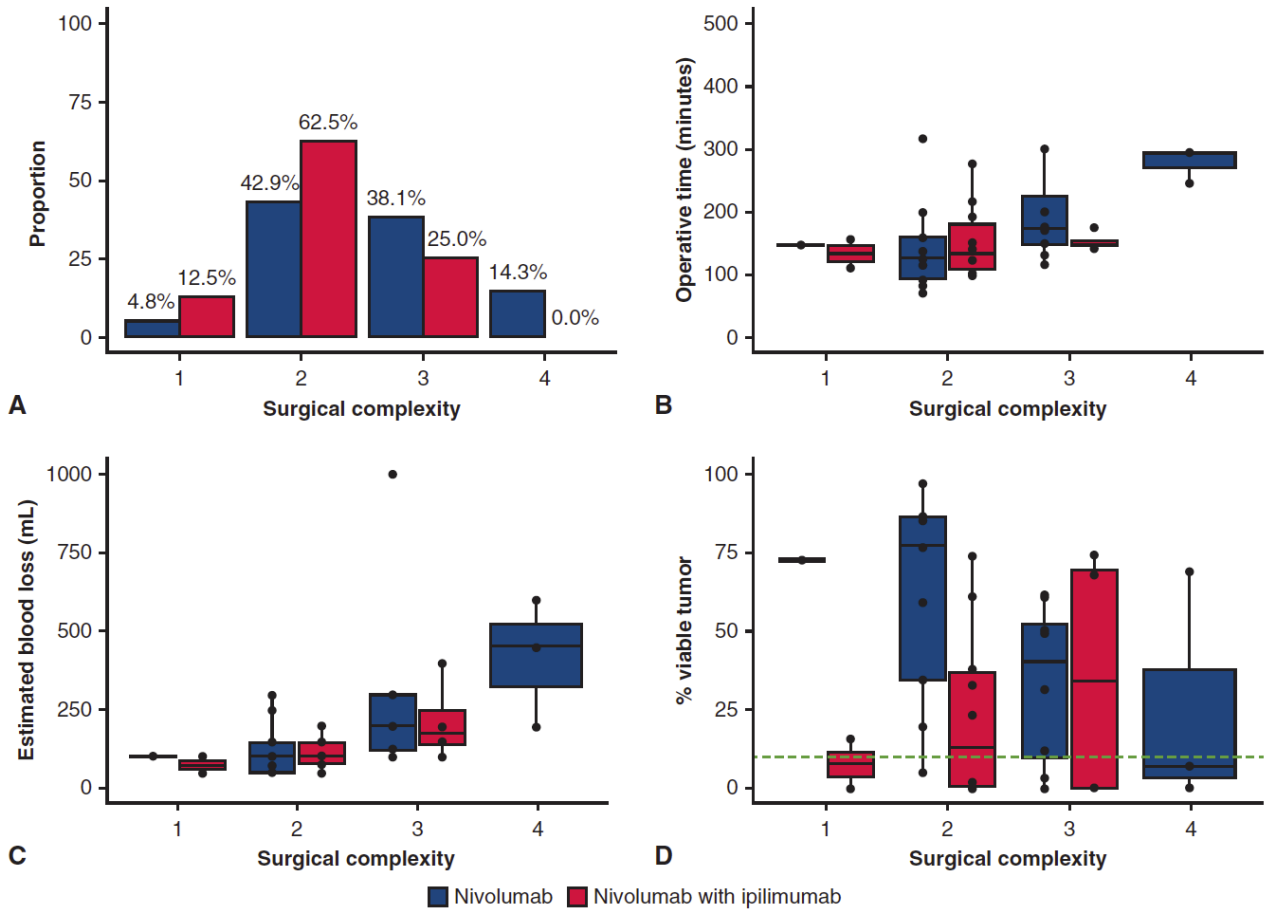


Heymach et al. Clinical Lung Cancer 2022

Surgical outcomes after neoadjuvant nivolumab or nivolumab with ipilimumab in patients with non–small cell lung cancer

Boris Sepesi, MD,[a] Nicolas Zhou, DO, MSc,[a] William N. William, Jr, MD,[b,c] Heather Y. Lin, PhD,[d] Cheuk H. Leung, MS,[d] Annikka Weissferdt, MD,[e] Kyle G. Mitchell, MD, MSc,[a] Apar Pataer, PhD,[a] Garrett L. Walsh, MD,[a] David C. Rice, MBBCh,[a] Jack A. Roth, MD,[a] Reza J. Mehran, MD,[a] Wayne L. Hofstetter, MD,[a] Mara B. Antonoff, MD,[a] Ravi Rajaram, MD, MSc,[a] Marcelo V. Negrao, MD,[b] Anne S. Tsao, MD,[b] Don L. Gibbons, MD, PhD,[b] J. Jack Lee, PhD,[d] John V. Heymach, MD, PhD,[b] Ara A. Vaporciyan, MD,[a] Stephen G. Swisher, MD,[a] and Tina Cascone, MD, PhD[b]





