(Neo)adjuvant Immunotherapy: The Next Step in Curing Cancer

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TENNESSEEONCOLOGY
a partner of OneOncology

Disclosures

No direct conflicts of interest

Sarah Cannon Research: ER Squibb, AstraZeneca, Boehringer Ingleheimer, Genetech, Eli Lilly and Company, Novartis, Pfizer, Celgene

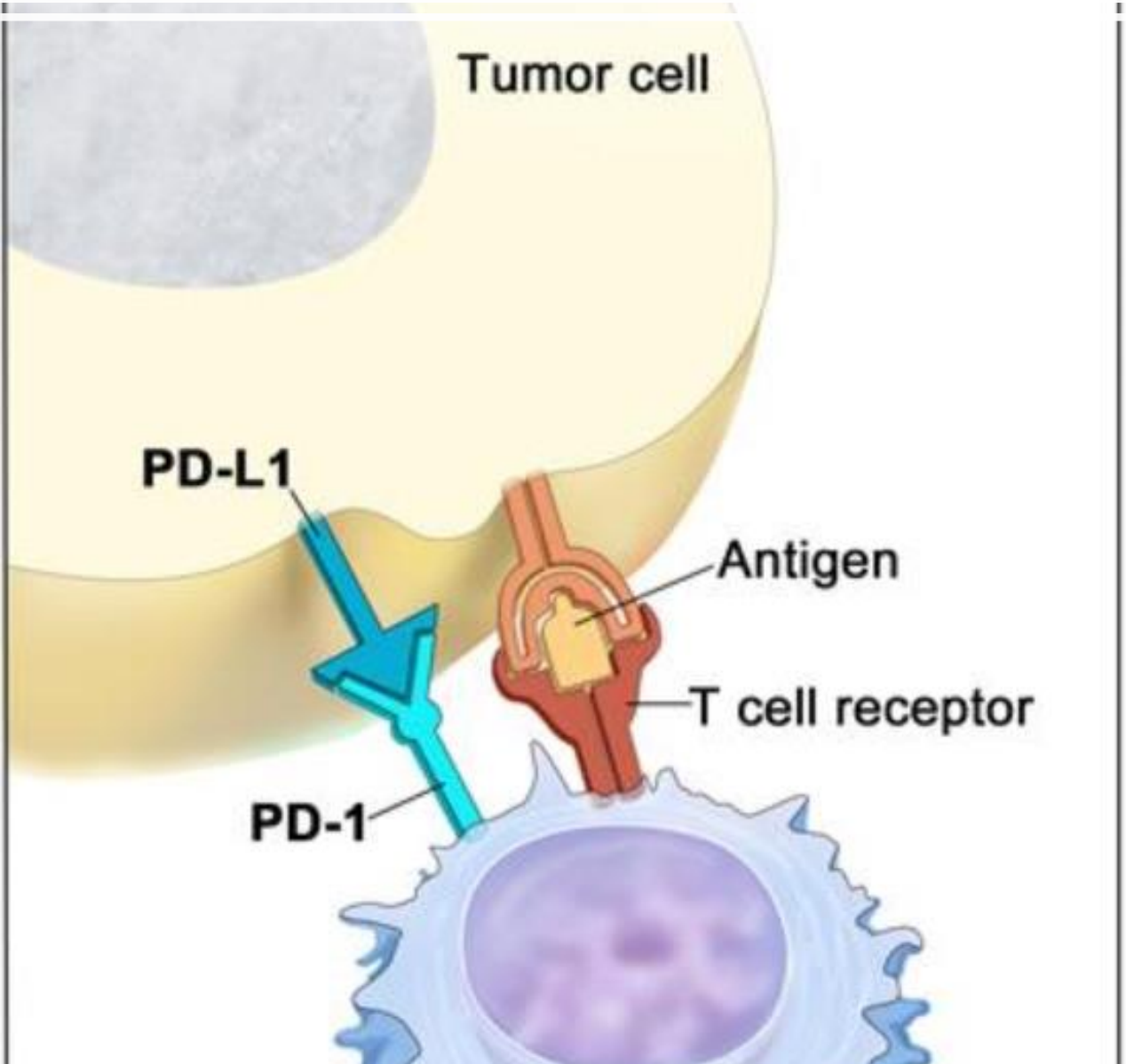
Today's Objectives

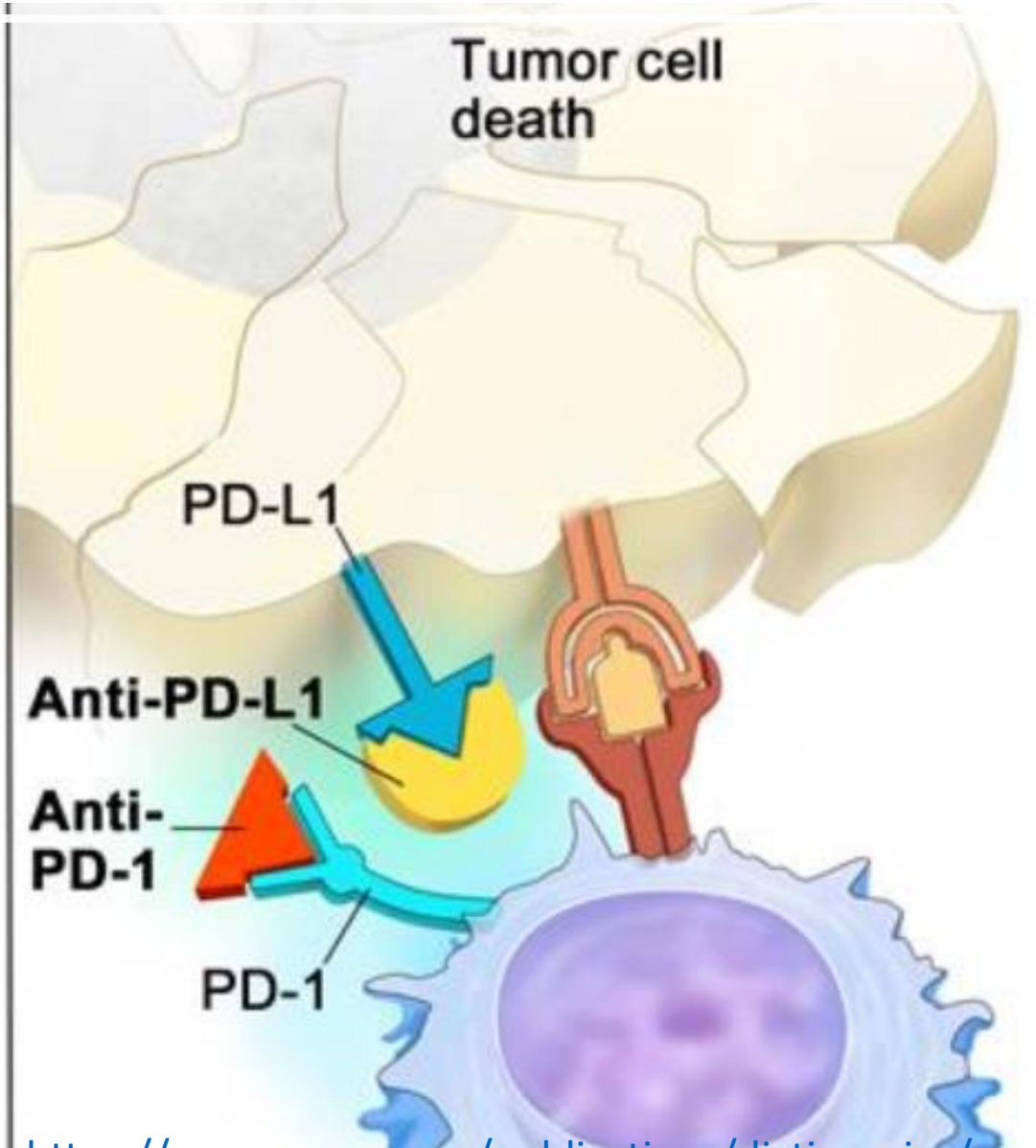
Identify alternative endpoints for development of cancer therapy

