Lung Cancer Initiative Summit Treatment Updates

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Director, Thoracic Oncology Program
Novant Health Cancer Institute
9.15.2023

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Lung Cancer Initiative Summit: Treatment Updates

- Historical perspectives/statistics
- Novel approaches in use today
  - Targeted therapies
  - Immunotherapies
- Future directions
- Questions

Where we started…

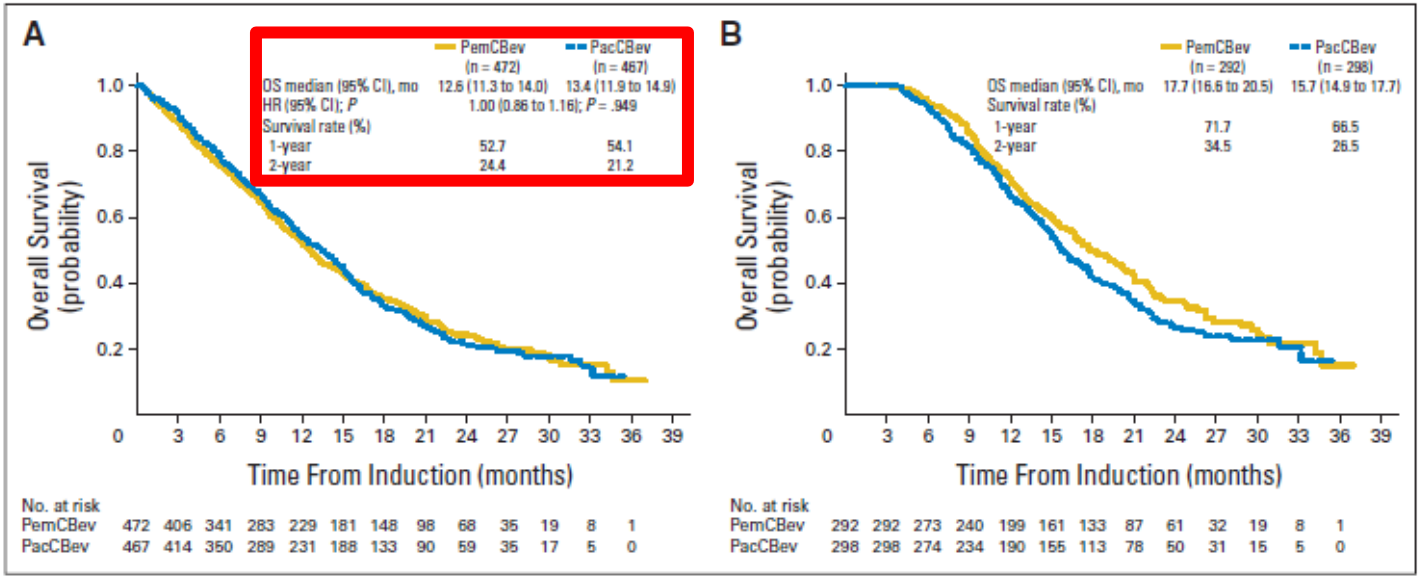
VOLUME 31 · NUMBER 34 · DECEMBER 1 2013

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

PointBreak: A Randomized Phase III Study of Pemetrexed Plus Carboplatin and Bevacizumab Followed by Maintenance Pemetrexed and Bevacizumab Versus Paclitaxel Plus Carboplatin and Bevacizumab Followed by Maintenance Bevacizumab in Patients With Stage IIIB or IV Nonsquamous Non–Small-Cell Lung Cancer

PointBreak: PemCBev Versus PacCBev Followed by Maintenance

Two year survival = 24%



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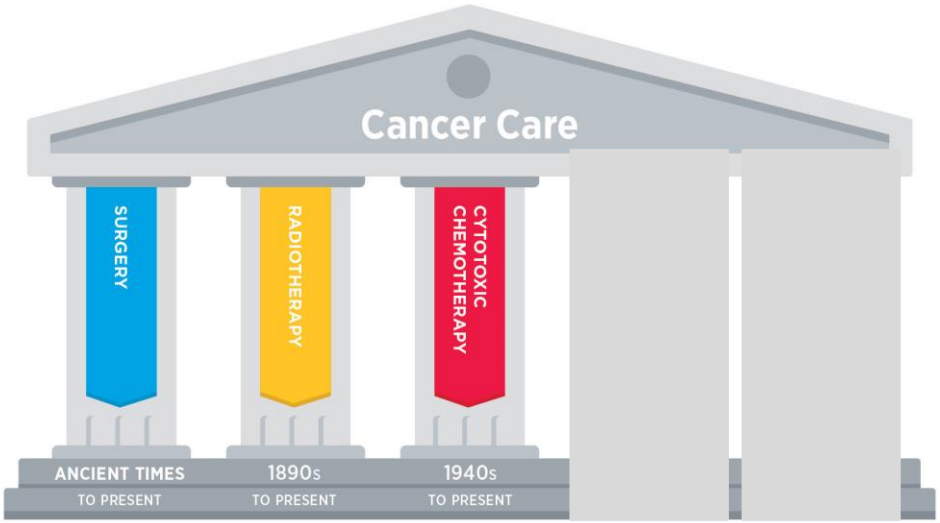
The Pillars of Cancer Care

FIGURE 9

The Pillars of Cancer Care

Physicians often refer to the "pillars" of cancer treatment. For many years, there was one treatment pillar: surgery. In 1896, a second pillar, radiotherapy, was added. The foundations for the third treatment pillar, cytotoxic chemotherapy, were laid in the early 1940s when a derivative of nitrogen mustard was explored as a treatment for lymphoma. These three pillars—surgery, radiation, and cytotoxic chemotherapy—continue to form the foundation of treatment for most patients with cancer. The first molecularly targeted therapeutics were introduced in the late 1990s, leading to the fourth pillar, molecularly targeted therapy, which continues to grow. Likewise, the late 1990s laid the groundwork for the fifth treatment pillar, immunotherapy. The number of anticancer therapeutics that form the most recent two pillars of cancer care continues to increase every year.



American Association for Cancer Research (AACR) Cancer Disparities Progress Report 2020

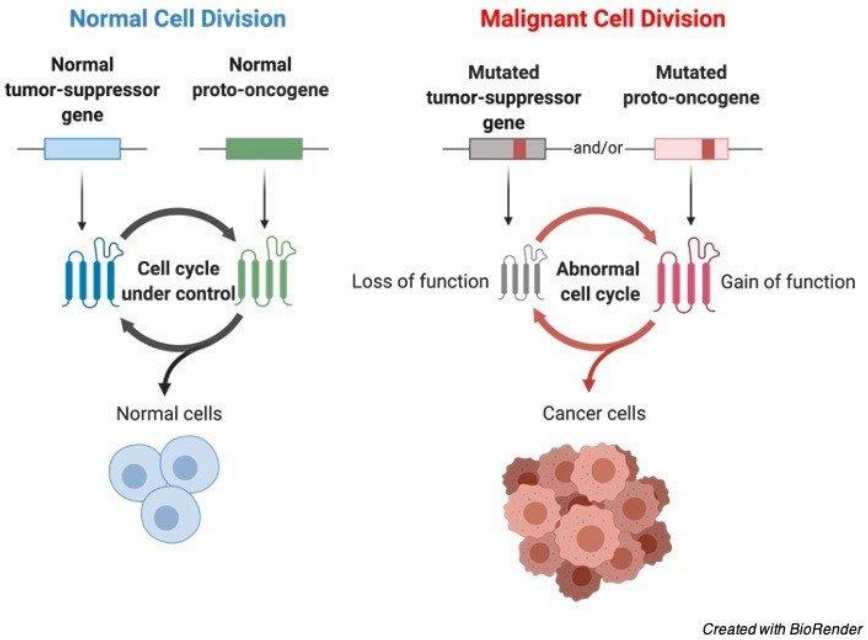
Oncogenes and Tumor Suppressors

(Proto) - Oncogenes

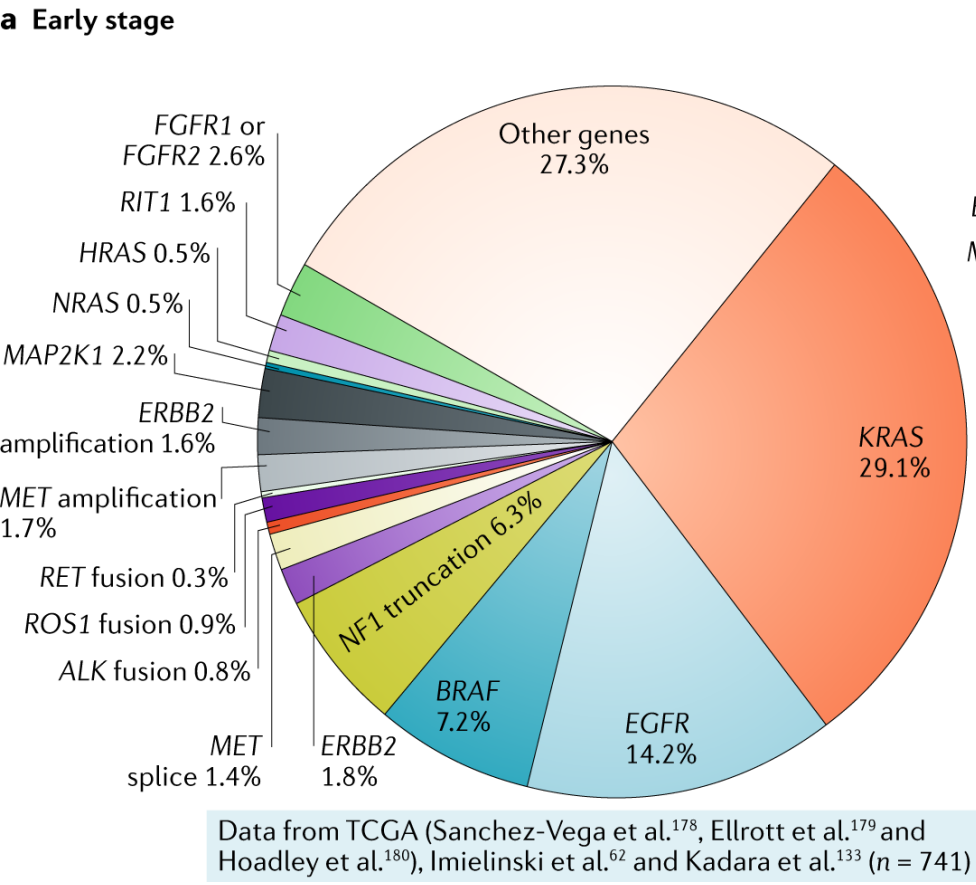
- Genes that normally help cells grow and divide. These can be mutated and allow cells to grow out of control. (Gas pedal)
- Example: EGFR