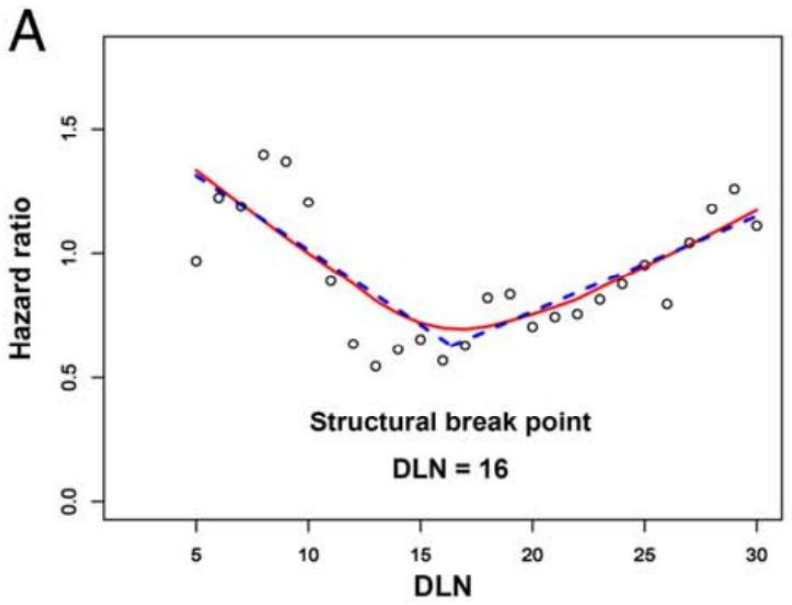
Sepesi et al. J Thorac Cardiovasc Surg 2022

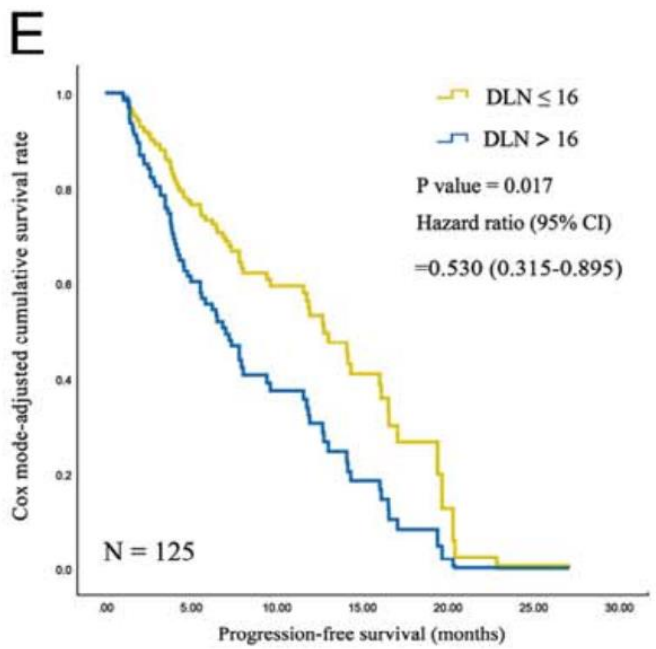
Surgeon as a clinician

- Optimal surgical technique (optimal surgical extent)
- Perioperative management
- Cytoreduction