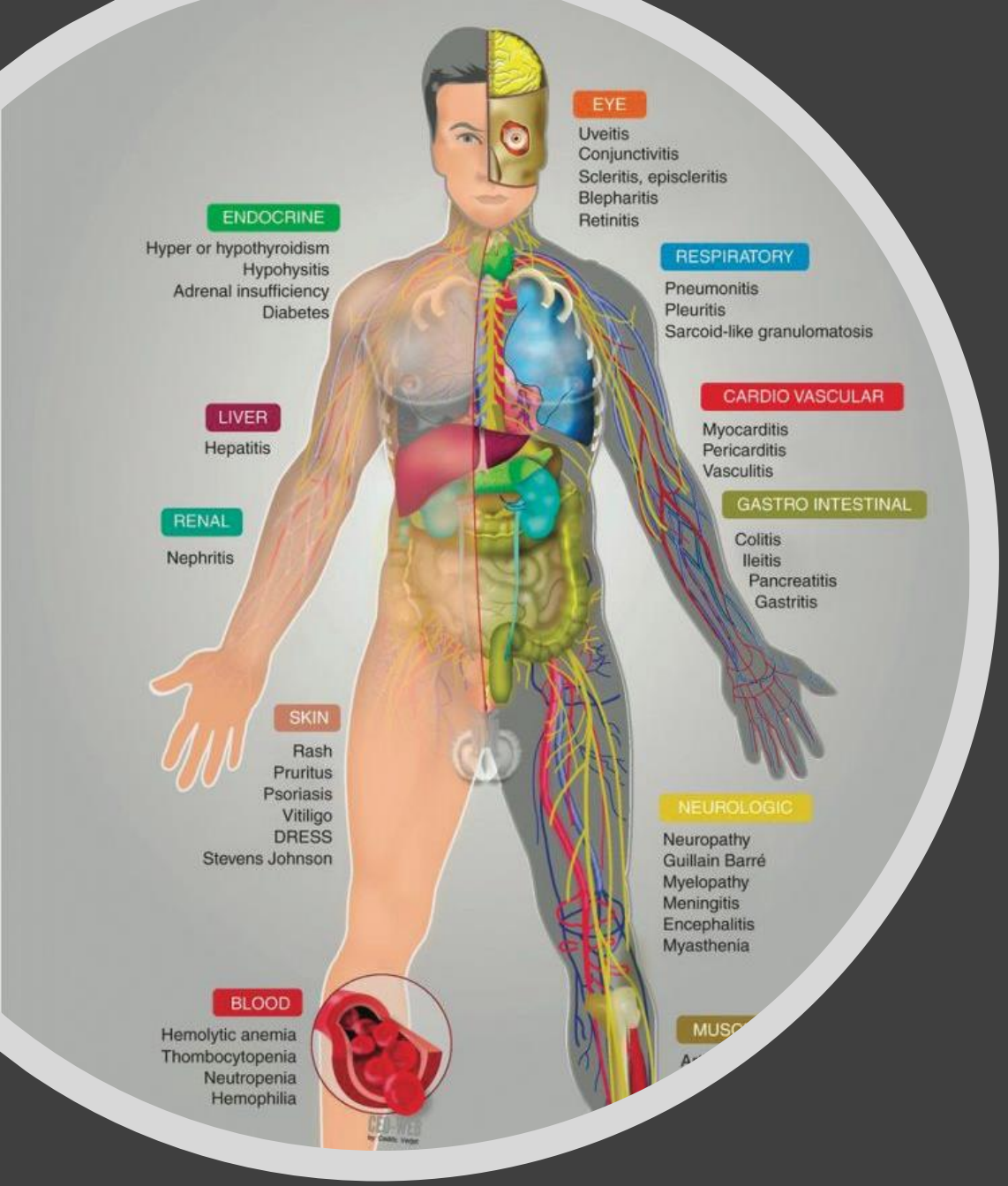
Neoadjuvant therapy is an increasing standard of care for many tumors.

Adjuvant immunotherapy is now a standard treatment in melanoma. Neoadjuvant therapy may be a new standard in breast cancer.

Immunotherapy – Checkpoint Inhibition



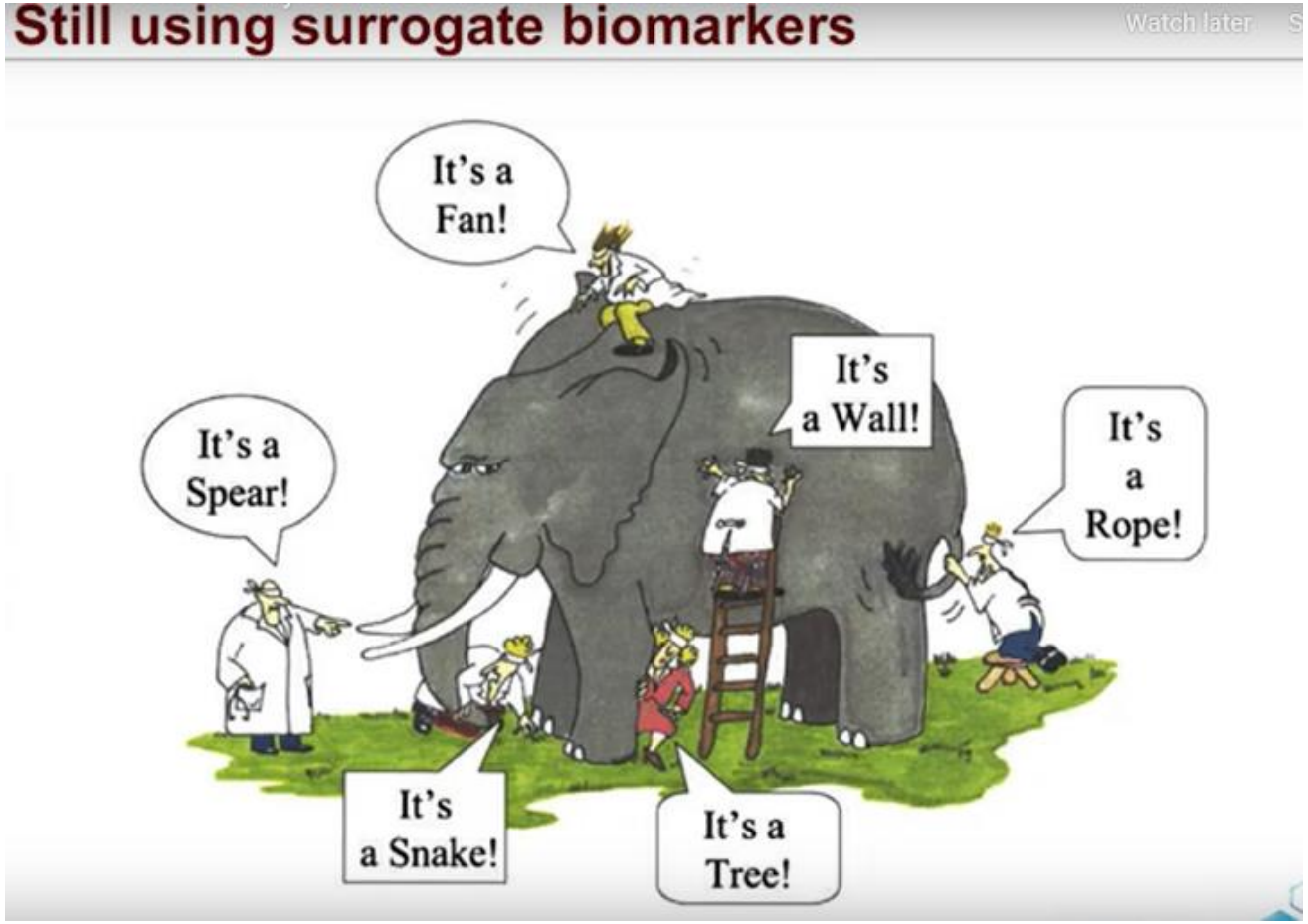




Immunotherapy Toxicity

https://cancerworld.net/e-grandround/management-of-toxicities-related-to-immunotherapies/