Tumor Suppressors

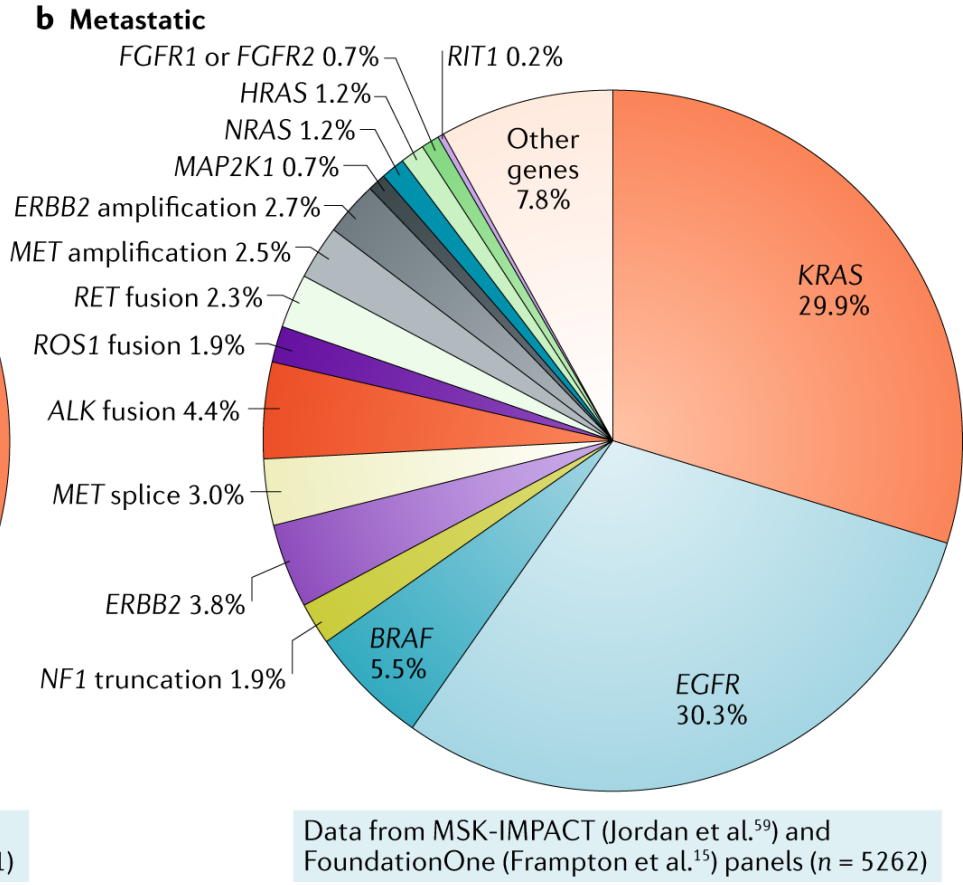
- A gene which tells cells to slow down division or die at the appropriate time. When these are mutated cells can grow out of control. (Brake pedal)
- Example: TP53



Genomic Drivers in NSCLC



Data from TCGA (Sanchez-Vega et al.[178], Ellrott et al.[179] and Hoadley et al.[180]), Imielinski et al.[62] and Kadara et al.[133] (n = 741)



Data from MSK-IMPACT (Jordan et al.[59]) and FoundationOne (Frampton et al.[15]) panels (n = 5262)

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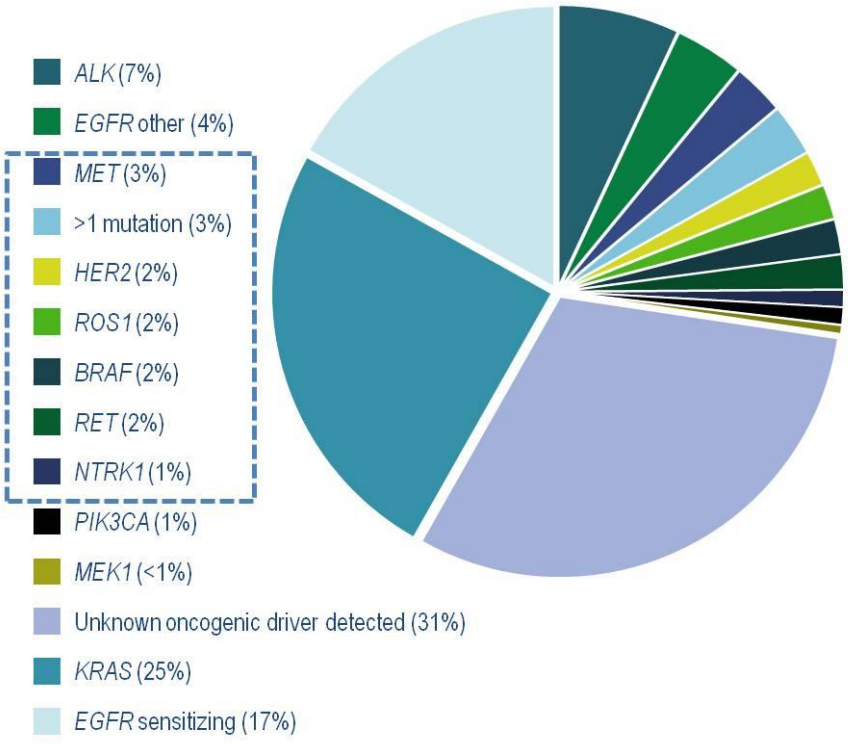
Oncogenic Drivers and Targeted Therapies

Great advances have been made in lung cancer therapy: targeting of oncogenic drivers



PRESENTED AT: 2018 ASCO ANNUAL MEETING

EGFR sensitizing
Gefitinib; Erlotinib; Afatinib; Osimertinib; Dacomitinib

ALK
Crizotinib; Alectinib; Ceritinib; Lorlatinib; Brigatinib

ROS1
Crizotinib; Cabozantinib; Ceritinib; Lorlatinib; Entrectinib; Ropotrectinib, DS-6051b

BRAF
Vemurafenib;Dabrafenib; Dabrafenib + Trametinib

MET
Crizotinib; Cabozantinib; Capmatinib; Savolitinib; Tepotinib; Merestinib; Glesatinib

HER2
Trastuzumab emtansine; Afatinib; Neratinib-temsirolimus; Dacomitinib; Poziotinib; XMT-1522; TAK-788; DS-8201a,

RET
Cabozantinib; Alectinib; Apatinib; Vandetanib; sunitinib; Ponatinib; Lenvatinib; BLU-667; LOXO-292

NTRK1
Entrectinib; LOXO-101 (larotrectinib); loxo-195; DS-6051b; ropotrectinib

PIK3CA
LY3023414; PQR 309

MEK1
Trametinib; Selumetinib;Cobimetinib

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What type of patients have driver mutations in NSCLC?

Young

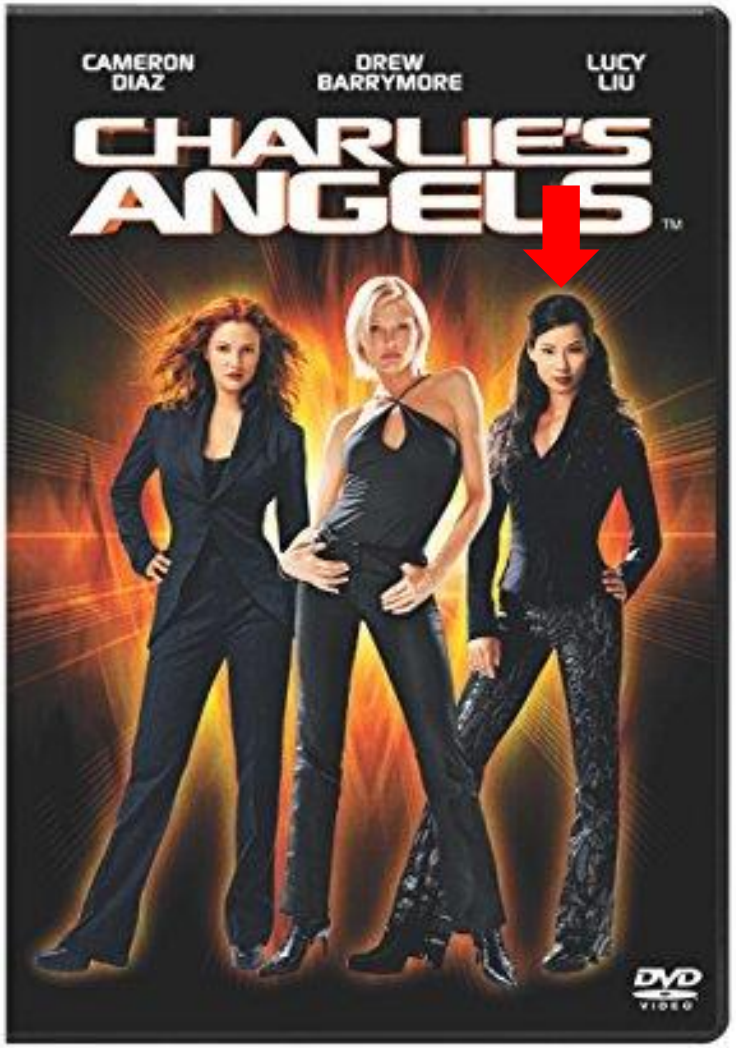
Never-smokers

Asian

Female

Adenocarcinoma

Brain metastases



ORIGINAL ARTICLE

Osimertinib in Untreated *EGFR*-Mutated Advanced Non–Small-Cell Lung Cancer

J.-C. Soria, Y. Ohe, J. Vansteenkiste, T. Reungwetwattana, B. Chewaskulyong, K.H. Lee, A. Dechaphunkul, F. Imamura, N. Nogami, T. Kurata, I. Okamoto, C. Zhou, B.C. Cho, Y. Cheng, E.K. Cho, P.J. Voon, D. Planchard, W.-C. Su, J.E. Gray, S.-M. Lee, R. Hodge, M. Marotti, Y. Rukazenkov, and S.S. Ramalingam, for the FLAURA Investigators*

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Osimertinib (N=279)	Standard EGFR-TKI (N=277)
Age — yr		
Median	64	64
Range	26–85	35–93
Male sex — no. (%)	101 (36)	105 (38)
Race — no. (%)†		
White	101 (36)	100 (36)
Asian	174 (62)	173 (62)
Other	4 (1)	4 (1)
Smoking status — no. (%)		
Never	182 (65)	175 (63)
Current	8 (3)	9 (3)
Former	89 (32)	93 (34)
WHO performance status — no. (%)‡		
0	112 (40)	116 (42)
1	167 (60)	160 (58)
Missing data	0	1 (<1)
Histologic type — no. (%)		
Adenocarcinoma	275 (99)	272 (98)
Other§	4 (1)	5 (2)
Overall disease classification — no. (%)		
Metastatic¶	264 (95)	262 (95)
Locally advanced‖	14 (5)	15 (5)
Missing data	1 (<1)	0
Metastases — no. (%)		
Visceral metastases**	94 (34)	103 (37)
CNS metastases††	53 (19)	63 (23)