Radical lymphadenectomy and Survival

144 patients with NSCLC
Surgery & anti-PD-1 for recurrence

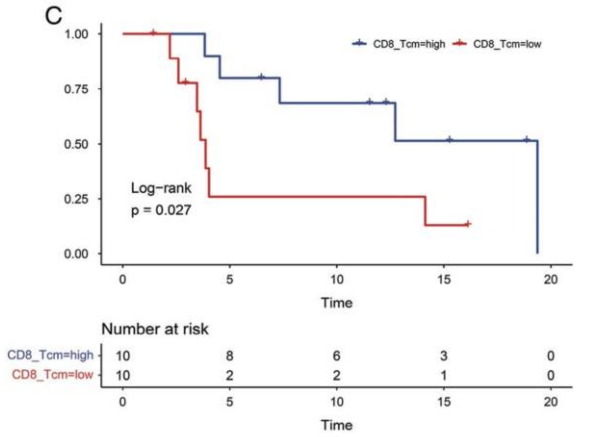


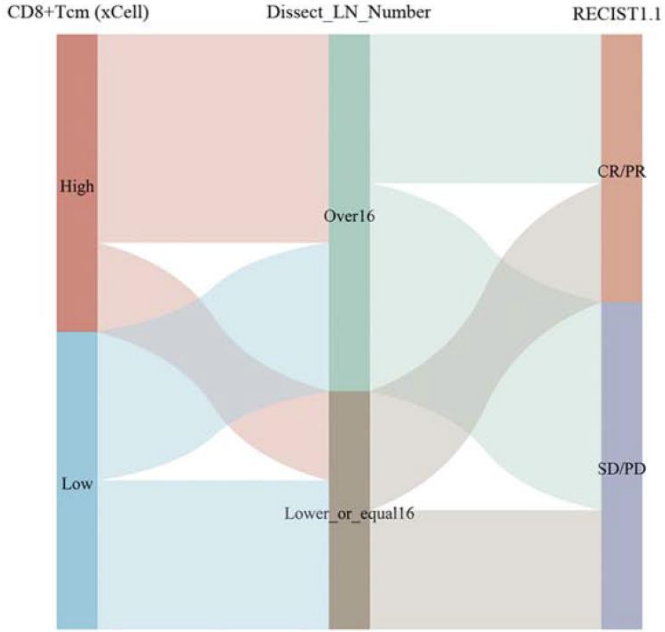


Survival probability

DLN ≤ 16	1.000	0.76	0.59	0.41	0.13	0
DLN > 16	1.000	0.60	0.37	0.19	0.02	0
PFS (mon)	0	5	10	15	20	25

Entire set





Deng et al. International Journal of Surgery 2024

Concepts of ideal resection for oncologic surgery

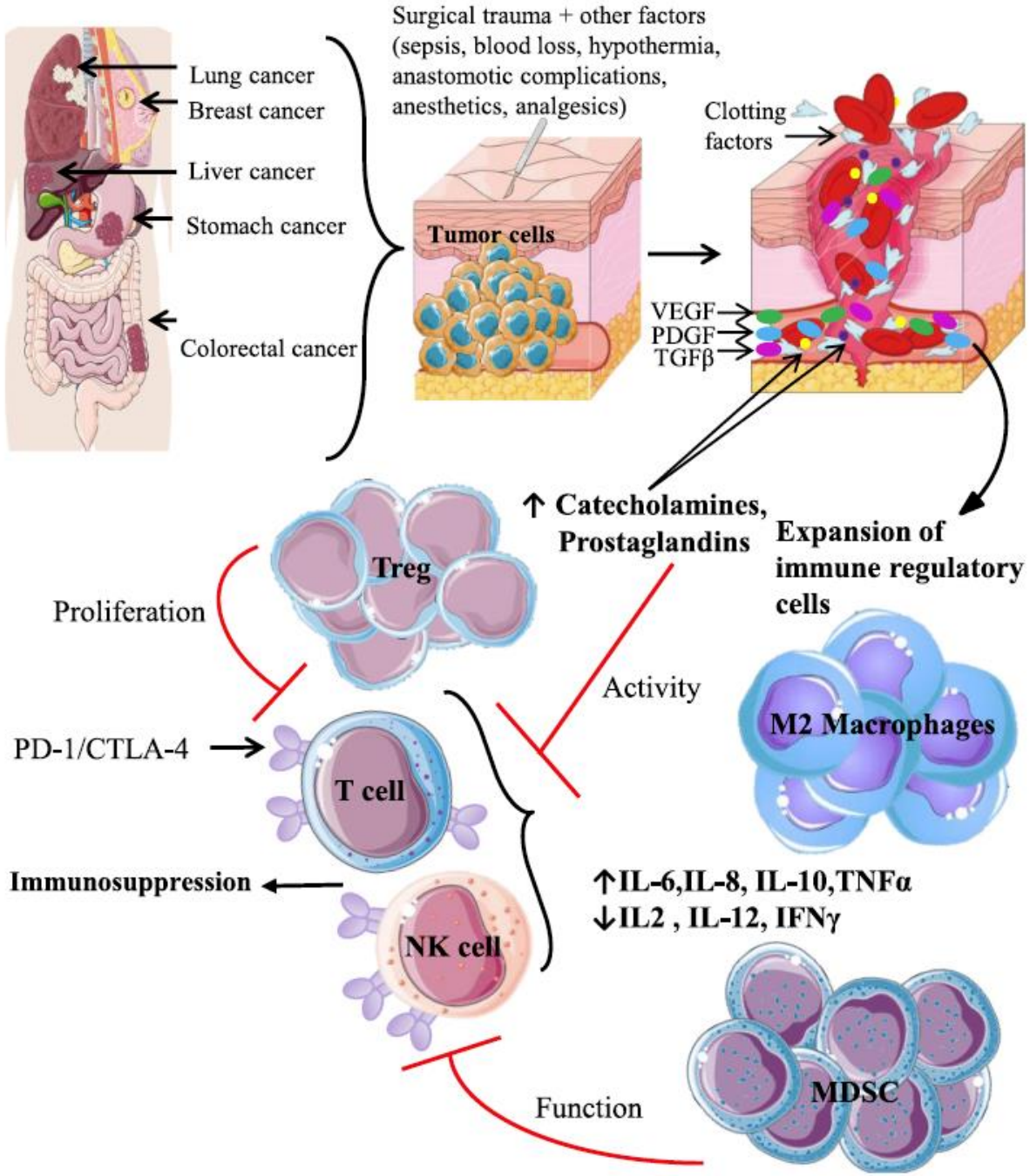
- Classic view-point
  - Complete resection
  - Complete lymphadenectomy & radical resection (3-FL, thoracic duct…)

