interdisipliner onkoloji derneği

GENÇLERLE ONKOLOJİYE BAKIŞ KONGRESİ

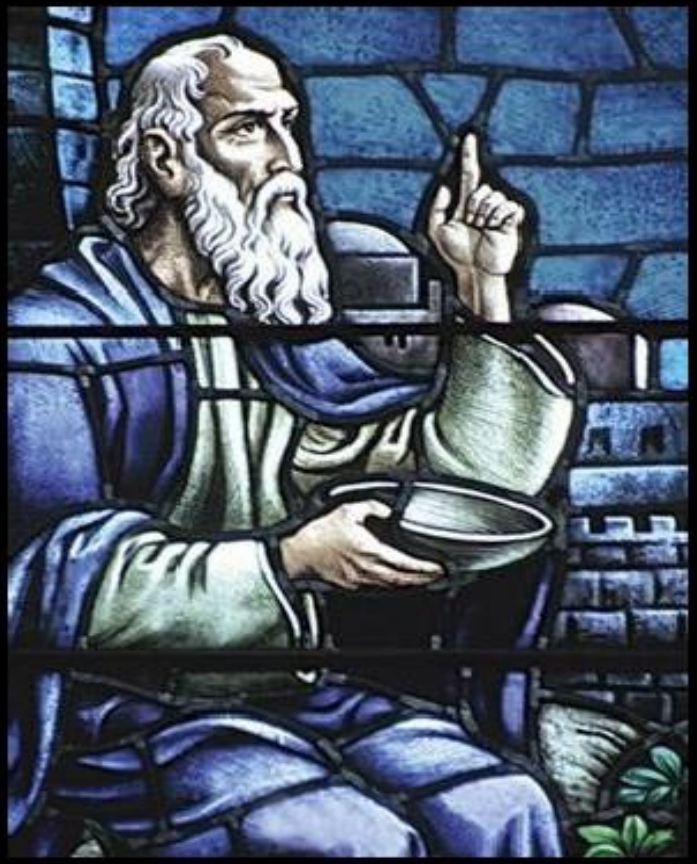
Kanserde Kür Vakti ☺ İmmünoterapi

Dr Ahmet Taner Sümbül

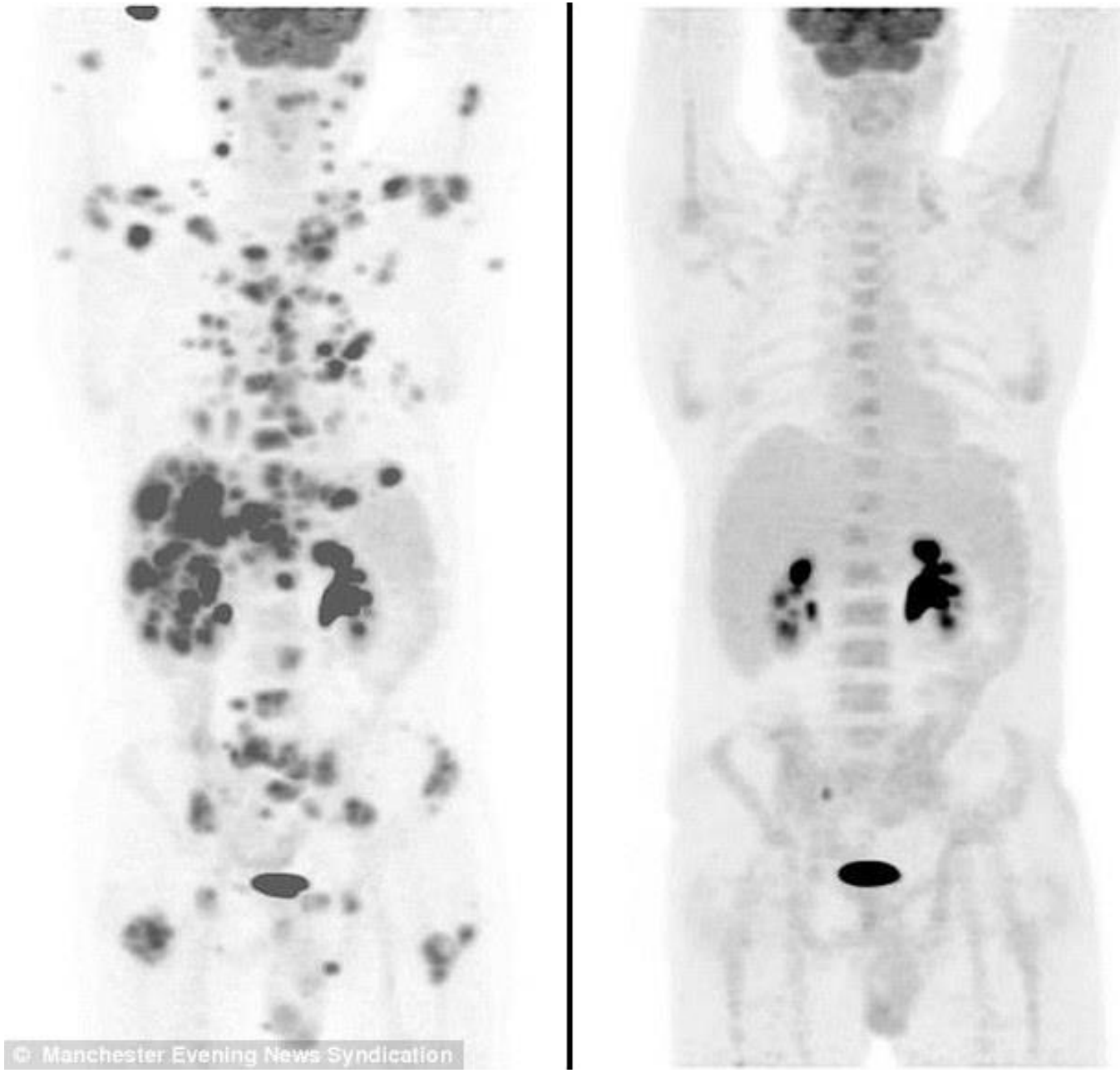
Başkent Üniversitesi Tıp Fakültesi

Tıbbi Onkoloji BD


EXTRA! EXTRA!
READ ALL ABOUT IT!
CANCER
CURED!!



"Sorgulanmayan hayat, yaşanmaya değmez" diyor Sokrat. Evet insan sorgulayıp hayat anlamını arayıp bulacak ve ondan sonra o çerçevede kendisine bir hayat kuracak. Buna hayatı temellendirme de deriz.



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 22, 2015 VOL. 372 NO. 4

PD-1 Blockade with Nivolumab in Relapsed or Refractory Hodgkin's Lymphoma

Stephen M. Ansell, M.D., Ph.D., Alexander M. Lesokhin, M.D., Ivan Borrello, M.D., Ahmad Halwani, M.D., Emma C. Scott, M.D., Martin Gutierrez, M.D., Stephen J. Schuster, M.D., Michael M. Millenson, M.D., Deepika Cattry, M.S., Gordon J. Freeman, Ph.D., Scott J. Rodig, M.D., Ph.D., Bjoern Chapuy, M.D., Ph.D., Azra H. Ligon, Ph.D., Lili Zhu, M.S., Joseph F. Grosso, Ph.D., Su Young Kim, M.D., Ph.D., John M. Timmerman, M.D., Margaret A. Shipp, M.D., and Philippe Armand, M.D., Ph.D.

ABSTRACT

BACKGROUND

Preclinical studies suggest that Reed–Sternberg cells exploit the programmed death 1 (PD-1) pathway to evade immune detection. In classic Hodgkin's lymphoma, alterations in chromosome 9p24.1 increase the abundance of the PD-1 ligands, PD-L1 and PD-L2, and promote their induction through Janus kinase (JAK)–signal transducer and activator of transcription (STAT) signaling. We hypothesized that nivolumab, a PD-1–blocking antibody, could inhibit tumor immune evasion in patients with relapsed or refractory Hodgkin's lymphoma.

METHODS

In this ongoing study, 23 patients with relapsed or refractory Hodgkin's lymphoma that had already been heavily treated received nivolumab (at a dose of 3 mg per kilogram of body weight) every 2 weeks until they had a complete response, tumor progression, or excessive toxic effects. Study objectives were measurement of safety and efficacy and assessment of the *PDL1* and *PDL2* (also called *CD274* and *PDCD1LG2*, respectively) loci and PD-L1 and PD-L2 protein expression.

RESULTS

Of the 23 study patients, 78% were enrolled in the study after a relapse following autologous stem-cell transplantation and 78% after a relapse following the receipt of brentuximab vedotin. Drug-related adverse events of any grade and of grade 3 occurred in 78% and 22% of patients, respectively. An objective response was reported in 20 patients (87%), including 17% with a complete response and 70% with a partial response; the remaining 3 patients (13%) had stable disease. The rate of progression-free survival at 24 weeks was 86%; 11 patients were continuing to participate in the study. Reasons for discontinuation included stem-cell transplantation (in 6 patients), disease progression (in 4 patients), and drug toxicity (in 2 patients). Analyses of pretreatment tumor specimens from 10 patients revealed copy-number gains in *PDL1* and *PDL2* and increased expression of these ligands. Reed–Sternberg cells showed nuclear positivity of phosphorylated STAT3, indicative of active JAK-STAT signaling.

CONCLUSIONS

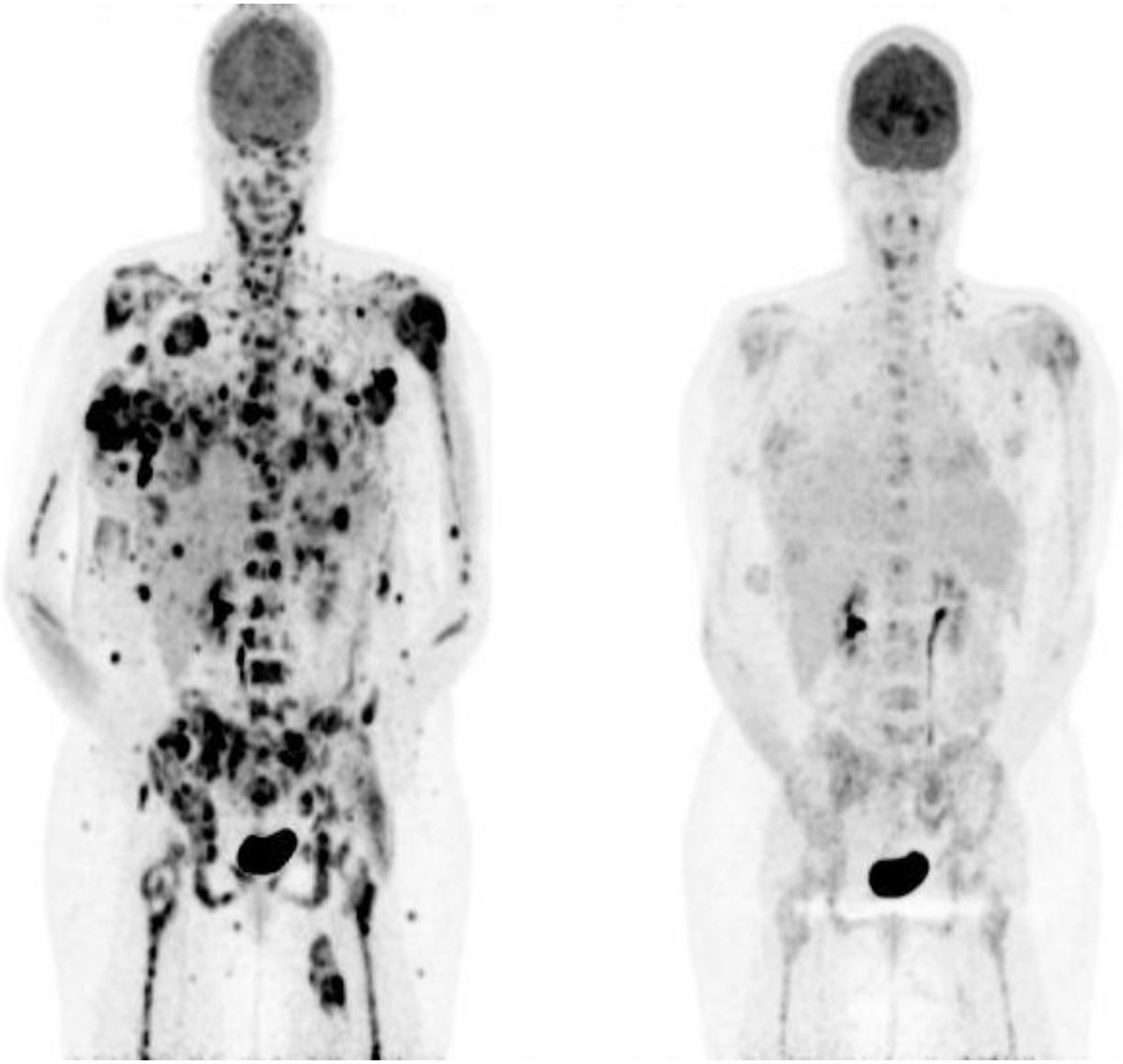
Nivolumab had substantial therapeutic activity and an acceptable safety profile in patients with previously heavily treated relapsed or refractory Hodgkin's lymphoma. (Funded by Bristol-Myers Squibb and others; ClinicalTrials.gov number, NCT01592370.)

From the Mayo Clinic, Rochester, MN (S.M.A.); Memorial Sloan Kettering Cancer Center (A.M.L., D.C.) and Weill Cornell Medical College (A.M.L.) — both in New York; Johns Hopkins University School of Medicine and the Sidney Kimmel Comprehensive Cancer Center, Baltimore (I.B.); University of Utah Huntsman Cancer Institute, Salt Lake City (A.H.); Oregon Health and Science University and the Knight Cancer Institute, Portland (E.C.S.); John Theurer Cancer Center, Hackensack University Medical Center, Hackensack (M.G.), and Bristol-Myers Squibb, Lawrenceville (L.Z., J.F.G., S.Y.K.) — both in New Jersey; Abramson Cancer Center, University of Pennsylvania (S.J.S.), and Fox Chase Cancer Center (M.M.M.) — both in Philadelphia; Dana–Farber Cancer Institute (G.J.F., B.C., M.A.S., P.A.) Brigham and Women's Hospital (S.J.R., A.H.L.), and Harvard Medical School (G.J.F., B.C., M.A.S., P.A., S.J.R., A.H.L.) — all in Boston; and Jonsson Comprehensive Cancer Center, University of California, Los Angeles, Los Angeles (J.M.T.). Address reprint requests to Dr. Ansell at the Mayo Clinic, 200 First St. SW, Rochester, MN 55905, or at ansell.stephen@mayo.edu; or to Dr. Armand at the Dana–Farber Cancer Institute, 450 Brookline Ave., Boston, MA 02215, or at philippe_armand@dfci.harvard.edu.

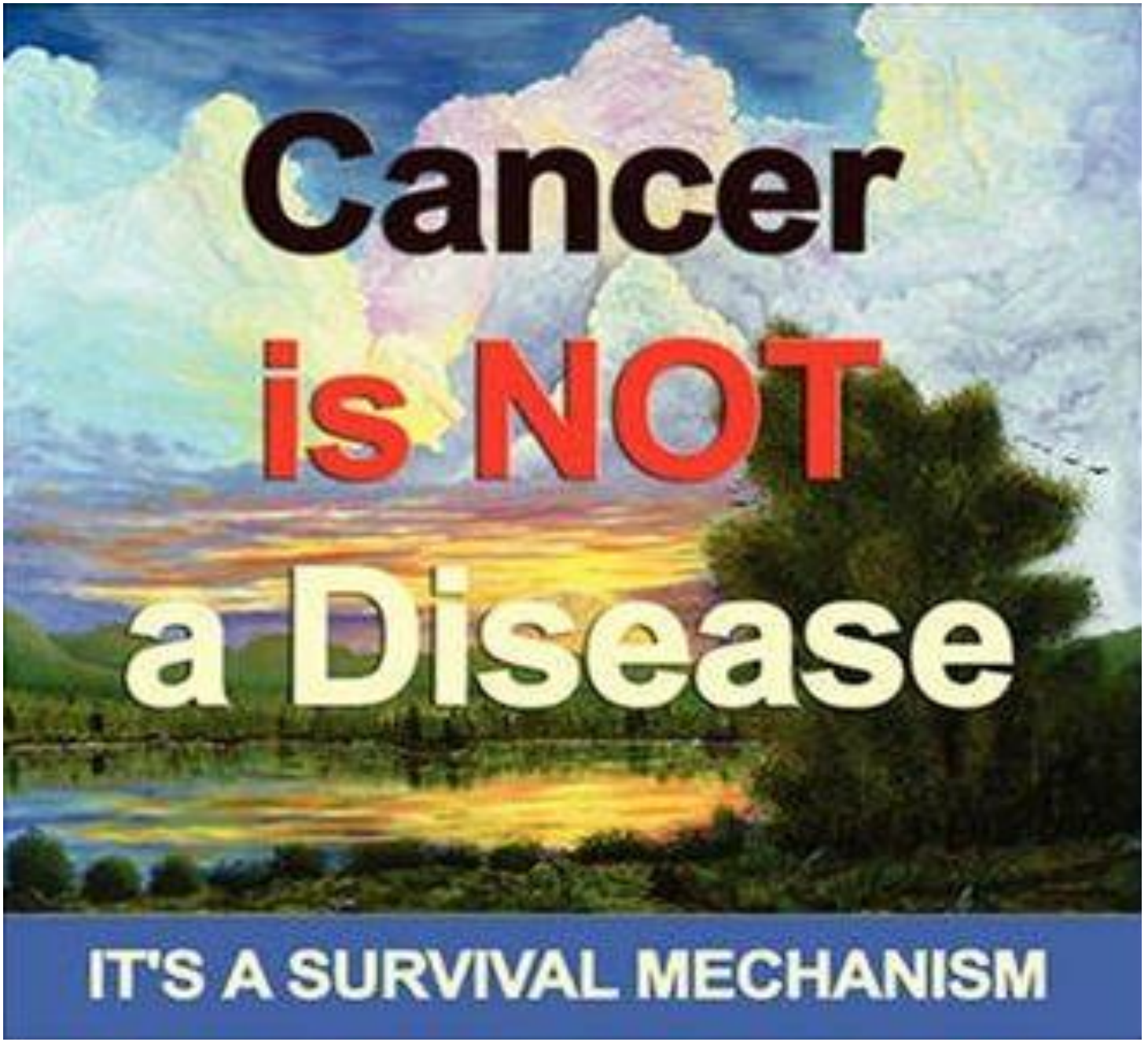
Drs. Ansell and Lesokhin and Drs. Shipp and Armand contributed equally to this article.

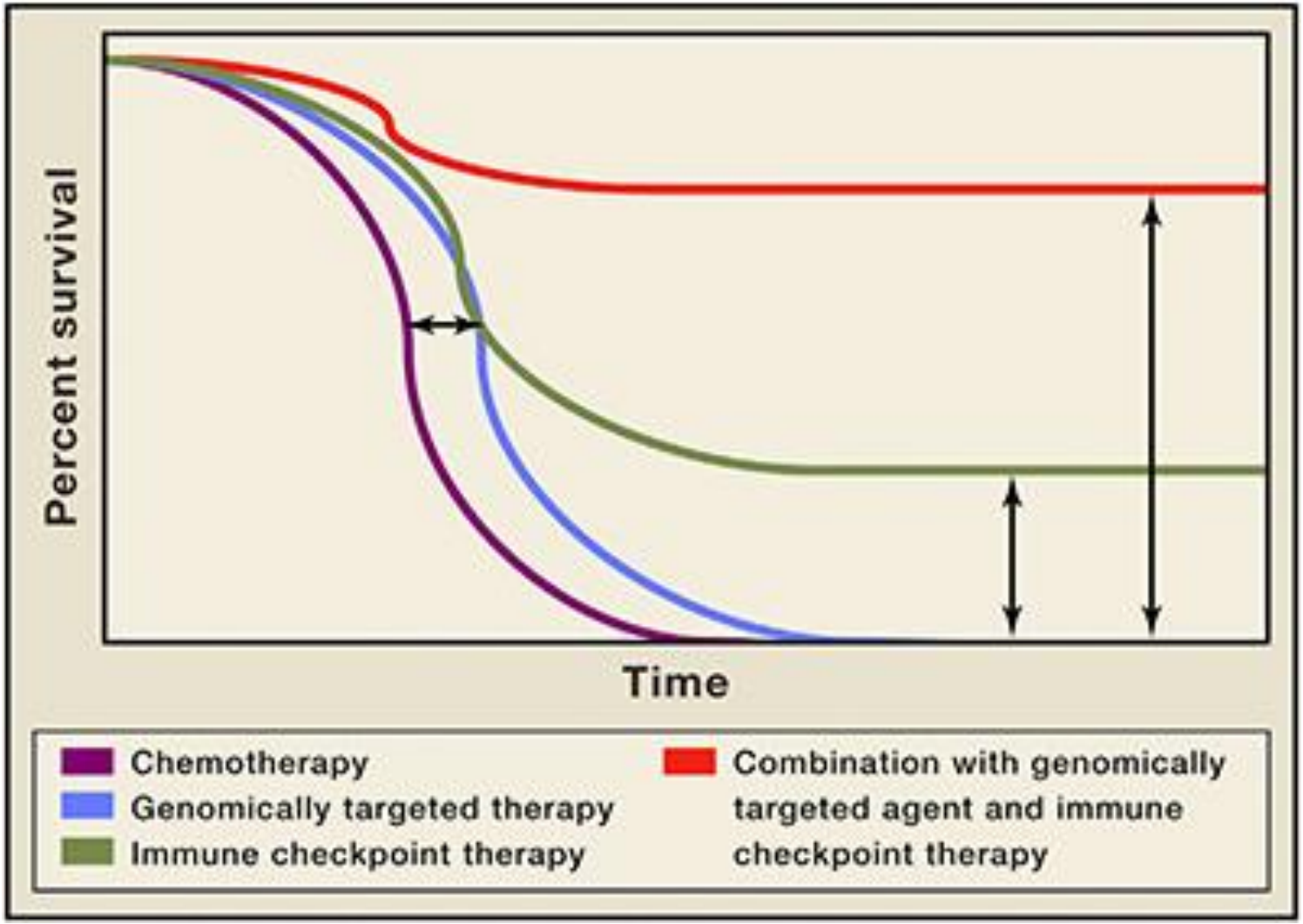
This article was published on December 6, 2014, at NEJM.org.