Targeted Therapies: From Waterfall to Sinkholes

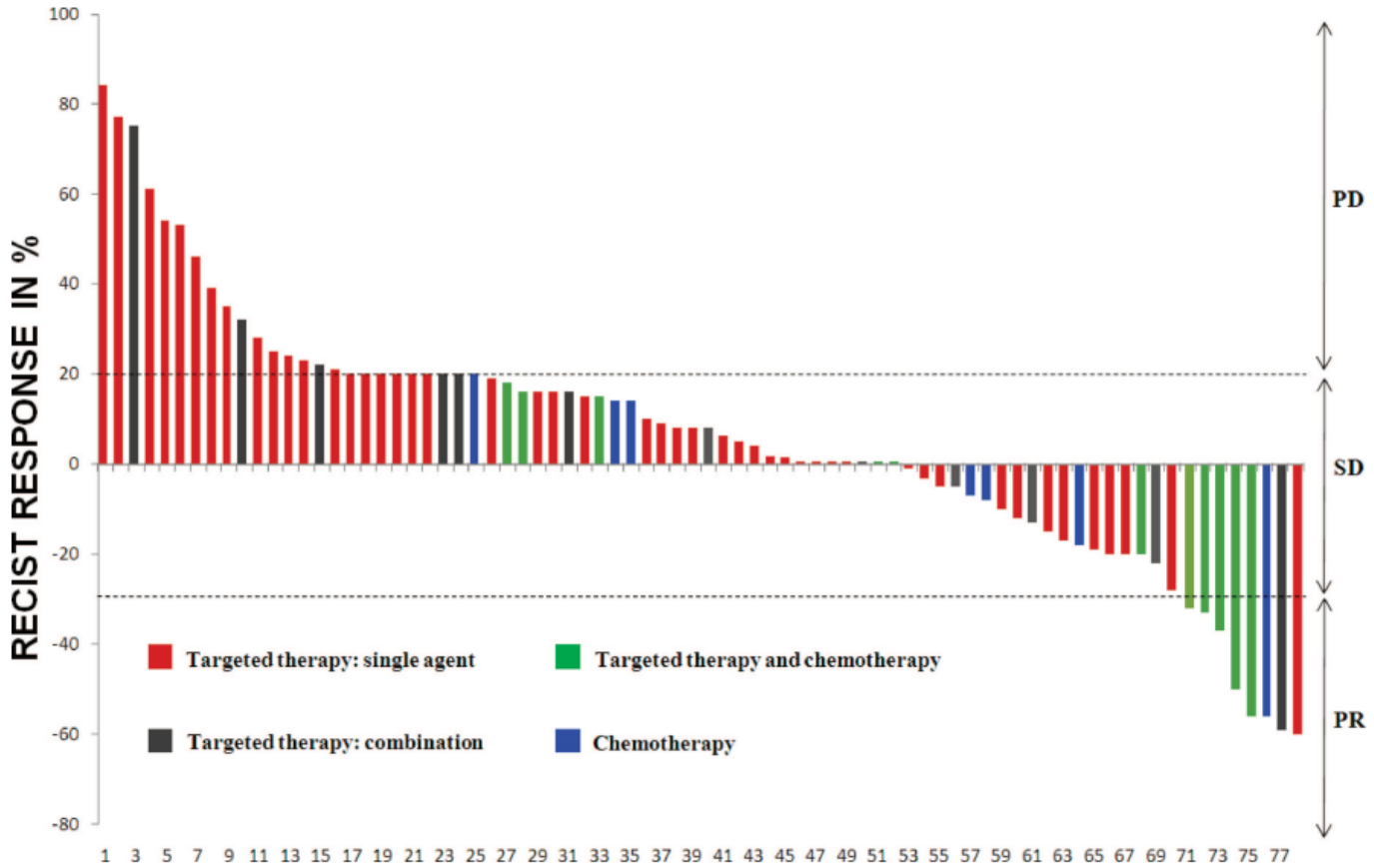


Figure 1. Waterfall plot of patients with non-small cell lung cancer treated in phase I clinical trials. Twenty-six (31%) patients had some tumor shrinkage, including eight partial responses (9.5%). Patients treated with a combination of targeted therapy and chemotherapy (green bars) were most likely to respond (5 of 13, 38.5%).

Abbreviations: PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

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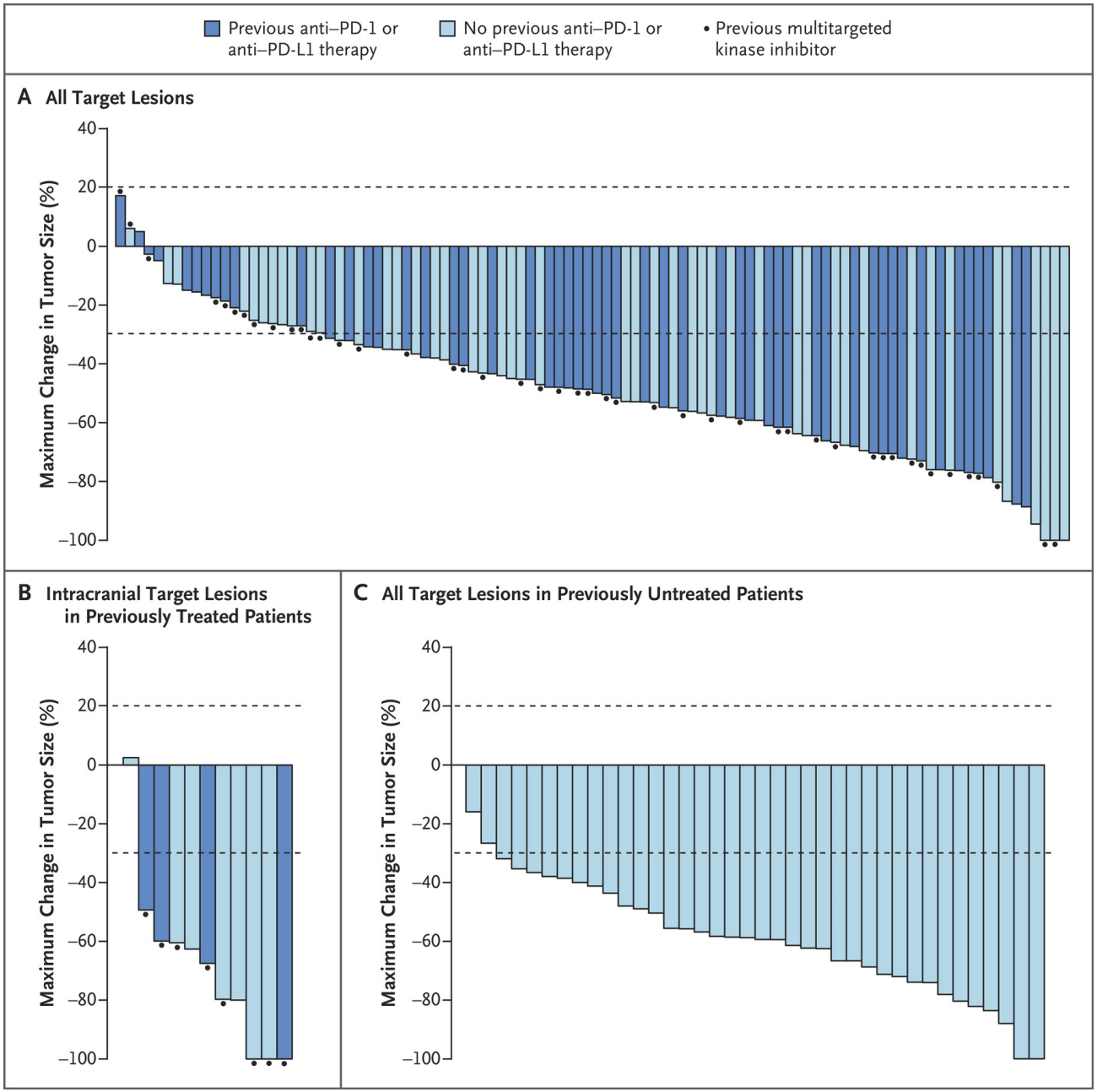

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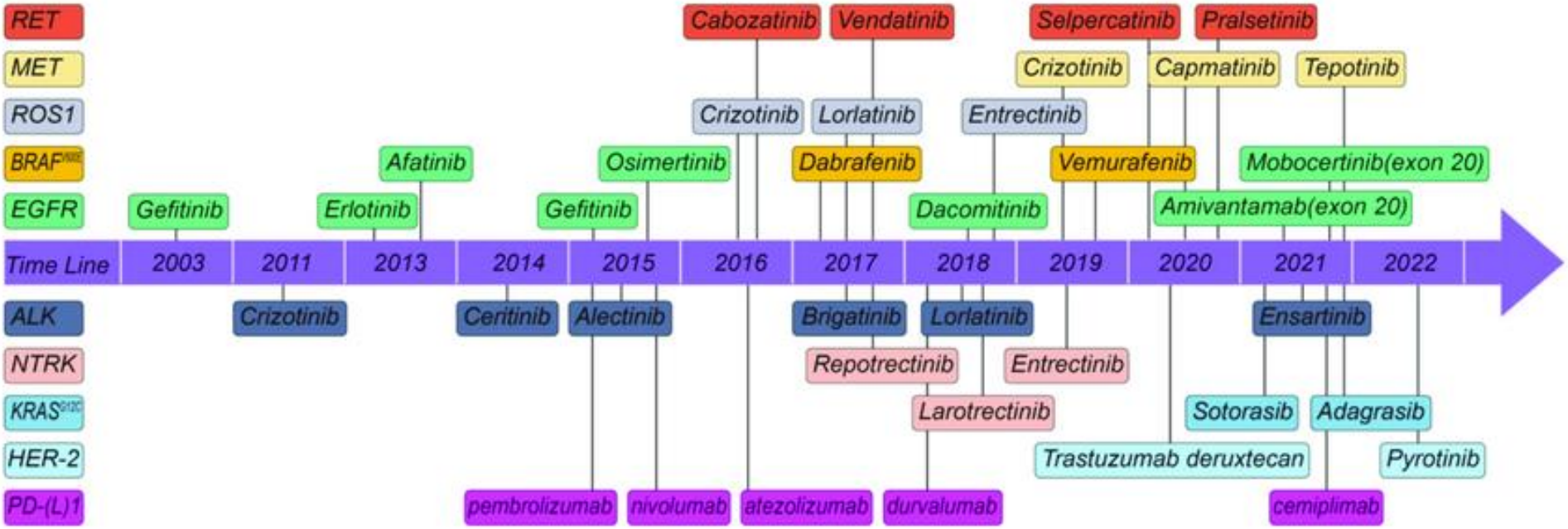
Timeline of Drug Approvals



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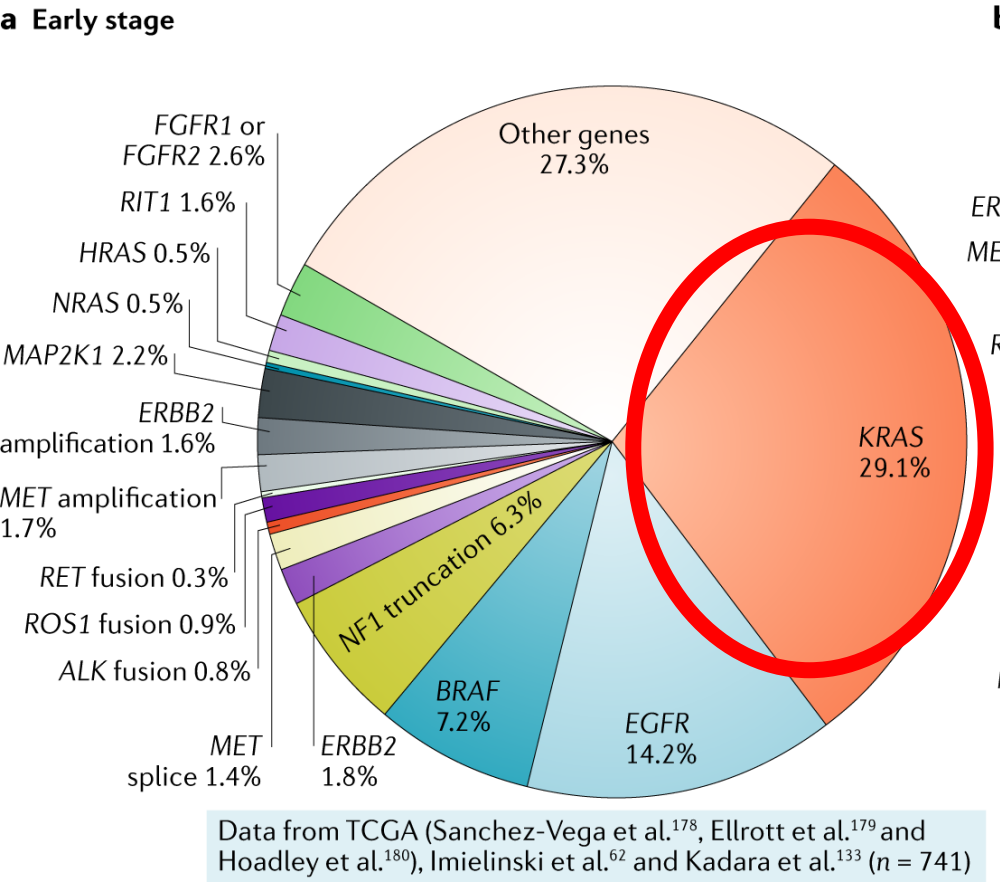
Genomic Drivers in NSCLC