- New concepts of operation (potentially)
  - Limited resection with R0
  - Patient-tailored lymph node dissection
    - Lobe-specific lymph node dissection, Selective lymph node dissection
    - Sentinel lymph node navigation
    - Image-guided detection & dissection

Surgery induced metastasis and progression

- Surgical resection itself can make cancer cells to metastasize and progress

- Surgical trauma disrupts the host immune system
  - Lasts days to weeks
  - “Immunosuppression window”



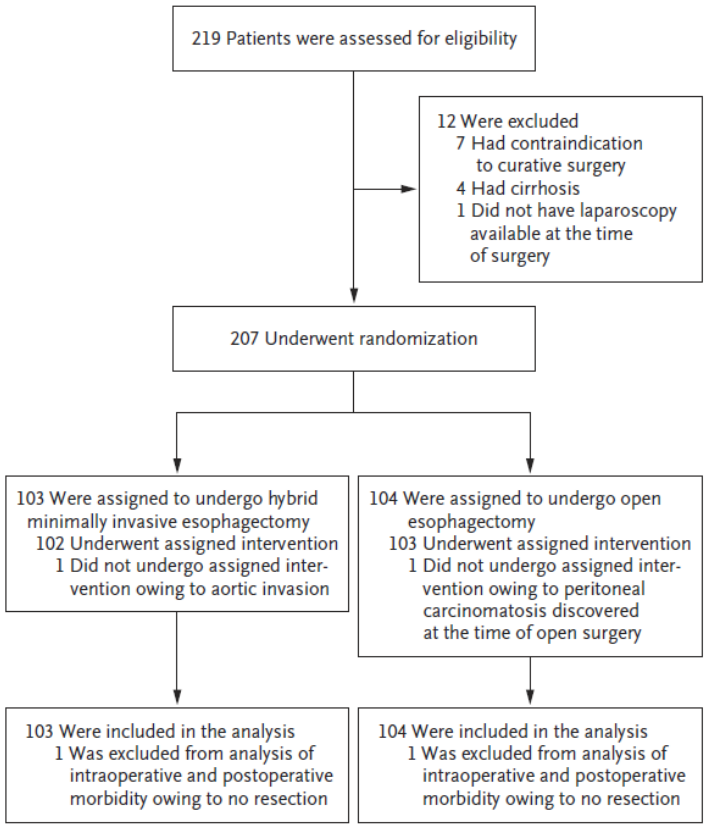
Bakos et al. Journal for ImmunoTherapy of Cancer 2018