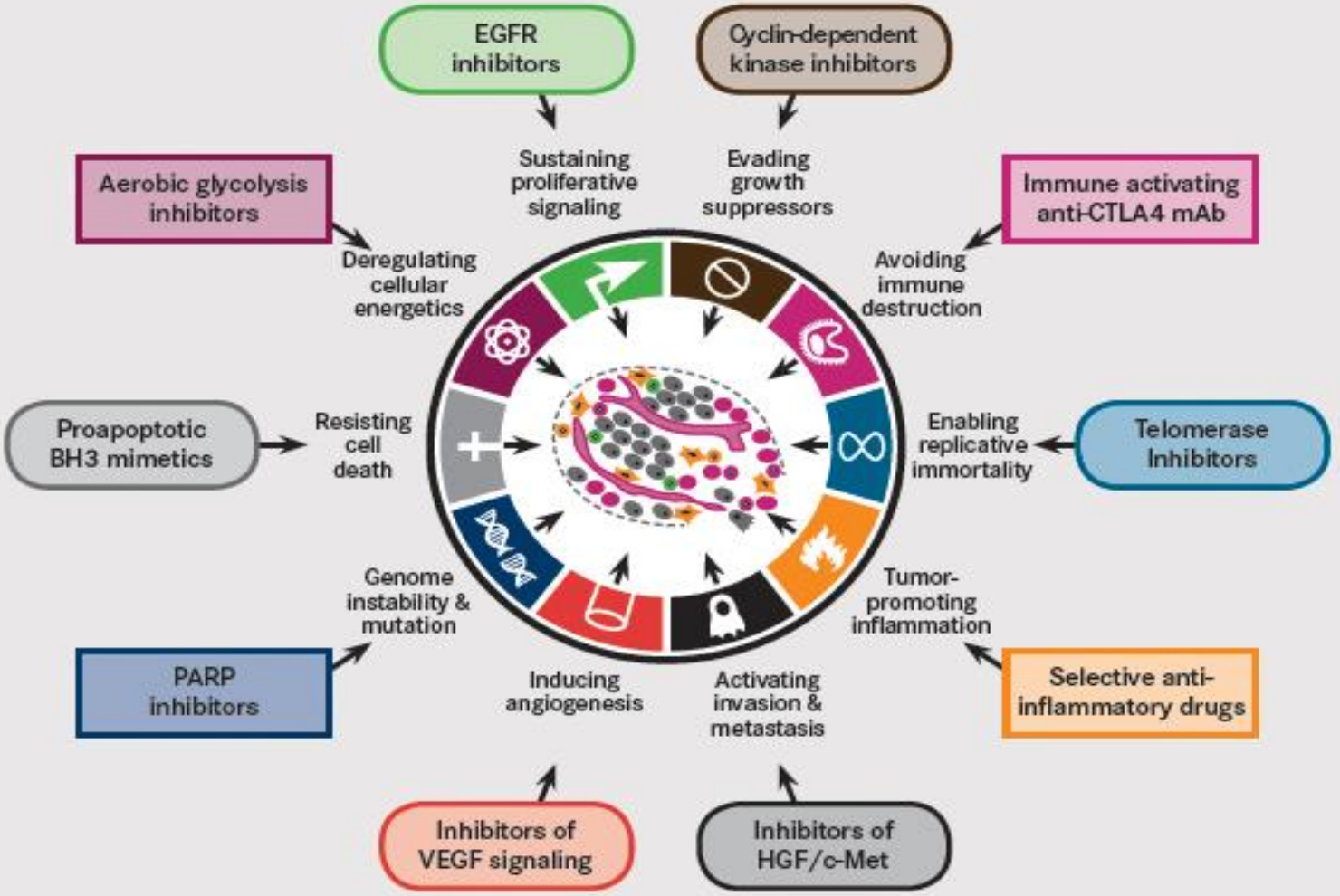
N Engl J Med 2015;372:311-9.
DOI: 10.1056/NEJMoa1411087




I'VE NEVER SEEN
ANYTHING LIKE THIS
IN MY
LIFE!


Cancer
is NOT
a Disease
IT'S A SURVIVAL MECHANISM

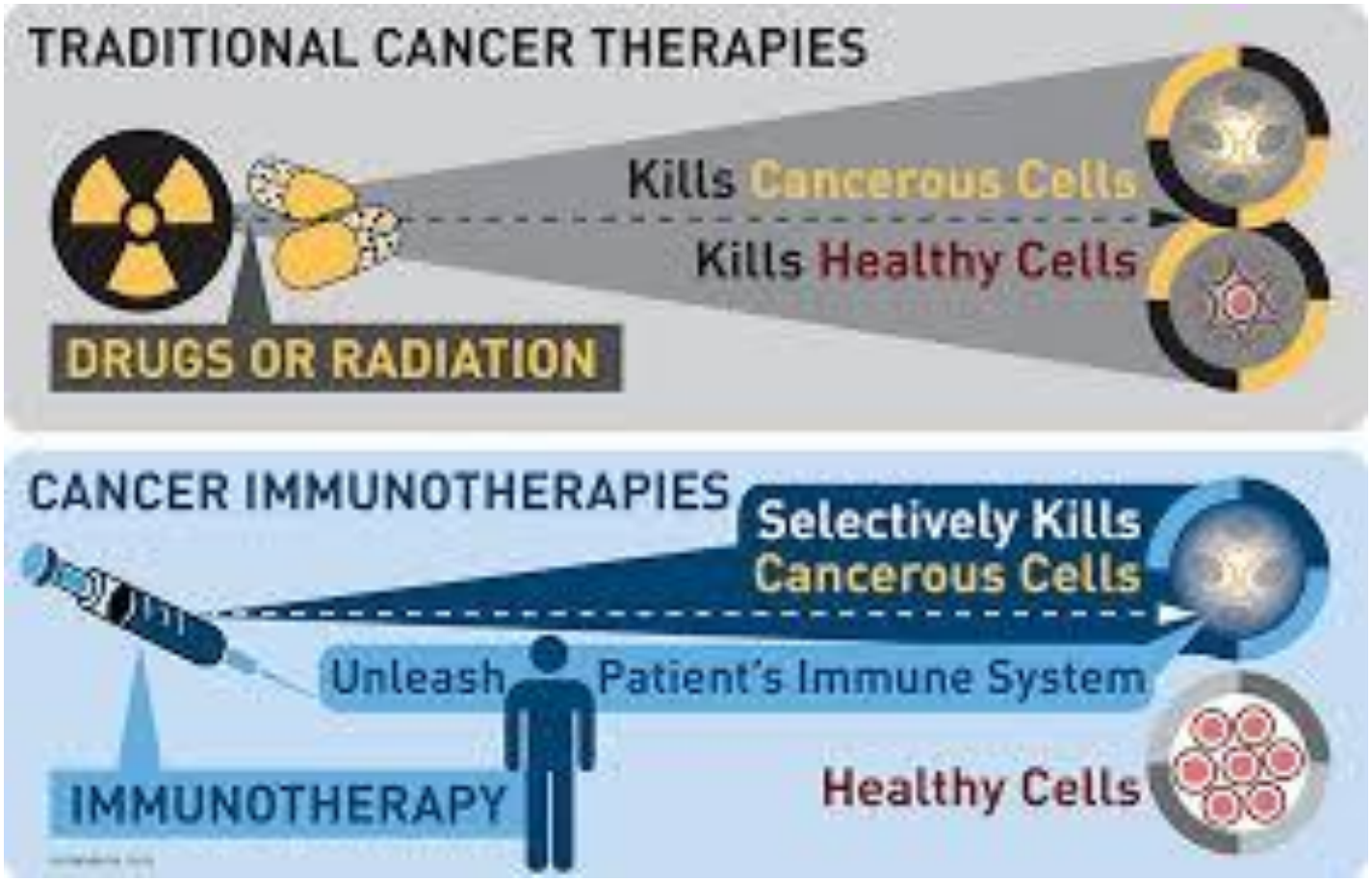

Percent survival
Time
Chemotherapy
Genomically targeted therapy
Immune checkpoint therapy
Combination with genomically targeted agent and immune checkpoint therapy



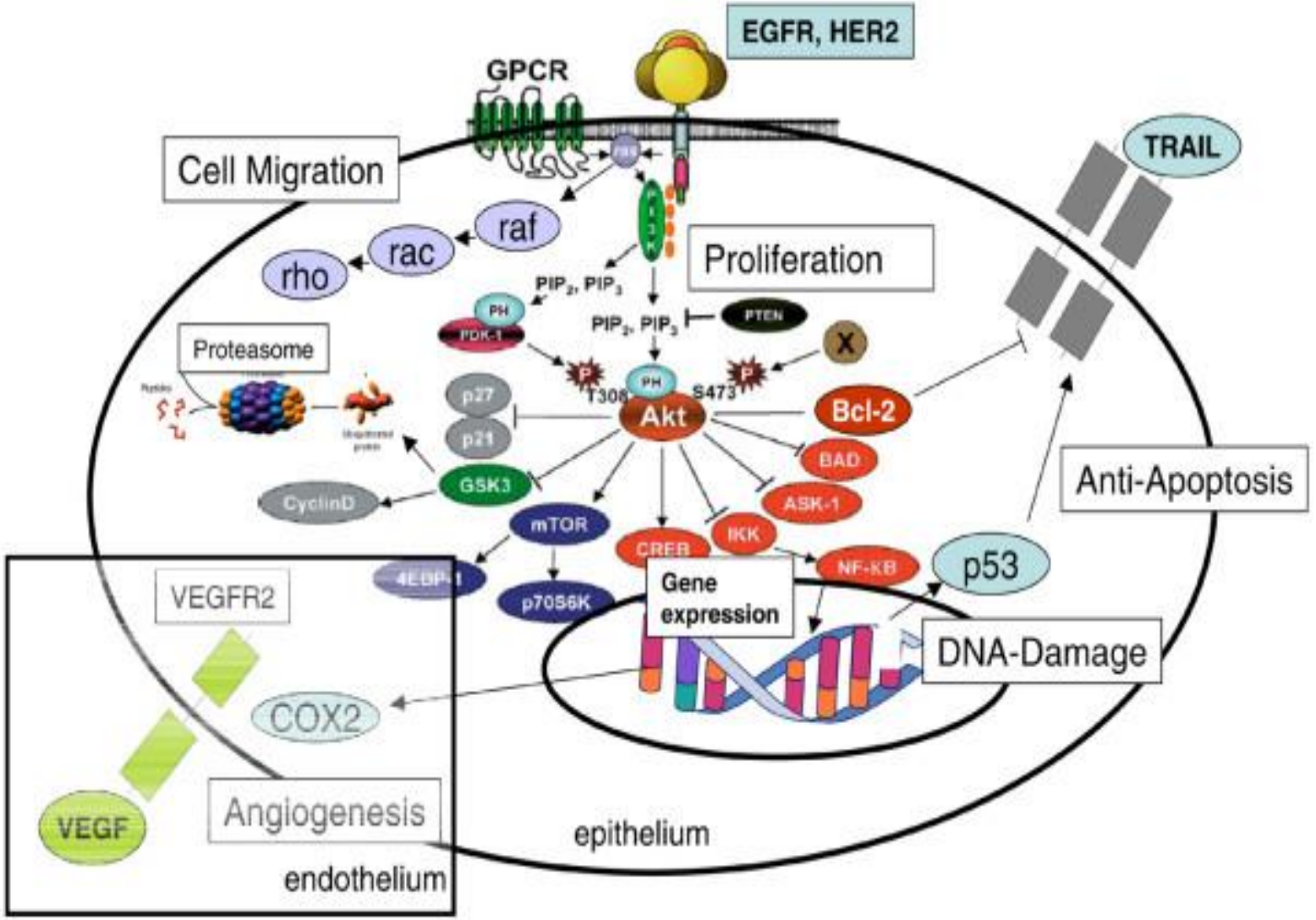
This figure illustrates some of the many approaches employed in developing therapeutics targeted to the known and emerging hallmarks of cancer.

EGFR indicates epidermal growth factor receptor; CTLA4, cytotoxic T lymphocyte-associated antigen 4; mAb, monoclonal antibody; HGF, hepatocyte growth factor; VEGF, vascular endothelial growth factor; PARP, poly-(ADP ribose) polymerase.

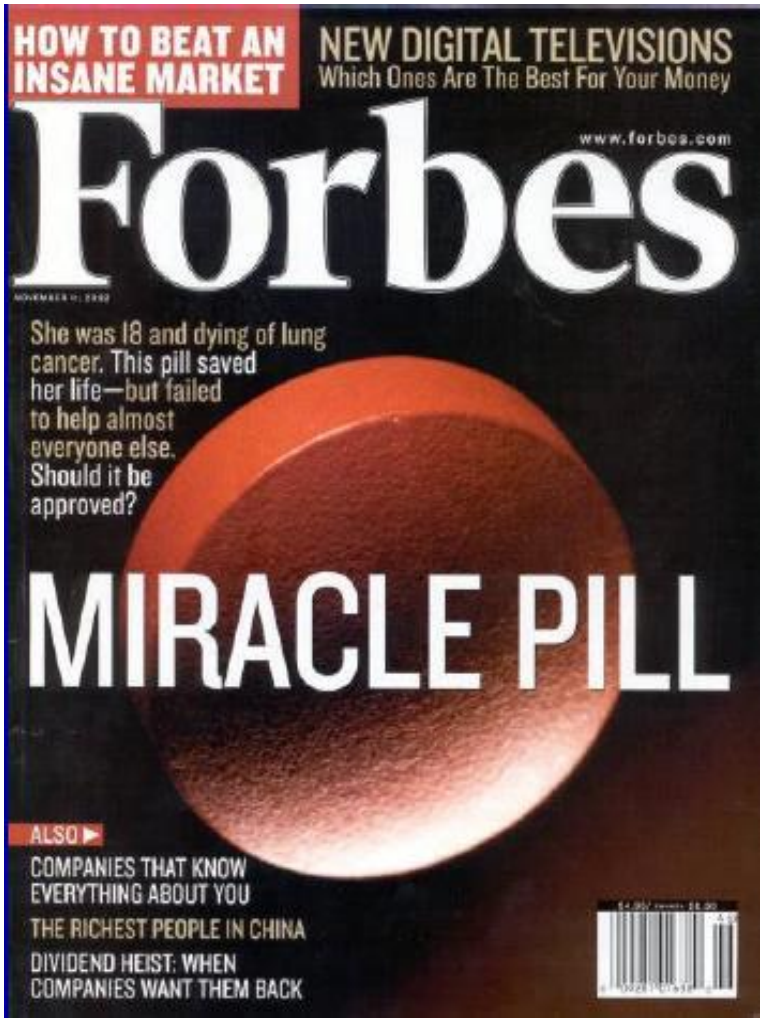
Source: Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011; 144:646-674. Reprinted with permission.


TRADITIONAL CANCER THERAPIES
Kills Cancerous Cells
Kills Healthy Cells
DRUGS OR RADIATION
CANCER IMMUNOTHERAPIES
Selectively Kills Cancerous Cells
Unleash Patient's Immune System
IMMUNOTHERAPY
Healthy Cells

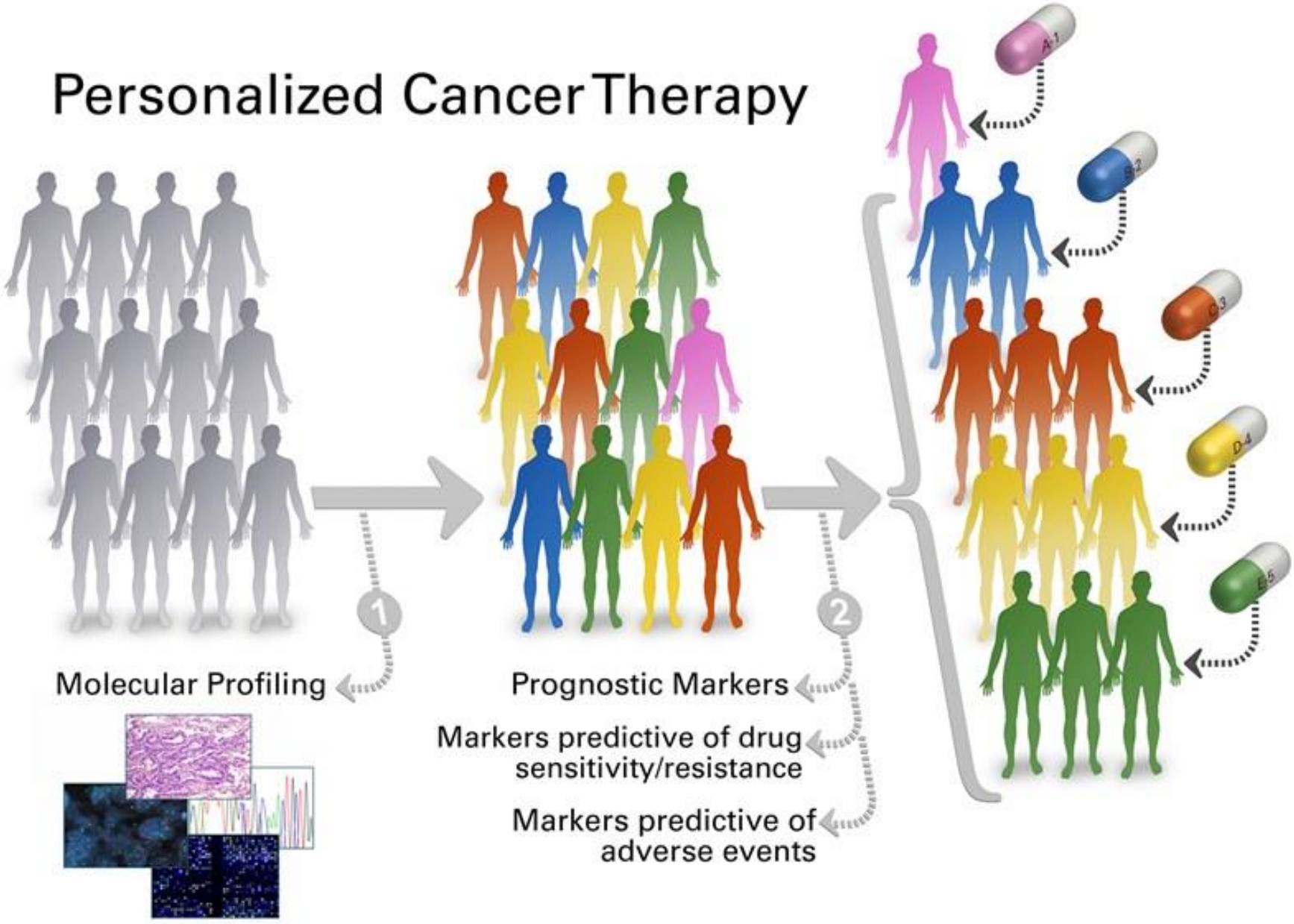
KANSER TEDAVİSİNDE HEDEF BÜTÜN MÜ YOKSA SINGLE CELL mi….?

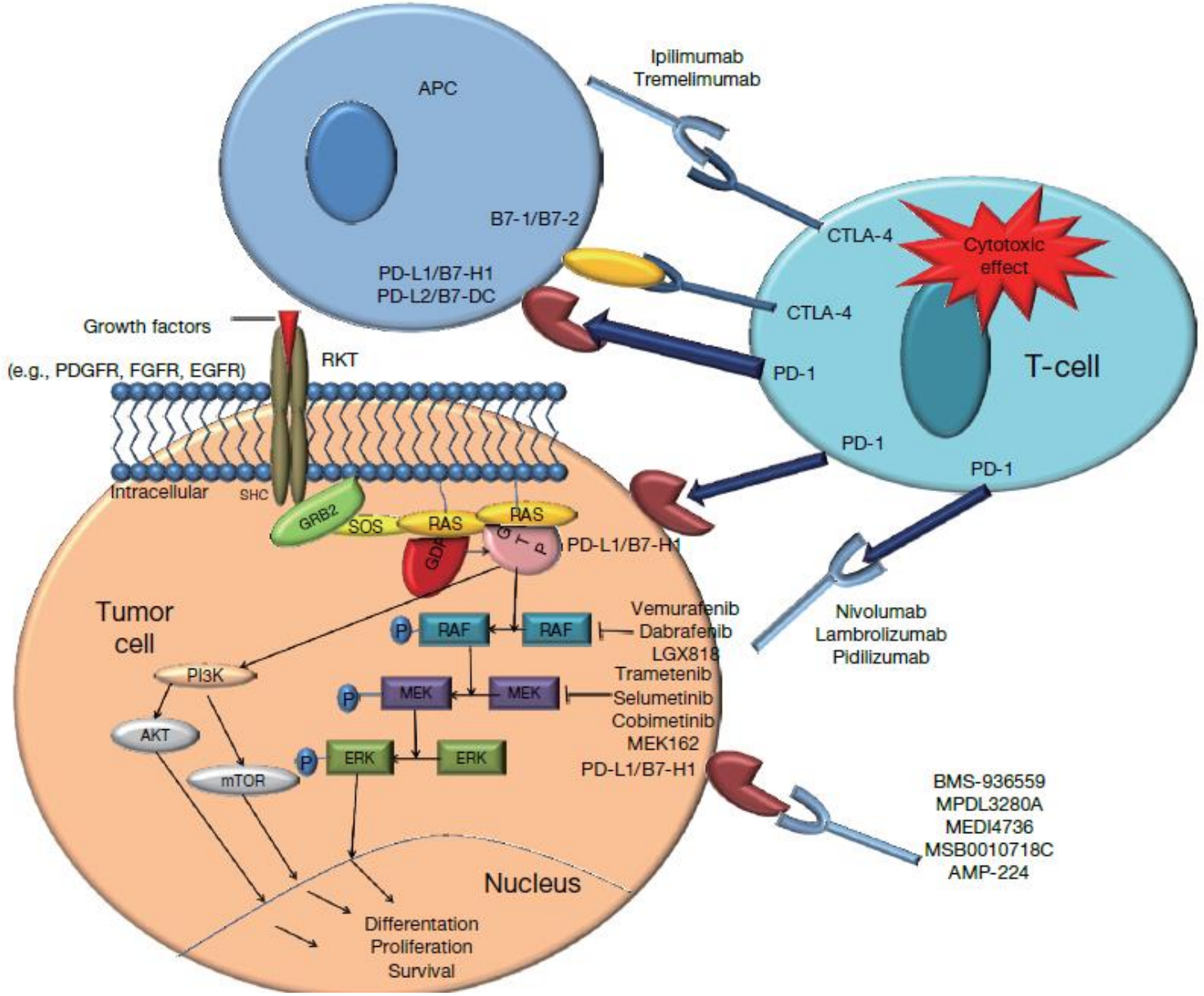

EGFR, HER2
GPCR
Cell Migration
raf
rac
rho
Proliferation
PIP2, PIP3
PH
PDK-1
PIP2, PIP3
PTEN
X
Proteasome
P
T308
PH
S473
P
p27
p21
Akt
Bcl-2
BAD
ASK-1
GSK3
CyclinD
mTOR
IKK
CREB
NF-KB
p53
4EBP-1
p70S6K
Gene expression
DNA-Damage
TRAIL
Anti-Apoptosis
VEGFR2
COX2
VEGF
Angiogenesis
endothelium
epithelium


MAY 28, 2001
TIME
THERE IS NEW AMMUNITION IN THE WAR AGAINST CANCER.
THESE ARE THE BULLETS.
Revolutionary new pills like GLIVEC combat cancer by targeting only the diseased cells. Is this the breakthrough we've been waiting for?
www.timeeurope.com AOL Keyword: TIME

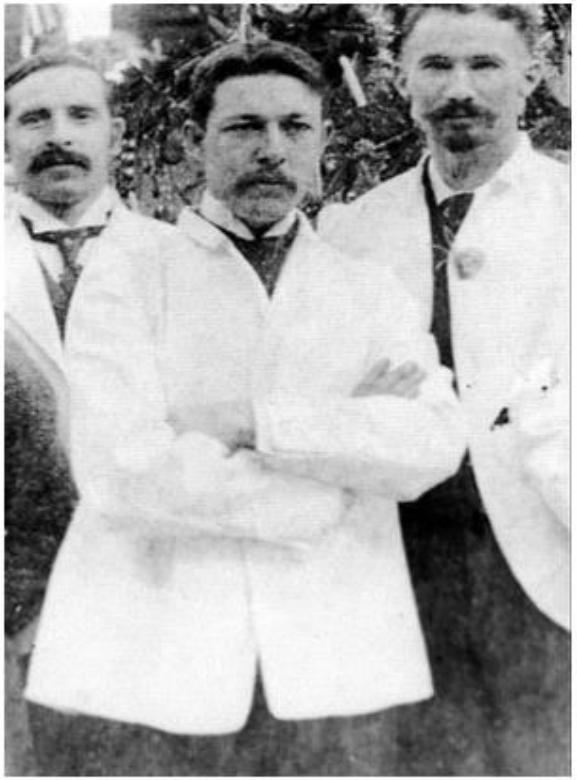

HOW TO BEAT AN INSANE MARKET
NEW DIGITAL TELEVISIONS
Which Ones Are The Best For Your Money
www.forbes.com
Forbes
She was 18 and dying of lung cancer. This pill saved her life—but failed to help almost everyone else. Should it be approved?
MIRACLE PILL
ALSO
COMPANIES THAT KNOW EVERYTHING ABOUT YOU
THE RICHEST PEOPLE IN CHINA
DIVIDEND HEIST: WHEN COMPANIES WANT THEM BACK

Personalized Cancer Therapy




APC
B7-1/B7-2
PD-L1/B7-H1
PD-L2/B7-DC
Ipilimumab
Tremelimumab
CTLA-4
Cytotoxic effect
CTLA-4
PD-1
T-cell
PD-1
PD-1
Growth factors
(e.g., PDGFR, FGFR, EGFR)
RKT
Intracellular
SHC
GRB2
SOS
RAS
RAS
GDP
GTP
PD-L1/B7-H1
Tumor cell
P
RAF
RAF
Vemurafenib
Dabrafenib
LGX818
PI3K
P
MEK
MEK
Trametenib
Selumetinib
Cobimetinib
MEK162
AKT
P
ERK
ERK
mTOR
PD-L1/B7-H1
Nivolumab
Lambrolizumab
Pidilizumab
BMS-936559
MPDL3280A
MEDI4736
MSB0010718C
AMP-224
Nucleus
Differentation
Proliferation
Survival