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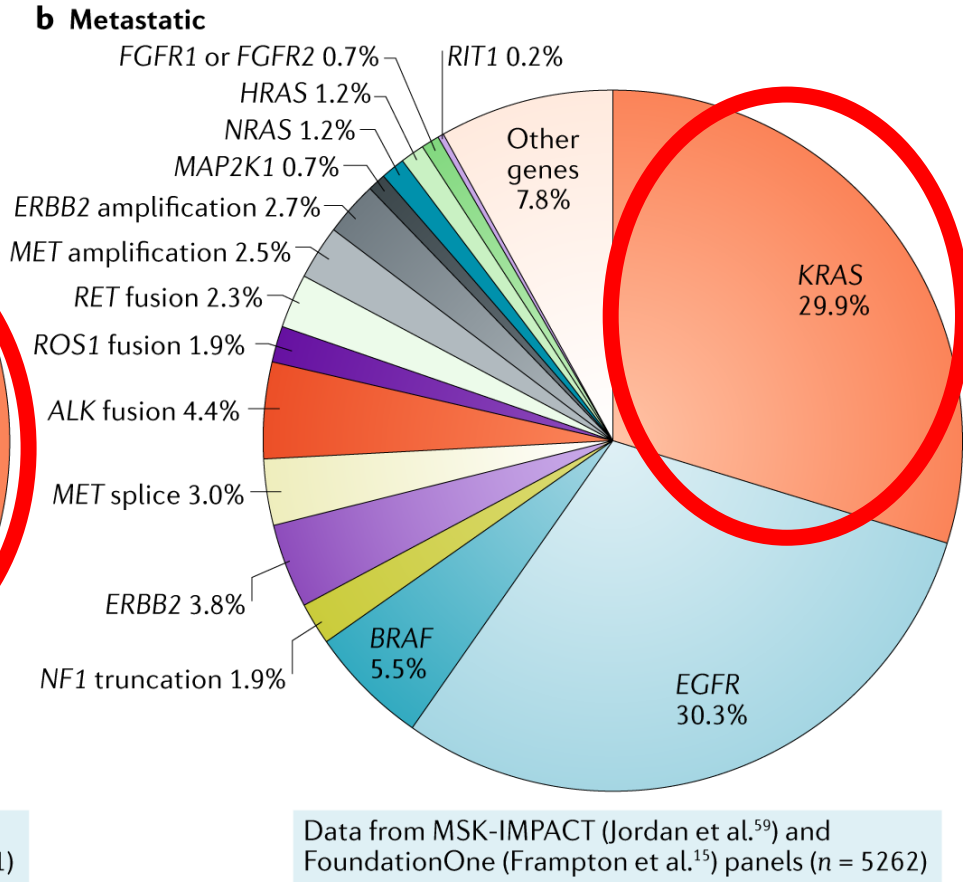

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KRAS: A Success Story

THE LANCET
Oncology

Sub
Arti

EDITORIAL | VOLUME 22, ISSUE 3, P289, MARCH 2021

Download Full Issue

Undruggable *KRAS*—time

The Lancet Oncology

ELSEVIER

Cancer Treatment Reviews

Volume 89, September 2020, 102070

Review Open Access | 10.1172/jci.insight.153688

Targeting the undruggable dawn of hope

Hande Asimgil,[1,2] Utku Ertetik,[2] Nedim Can Çevik,[2] Menar Ekizce,[2] Alper Doğruöz,[1,2] Muazzez Gökalp,[2] Elif Arık-Sever,[2] Rouzanna Istvanffy,[1,3,4] Helmut Friess,[1,3,4] Güralp Onur Ceyhan,[2] and Ihsan Ekin Demir[1,2,3,4,5]

Published January 11, 2022 - More info

Hot Topic

KRAS: From undruggable to a druggable Cancer Target

Dipesh Uprety, Alex A. Adjei

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KRAS: A Success Story

REVIEW ARTICLE **OPEN**

KRAS mutation: from undruggable to druggable in cancer

Lamei Huang[1], Zhixing Guo[1], Fang Wang[1] and Liwu Fu[1]✉

Table 1. The frequency of KRAS mutations in cancer

Tumour types	Sample	KRAS mutations (%)								
		Total rate	Mutation sites					Top 1		
			G12	G13	Q61	A146	Other			
Pancreatic adenocarcinoma	1207	67.61	62.30	0.83	4.23	0.08	0.17	G12D	26.84	
Colorectal adenocarcinoma	3953	35.77	22.82	6.68	1.67	2.76	1.85	G12D	9.87	
Nonsmall-cell lung cancer	7135	20.42	17.39	0.85	0.31	0.06	1.81	G12C	8.38	
Cholangiocarcinoma	1072	12.69	8.96	1.12	1.12	1.87	0.37	G12D	4.29	
Uterine endometrial carcinoma	1907	14.11	10.38	1.78	0.63	0.10	1.21	G12D	4.20	
Testicular germ cell cancer	506	11.66	6.92	0.00	1.98	1.58	1.19	G12V	2.77	
Cervical squamous cell carcinoma	607	4.28	2.47	0.99	0.00	0.49	0.33	G12D	1.32	
Myelodysplastic	6940	3.83	1.86	0.75	0.29	0.23	0.71	G12D	0.84	

Data sources from cBioPortal.org. G12: codon 12 encoding glycine; G13: codon 13 encoding glycine; Q61: codon 61 encoding glutamine; A146: codon 146 encoding

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CodeBreak: Sotorasib in KRAS G12C Mutated NSCLC

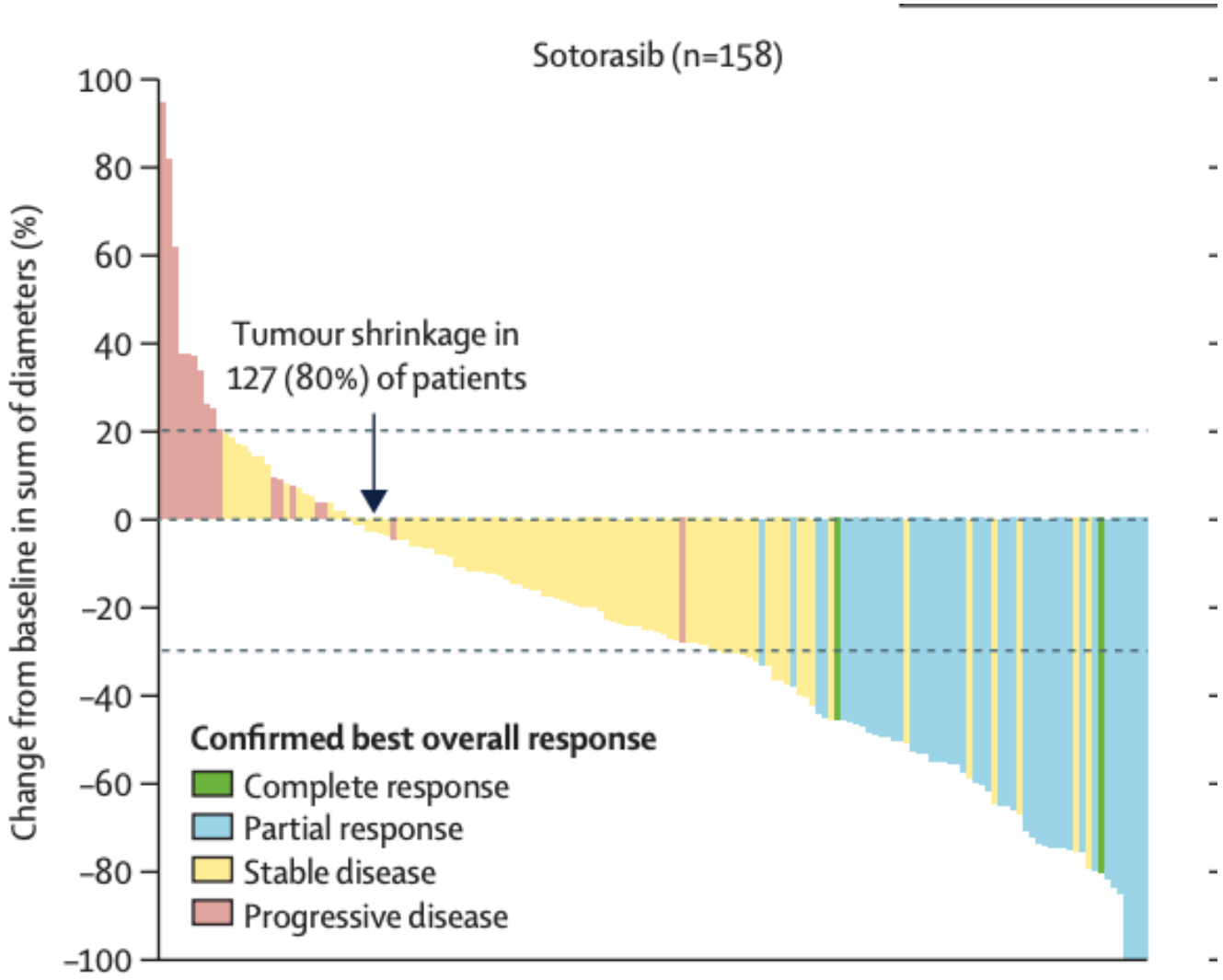

Table 3. Combination therapy of KRAS (G12C) inhibitors in clinical trials

ClinicalTrials.gov registration	Drug	Disease setting	Study phase	Recruitment status
Combined with chemotherapy				
NCT04303780	AMG510 Docetaxel	NSCLC	III	Recruiting
NCT04185883	AMG510 Docetaxel	Advanced NSCLC	I b	Recruiting
NCT04165031	LY3499446 Docetaxel	Solid tumours	I/II	Terminated
NCT04685135	MRTX849 Docetaxel	Metastatic NSCLC	III	Recruiting
Combined with targeted therapy				
NCT04185883	AMG510 Erlotinib	Solid tumours	I b	Recruiting
NCT04185883	AMG510 TNO155	Solid tumours	I b	Recruiting
NCT04185883	AMG510 Selumetinib	Solid tumours	I b	Recruiting
NCT04185883	AMG510 Everolimus	Solid tumours	I b	Recruiting
NCT03785249	MRTX849 Afatinib	NSCLC	I/II	Recruiting
NCT03785249	MRTX849 Cetuximab	Solid tumours	I/II	Recruiting
NCT04793958	MRTX849 Cetuximab	Metastatic CRC	III	Recruiting
NCT04330664	MRTX849 TNO155	NSCLC	I/II	Recruiting
NCT04165031	LY3499446 Abemaciclib	Advanced NSCLC	I/II	Terminated
NCT04165031	LY3499446 Erlotinib	Advanced NSCLC	I/II	Active not recruiting
NCT04449874	GDC-6036 Erlotinib	Solid tumours	I a/I b	Recruiting
NCT04449874	GDC-6036 Cetuximab	Solid tumours	I a/I b	Recruiting
NCT04449874	GDC-6036 Bevacizumab	Solid tumours	I a/I b	Recruiting
Combined with immune therapy				
NCT03600883	AMG510 Pembrolizumab	NSCLC	II	Recruiting
NCT03600883	AMG510 Atezolizumab	NSCLC	II	Recruiting
NCT03785249	MRTX849 Pembrolizumab	NSCLC	I/II	Recruiting
NCT04613596	MRTX849 Pembrolizumab	NSCLC	II	Not yet recruiting
NCT04449874	GDC-6036 Atezolizumab	Solid tumours	I a/I b	Recruiting

NSCLC: nonsmall-cell lung cancer; CRC: colorectal adenocarcinoma. Data from ClinicalTrial.gov, accessed September 18, 2021

What type of patients have driver mutations in NSCLC?