Optimal operation in the view-point of immunology

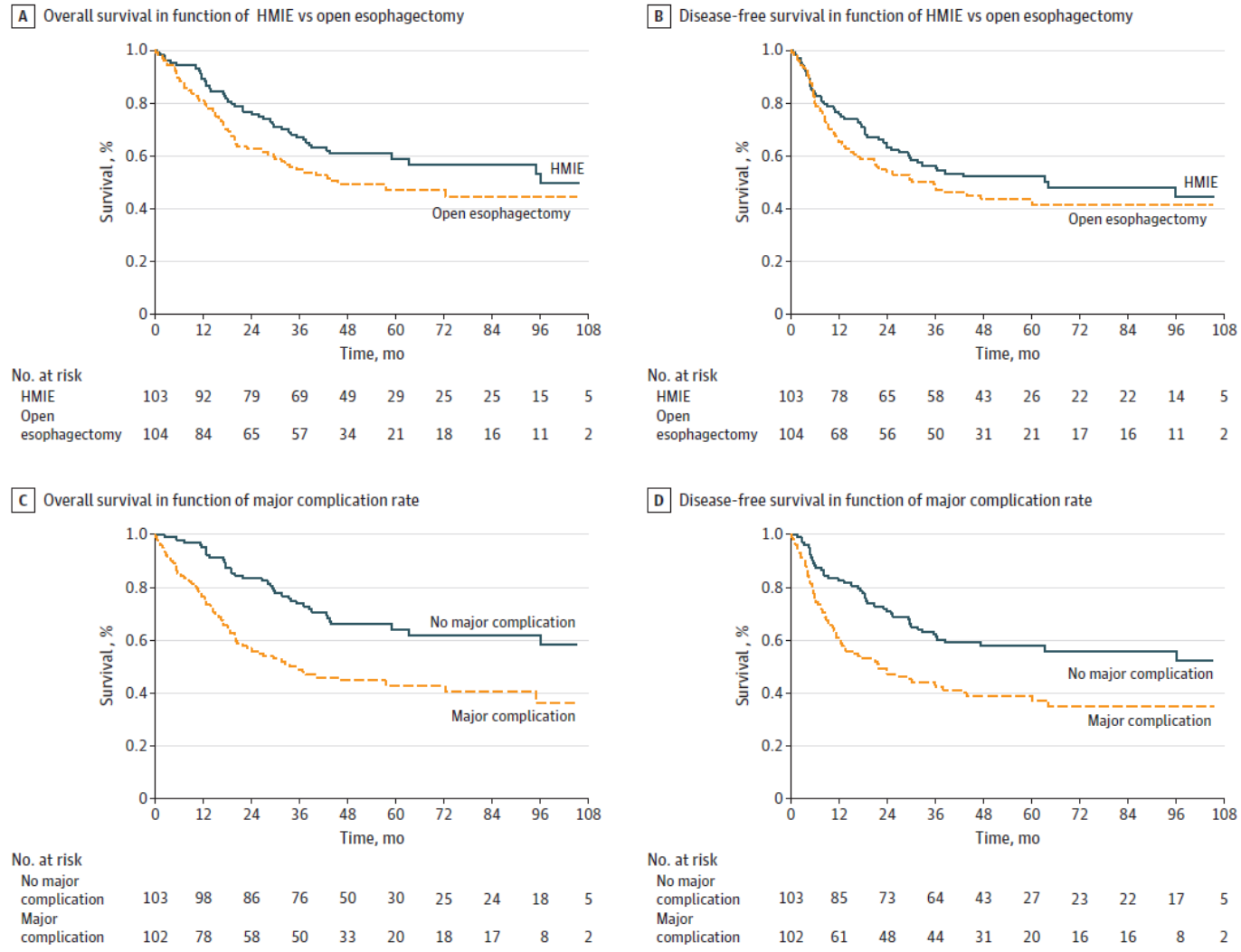
- Perioperative periods; maximal risk of immunosuppression

- Shorten the anesthetic time and operation time
- Perform the minimally invasive surgery
- Prevent blood transfusion and use of morphine
- Prevent complications

MIRO trials; 5-year follow-up data



- Intraoperative and postoperative complications (HR 2.21, p<0.001)
- Pulmonary complications (HR 1.94, p=0.005)