William Coley and the birth of cancer immunotherapy



New York Times - July 29, 1908

ERYSIPELAS GERMS AS CURE FOR CANCER

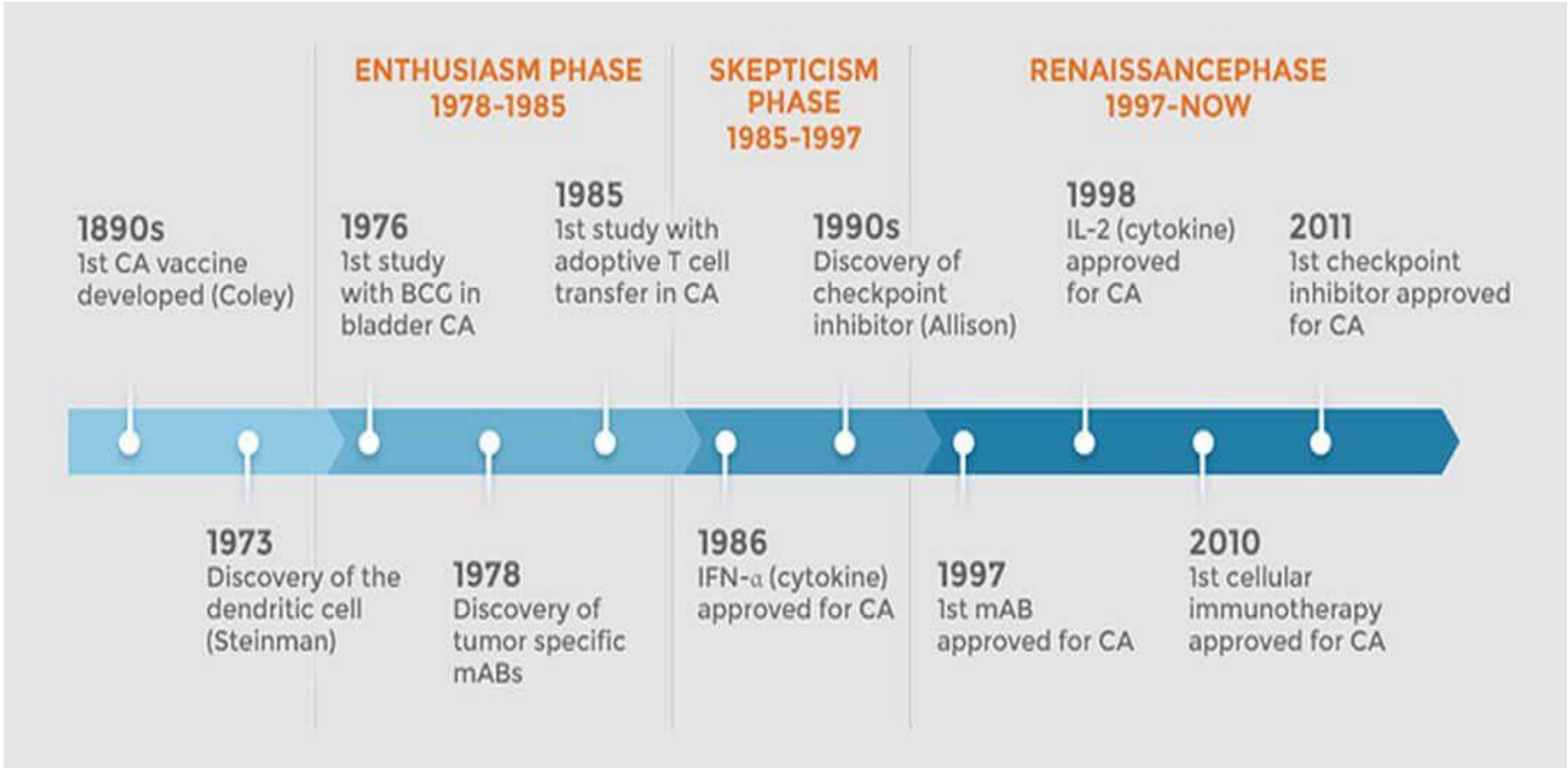
Dr. Coley's Remedy of Mixed Toxins Makes One Disease Cast Out the Other.

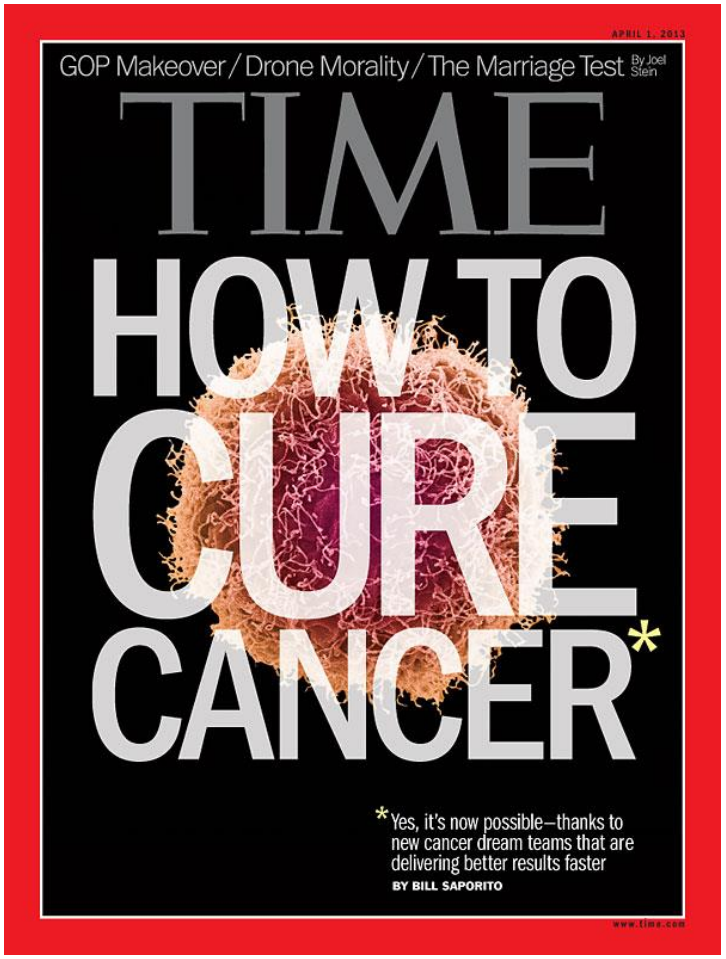
MANY CASES CURED HERE

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-

Elie Metchnikoff & Paul Ehrlich won the Nobel Prize 3 months later


ENTHUSIASM PHASE
1978-1985
SKEPTICISM PHASE
1985-1997
RENAISSANCEPHASE
1997-NOW
1890s
1st CA vaccine developed (Coley)
1973
Discovery of the dendritic cell (Steinman)
1976
1st study with BCG in bladder CA
1978
Discovery of tumor specific mABs
1985
1st study with adoptive T cell transfer in CA
1986
IFN-α (cytokine) approved for CA
1990s
Discovery of checkpoint inhibitor (Allison)
1997
1st mAB approved for CA
1998
IL-2 (cytokine) approved for CA
2010
1st cellular immunotherapy approved for CA
2011
1st checkpoint inhibitor approved for CA



CURING CANCER with IMMUNO THERAPY

How it happened a century ago,

What we learned as we attempted it, and

Why it is possible today.

RENE CHEE, PhD & EDWARD CHEE, MS

APRIL 4, 2016

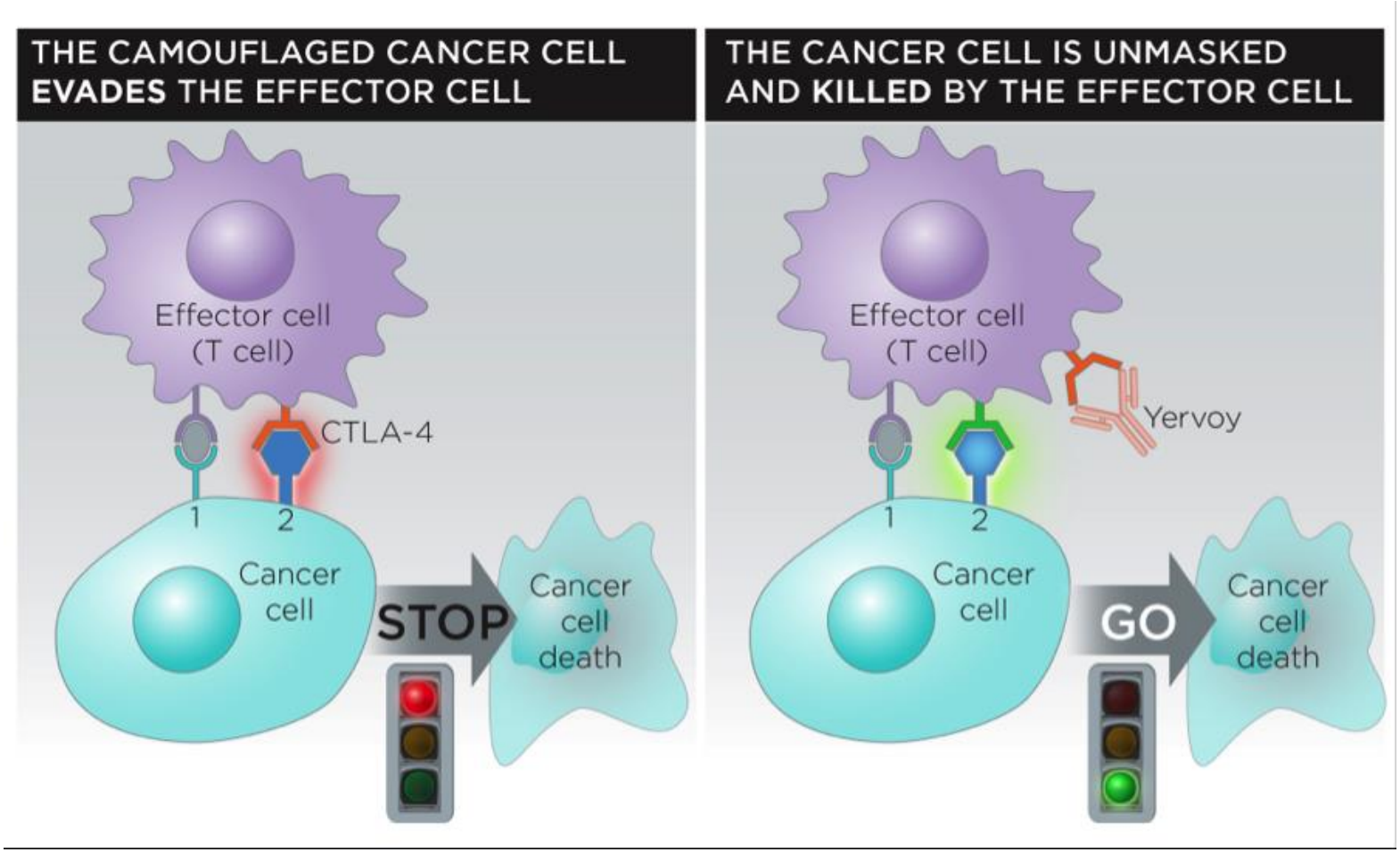
TIME

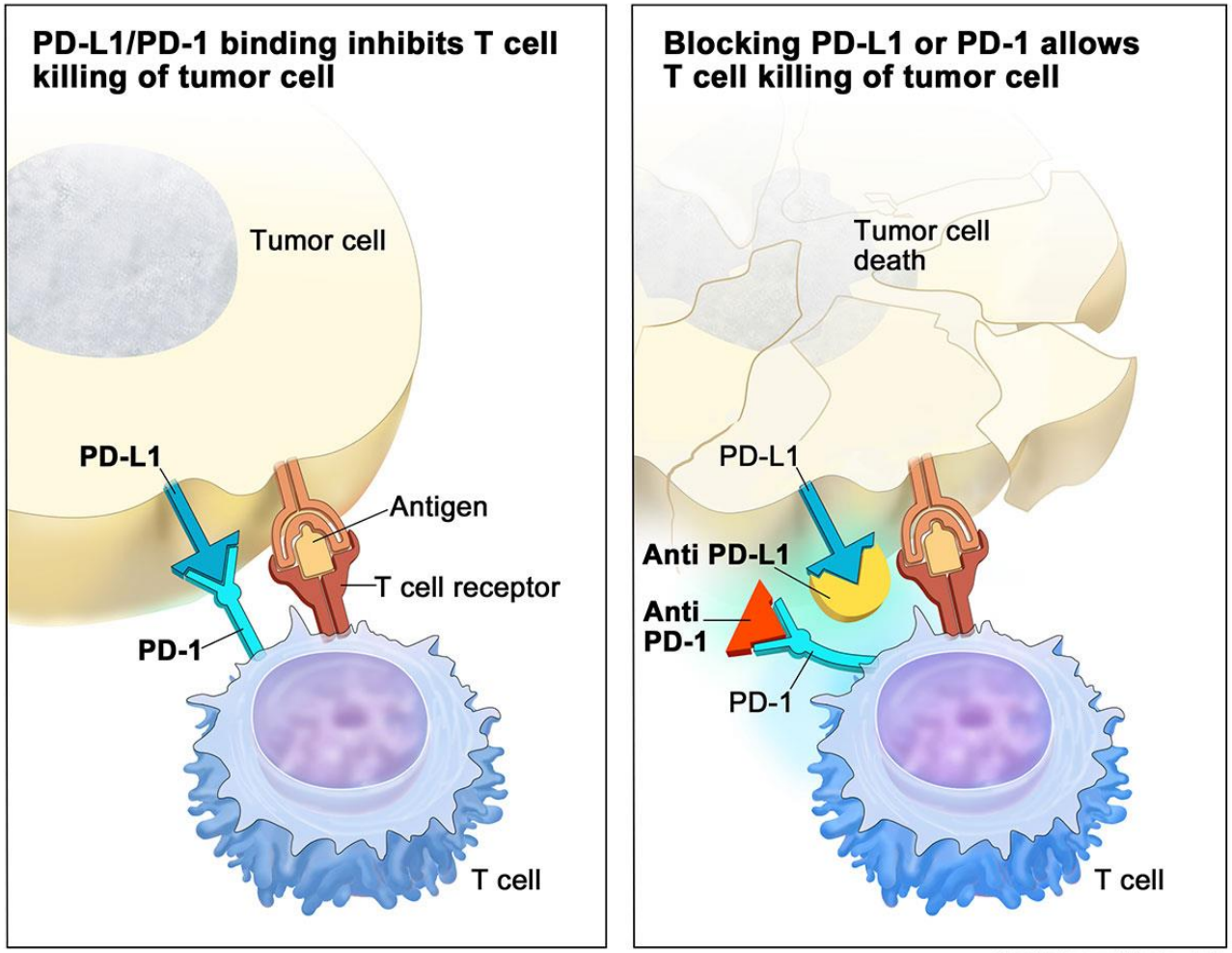
What if your immune system could be taught to kill cancer?

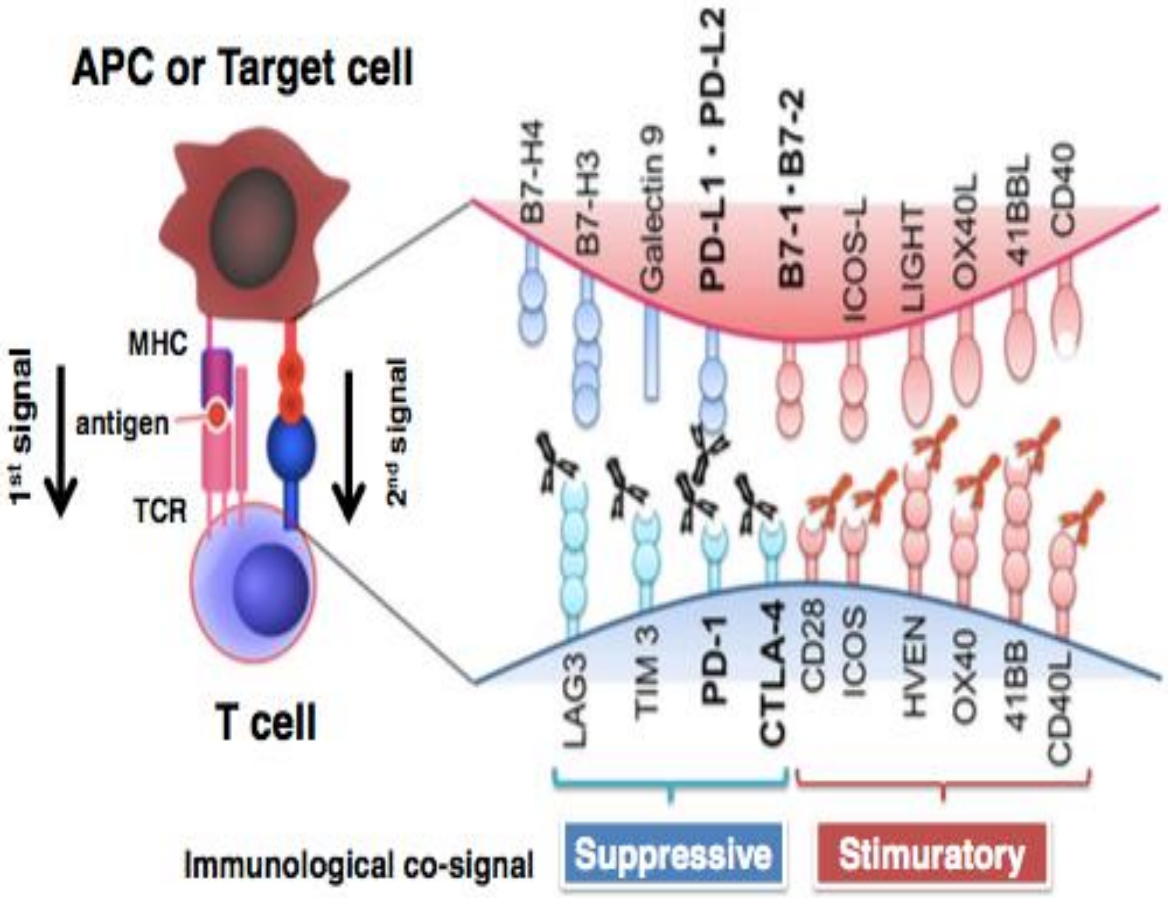
Inside the brutally selective, hugely expensive, lifesaving trials of immunotherapy.

By Alice Park

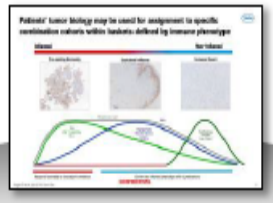
time.com

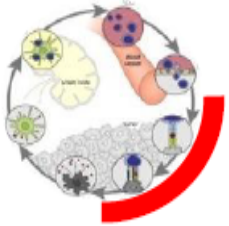
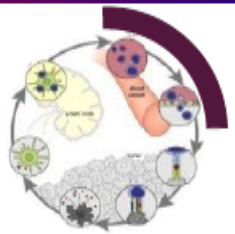
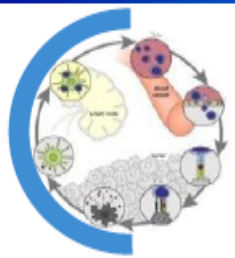

THE CAMOUFLAGED CANCER CELL
EVADES THE EFFECTOR CELL
Effector cell
(T cell)
CTLA-4
1
2
Cancer
cell
STOP
Cancer
cell
death
THE CANCER CELL IS UNMASKED
AND KILLED BY THE EFFECTOR CELL
Effector cell
(T cell)
Yervoy
1
2
Cancer
cell
GO
Cancer
cell
death



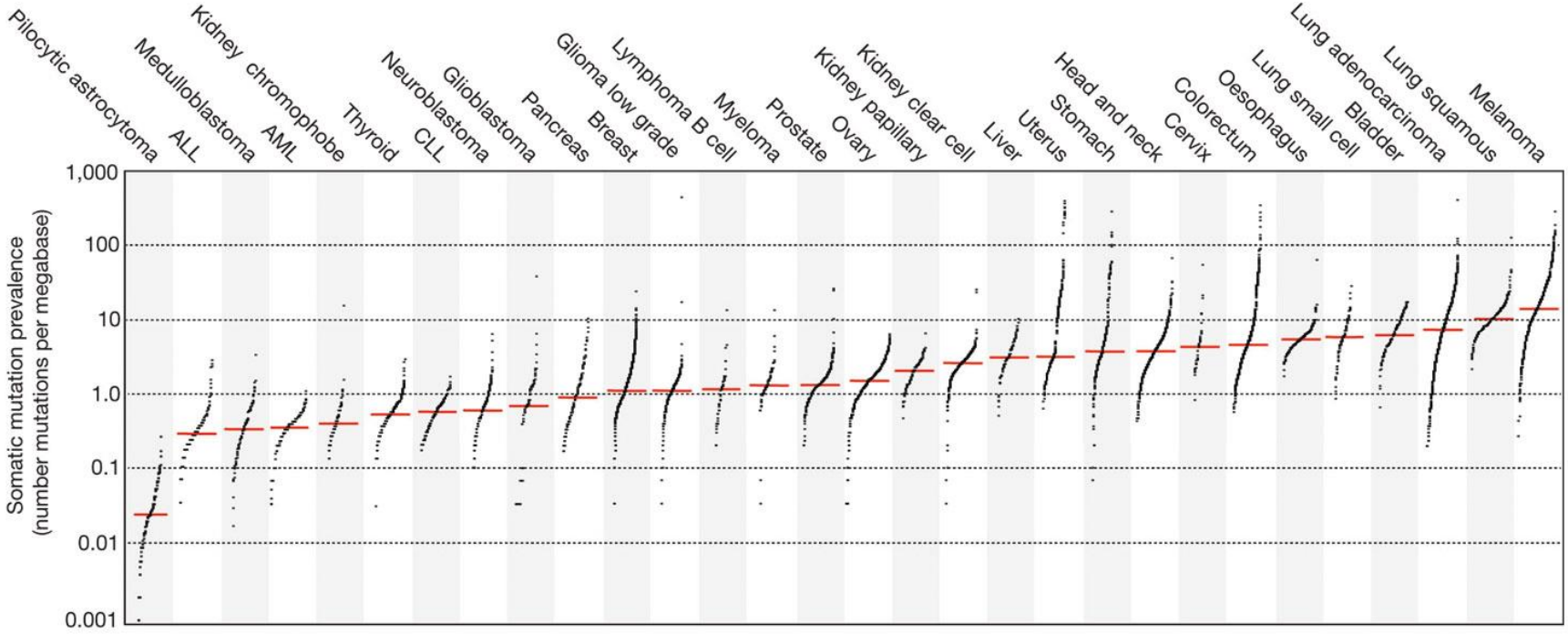

APC or Target cell
MHC
antigen
TCR
1st signal
2nd signal
T cell
B7-H4
B7-H3
Galectin 9
PD-L1 • PD-L2
B7-1 • B7-2
ICOS-L
LIGHT
OX40L
41BBL
CD40
LAG3
TIM 3
PD-1
CTLA-4
CD28
ICOS
HVEN
OX40
41BB
CD40L
Immunological co-signal
Suppressive
Stimuratory