Young MYTH BUSTED

- Median age 50s (ALK, ROS1), 60s (EGFR, BRAF)

Never-smokers MYTH BUSTED

- ~40% current/former smokers (EGFR, ALK, ROS1); 75% BRAF

Asian MYTH BUSTED

- > 50% are white for ALK, ROS1
- > 80% white for BRAF

Female MYTH BUSTED

- Female predominance, but 35-45% male

Adenocarcinoma PLAUSIBLE

- < 10% non-adenocarcinoma

Brain metastases PLAUSIBLE

- ~35% (ALK), 20% (EGFR)

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234,000

Small cell (13%)

Adeno (48%)

Squamous (24%)

112,320

KRAS G12C	13%
EGFR	15%
ALK	5%
ROS1	1%
BRAF	3%
MET	3%
HER2	2%
RET	2%
NTRK	1%
	45%

Estimated New Cases

			Males	Females			
Prostate	174,650	20%			Breast	268,600	30%
Lung & bronchus	116,440	13%			Lung & bronchus	111,710	13%
Colon & rectum	78,500	9%			Colon & rectum	67,100	8%
Urinary bladder	61,700	7%			Uterine corpus	61,880	7%
Melanoma of the skin	57,220	7%			Melanoma of the skin	39,260	4%
Kidney & renal pelvis	44,120	5%			Thyroid	37,810	4%
Non-Hodgkin lymphoma	41,090	5%			Non-Hodgkin lymphoma	33,110	4%
Oral cavity & pharynx	38,140	4%			Kidney & renal pelvis	29,700	3%
Leukemia	35,920	4%			Pancreas	26,830	3%
Pancreas	29,940	3%			Leukemia	25,860	3%
All Sites	**870,970**	**100%**			**All Sites**	**891,480**	**100%**

28,810

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Immunotherapy:
Hope for Durable Remission

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Early Immunotherapy

William Coley

- Bone surgeon, late 1800s

Observed spontaneous cancer remissions after erysipelas infection

Began injecting lives/attenuated bacteria into patient's tumors in 1891

- Called this approach Coley's toxins

New York Times - July 29, 1908

ERYSIPELAS GERMS AS CURE FOR CANCER

Dr. Coley's Remedy of Mixed Toxins Makes One Disease Cast Out the Other.

MANY CASES CURED HERE

Physician Has Used the Cure for 15 Years and Treated 430 Cases— Probably 150 Sure Cures.

Following news from St. Louis that two men have been cured of cancer in the City Hospital there by the use of a fluid discovered by Dr. William B. Coley of New York, it came out yester-

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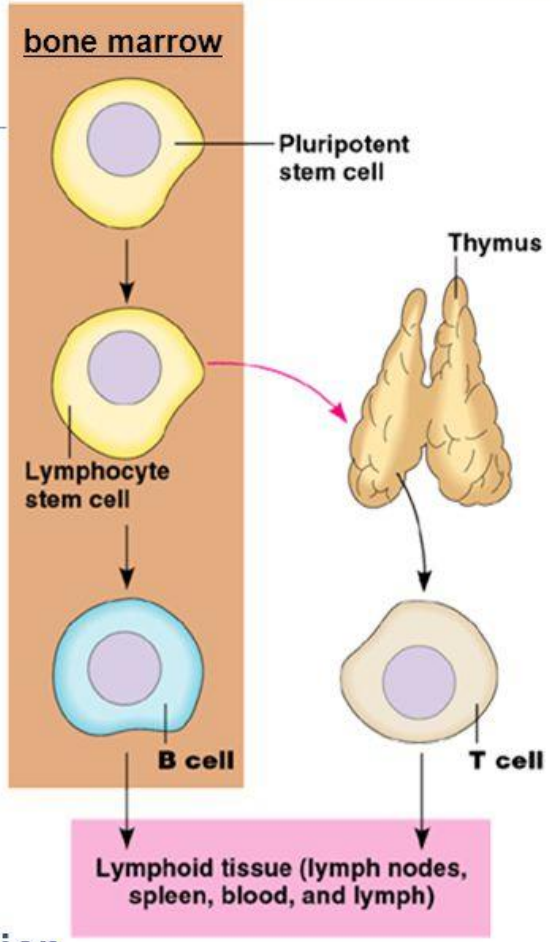
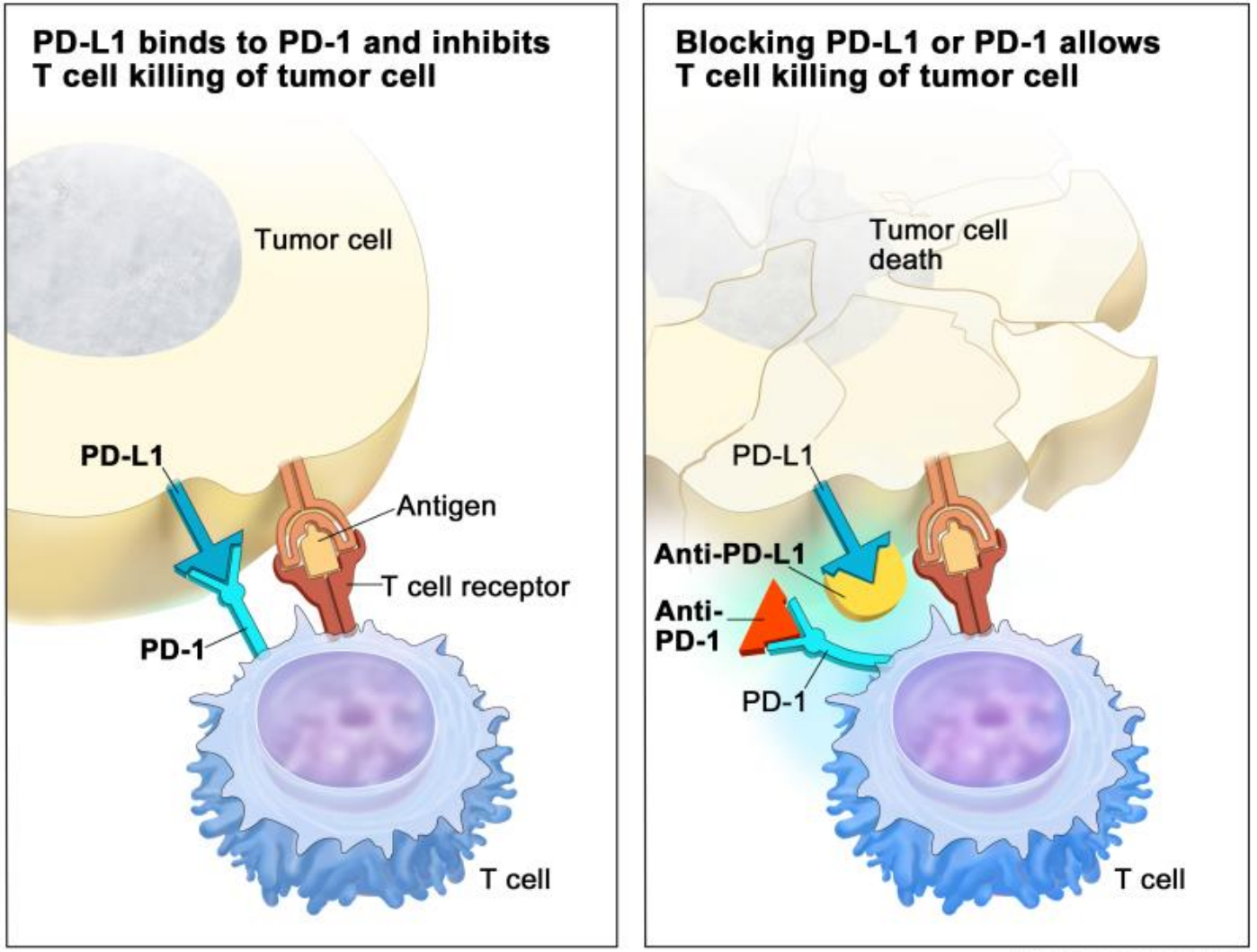
Immunology 101

Lymphocytes

- **B cells**
  - mature in **bone marrow**
  - **humoral** response system
    - "humors" = body fluids
    - produce antibodies
- **T cells**
  - mature in **thymus**
  - **cellular** response system
- **Learn to distinguish "self" from "non-self" antigens during maturation**
  - if they react to "self" antigens, they are destroyed during maturation