Searching for Predictors of Response



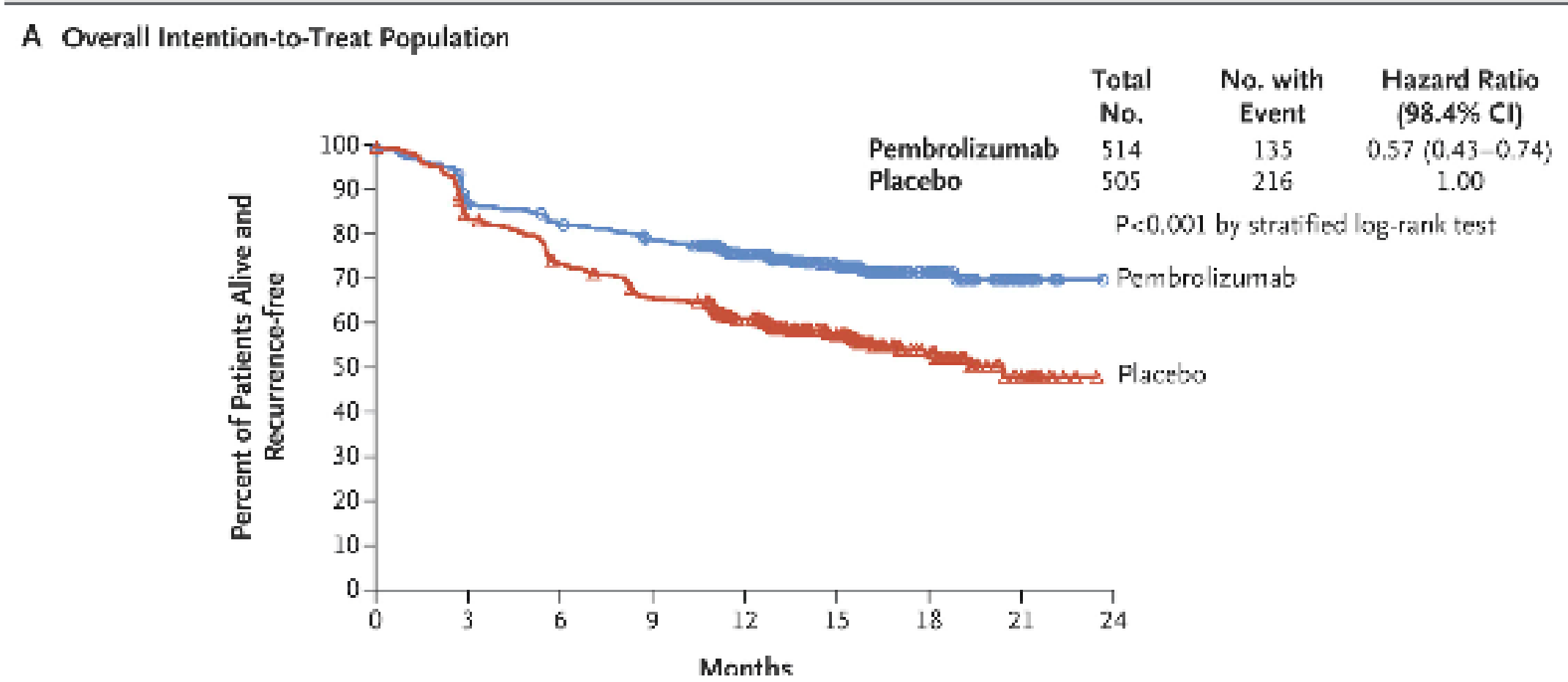
https://www.philipchircop.com/post/25783275888/seeing-the-full-elephant-its-a-tree-its-a

Adjuvant Immunotherapy

- Standard of care in stage III/IV resected melanoma
- Other cancers: Jury is out

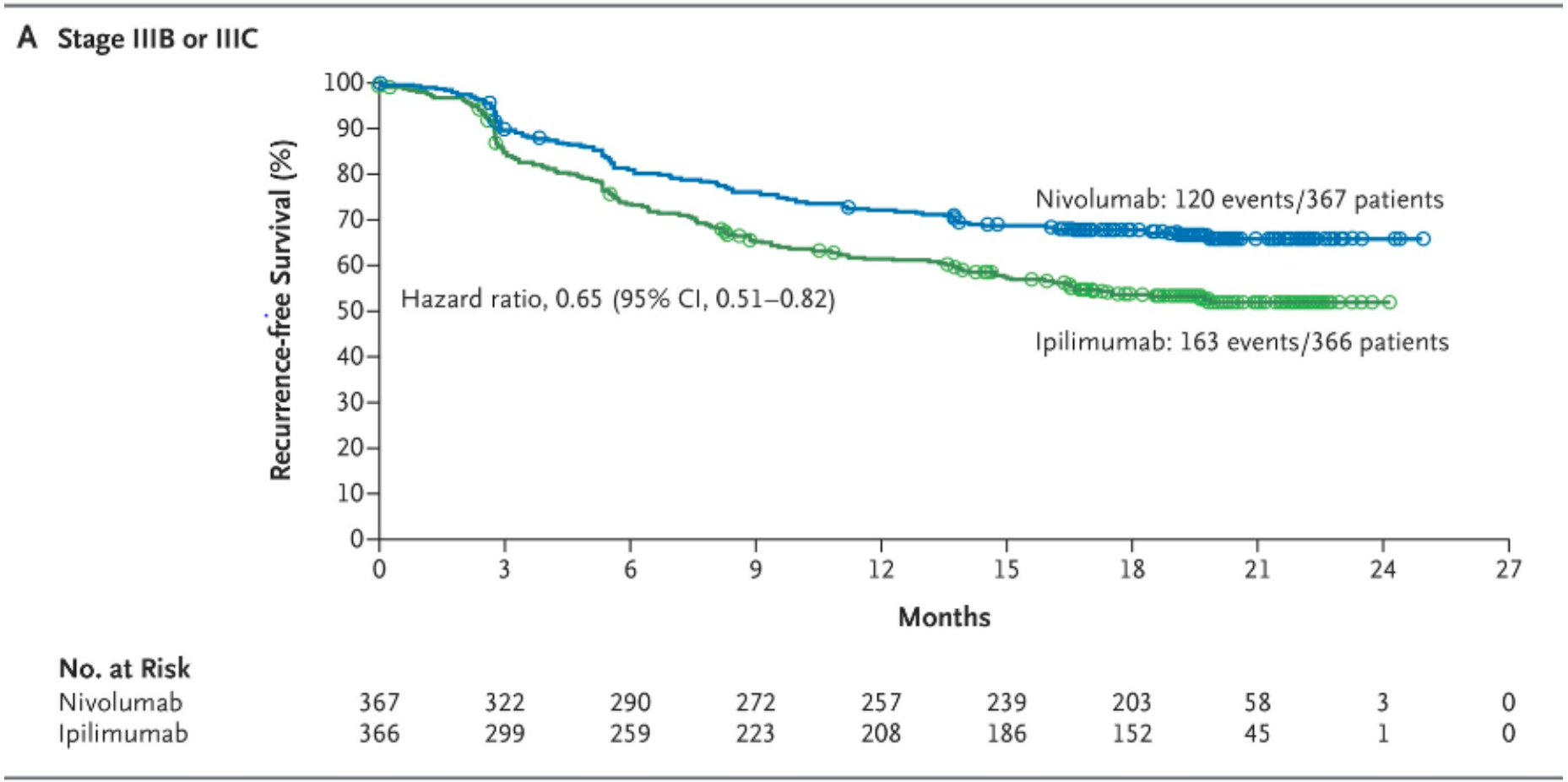
LUNG CANCER	KIDNEY CANCER	BLADDER CANCER
IMPOWER 010 (Atezolizumab) 10/2015	PROSPER RCC (Nivolumab) ONGOING	Imvigor0101 (Atezolizumab)
KEYNOTE 091 – PEARLS Pembrolizumab 11/2015	Nivolumab +/- Ipilumumab Ongoing	Checkmate 274 (Nivolumab) 2/2016 (completed)
ANVIL trial (Nivolumab) 5/2016	MK3475 (Pembrolizumab) COMPLETED	AMBASSADOR (Pembrolizumab)
Durvalumab 11/2014		

Adjuvant Melanoma Therapy- Keynote 054



AM Eggermont et al. N Engl J Med 2018;378:1789-1801.