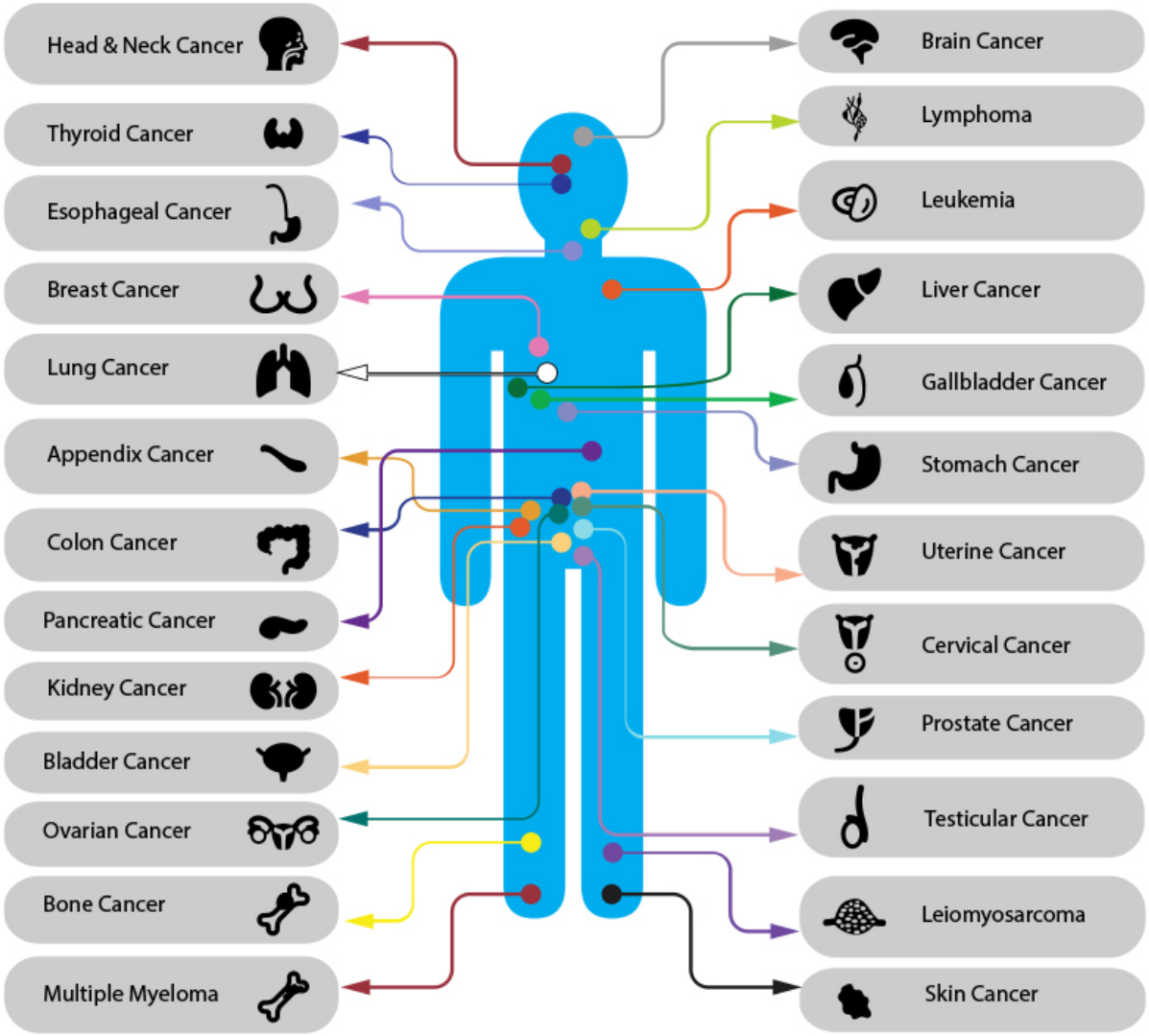
Targeting Treatment Options to Different Cancer Immune Phenotypes



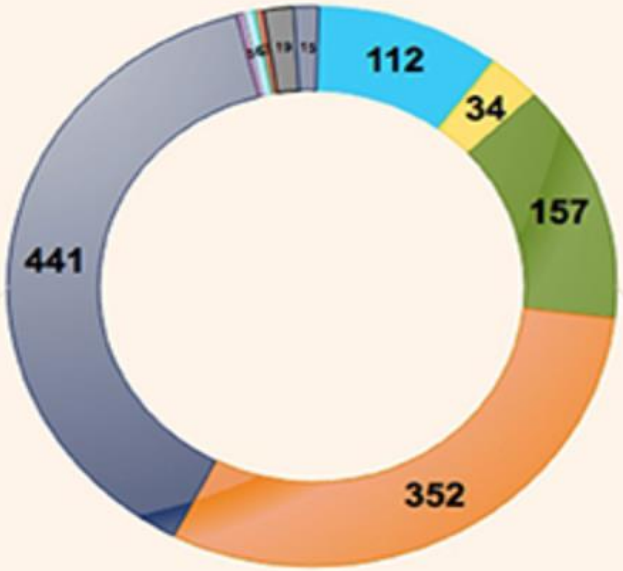
Inflamed	Immune Excluded	Immune Desert
Melanoma Lung Bladder RCC	TNBC Colorectal Gastric Pancreatic	Ovarian Prostate
		
CD8+ T cells infiltrated, but non-functional	CD8+ T cells accumulated but not efficiently infiltrated	CD8+ T cells absent from tumor and periphery
Accelerate or remove brakes on T-cell response	Bring T-cells in contact with cancer cells	Increase number of antigen-specific T-cells or increase antigen presentation
aTIGIT, aCSF-1R	aCXCR4, TCBs	MEKi, FAP IL-2v, aVEGF, chemo

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE


Pilocytic astrocytoma
ALL
Medulloblastoma
AML
Kidney chromophobe
Thyroid
CLL
Neuroblastoma
Glioblastoma
Pancreas
Breast
Glioma low grade
Lymphoma B cell
Myeloma
Prostate
Ovary
Kidney papillary
Kidney clear cell
Liver
Uterus
Stomach
Head and neck
Cervix
Colorectum
Oesophagus
Lung small cell
Bladder
Lung adenocarcinoma
Lung squamous
Melanoma
Somatic mutation prevalence
(number mutations per megabase)
1,000
100
10
1.0
0.1
0.01
0.001

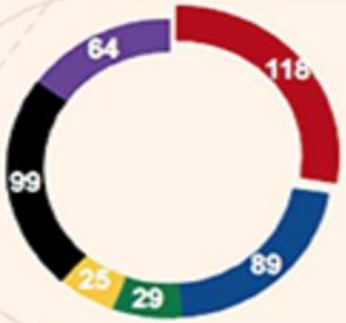

Head & Neck Cancer
Thyroid Cancer
Esophageal Cancer
Breast Cancer
Lung Cancer
Appendix Cancer
Colon Cancer
Pancreatic Cancer
Kidney Cancer
Bladder Cancer
Ovarian Cancer
Bone Cancer
Multiple Myeloma
Brain Cancer
Lymphoma
Leukemia
Liver Cancer
Gallbladder Cancer
Stomach Cancer
Uterine Cancer
Cervical Cancer
Prostate Cancer
Testicular Cancer
Leiomyosarcoma
Skin Cancer

Number of Clinical Trials of Checkpoint Inhibitors (PD-1/PDL-1)

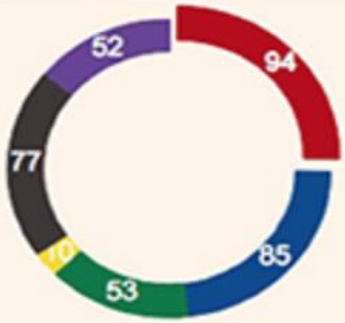


- Atezolizumab(AntiPD-L1)
- Avelumab (Anti PD-L1)
- Durvalumab(Anti PD-L1)
- Nivolumab (Anti PD-1)
- Pembrolizumab (Anti PD-1)
- Pidilizumab (Anti PD-1)
- REGN2810 (Anti PD-1)
- AMP-224 (Anti PD-1)
- MEDI0680 (Anti PD-1)
- PDR001 (Anti PD-1)
- CT-001 (Anti PD-1)

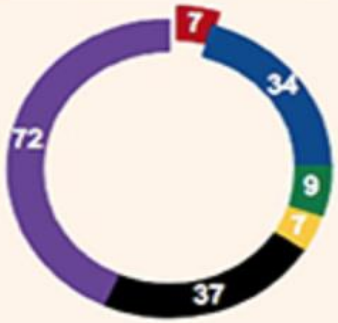
Pembrolizumab



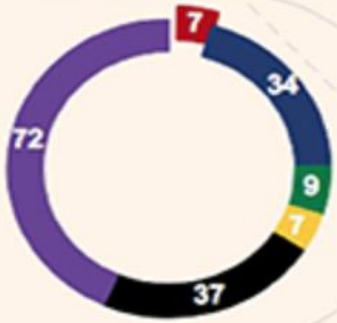
Nivolumab



MEDI4736



Atezolizumab



- Melanoma
- NSCLC
- RCC
- Urothelila Cancer
- solid tumor
- Advanced solid and hematological malignancies

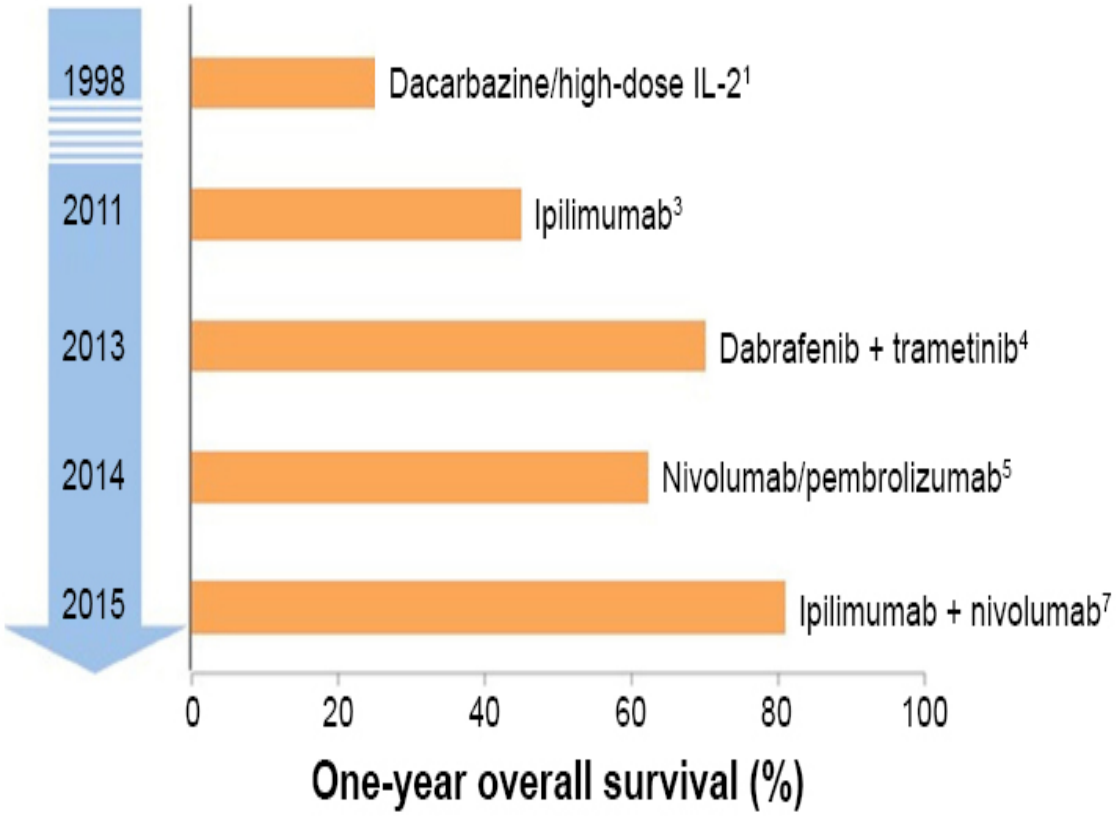
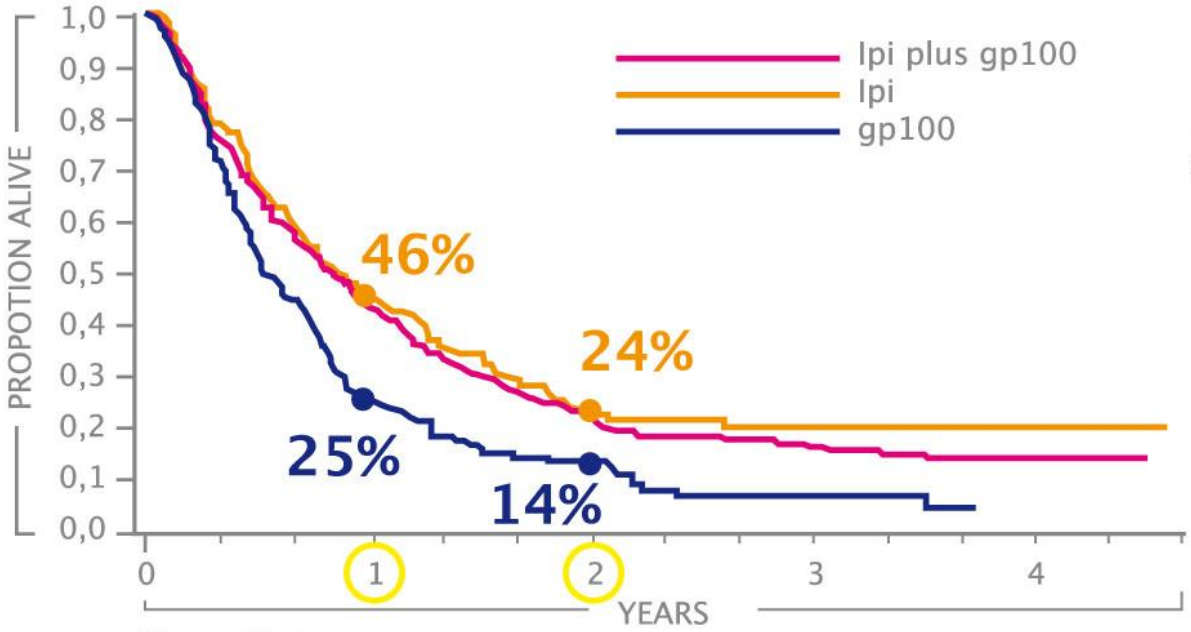


Figure 1 One-year overall survival for patients with advanced-stage melanoma.
Note: Data from previous studies.[1,3,4]



No. at Risk

Ipi plus gp100	403	297	223	163	115	81	54	42	33	24	17	7	6	4	0
Ipi	137	106	79	56	38	30	24	18	13	13	8	5	2	1	0
gp100	136	93	58	32	23	17	16	7	5	5	3	1	0	0	0

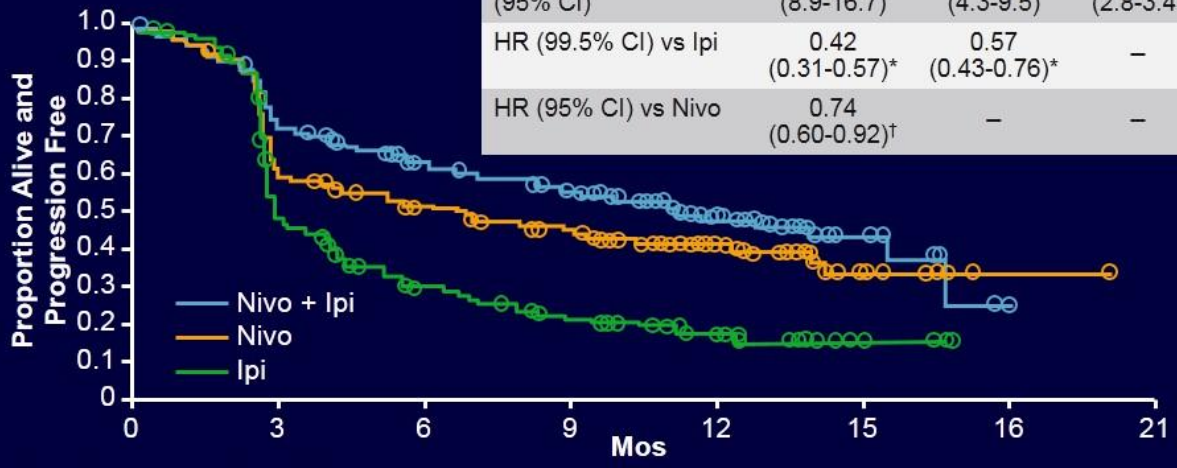
24% 2-YEAR
survival rate

Some patients were alive up to

4.5 YEARS

CheckMate 067: Improved PFS with Nivo + Ipi or Nivo Alone vs Ipi Alone

	Nivo + Ipi (n = 314)	Nivo (n = 316)	Ipi (n = 315)
Median PFS, mos (95% CI)	11.5 (8.9-16.7)	6.9 (4.3-9.5)	2.9 (2.8-3.4)
HR (99.5% CI) vs Ipi	0.42 (0.31-0.57)*	0.57 (0.43-0.76)*	–
HR (95% CI) vs Nivo	0.74 (0.60-0.92)†	–	–



*Stratified log-rank $P < .00001$ vs Ipi.

†Exploratory endpoint. Study not powered to detect a statistical difference between Nivo + Ipi and Nivo.

Wolchok JD, et al. ASCO 2015. Abstract LBA1. *Reprinted with permission.*

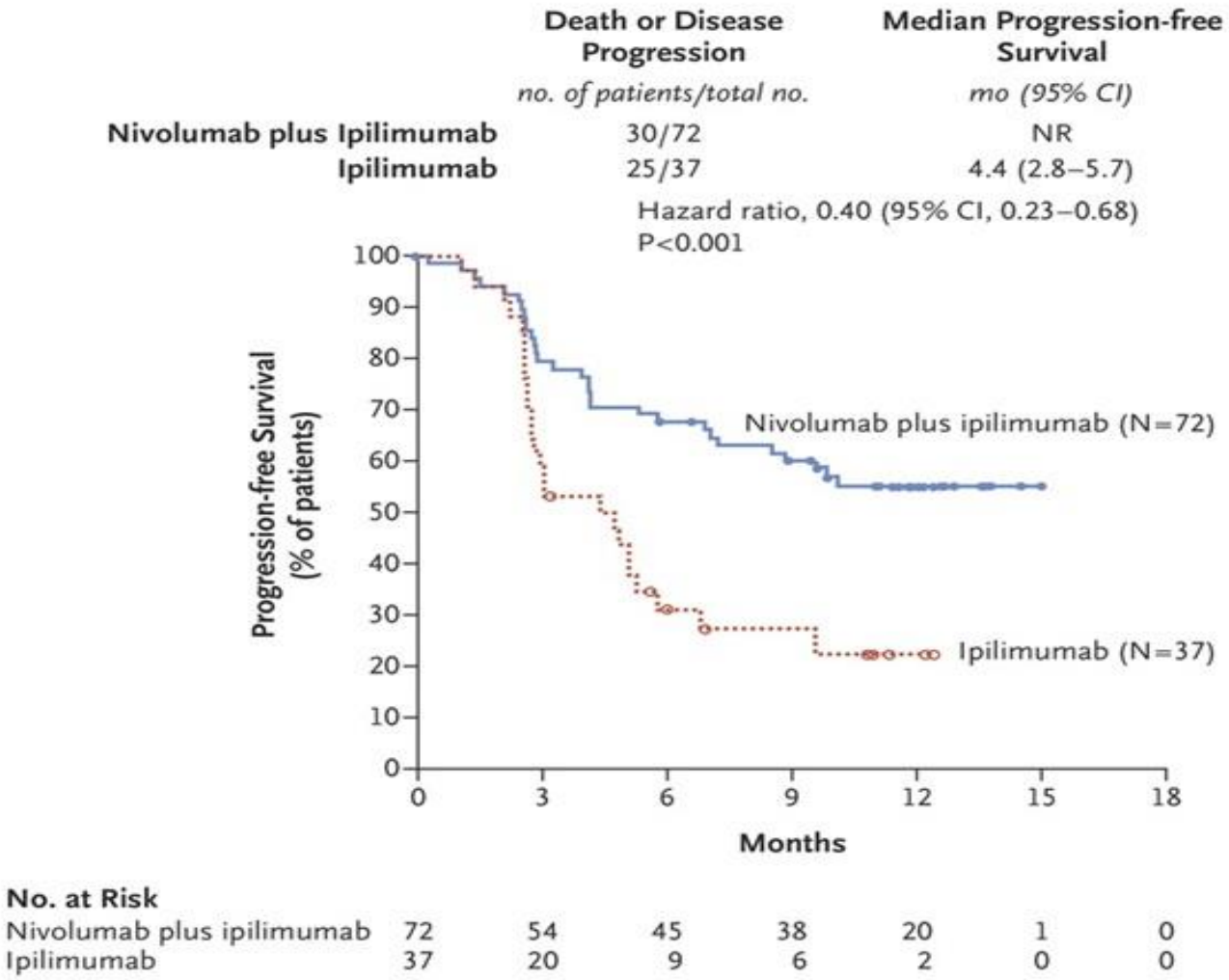


Image taken from: Postow MA et al. N Engl J Med 2015.
DOI: 10.1056/NEJMoa1414428

Adjuvant Ipilimumab

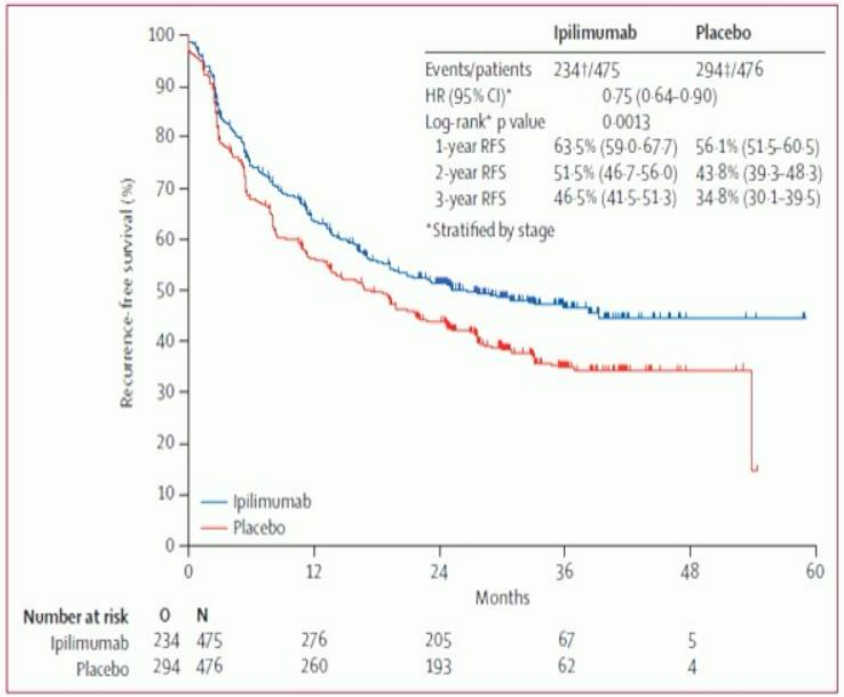


Figure 2: **Kaplan-Meier curves of recurrence-free survival, as assessed by IRC**

RFS=recurrence-free survival. IRC=independent review committee. O=observed number of events (recurrence or death). N=number of patients. *We compared the RFS distributions of the treatment groups with a log-rank test at a two-sided alpha level of 0·05, stratified by stage as indicated at randomisation. †Type of RFS event: locoregional recurrence (n=87), distant metastasis or death due to melanoma (n=138), death due to another cause or unknown cause (n=9). ‡Type of RFS event: locoregional recurrence (n=106), distant metastasis or death due to melanoma (n=186), death due to another cause or unknown cause (n=2).