PD-L1: The Basics



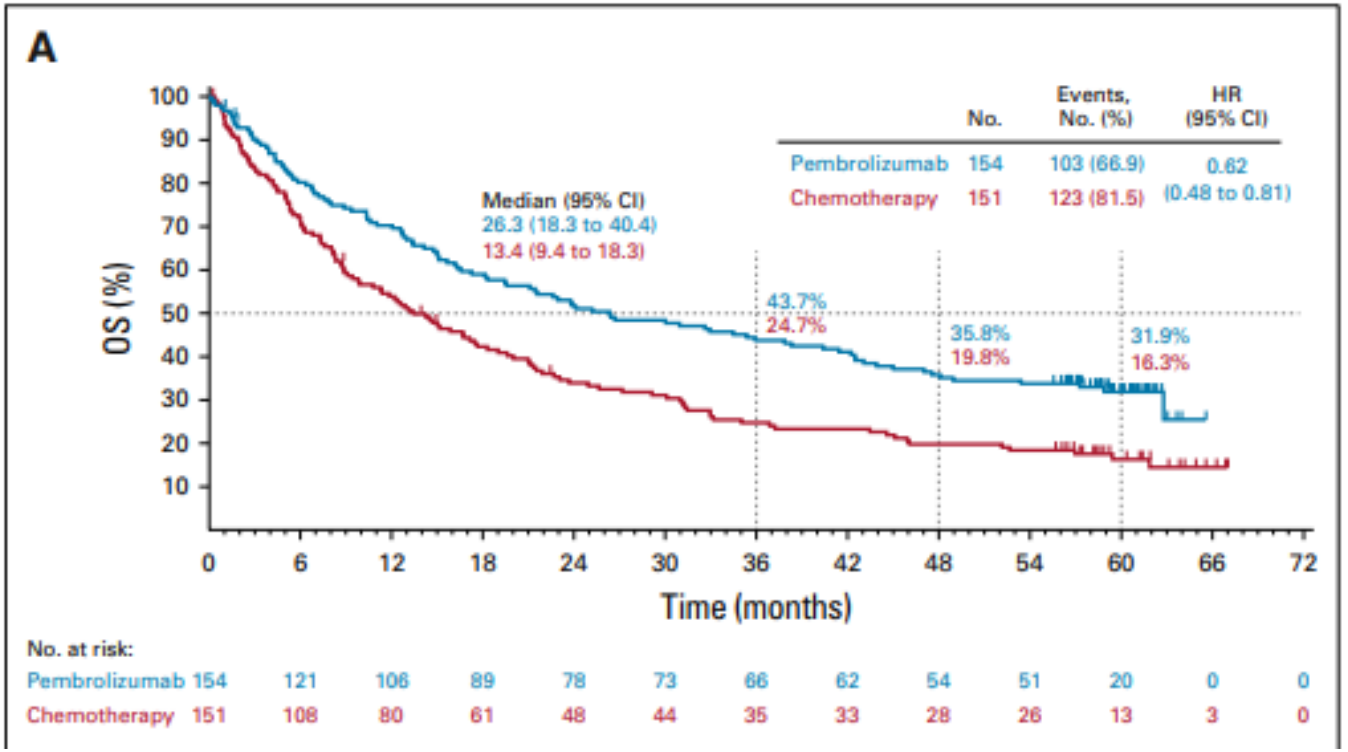
Keynote 024: The Gamechanger

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 10, 2016 VOL. 375 NO. 19

Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer

Martin Reck, M.D., Ph.D., Delvys Rodríguez-Abreu, M.D., Andrew G. Robinson, M.D., Rina Hui, M.B., B.S., Ph.D., Tibor Csőszi, M.D., Andrea Fülöp, M.D., Maya Gottfried, M.D., Nir Peled, M.D., Ph.D., Ali Tafreshi, M.D., Sinead Cuffe, M.D., Mary O'Brien, M.D., Suman Rao, M.D., Katsuyuki Hotta, M.D., Ph.D., Melanie A. Leiby, Ph.D., Gregory M. Lubiniecki, M.D., Yue Shentu, Ph.D., Reshma Rangwala, M.D., Ph.D., and Julie R. Brahmer, M.D., for the KEYNOTE-024 Investigators*



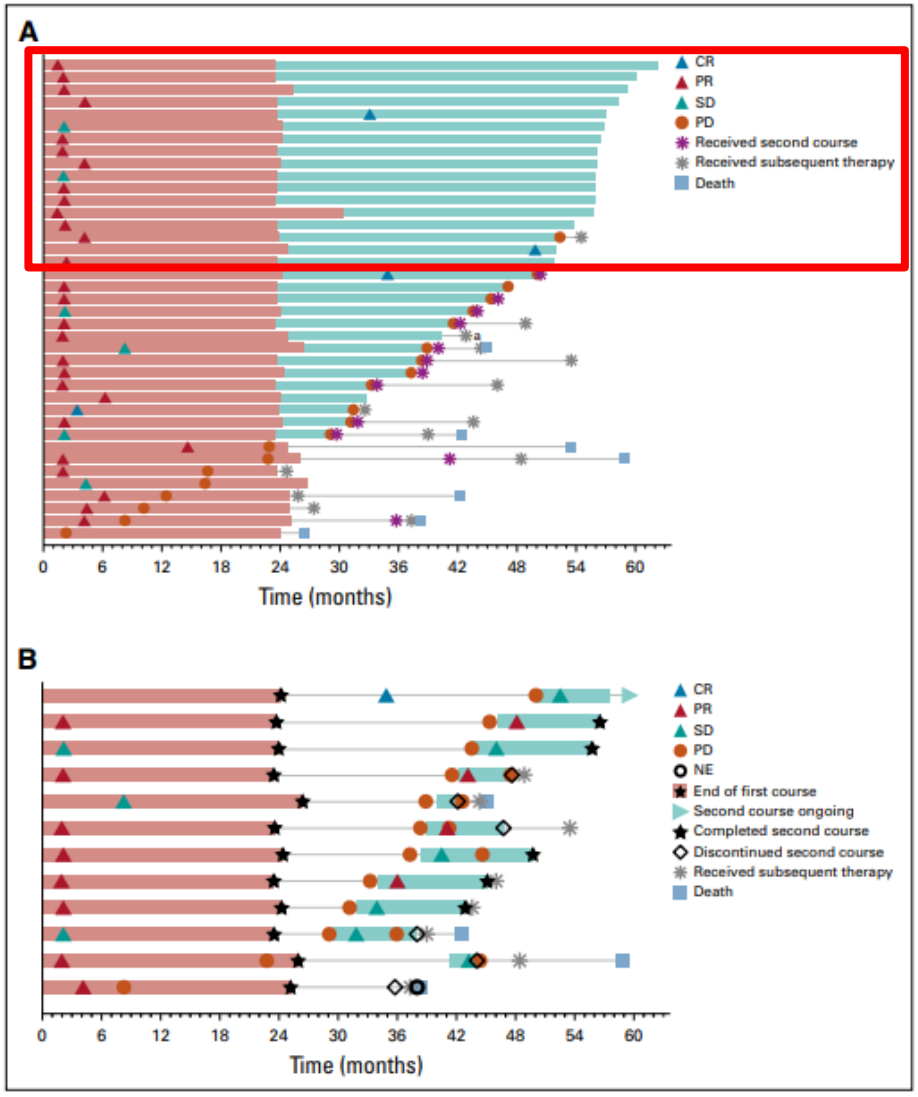


FIG 4. Treatment duration and time to response in (A) patients completing 35 cycles of pembrolizumab treatment and (B) patients who received a second course of pembrolizumab treatment. Light red bars indicate the first course of pembrolizumab treatment duration. Light teal bars indicate the (A) first course follow-up duration or (B) second course of treatment duration. Follow-up was defined as the time to progression or last nonprogression assessment by investigator. Response was assessed by RECIST v1.1 per investigator review. The maximum treatment duration for the second course was 17 cycles. [a]Patient developed a secondary malignancy. CR, complete response; NE, nonevaluable; PD, progressive disease; PR, partial response; SD, stable disease.

N =16/35 without relapse

N = 12 second course

- 4 PR, 6 SD
- 5 completed

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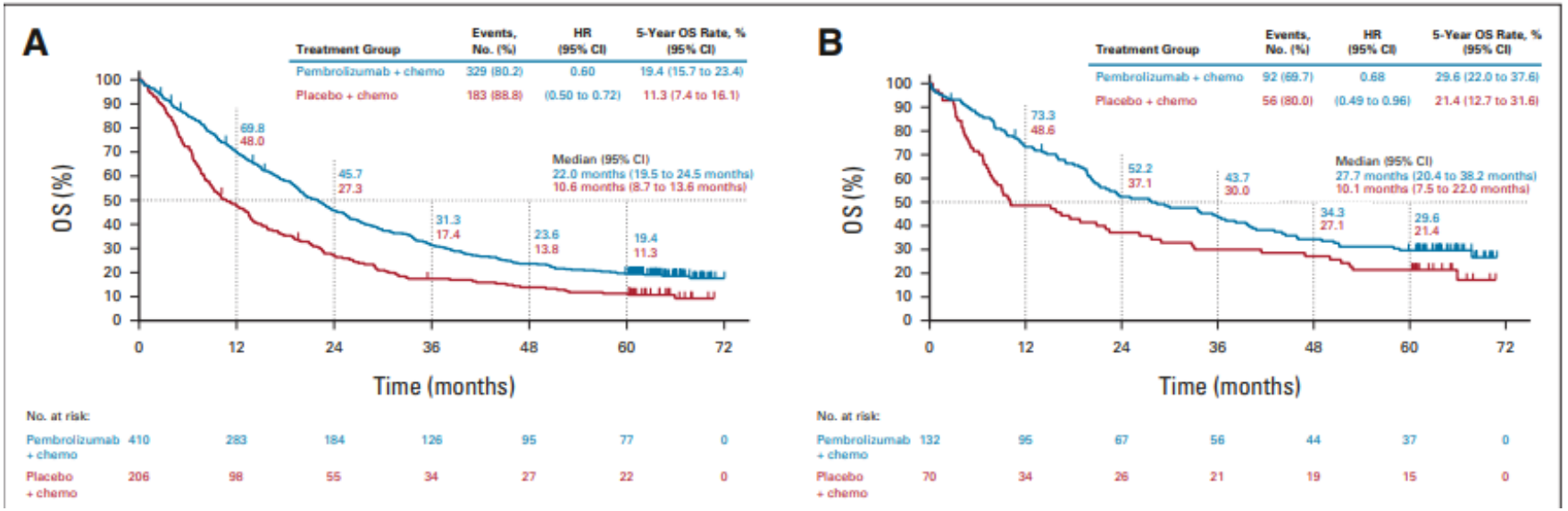
clinical trial updates

Pembrolizumab Plus Pemetrexed and Platinum in Nonsquamous Non–Small-Cell Lung Cancer: 5-Year Outcomes From the Phase 3 KEYNOTE-189 Study

Marina C. Garassino, MD[1,2]; Shirish Gadgeel, MD[3]; Giovanna Speranza, MD, MSc[4]; Enriqueta Felip, MD, PhD[5]; Emilio Esteban, MD[6]; Manuel Dómine, MD[7]; Maximilian J. Hochmair, MD[8]; Steven F. Powell, MD[9]; Helge G. Bischoff, MD[10]; Nir Peled, MD[11]; Francesco Grossi, MD[12]; Ross R. Jennens, MBBS[13]; Martin Reck, MD, PhD[14]; Rina Hui, MBBS, PhD[15]; Edward B. Garon, MD[16]; Takayasu Kurata, MD[17]; Jhanelle E. Gray, MD[18]; Paul Schwarzenberger, MD[19]; Erin Jensen, MS[19]; M. Catherine Pietanza, MD[19]; and Delvys Rodríguez-Abreu, MD, PhD[20]