Nuytens et al. JAMA Surgery 2021

Maximal risk of immunosuppression during immediate postoperative periods

= Therapeutic window of opportunity

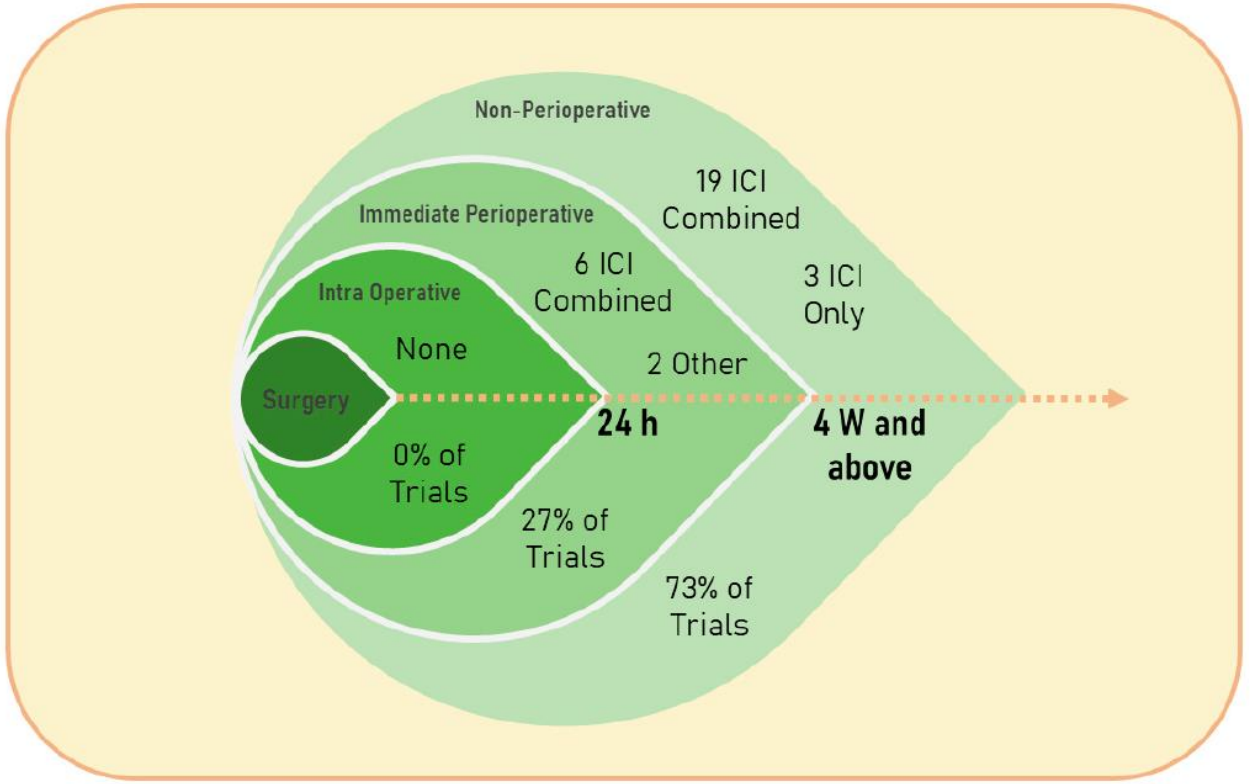
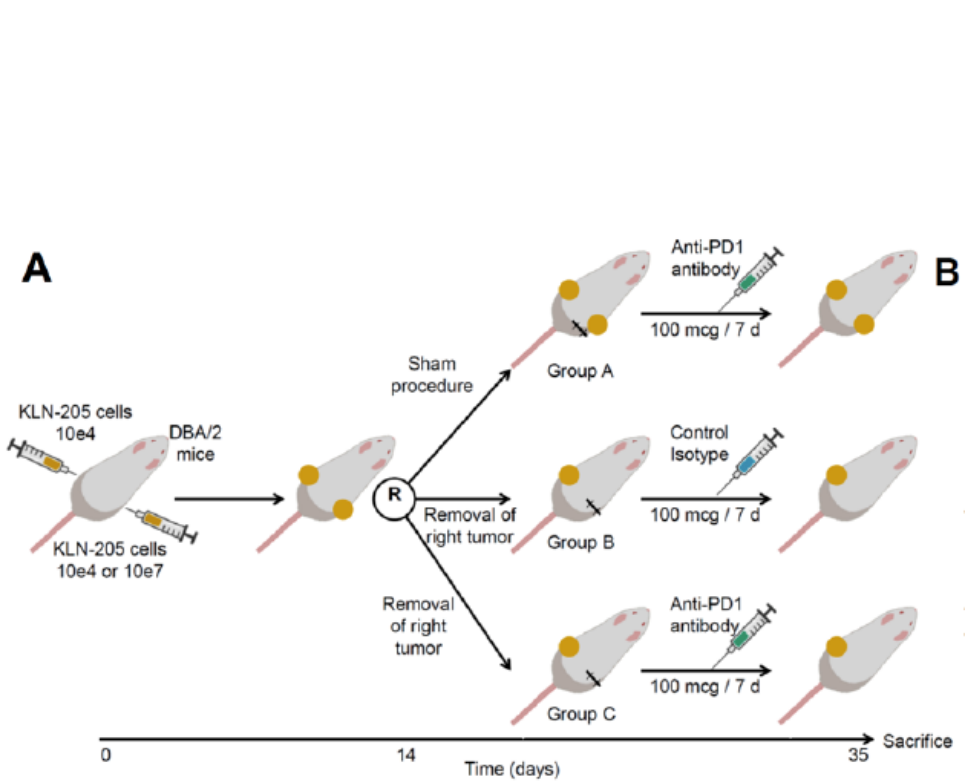
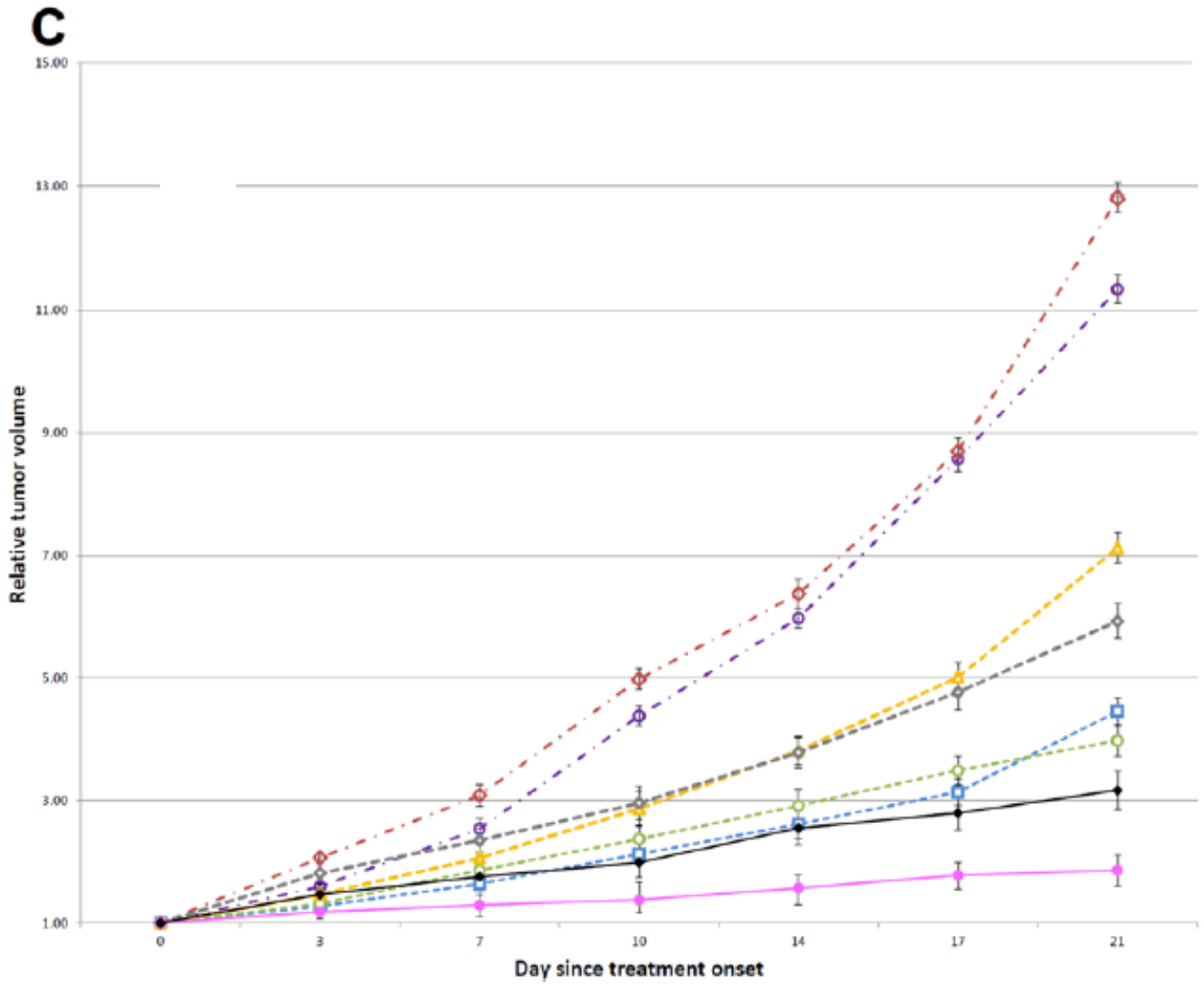