Eggermont et al. Lancet Oncol 2015

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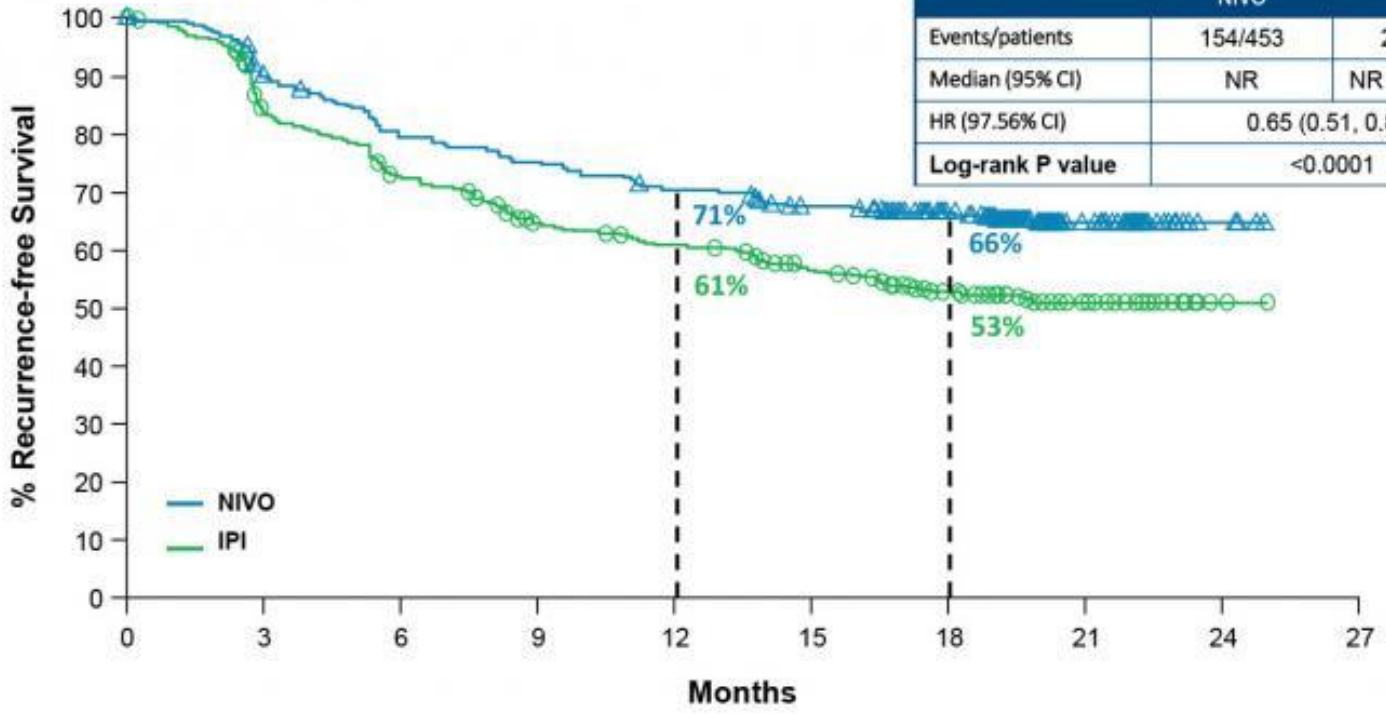
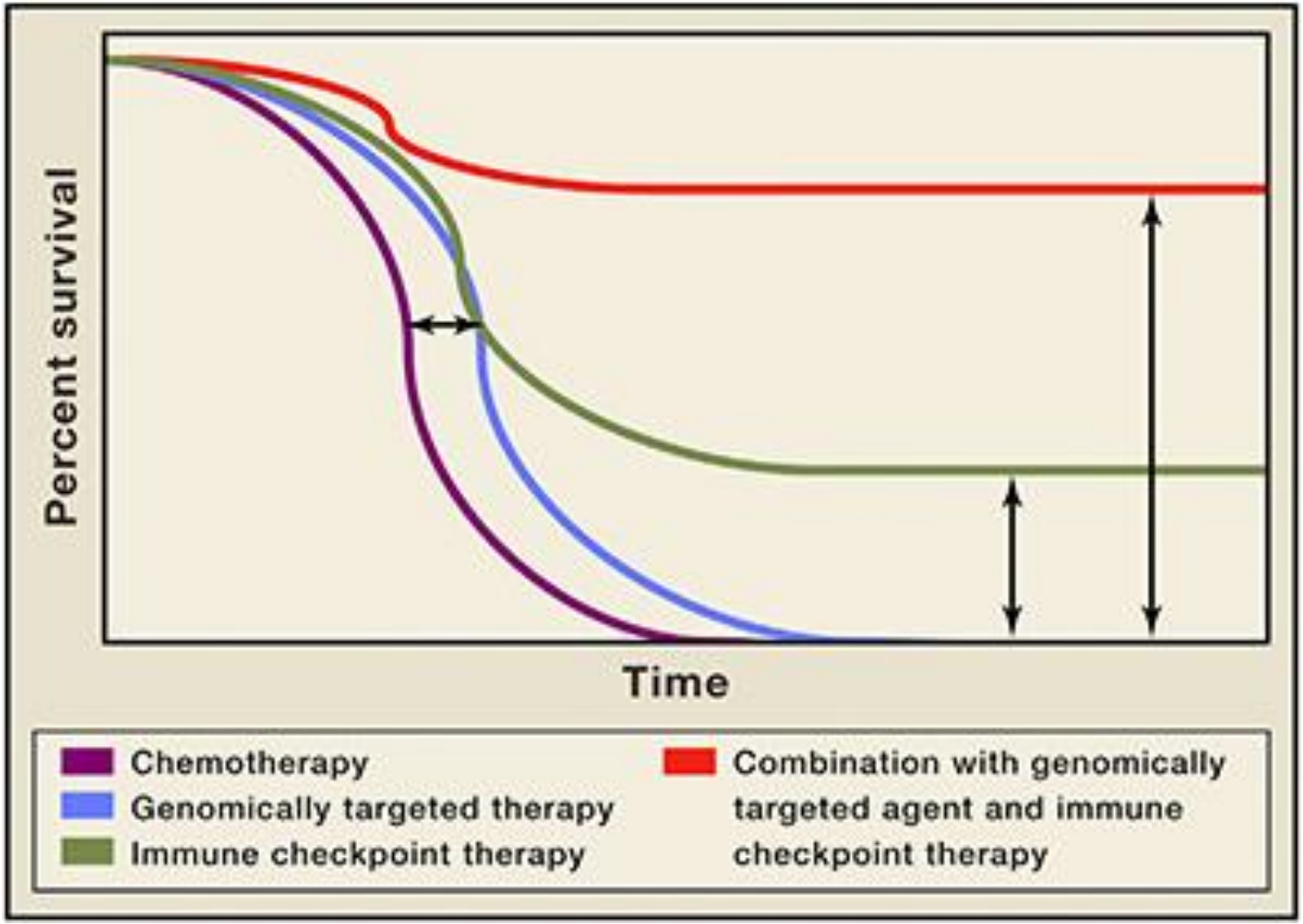
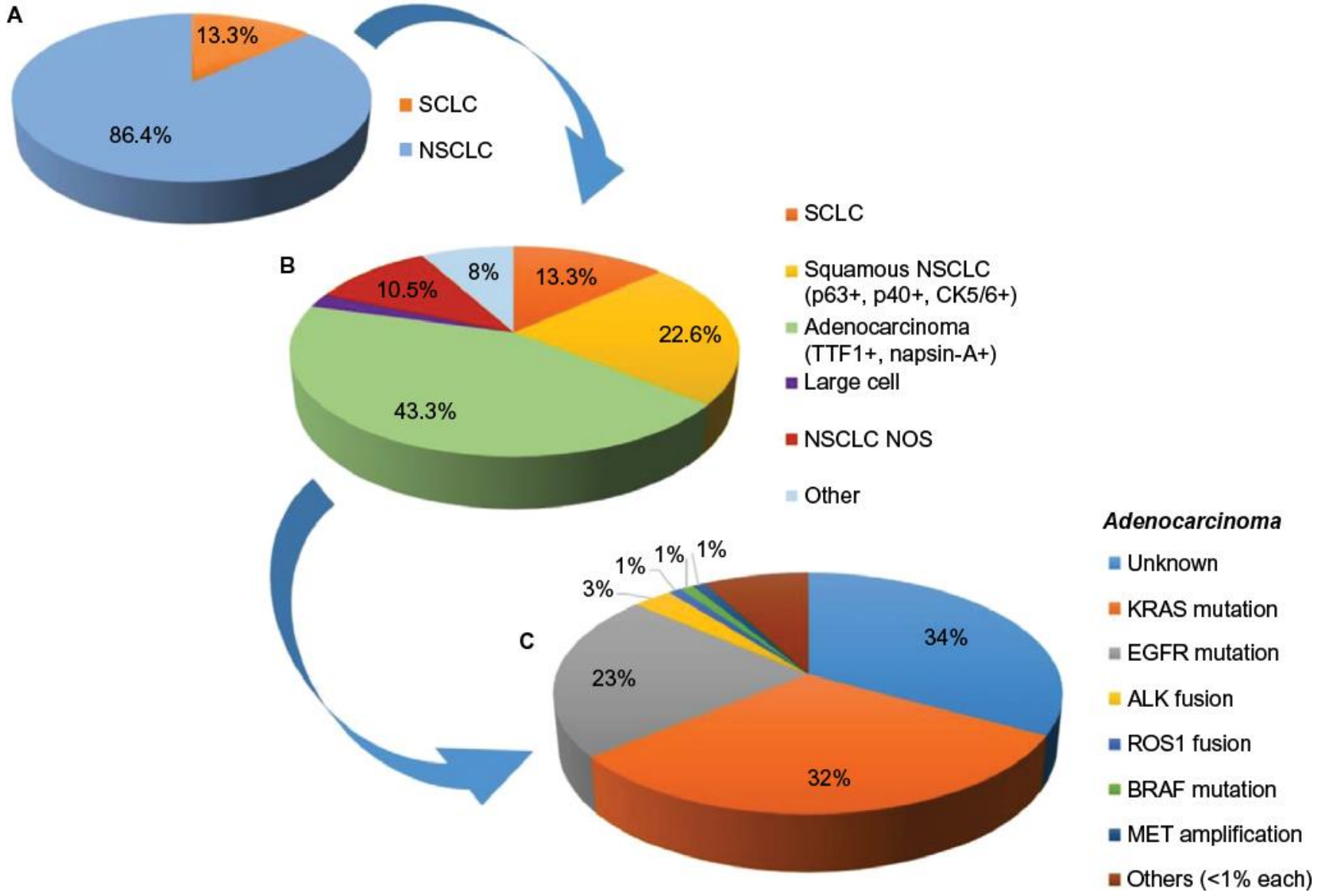


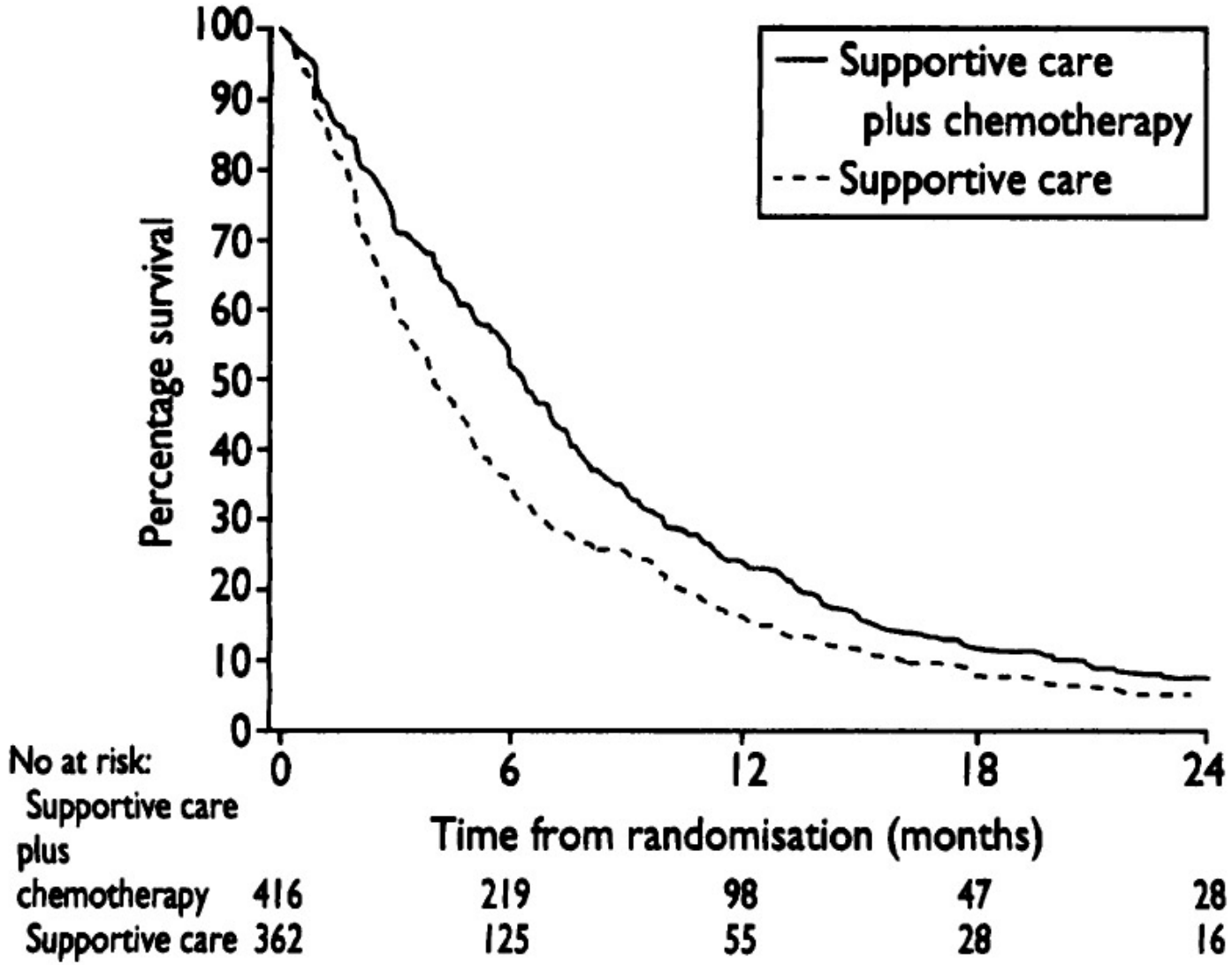
	NIVO	IPI
Events/patients	154/453	206/453
Median (95% CI)	NR	NR (16.6, NR)
HR (97.56% CI)	0.65 (0.51, 0.83)	
Log-rank P value	<0.0001	

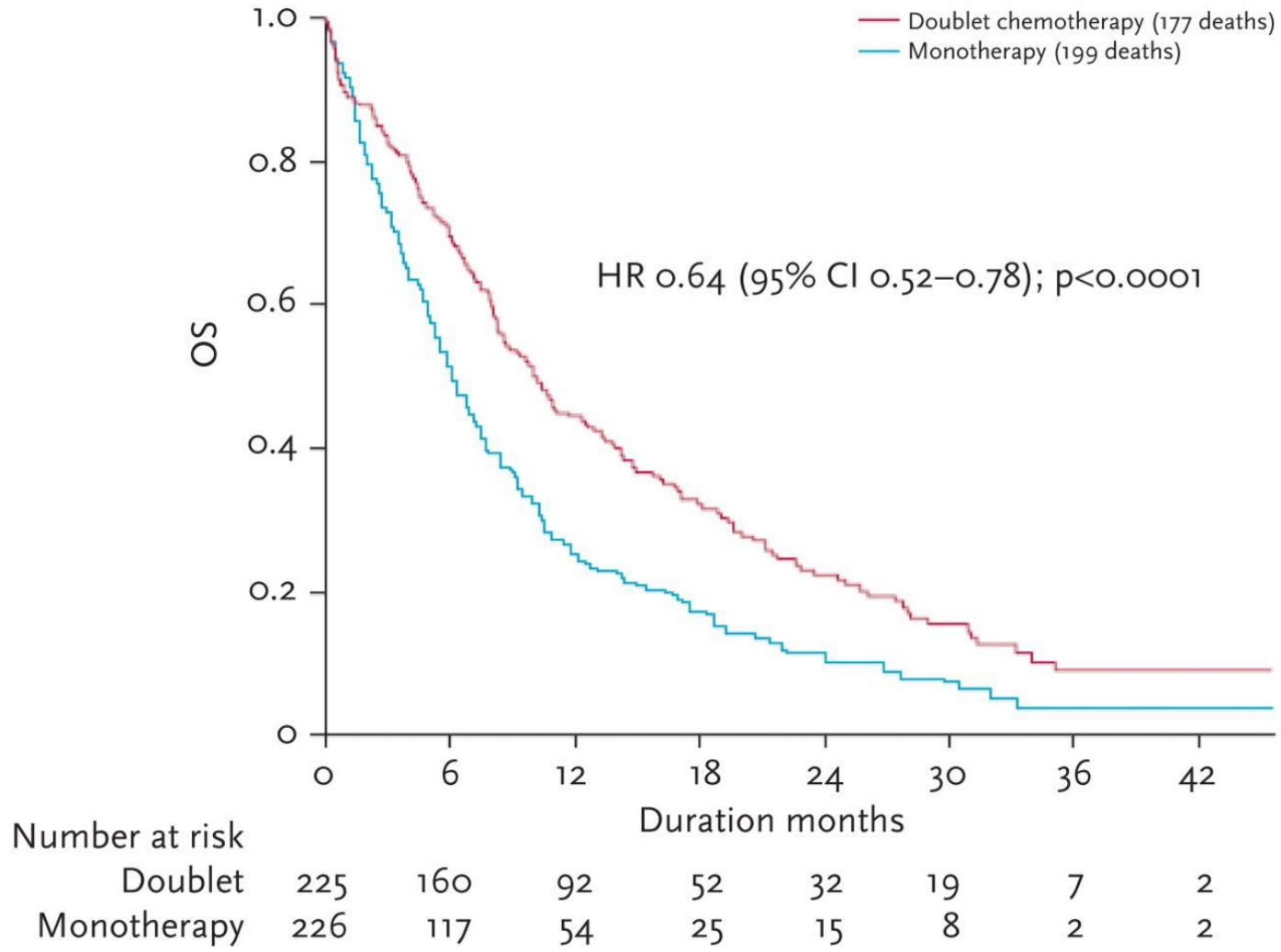
Number of patients at risk

NIVO	453	399	353	332	311	291	249	71	5	0
IPI	453	364	314	269	252	225	184	56	2	0

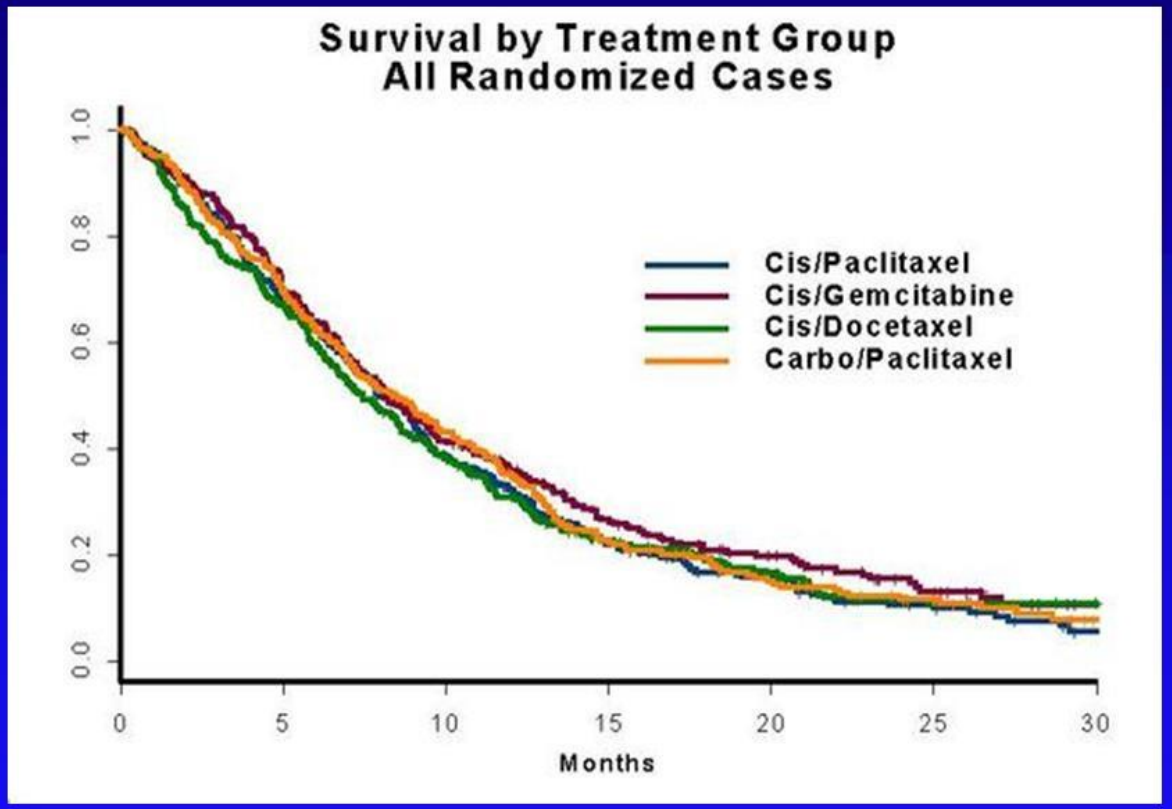

Percent survival
Time
Chemotherapy
Genomically targeted therapy
Immune checkpoint therapy
Combination with genomically targeted agent and immune checkpoint therapy


A
13.3%
86.4%
SCLC
NSCLC
B
8%
13.3%
10.5%
22.6%
43.3%
SCLC
Squamous NSCLC (p63+, p40+, CK5/6+)
Adenocarcinoma (TTF1+, napsin-A+)
Large cell
NSCLC NOS
Other
C
1%
1%
1%
3%
34%
23%
32%
Adenocarcinoma
Unknown
KRAS mutation
EGFR mutation
ALK fusion
ROS1 fusion
BRAF mutation
MET amplification
Others (<1% each)

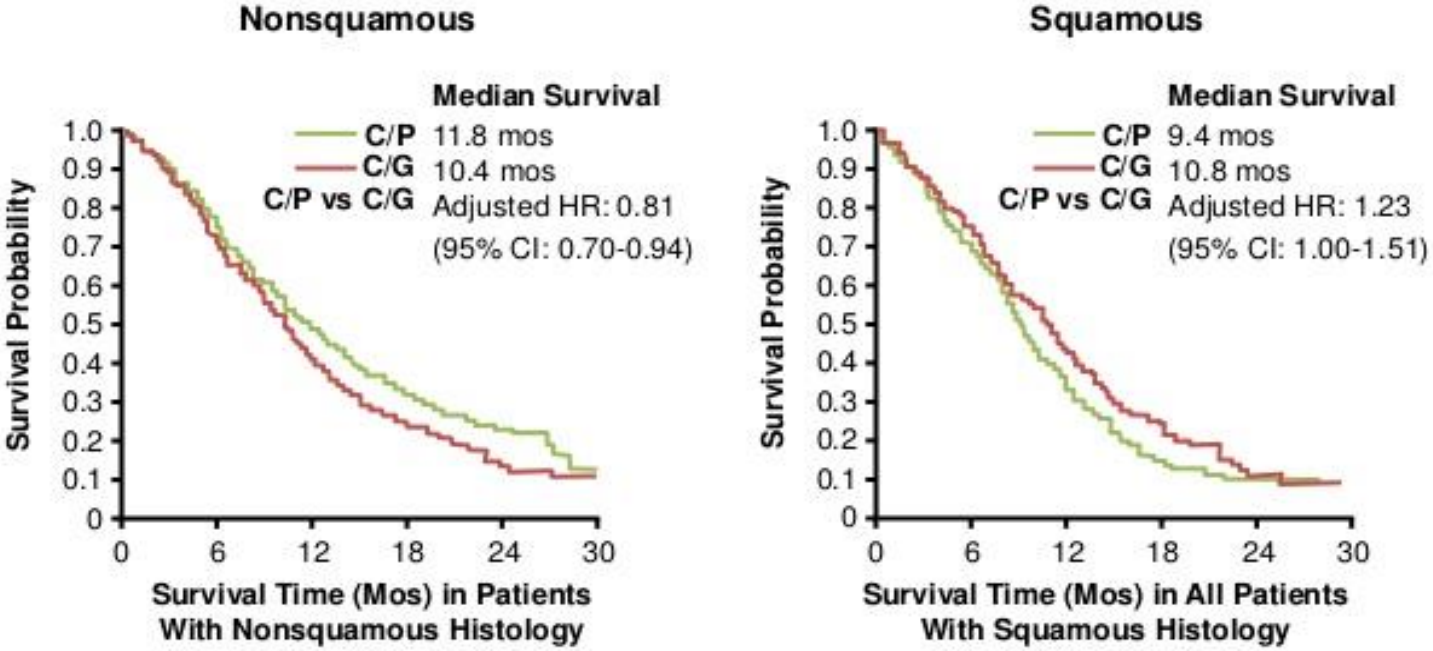

Supportive care plus chemotherapy
Supportive care
Percentage survival
100
90
80
70
60
50
40
30
20
10
0
0
6
12
18
24
Time from randomisation (months)
No at risk:
Supportive care plus chemotherapy 416 219 98 47 28
Supportive care 362 125 55 28 16


Doublet chemotherapy (177 deaths)
Monotherapy (199 deaths)
HR 0.64 (95% CI 0.52–0.78); p<0.0001
OS
1.0
0.8
0.6
0.4
0.2
0
0
6
12
18
24
30
36
42
Duration months
Number at risk
Doublet 225 160 92 52 32 19 7 2
Monotherapy 226 117 54 25 15 8 2 2