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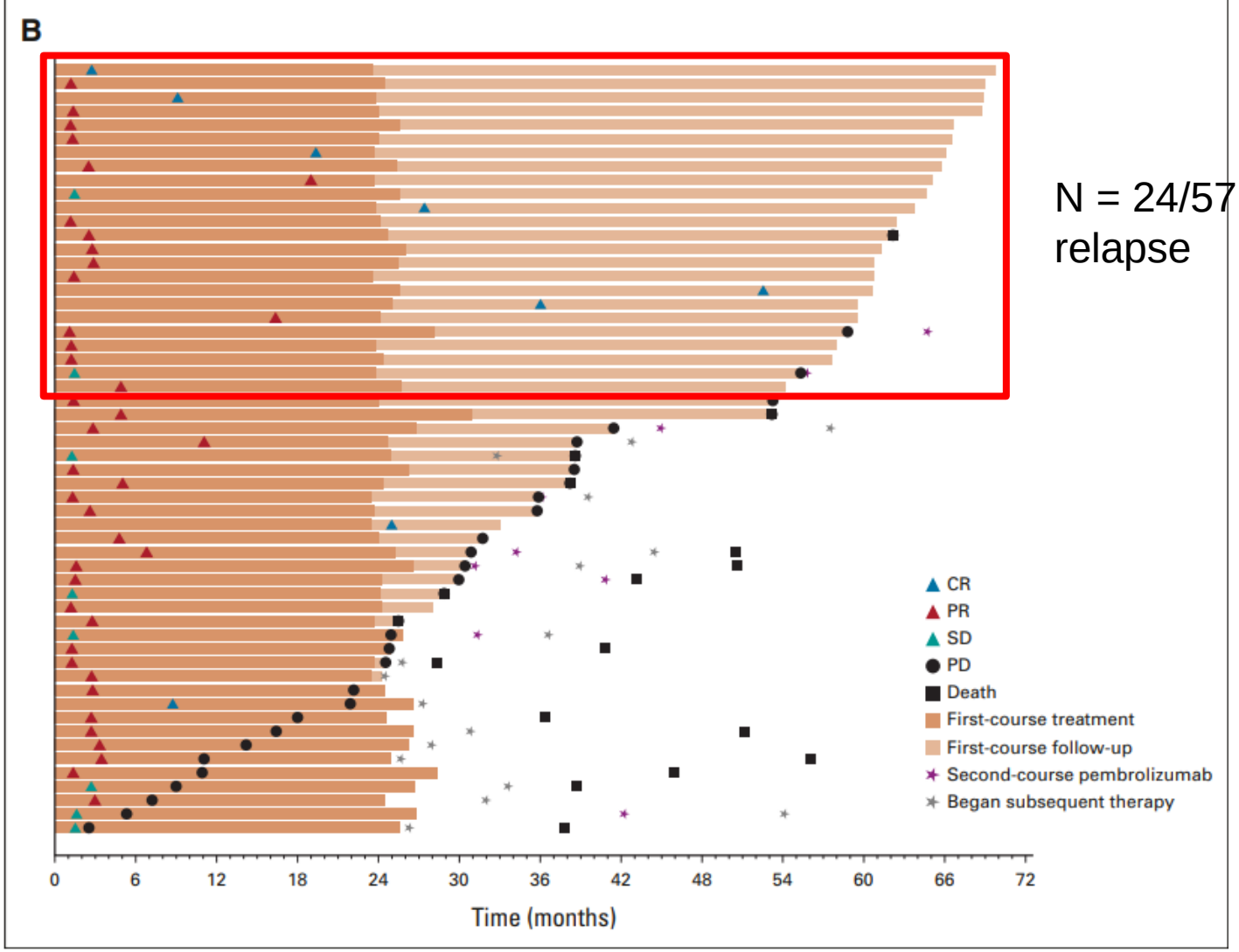
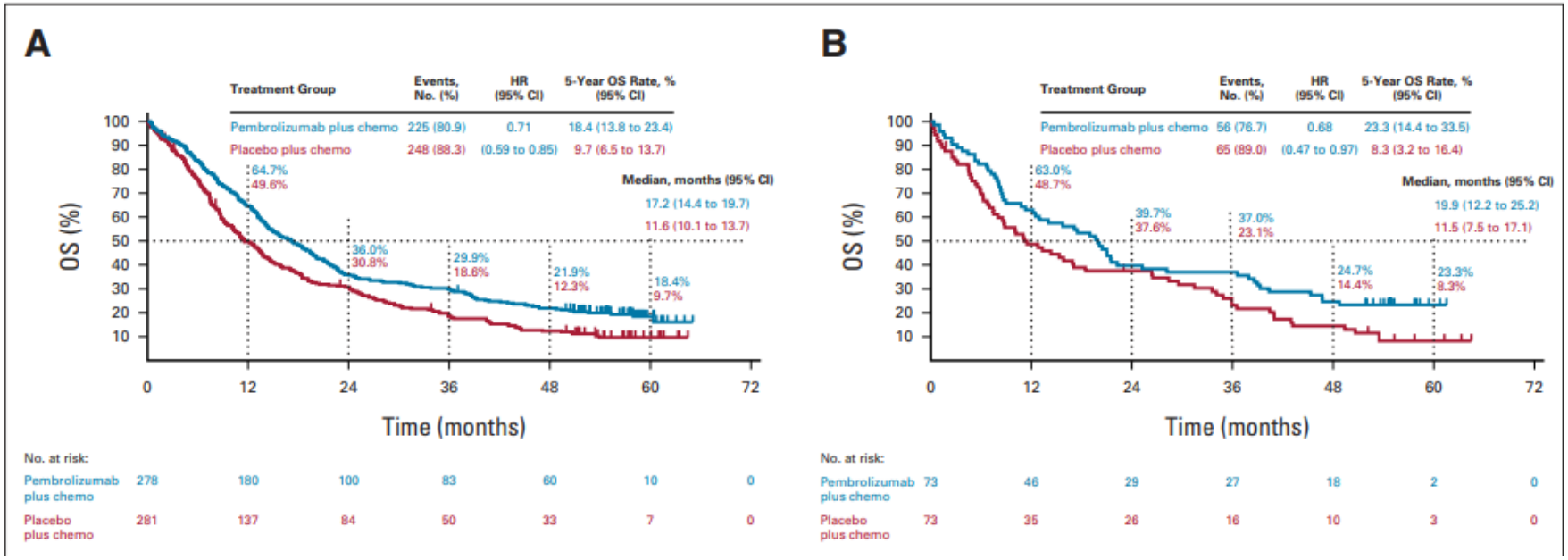


N = 24/57 without relapse

FIG 2. (A) Duration of response in the ITT population and (B) treatment duration and time to response in patients who completed 35 cycles of pembrolizumab. Response assessments are shown per RECIST version 1.1 by BICR. Median PFS was not reached (95% CI, 14.7 months to not reached). PFS rate 3 years after completion of 35 cycles was 56.2% (95% CI, 39.7 to 69.8). BICR, blinded independent central review; chemo, chemotherapy; CR, complete response; ITT, intention-to-treat; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Pembrolizumab Plus Chemotherapy in Squamous Non–Small-Cell Lung Cancer: 5-Year Update of the Phase III KEYNOTE-407 Study

Silvia Novello, MD, PhD[1]; Dariusz M. Kowalski, MD, PhD[2]; Alexander Luft, MD, PhD[3]; Mahmut Gümüş, MD[4]; David Vicente, MD[5]; Julien Mazières, MD, PhD[6]; Jeronimo Rodríguez-Cid, MD[7]; Ali Tafreshi, MD[8]; Ying Cheng, MD[9]; Ki Hyeong Lee, MD, PhD[10]; Alexander Golf, MD[11]; Shunichi Sugawara, MD, PhD[12]; Andrew G. Robinson, MD[13]; Balazs Halmos, MD[14]; Erin Jensen, MS[15]; Paul Schwarzenberger, MD[16]; M. Catherine Pietanza, MD[16]; and Luis Paz-Ares, MD, PhD[17]



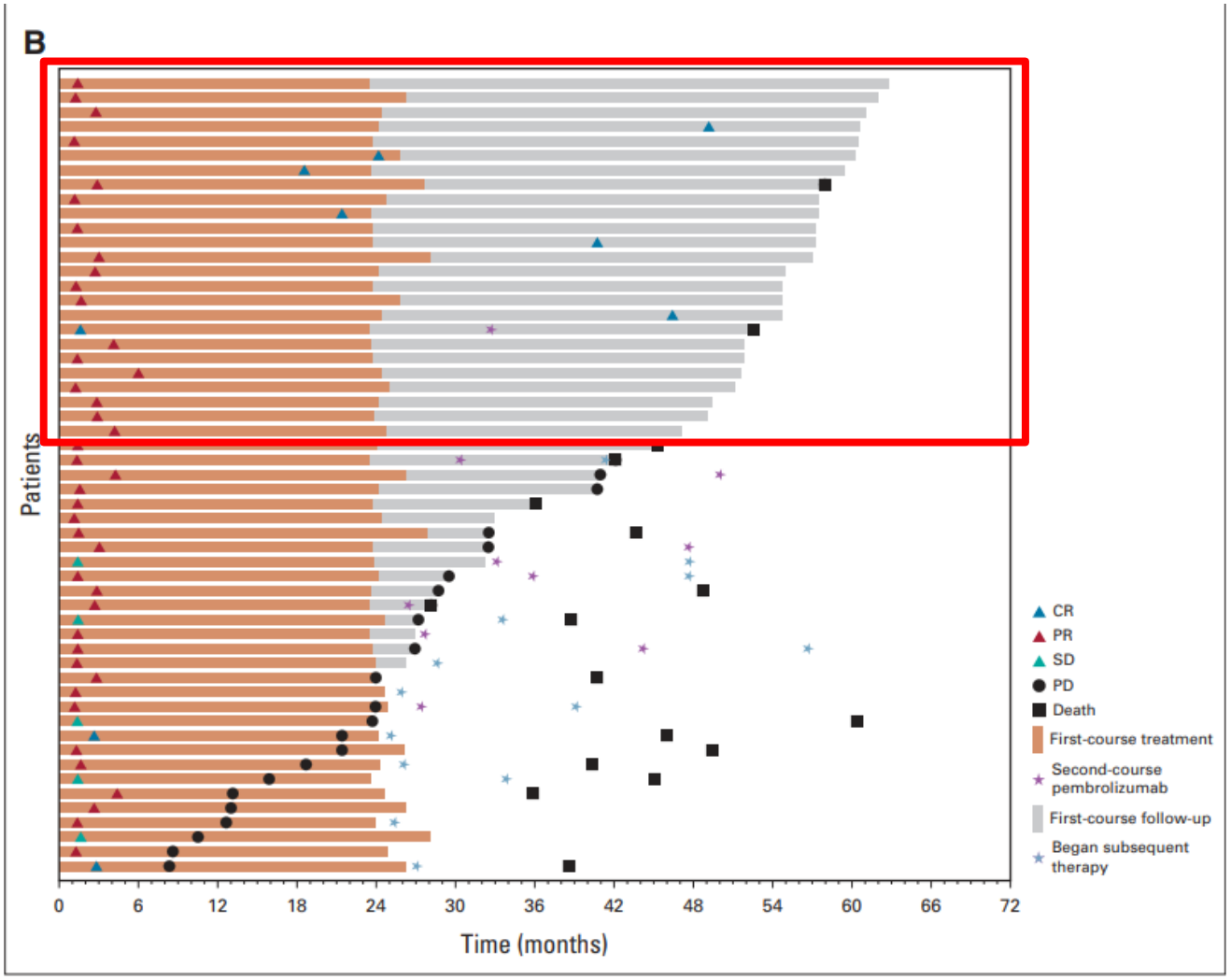
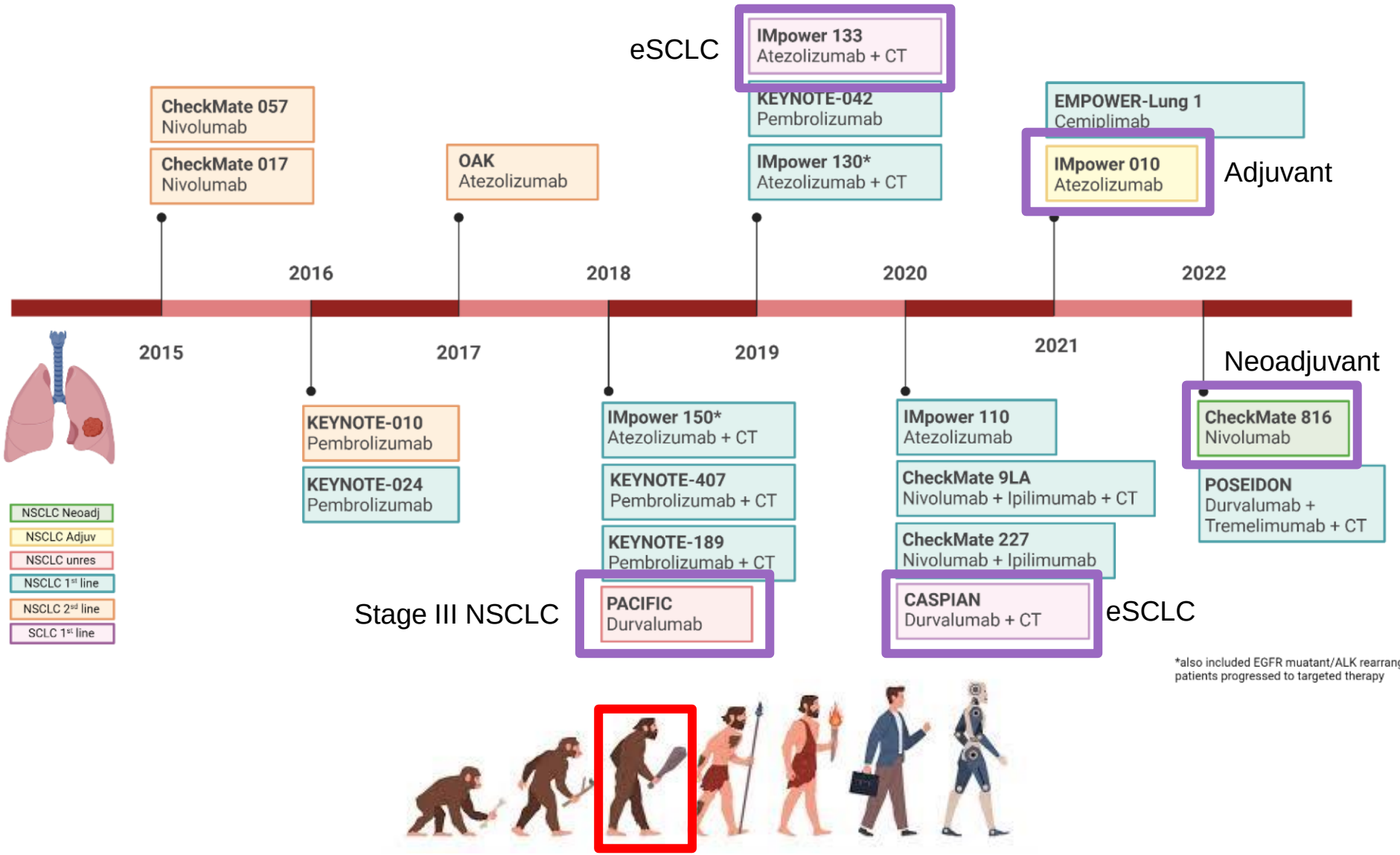