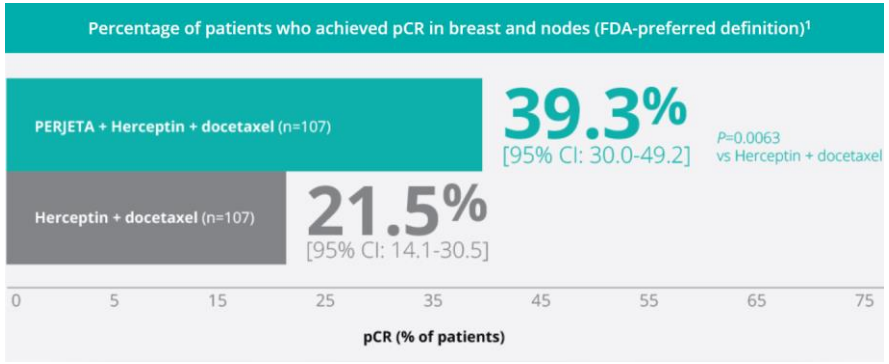
Adjuvant Immunotherapy – Checkmate 238



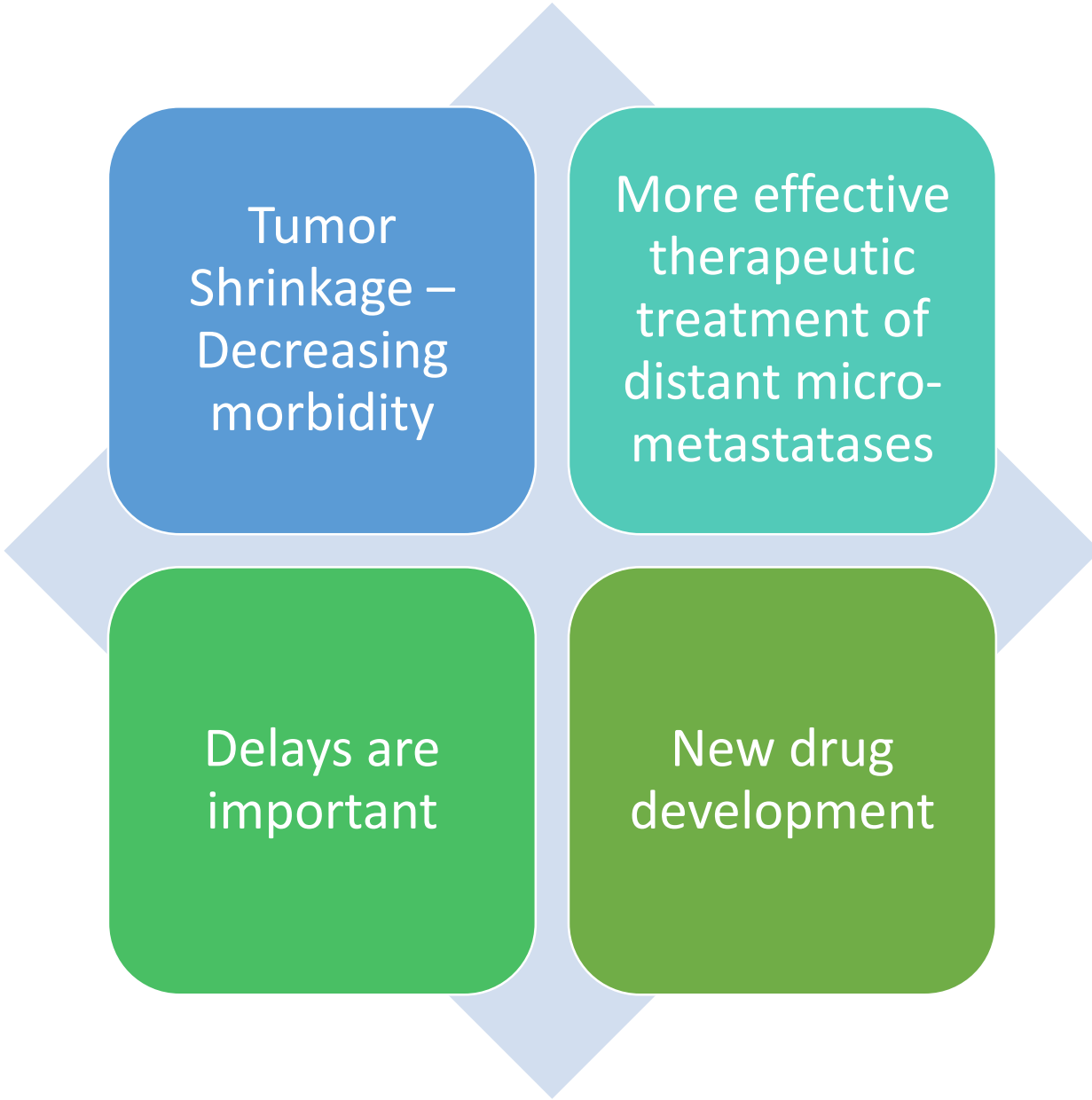
Weber J et al. N Engl J Med 2017;377:1824-1835.

Neoadjuvant therapy as surrogate endpoint

- Pathological Complete Response and Accelerated Drug Approval in Early Breast Cancer
  - T Prowell MD, R. Pazdur MD N Engl J Med 2012; 366:2438-2441



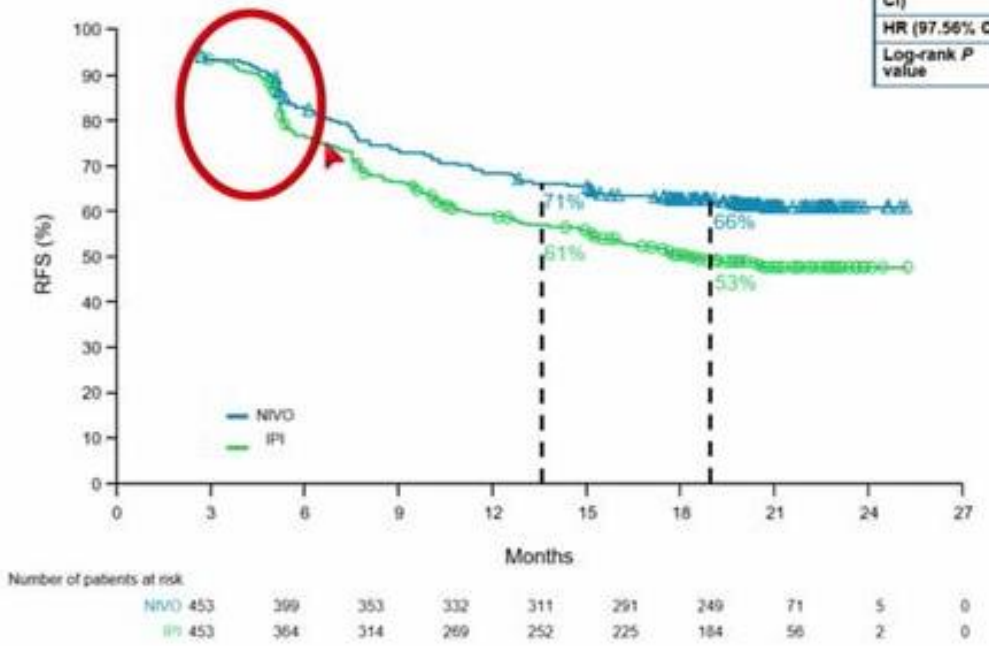
Rationale for Neoadjuvant Immunotherapy



Check Mate 238

Primary Endpoint: RFS

	NIVO	IPI
Events/patients	154/453	206/453
Median (95% CI)	NR	NR (16.6, NR)
HR (97.56% CI)	0.65 (0.51, 0.83)	
Log-rank *P* value	<0.0001	



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Timing matters

Weber J et al. N Engl J Med 2017;377:1824-1835.