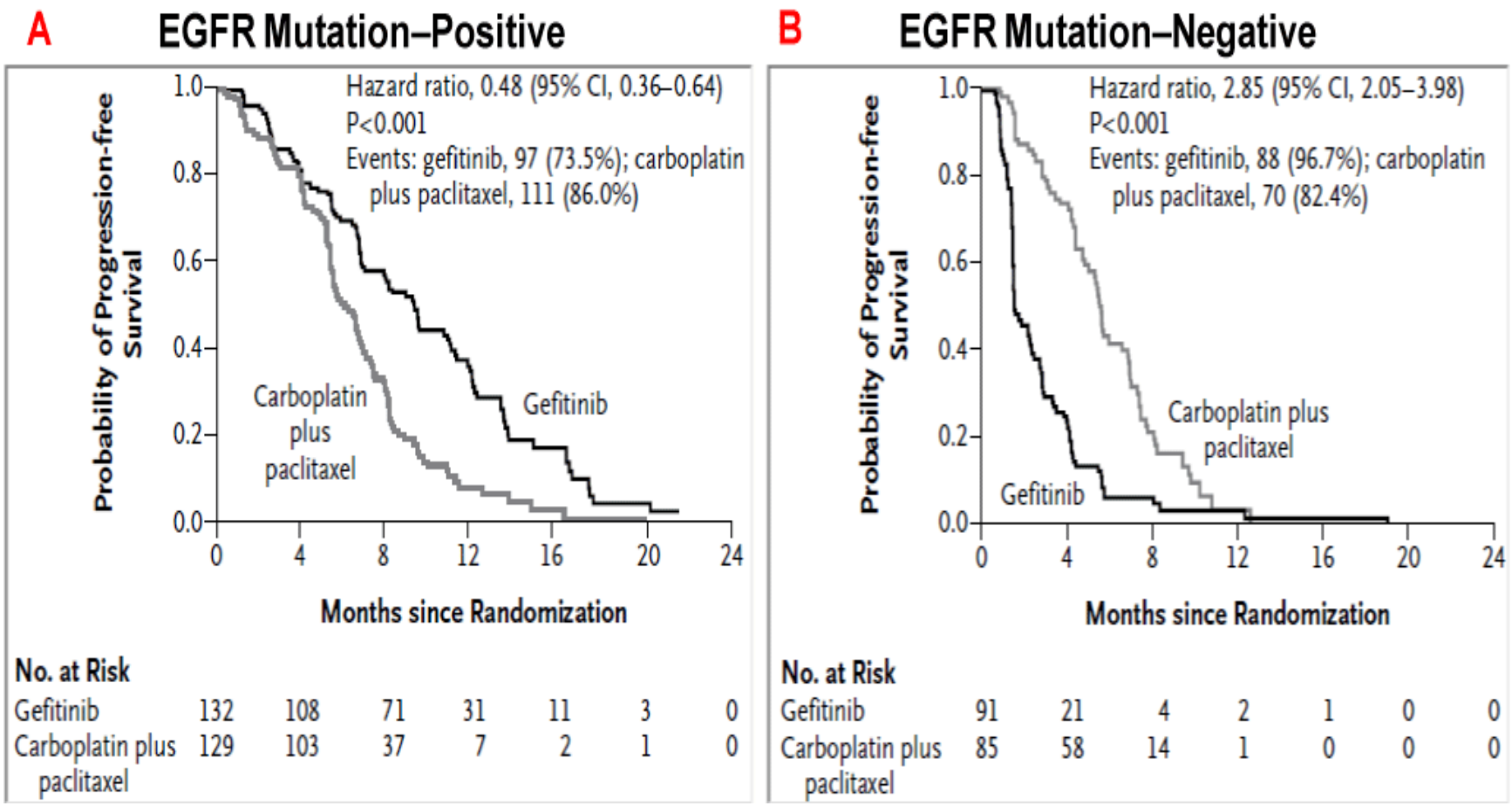
ECOG 1594: Overall Survival by Treatment Group



Cisplatin + Pemetrexed (C/P) vs Cisplatin + Gemcitabine (C/G) in Advanced NSCLC: OS by Histology



Scagliotti GV, et al. J Clin Oncol. 2008;26:3543-3551.


A
EGFR Mutation–Positive
Hazard ratio, 0.48 (95% CI, 0.36–0.64)
P<0.001
Events: gefitinib, 97 (73.5%); carboplatin plus paclitaxel, 111 (86.0%)
Probability of Progression-free Survival
1.0
0.8
0.6
0.4
0.2
0.0
Carboplatin plus paclitaxel
Gefitinib
0
4
8
12
16
20
24
Months since Randomization
No. at Risk
Gefitinib 132 108 71 31 11 3 0
Carboplatin plus paclitaxel 129 103 37 7 2 1 0
B
EGFR Mutation–Negative
Hazard ratio, 2.85 (95% CI, 2.05–3.98)
P<0.001
Events: gefitinib, 88 (96.7%); carboplatin plus paclitaxel, 70 (82.4%)
Probability of Progression-free Survival
1.0
0.8
0.6
0.4
0.2
0.0
Carboplatin plus paclitaxel
Gefitinib
0
4
8
12
16
20
24
Months since Randomization
No. at Risk
Gefitinib 91 21 4 2 1 0 0
Carboplatin plus paclitaxel 85 58 14 1 0 0 0

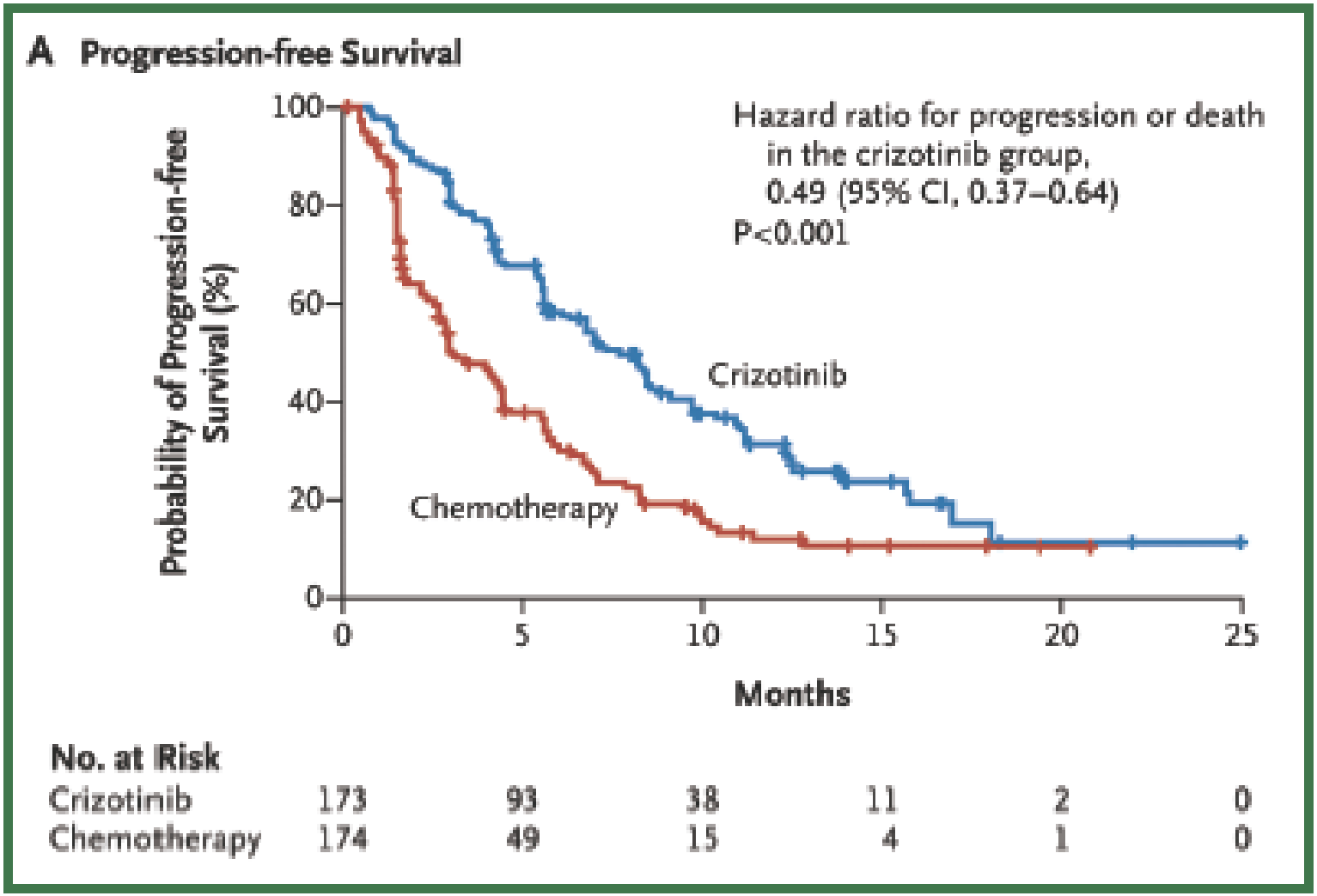
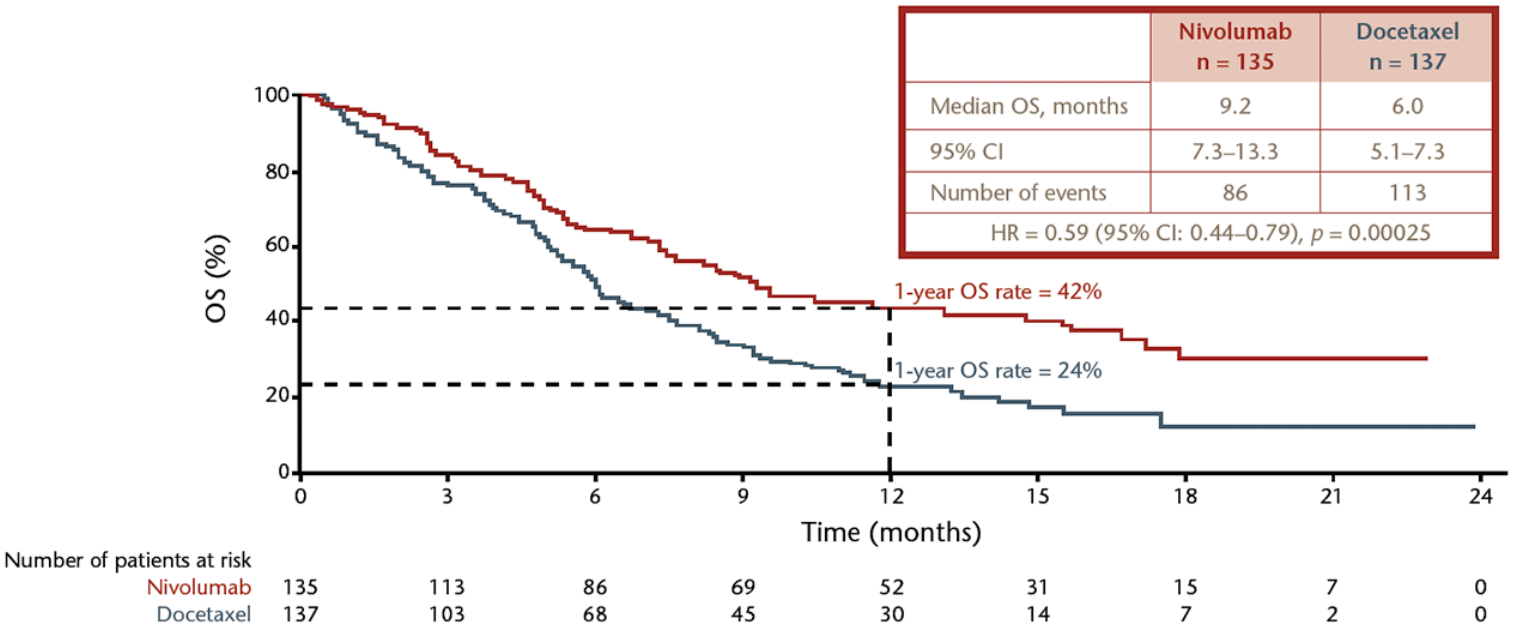
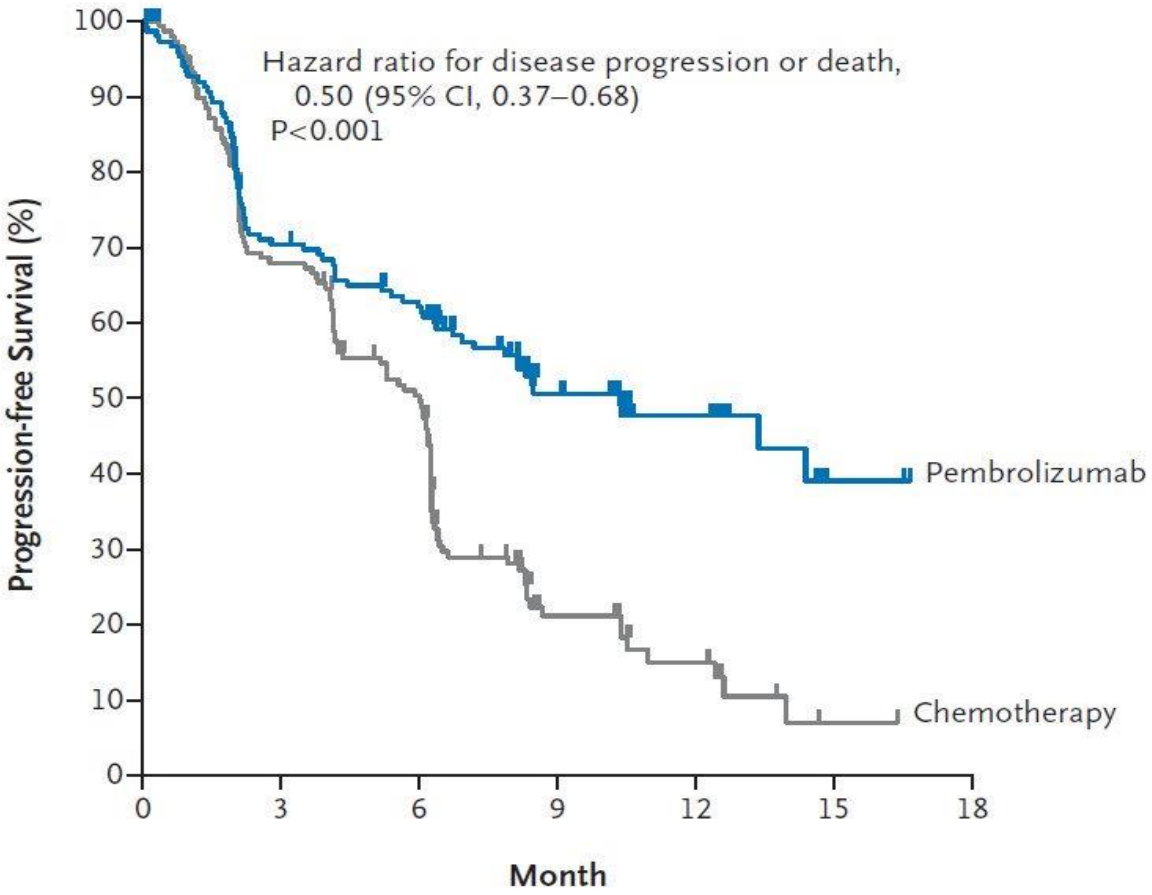

A Progression-free Survival
Probability of Progression-free Survival (%)
100
80
60
40
20
0
Hazard ratio for progression or death in the crizotinib group, 0.49 (95% CI, 0.37–0.64)
P<0.001
Crizotinib
Chemotherapy
0
5
10
15
20
25
Months
No. at Risk
Crizotinib 173 93 38 11 2 0
Chemotherapy 174 49 15 4 1 0

Figure 1. Overall survival

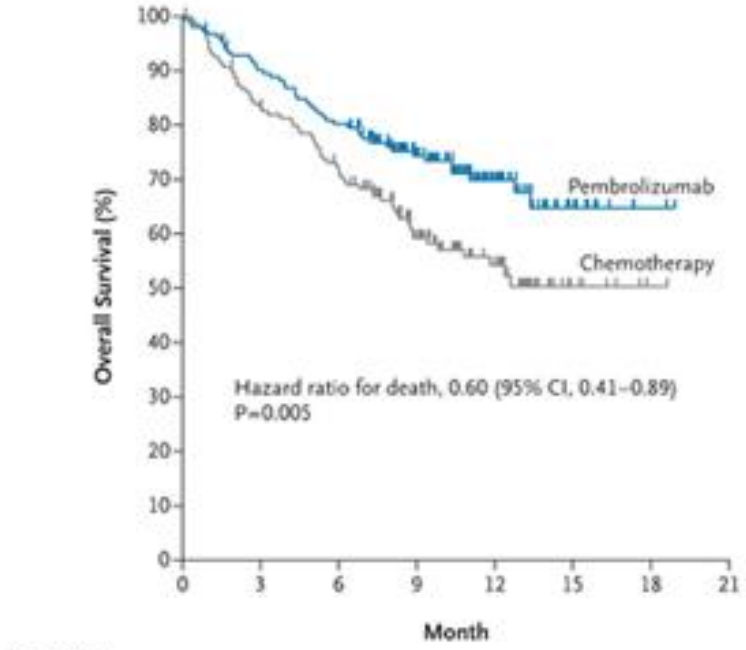


CI = confidence interval; HR = hazard ratio; OS = overall survival

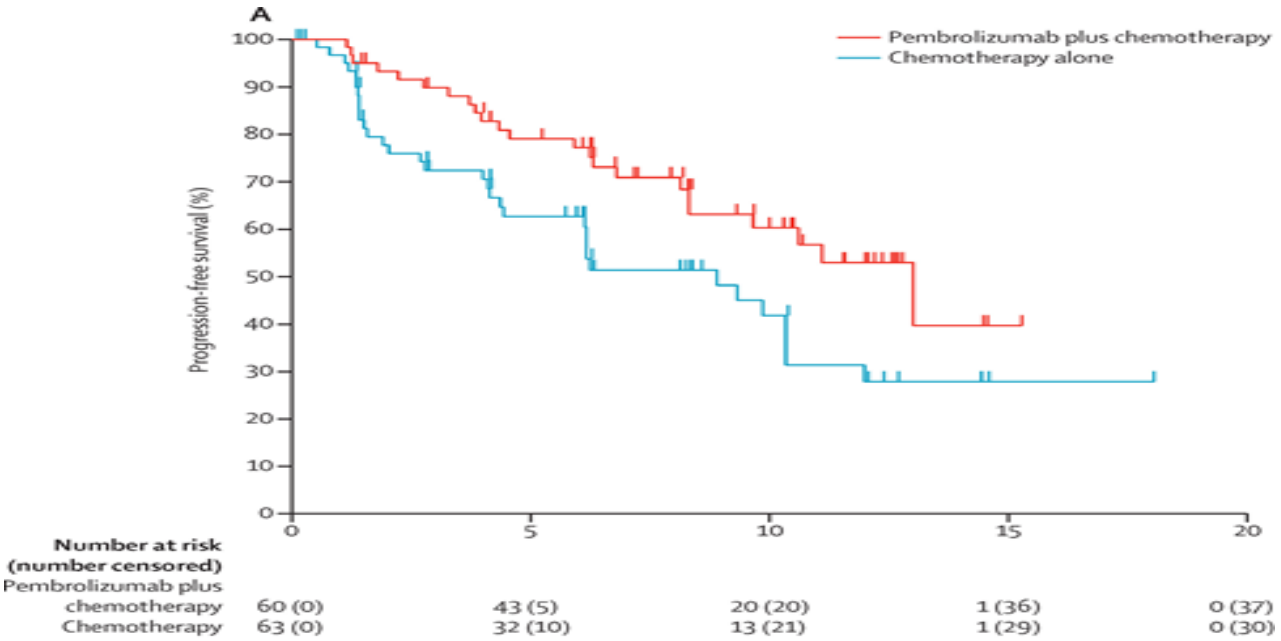


No. at Risk							
Pembrolizumab	154	104	89	44	22	3	1
Chemotherapy	151	99	70	18	9	1	0

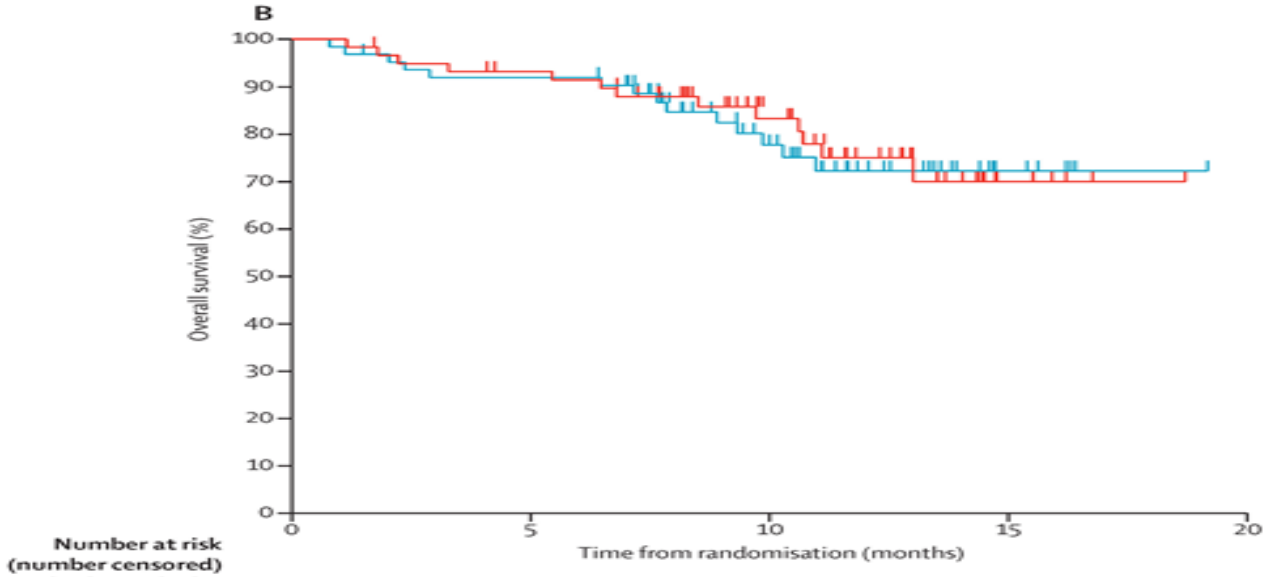
First-Line Pembrolizumab: 024 OS



From N Engl J Med, Reck M, et al., Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer, 375., 1823-1833. Copyright ©2016 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