FIG 2. Patient response to pembrolizumab plus chemotherapy and placebo plus chemotherapy. (A) DOR in the ITT population and (B) time to response and DOR in patients who completed 35 cycles of pembrolizumab. Median PFS was NR (95% CI, 21.2 months to NR) among patients who completed 35 cycles. The PFS rate 3 years after completion of 35 cycles was 58.4% (95% CI, 39.8 to 73.0). chemo, chemotherapy; CR, complete response; DOR, duration of response; ITT, intention to treat; NR, not reached; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

N = 27/55 without relapse

Immunotherapy Drug Approval Timeline



Future Directions: Harnessing The Cancer-Immunity Cycle

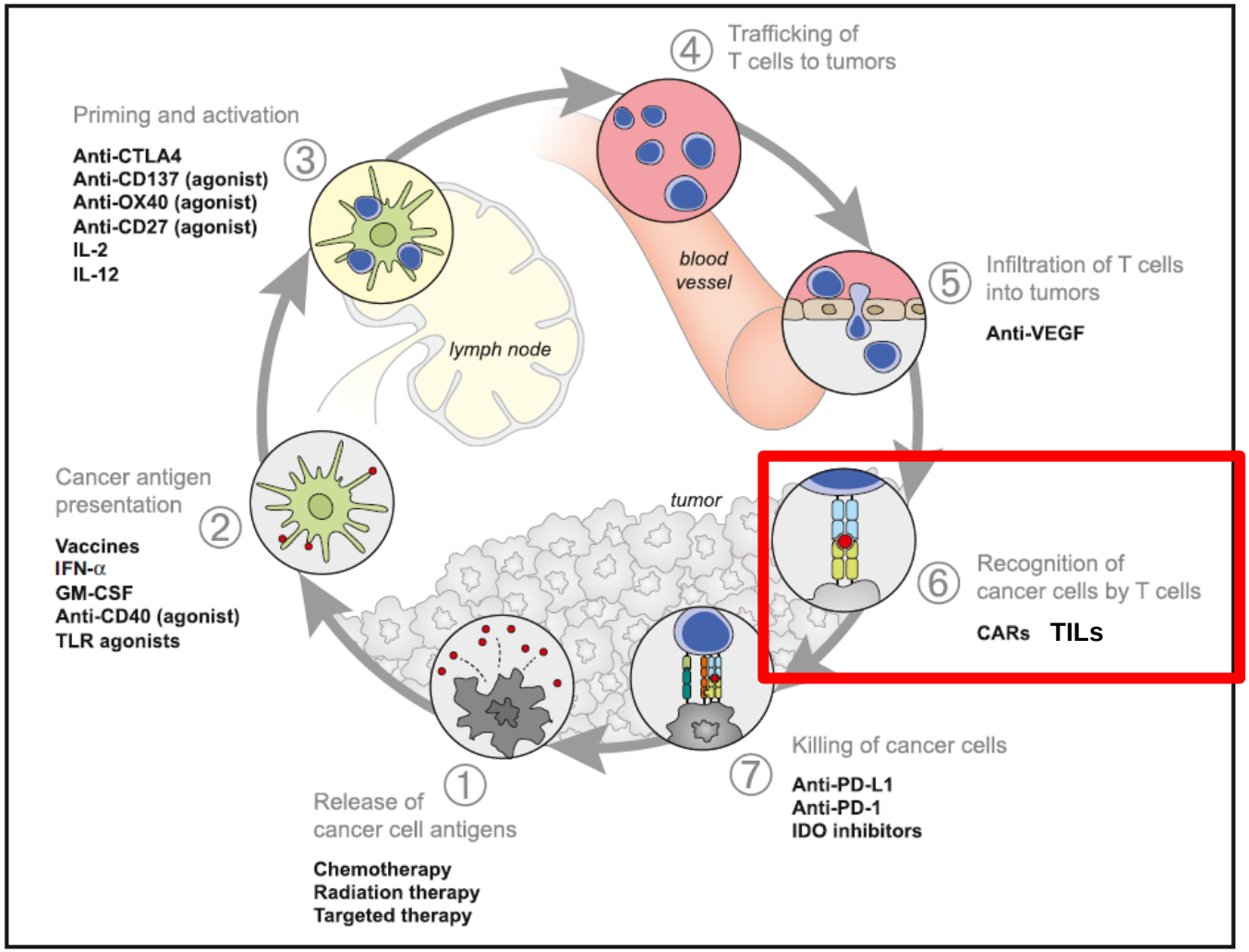
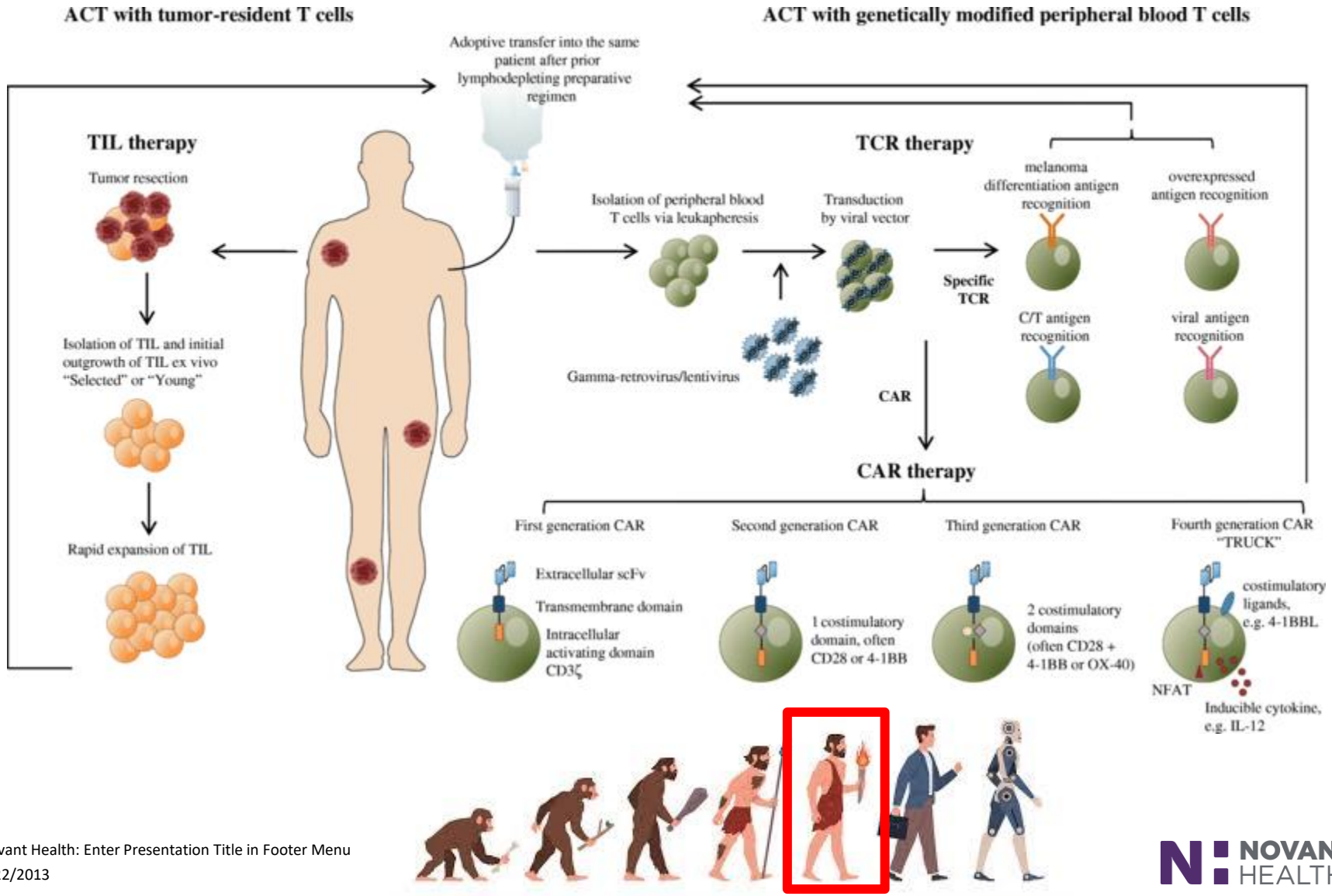


Figure 3. Therapies that Might Affect the Cancer-Immunity Cycle

Cellular Therapies



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