Melenoma - Neoadjuvant

	Immunotherapy	Targeted Therapy
Pathologic Complete Response (pCR)	38%	47%
12m PFS	83%	65%
pCR Recurrences	0 /51	7/17
Non-pCR Recurrence	18/82	19/27

ASCO 2019 – International Neoadjuvant Melanoma Consortium Meta-analysis

- 6 trials of Neoadjuvant therapy
- 184 patients (133 immunotherapy / 55 targeted

Neoadjuvant Breast Cancer

2 trials presented in December 2019

Divergent conclusions

Stage and pathology

NeoTRIP Michaelangelo Trial

Population:

- Triple negative breast cancer (ER-,PR-, Her2-)
- N1 Node + or large mass

Treatment - 8 cycles of neoadjuvant chemotherapy

- Carboplatin / nab-paclitaxel
- Carboplatin / nab- paclitaxel / atezolizumab

Endpoints

- Event Free Survival
- Pathologic complete response

NeoTripaPDL1 Michalango Trial
Luco Gianni et a. San Antonio Breast Conference 2019.

Results – Pathologic Complete Response

	Chemotherapy + Atezolizumab	**Chemotherapy**
# of patients	138	142
Path Complete Responses	43.5%	40.8%
Odds ratio	1.11 (0.69-1.79)	

NeoTripaPDL1 Michaelango Trial
Luco Gianni et a. San Antonio Breast Conference 2019.

KEYNOTE-522

Phase 3 trial of Neoadjuvant Pembrolizumab with chemotherapy

- Followed by Adjuvant Pembrolizumab versus Placebo for Early Triple Negative Breast Cancer

Higher risk patients included:

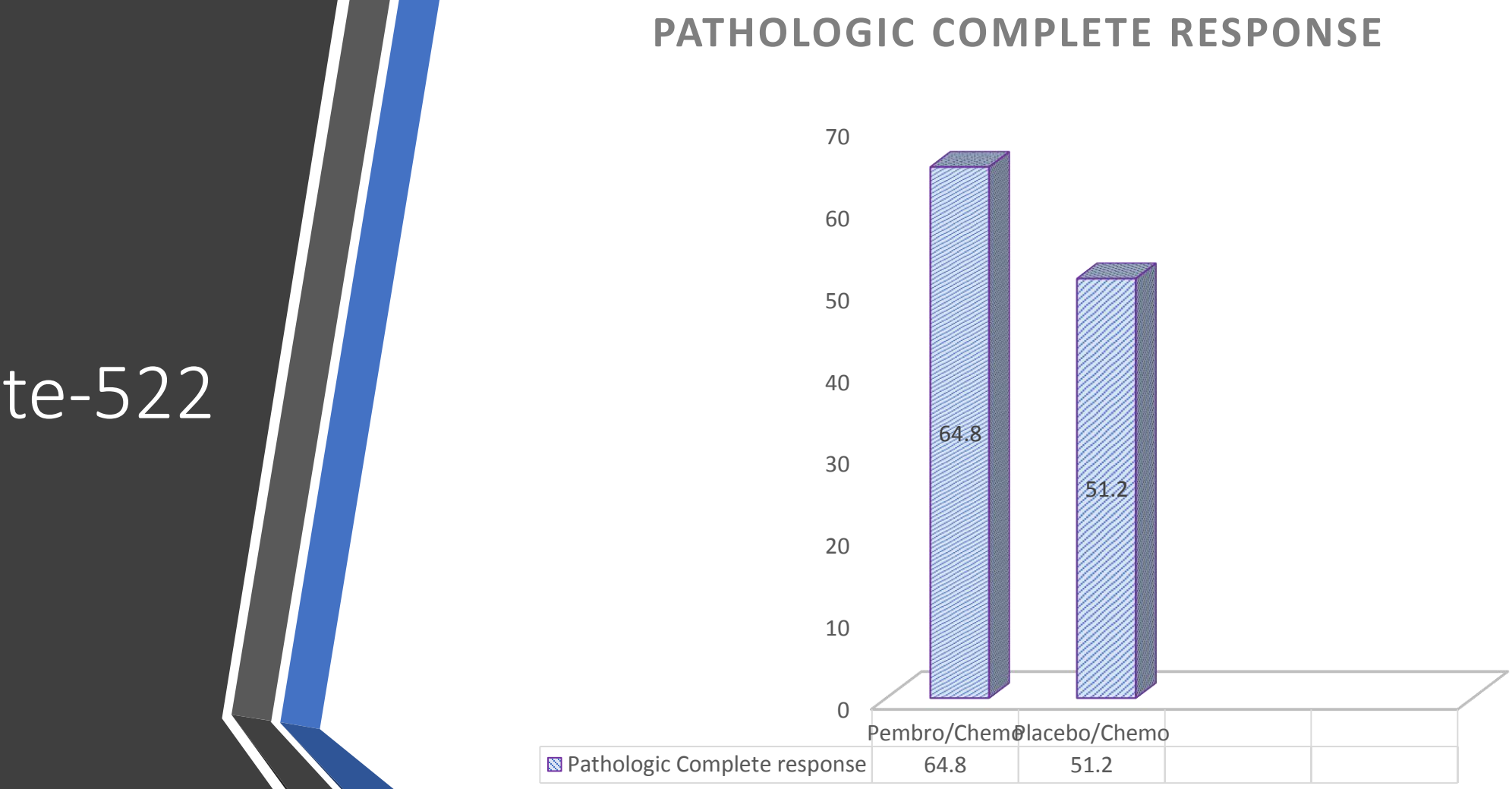
- N1 or N2 disease

Treatment

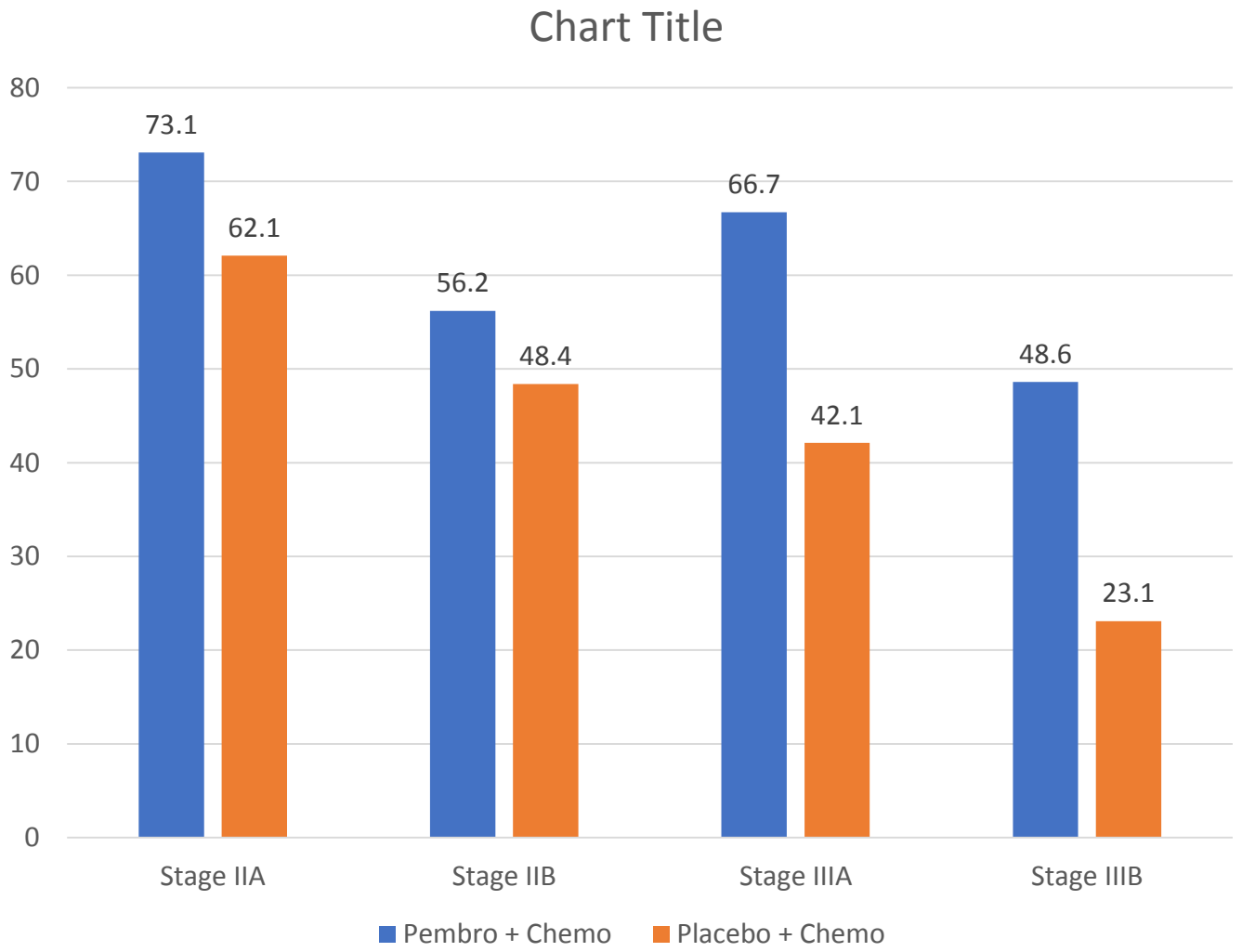
- Chemotherapy for 4 cycles (Carboplatin / paclitaxel) then Epirubicin / Cyclophosphamide x 4 cycles +/- Pembrolizumab
- Surgery
- Pembrolizumab or placebo x 8 cycles

Peter Schmid et al. San Antonio Breast Cancer Symposium December 2019

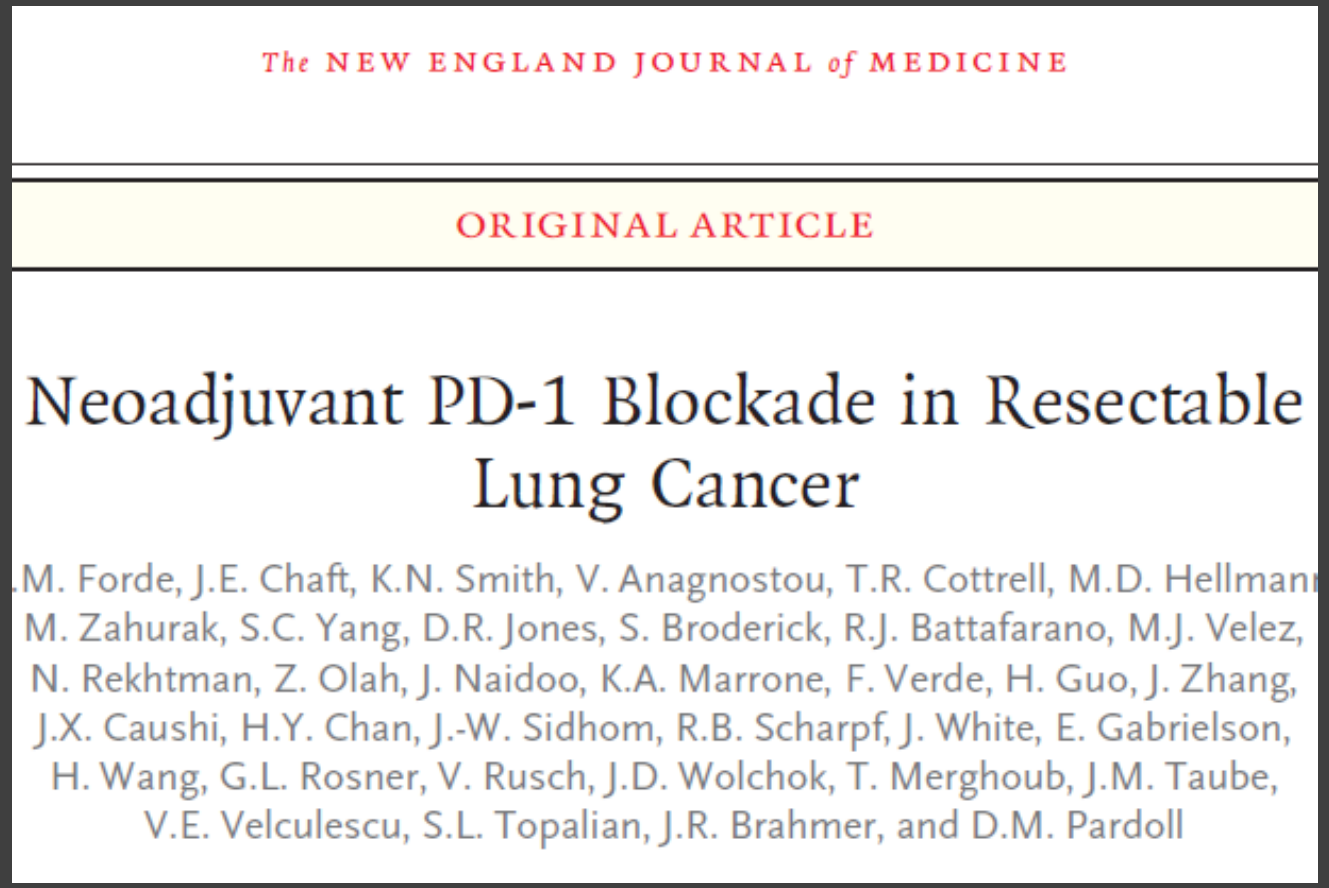
Keynote-522


PATHOLOGIC COMPLETE RESPONSE
70
60
50
40
30
20
10
0
64.8
51.2
Pembro/Chemo
Placebo/Chemo
Pathologic Complete response
64.8
51.2