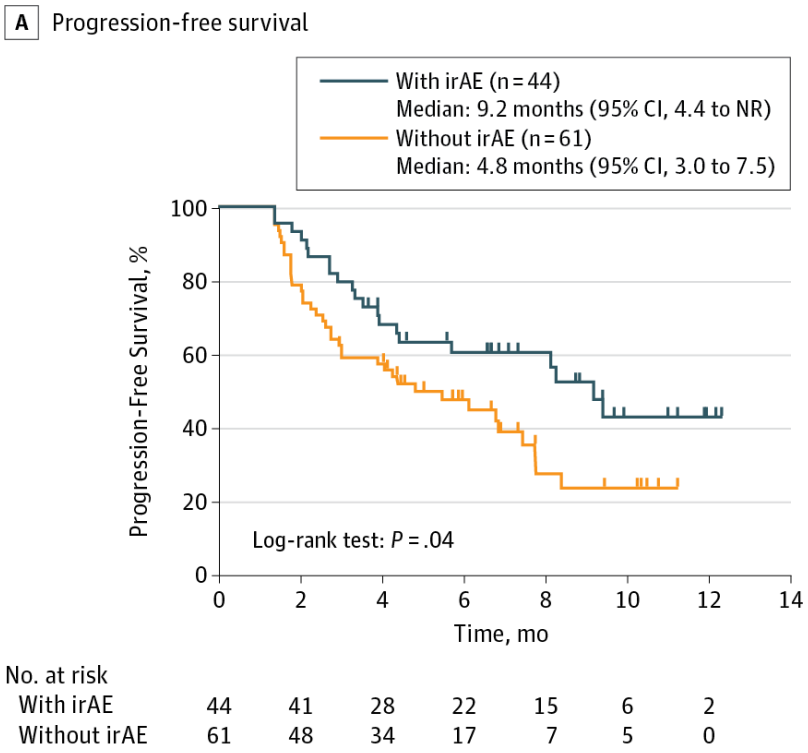


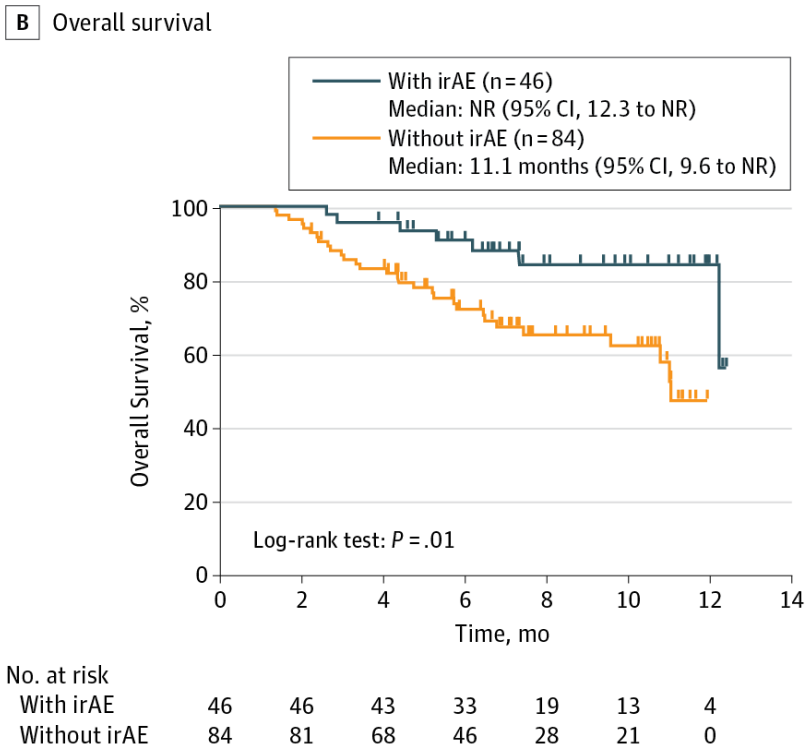
Number at risk (number censored)					
Pembrolizumab plus chemotherapy	60 (0)	43 (5)	20 (20)	1 (36)	0 (37)
Chemotherapy	63 (0)	32 (10)	13 (21)	1 (29)	0 (30)

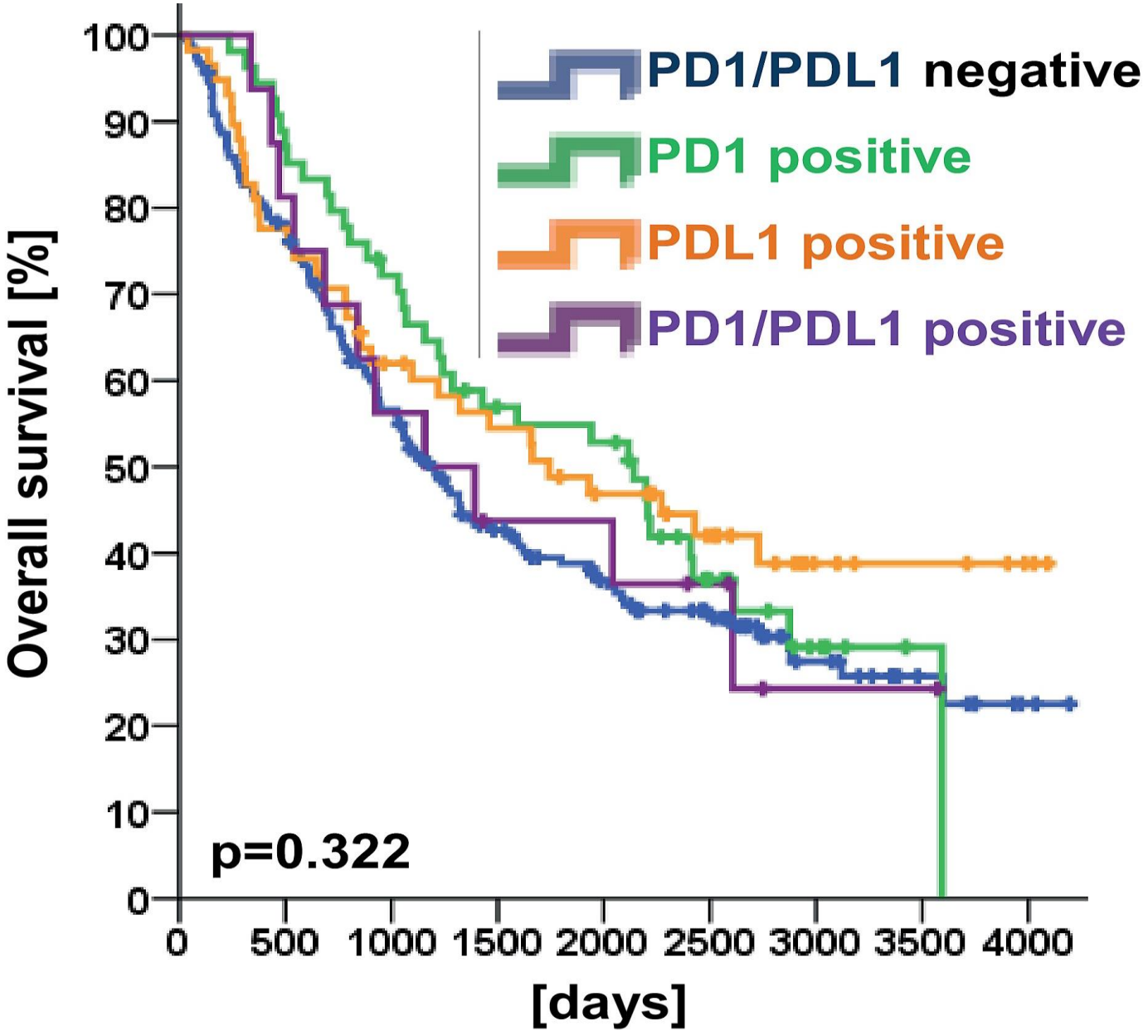


Number at risk (number censored)					
Pembrolizumab plus chemotherapy	60 (0)	53 (3)	33 (18)	5 (42)	0 (47)
Chemotherapy	63 (0)	57 (1)	31 (20)	6 (43)	0 (49)

Yan Etki Cevap Üzerinde Etkili mi?






PD1/PDL1 negative
PD1 positive
PDL1 positive
PD1/PDL1 positive
Overall survival [%]
100
90
80
70
60
50
40
30
20
10
0
p=0.322
0
500
1000
1500
2000
2500
3000
3500
4000
[days]

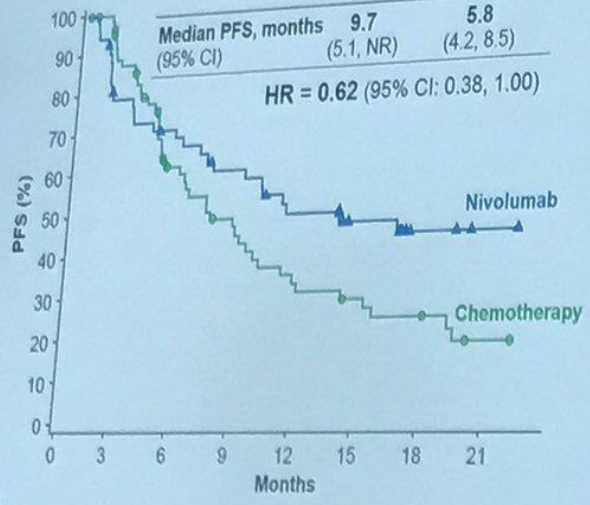
PFS by Tumor Mutation Burden Subgroup

CheckMate 026 TMB Analysis: Nivolumab in First-line NSCLC

High TMB

	Nivolumab n = 47	Chemotherapy n = 60
Median PFS, months (95% CI)	9.7 (5.1, NR)	5.8 (4.2, 8.5)

HR = 0.62 (95% CI: 0.38, 1.00)



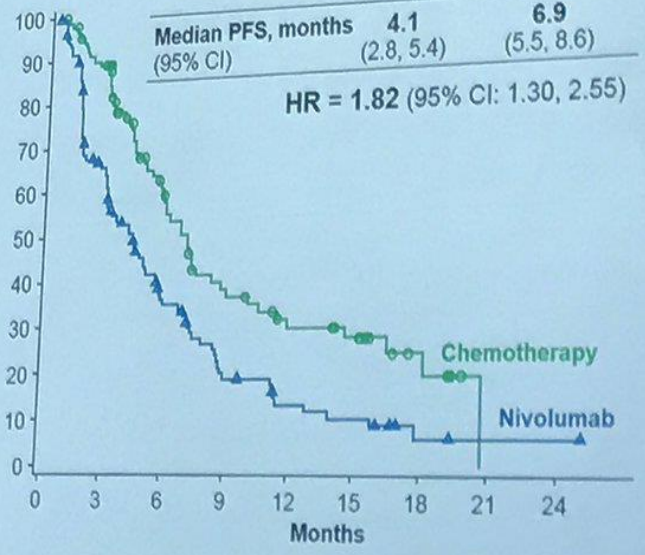
No. at Risk

Nivolumab	47	30	26	21	16	12	4	1
Chemotherapy	60	42	22	15	9	7	4	1

Low/medium TMB

	Nivolumab n = 111	Chemotherapy n = 94
Median PFS, months (95% CI)	4.1 (2.8, 5.4)	6.9 (5.5, 8.6)

HR = 1.82 (95% CI: 1.30, 2.55)

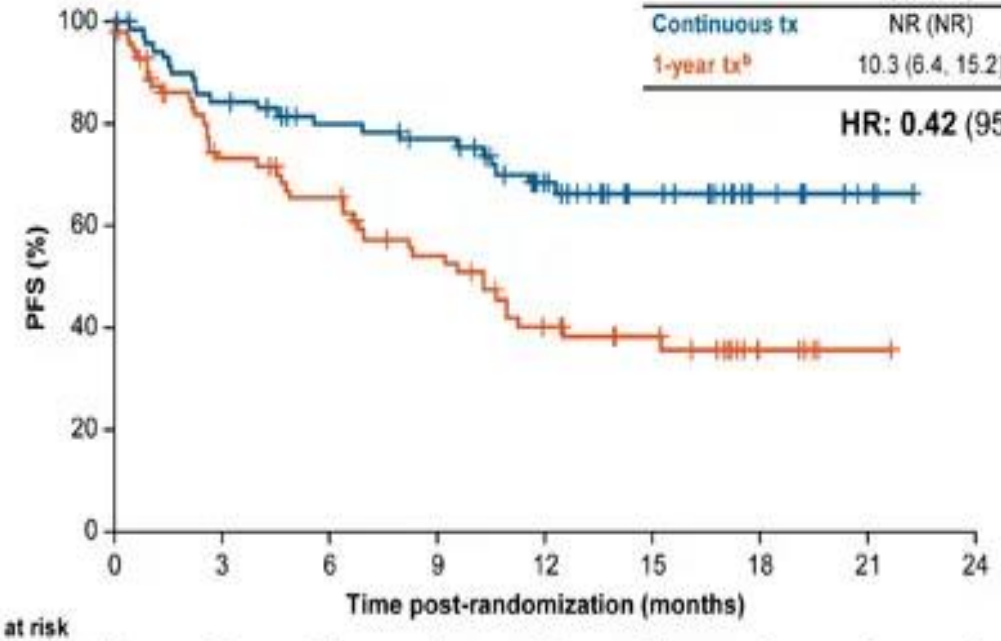


	111	54	30	15	9	7	2	1	1
	94	65	37	23	15	12	5	0	0

Aralıklı Sürekli ??

CheckMate 153: Continuous vs 1-Year Nivolumab

PFS From Randomization[a]



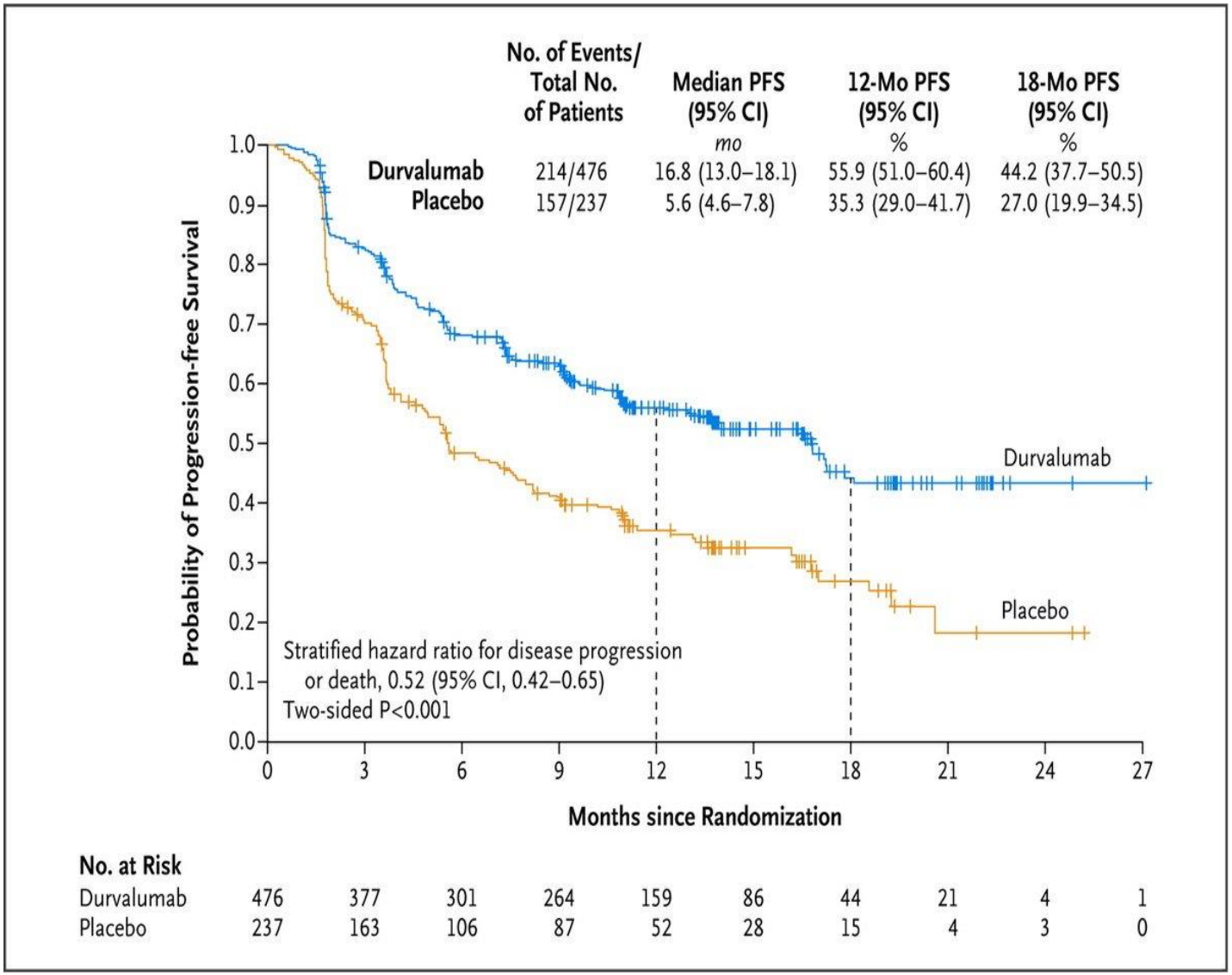
	Median, months (95% CI)	PFS rate, % 6-month	1-year
Continuous tx	NR (NR)	80	65
1-year tx[b]	10.3 (6.4, 15.2)	69	40

HR: 0.42 (95% CI: 0.25, 0.71)

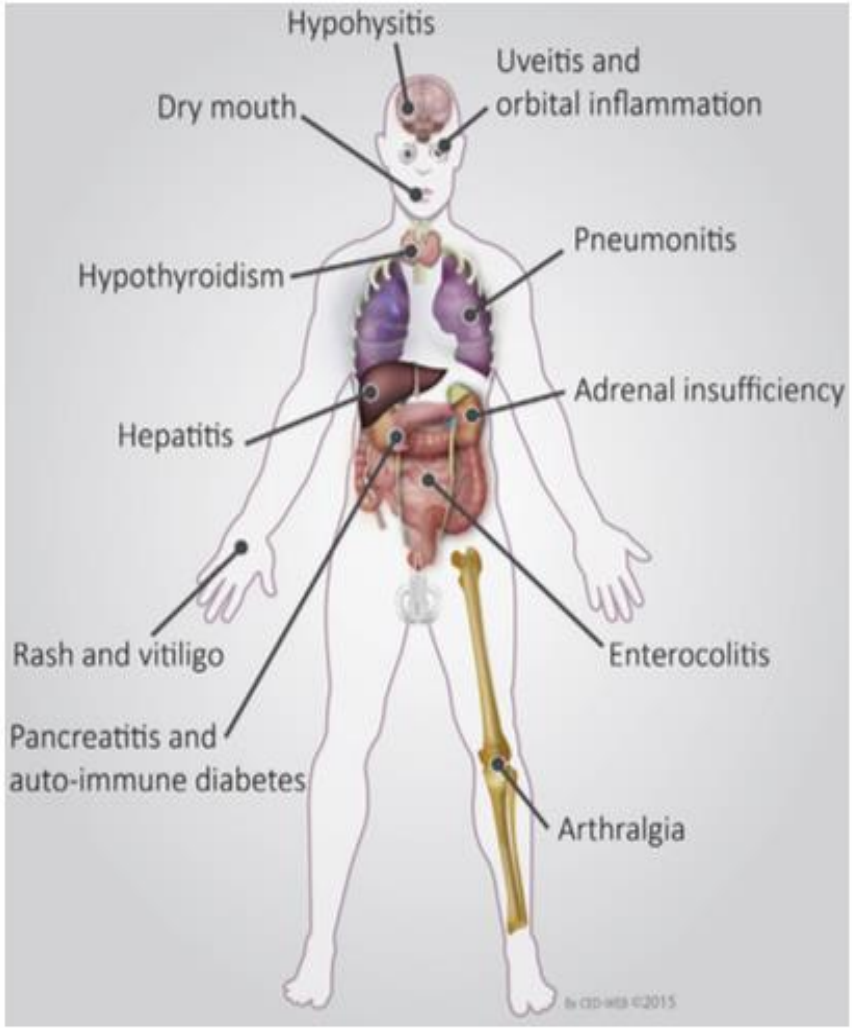
No. at risk									
Continuous tx	76	60	53	49	35	22	10	3	0
1-year tx	87	50	43	33	21	16	5	1	0

[a]Patients who did not have PD at randomization; minimum/median follow-up time post-randomization, 10.0/14.9 months
[b]With optional retreatment allowed at PD
NR = not reached; tx = treatment

Daha erken safhada



Peki Yan Etki???



RESEARCH ARTICLE

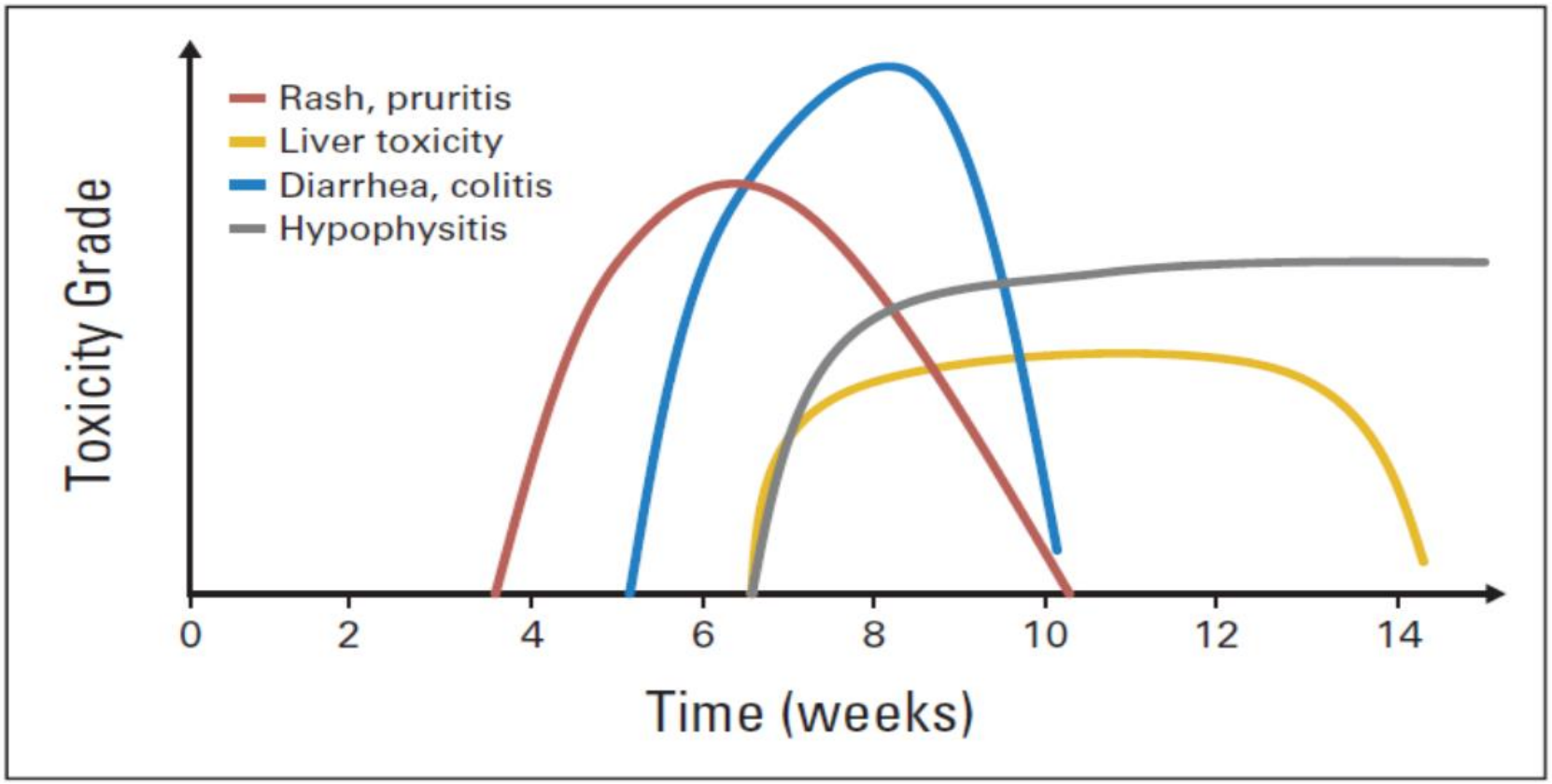
Adverse Events Associated with Immune Checkpoint Blockade in Patients with Cancer: A Systematic Review of Case Reports

Noha Abdel-Wahab[1,2], Mohsin Shah[1], Maria E. Suarez-Almazor[1]*

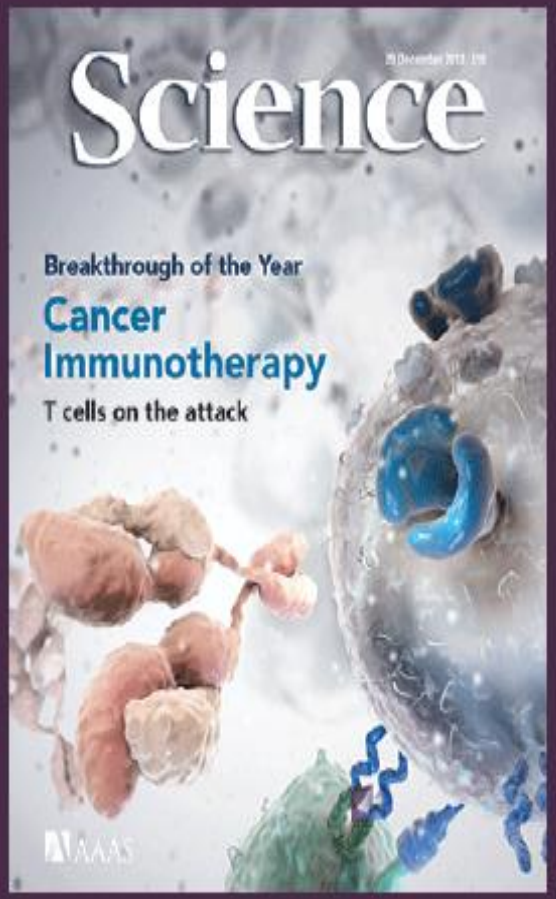
1 Section of Rheumatology and Clinical Immunology, Department of General Internal Medicine, University of Texas MD Anderson Cancer Center, Houston, Texas, United States of America, **2** Rheumatology and Rehabilitation Department, Assiut University Hospitals, Assiut, Egypt