Figure 1. A schematic representation of Table 1. Timing relative to surgery and type of the treatment given to cancer patients in clinical trials found on search results of the keywords "cancer" and "perioperative immunotherapy" in the past five years (since 1 January 2018) on https://clinicaltrials.gov/ (accessed on 14 April 2023). 24 h, 24 hours; 4 W and above, 4 weeks and above; ICI, immune checkpoint inhibition; Combined, ICI therapy combined with other types of interventions.

Sandbank et al. Curr Oncol 2023

Rationale of surgical debulking

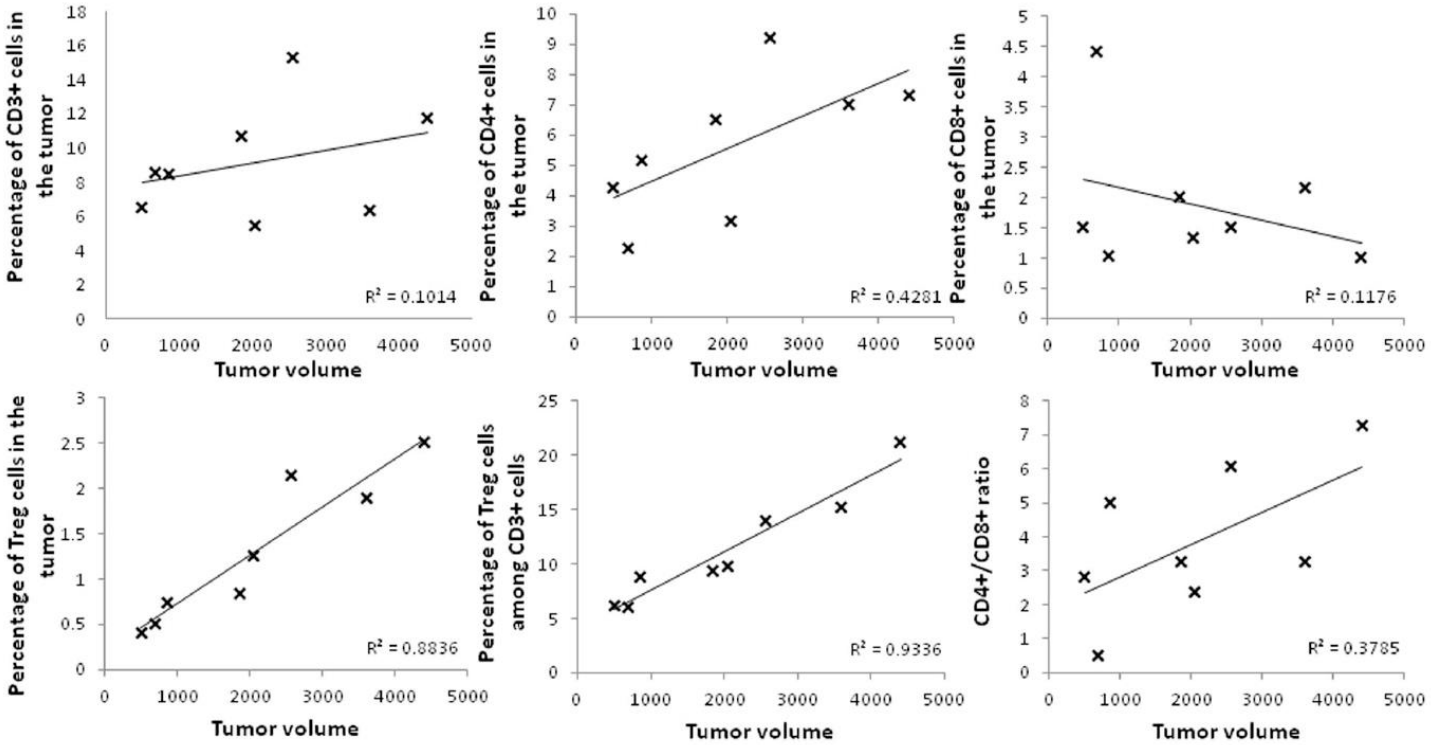




Guisier et al. Scientific reports 2019

Rationale of surgical debulking

	High MTV (n = 19)	Low MTV (n = 29)	p-value
Best response			
Partial response	4	8	
Stable disease	11	17	
Progression disease	4	4	
Progression-free survival (months)	3.1 [1.6–5.2]	5.2 [3.1–12.3]	0.13
6-months progression-free survival	3 (16%)	11 (38%)	0.049
1-year overall survival	7 (37%)	21 (73%)	**0.013**



- Bigger tumors have higher densities of Treg, and establish a tolerogenic state
- Metabolic competition between immune cells and cancer cells
- Hypoxia-induced recruitment of immunosuppressive cells and dysfunction of effector immune cells

Guisier et al. Scientific reports 2019

Conclusion

- Even though the immuno-oncology develops, the role of thoracic surgeon is still valid for treating the cancer patients.
- More collaboration between surgeons and oncologists is needed in the era of immunotherapy.
- The concept of ideal surgery may be redefined in the future.

Thank you for attention!!!

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