Response by Stage



Neoadjuvant Lung Cancer



The NEW ENGLAND JOURNAL of MEDICINE

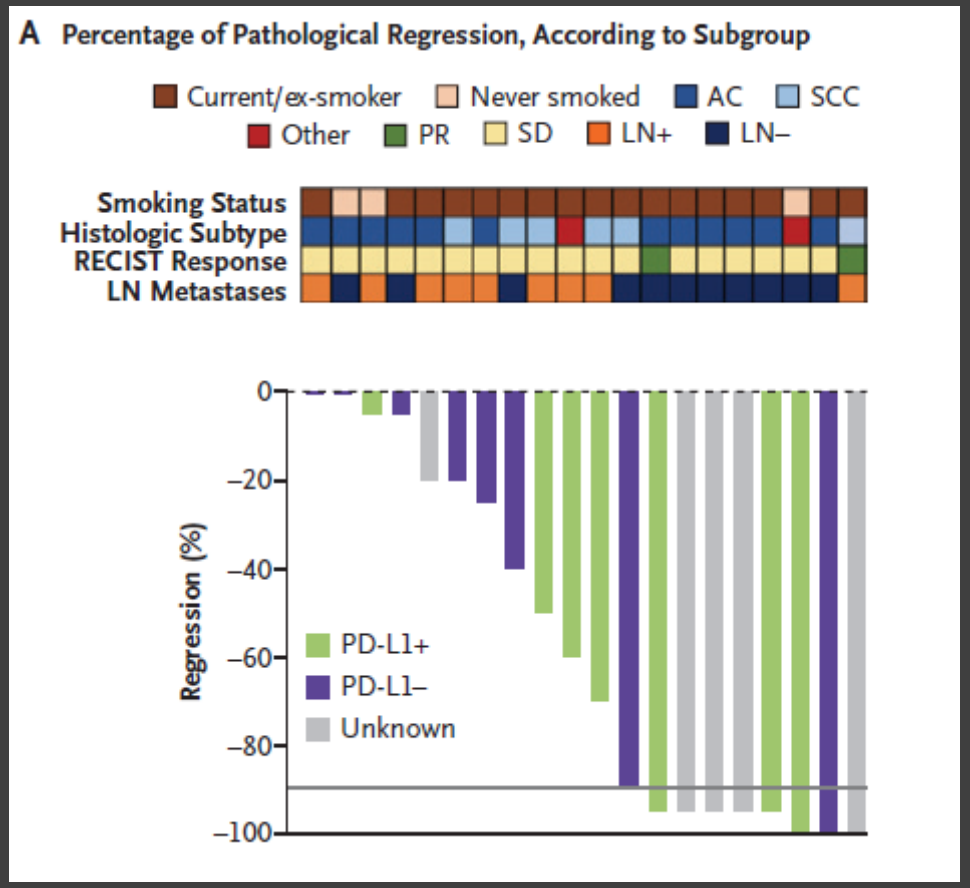
ORIGINAL ARTICLE

Neoadjuvant PD-1 Blockade in Resectable Lung Cancer

M. Forde, J.E. Chaft, K.N. Smith, V. Anagnostou, T.R. Cottrell, M.D. Hellmann
M. Zahurak, S.C. Yang, D.R. Jones, S. Broderick, R.J. Battafarano, M.J. Velez,
N. Rekhtman, Z. Olah, J. Naidoo, K.A. Marrone, F. Verde, H. Guo, J. Zhang,
J.X. Caushi, H.Y. Chan, J.-W. Sidhom, R.B. Scharpf, J. White, E. Gabrielson,
H. Wang, G.L. Rosner, V. Rusch, J.D. Wolchok, T. Merghoub, J.M. Taube,
V.E. Velculescu, S.L. Topalian, J.R. Brahmer, and D.M. Pardoll

- Surgically Operable stage I or II Non-Small cell cancer
- 2 doses of Nivolumab (4 weeks)
- Endpoint: Major Pathologic Response (<10% residual tumor)

Results

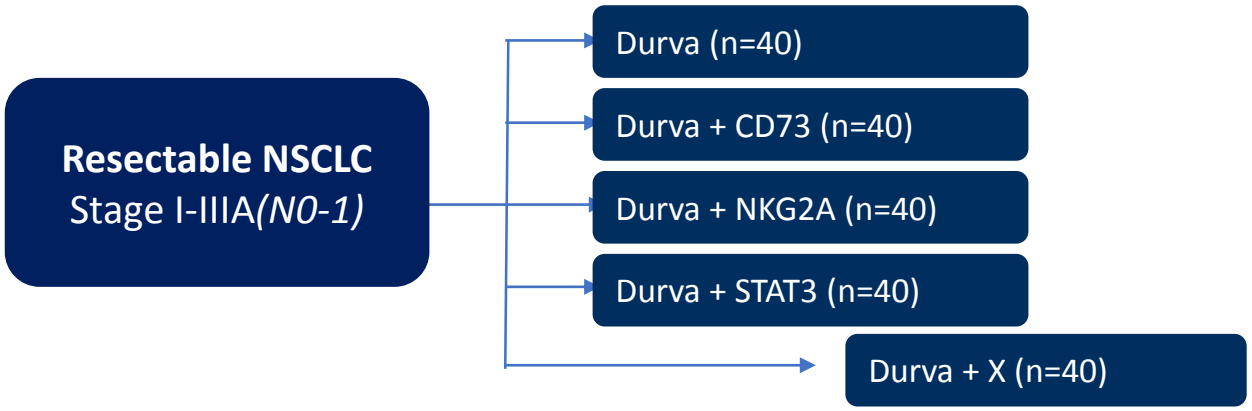


- No significant toxicity
- 9/21 patient had MPR
- Major Pathologic Response
  <10% viable cancer cells

PM Forde et al. N Engl J Med 2018;378:1976-1986.

NeoCOAST – Study Design

- Subjects will be randomized to one of four treatment arms
- Additional arms may be added in the future



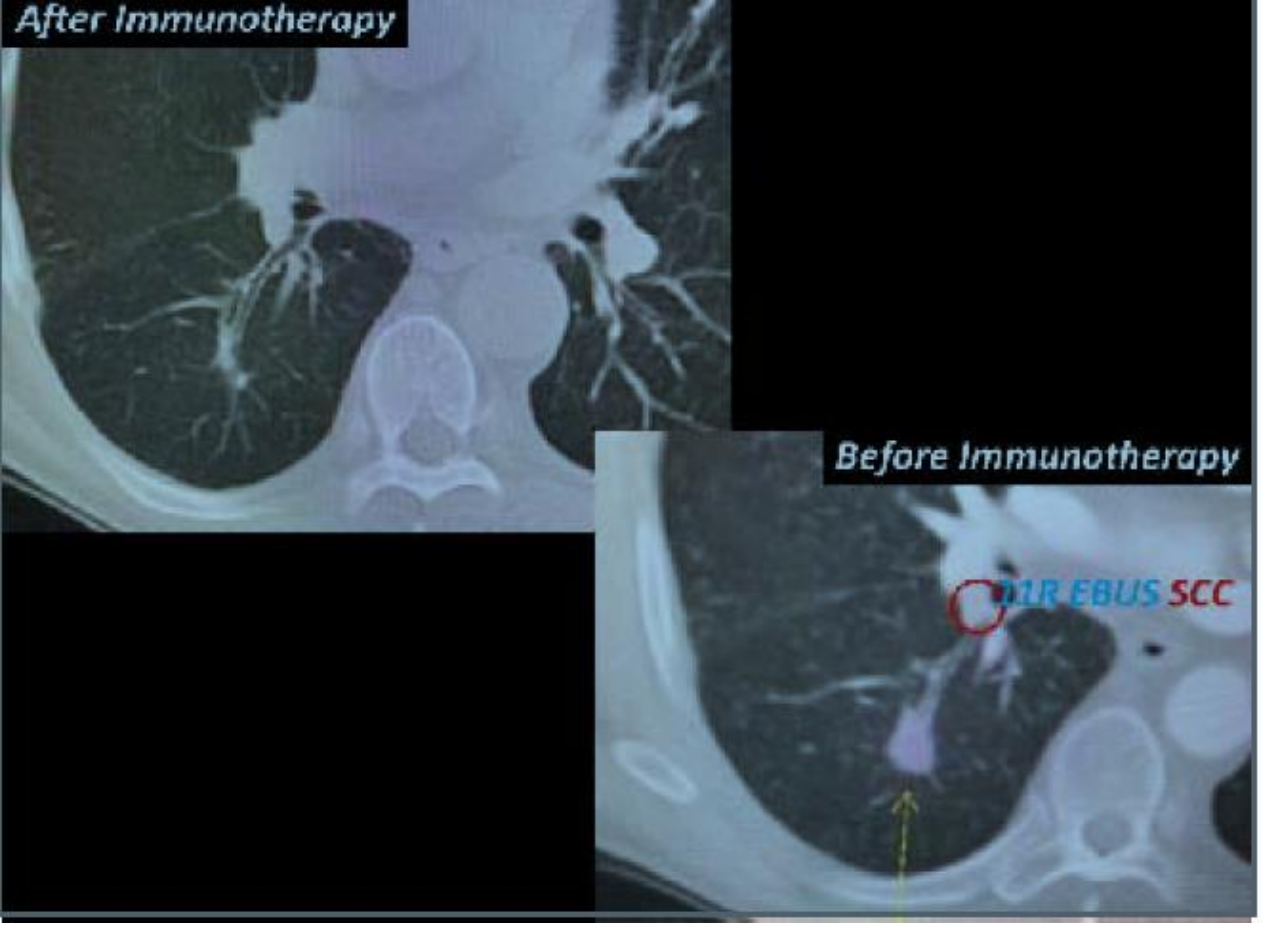
Primary endpoints: MPR

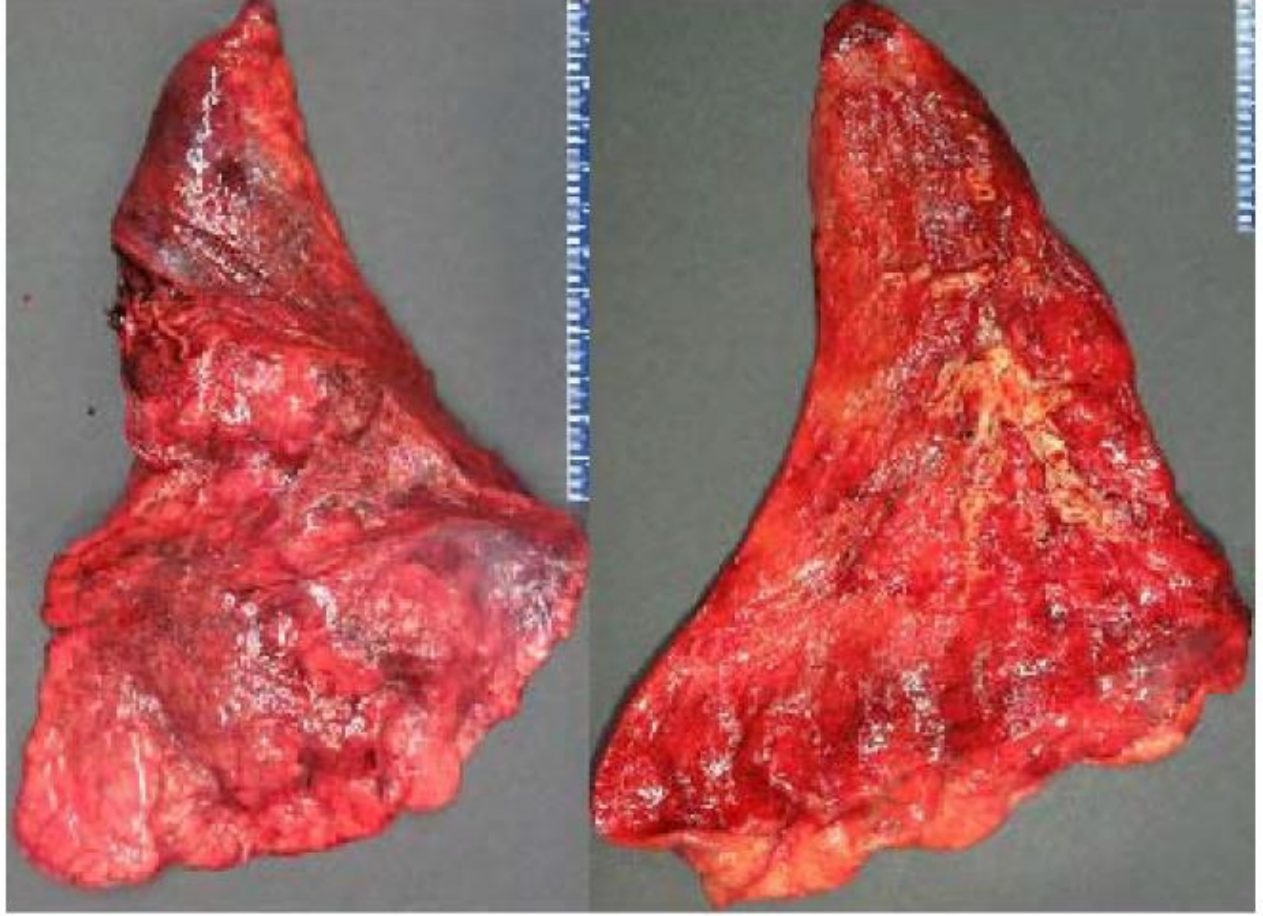
Secondary endpoints:

- Feasibility to Surgery
- Pathological Complete Response (pCR)
- ORR, safety, PK, immunogenicity

Exploratory endpoints:

- ctDNA, TMB, TILs, IFN-g signature, etc





NeoCoast Trial at Memorial

Single-Agent Therapy	Location	Eligibility	Cisplatin Eligibility	Trial Identifier	Status
Pembrolizumab (PURE-01)	Italy	T2-3aN0M0	Yes	NCT02736266	Has results
Pembrolizumab (PANDORE)	France	T2-4N0 or Nx	No	NCT03212651	Enrolling
Atezolizumab	South Korea	T2-4aN0M0	N/A	NCT03577132	Enrolling
Atezolizumab	United States	T < 2, T2-4N0M0	No	NCT02451423	Enrolling
Avelumab (BL-AIR)	United States	T2-4aN0M0	No	NCT03498196	Enrolling
Atezolizumab (ABACUS)	Europe	T2-4aN0M0	No	NCT02662309	Has results
Immune Combination Therapy					
Nivolumab/urelumab	United States	T2-4aN0M0	No	NCT02845323	Enrolling
Nivolumab/ipilimumab (NABUCCO)	Netherlands	T3-4N0 or N+	No	NCT03387761	Enrolling
Durvalumab/tremelimumab vs. chemotherapy (DUTRENEO)	Spain	T2-4N0 or N1	Yes	NCT03472274	Enrolling
Durvalumab/tremelimumab (NITIMIB)	Switzerland	T2-4N0 or N+	No	NCT03234153	Enrolling
Durvalumab/tremelimumab	United States (MDACC)	T2-4aN0M0	No	NCT02812420	Enrolling
Nivolumab ± ipilimumab (CA209-9DJ)	United States (MSKCC)	T2-4aN0M0	No	NCT03520491	Enrolling
Durvalumab + olaparib (NEODURVARIB)	Spain	T2-4aN0M0	No	NCT03534492	Enrolling
Chemoimmunotherapy Combinations					
Nivolumab + gemcitabine/cisplatin (BLASST-1)	United States	T2-4aN0M0	Yes	NCT03294304	Enrolling
Avelumab (AURA) ± chemotherapy	Belgium	T2-4N0 or N+	Yes/No	NCT03674424	Enrolling
Pembrolizumab + gemcitabine/cisplatin	United States	T2-4N0 or Nx	Yes	NCT02690558	Enrolling
Pembrolizumab + gemcitabine/cisplatin	United States (UU)	T2-4aN0M0	Yes	NCT02365766	Has results

Neoadjuvant Bladder

Summary

- Adjuvant and neoadjuvant therapy now standard in some cases.
  - Adjuvant Stage III melanoma.
  - Neoadjuvant in SOME breast patients.
- Answers will vary.
- Trials are the key.