* msalmazor@mdanderson.org

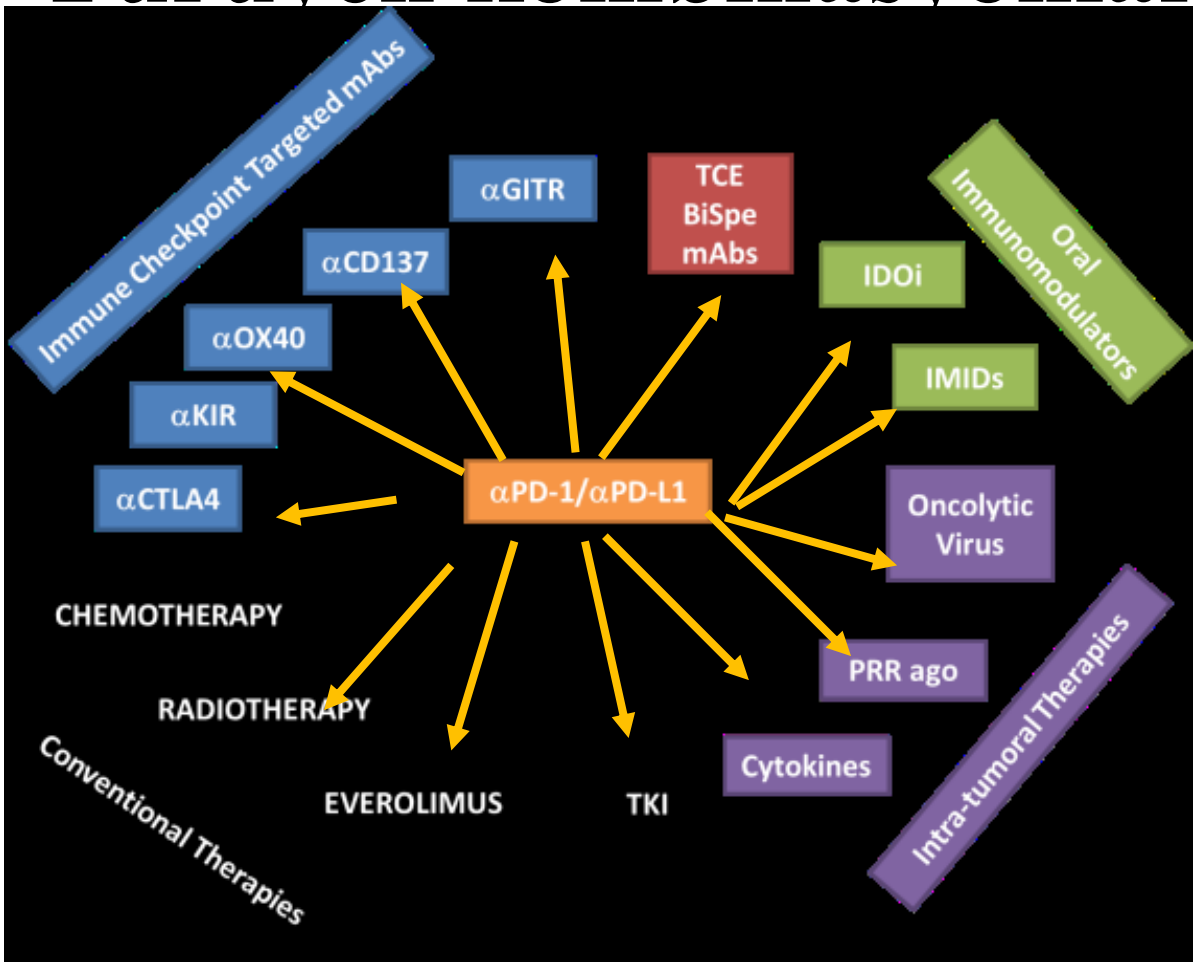
İmmunoterapi Yan Etki Gelişim Süreleri ve Dereceleri



Where are we going?
Immune checkpoint inhibitors

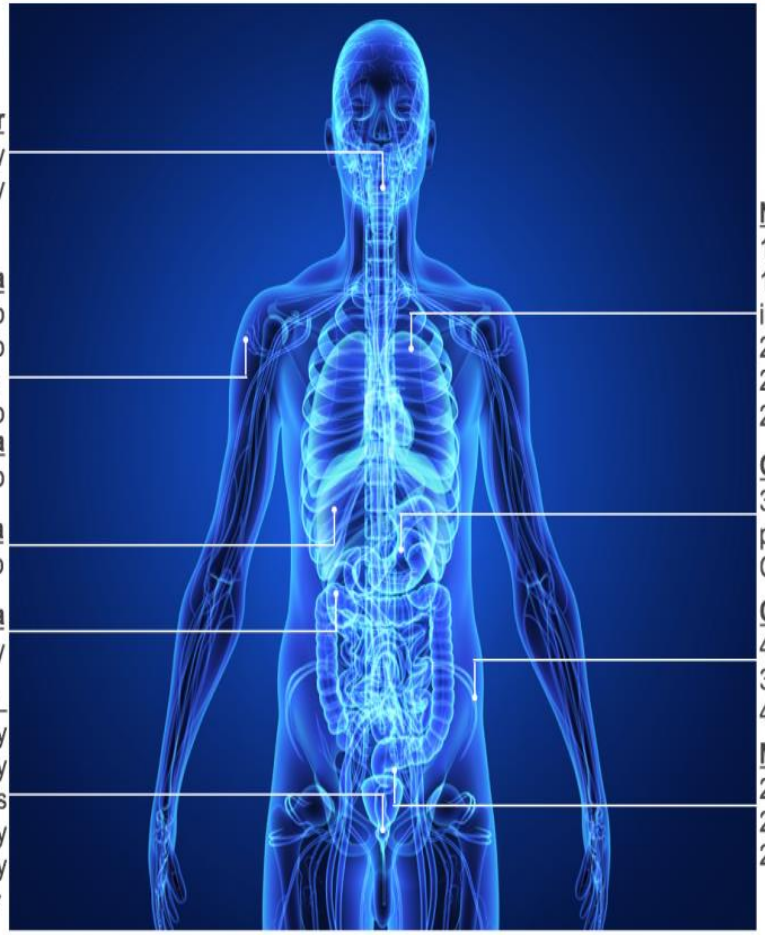


Yürüyen kombinasyonlar



	NSCLC	RCC
Nivolumab	+ Bevacizumab Nintedanib	+ Sunitinib / Pazopanib Cabozantinib
Pembrolizumab	Ramucirumab + Nintedanib Bevacizumab	Axitinib + Lenvatinib Bevacizumab Pazopanib
Atezolizumab	+ Bevacizumab	+ Bevacizumab Bevacizumab + MOXR0916
Avelumab		+ Axitinib

U.S. FDA Approved Immune-Checkpoint Inhibitors



Squamous Cell Head & Neck Cancer
1L nivolumab after platinum chemotherapy
1L pembrolizumab after platinum chemotherapy

Malignant Melanoma
Adj./1L ipilimumab
1L nivolumab ± ipilimumab
Adj. nivolumab
1L pembrolizumab

Merkel Cell Carcinoma
2L avelumab

Hepatocellular Carcinoma
2L nivolumab after sorafenib

Adv. Renal Cell Carcinoma
2L nivolumab after anti-angiogenic therapy

Locally Adv. or Met. Urothelial Cancer
1L nivolumab after platinum chemotherapy
1L pembrolizumab after platinum chemotherapy
or in platinum-ineligible patients
1/L atezolizumab after platinum chemotherapy
1L avelumab after platinum chemotherapy
1L durvalumab after platinum chemotherapy

Non-Small Cell Lung Cancer
1L pembrolizumab TPS≧50%
1L pembrolizumab +pemetrexed/carboplatin
in non-squamous NSCLC
2L pembrolizumab TPS≧1%
2L nivolumab
2L atezolizumab NSCLC

Gastric & GEJ Carcinoma
3L pembrolizumab after fluoropyrimidine- and
platinum-chemotherapy +/- HER2/neu therapy
CPS≧1

Classical Hodkin Lymphoma
4L pembrolizumab
3L nivolumab after auto-HSCT and BV
4L nivolumab and after auto-HSCT

MSI-H or dMMR Cancers
2L nivolumab in CRC after FOLFOXIRI
2L pembrolizumab in CRC after FOLFOXIRI
2L pembrolizumab in any MSI-H/dMMR cancer

1 Prescribing information pembrolizumab (Keytruda®), revised: 11/2017
2 Prescribing information nivolumab (Opdivo®), revised: 12/2017
3 Prescribing information ipilimumab (Yervoy®), revised: 12/2017
4 Prescribing information atezolizumab (Tecentriq®), Revised: 04/2017
5 Prescribing information avelumab (Bavencio®), Revised: 10/2017
6 Prescribing information durvalumab (Imfinzi®), Revised: 05/2017

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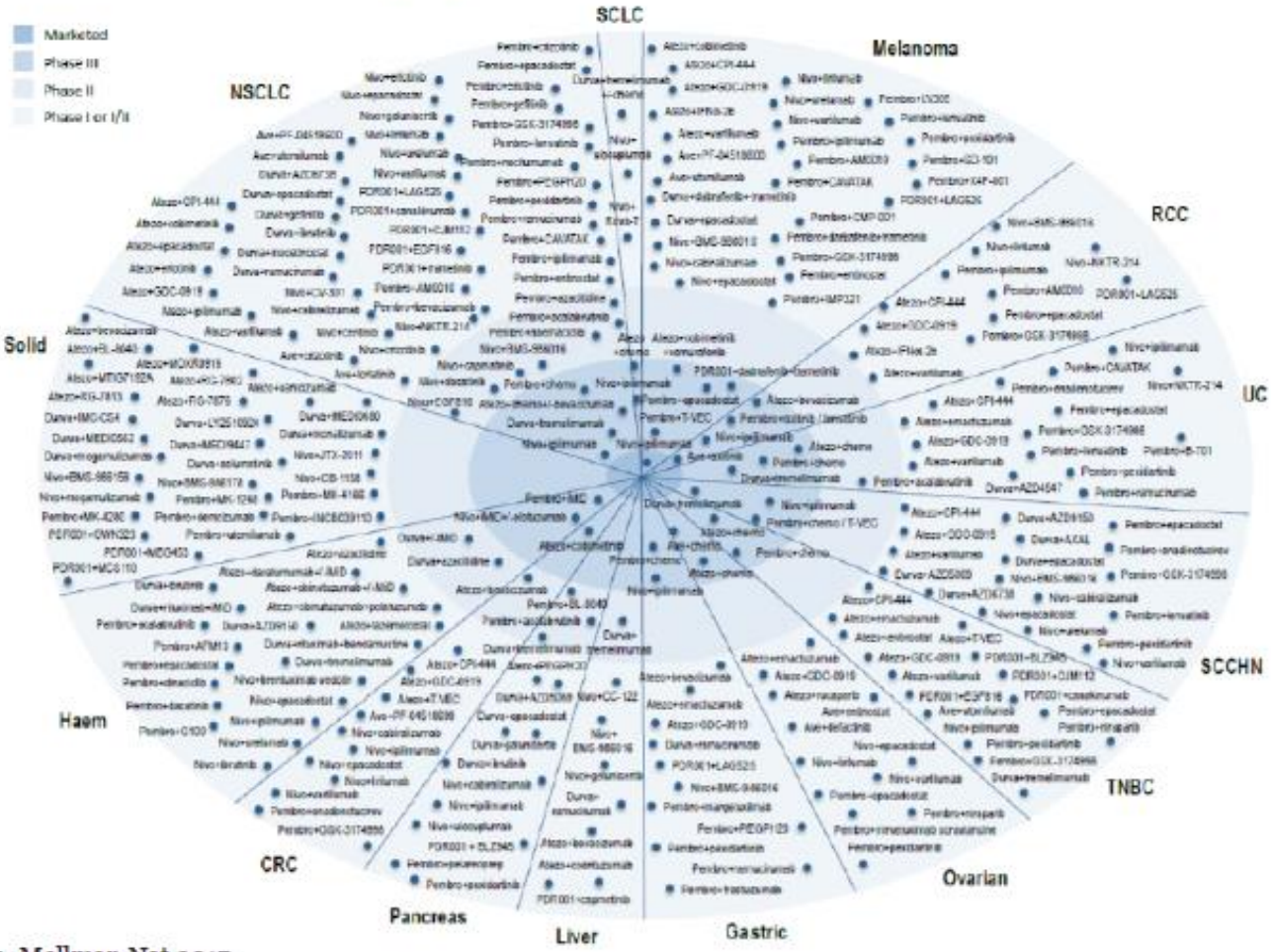
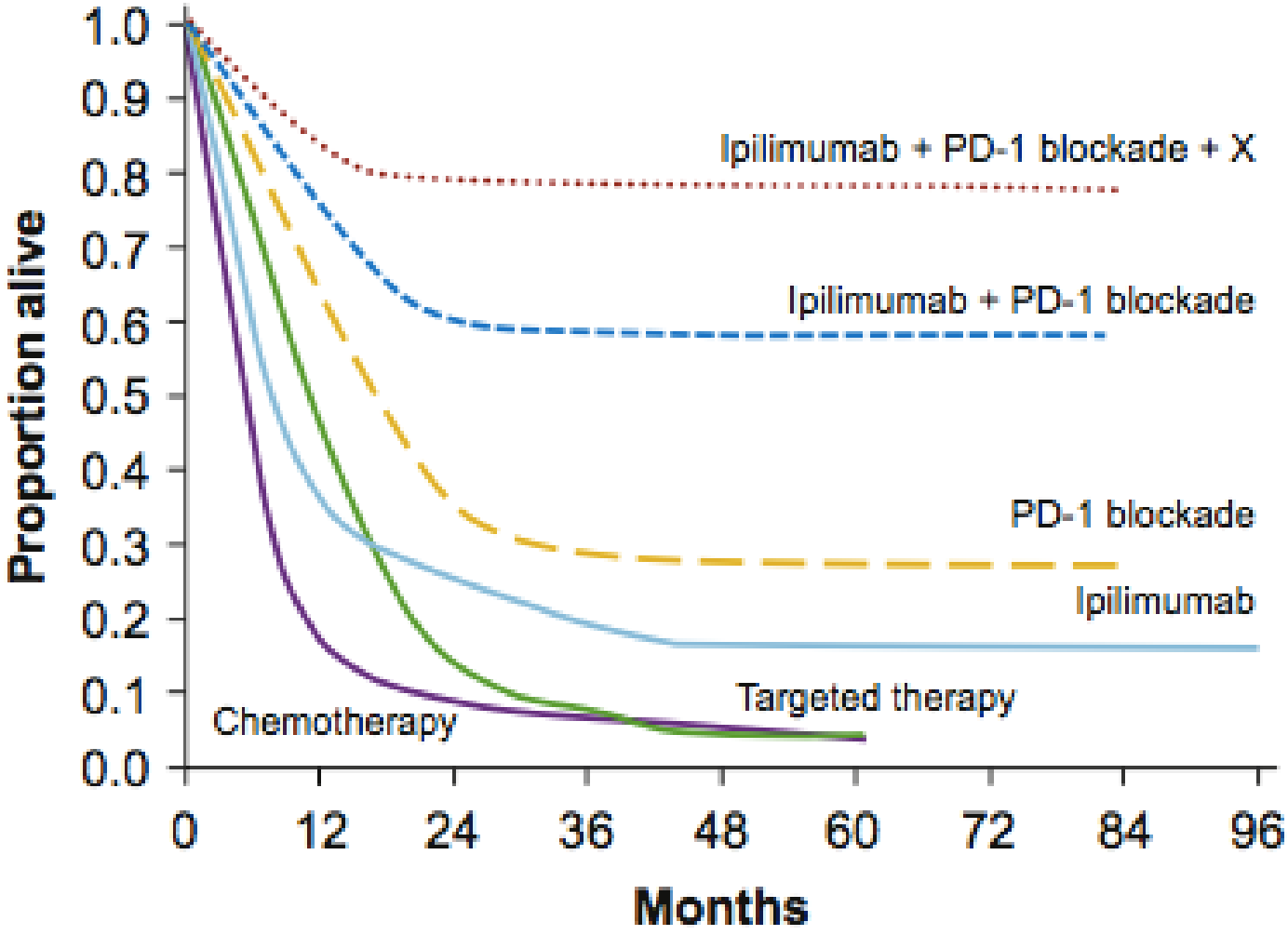
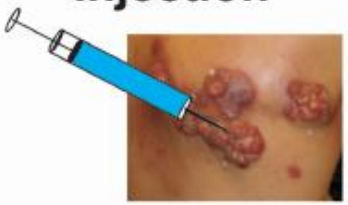
The immunotherapy tsunami: combinations



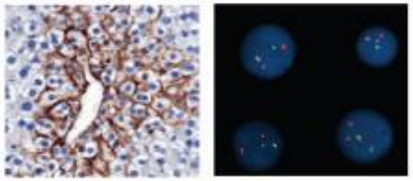
Chen, Mellman Nat 2017


Proportion alive
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
12
24
36
48
60
72
84
96
Months
Ipilimumab + PD-1 blockade + X
Ipilimumab + PD-1 blockade
PD-1 blockade
Ipilimumab
Targeted therapy
Chemotherapy

Intratumoral Injection



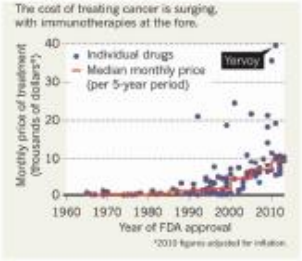
Predictive Biomarkers



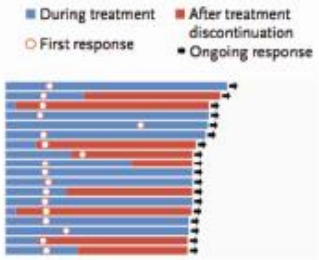
All Patients in Clinical Trial?

Toxicity

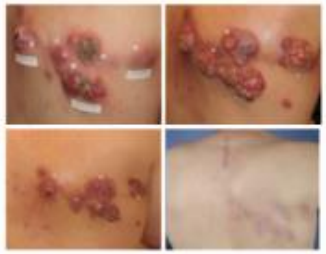
Financial Toxicity



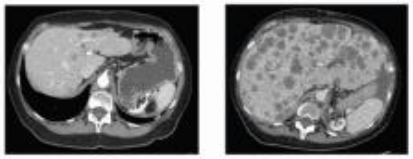
Treatment Duration



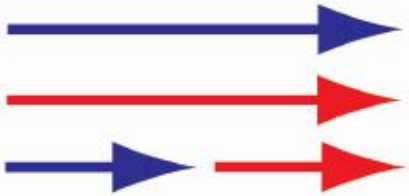
Pseudoprogression



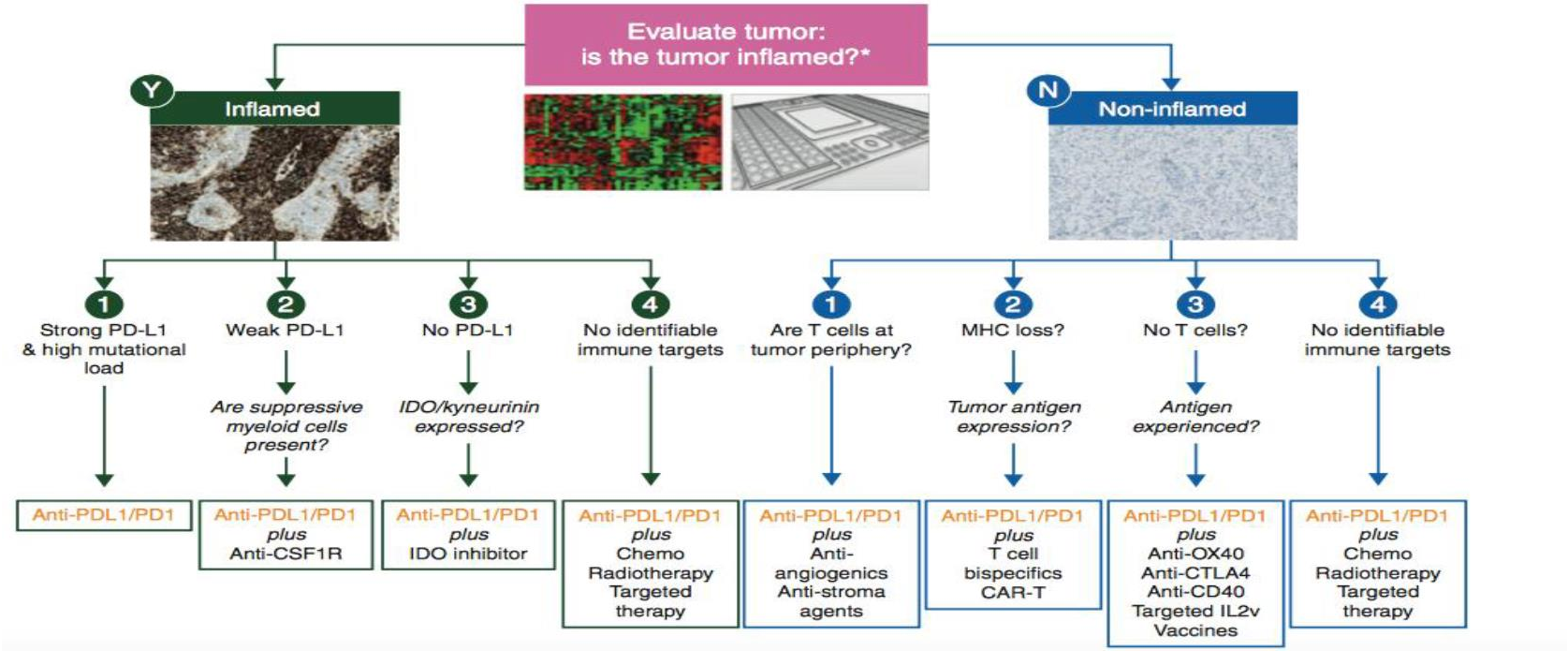
Hyperprogression



Parallel vs Sequential



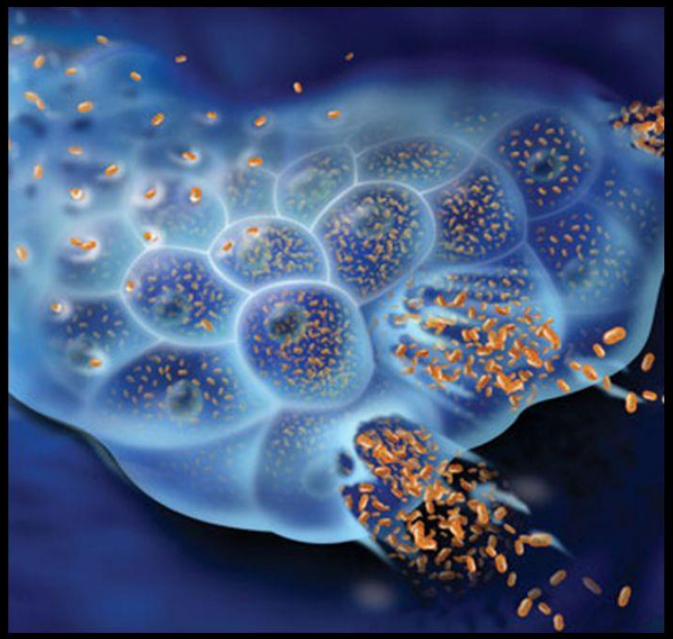
A model for future decision making….



ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

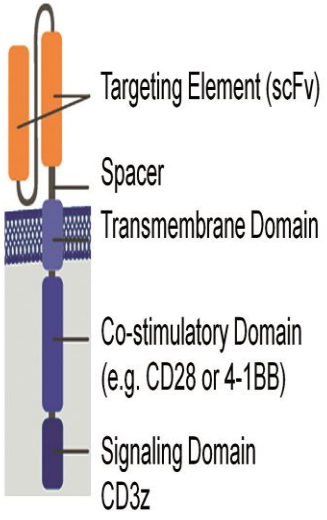
Chen Immunity 39, July 25, 2013

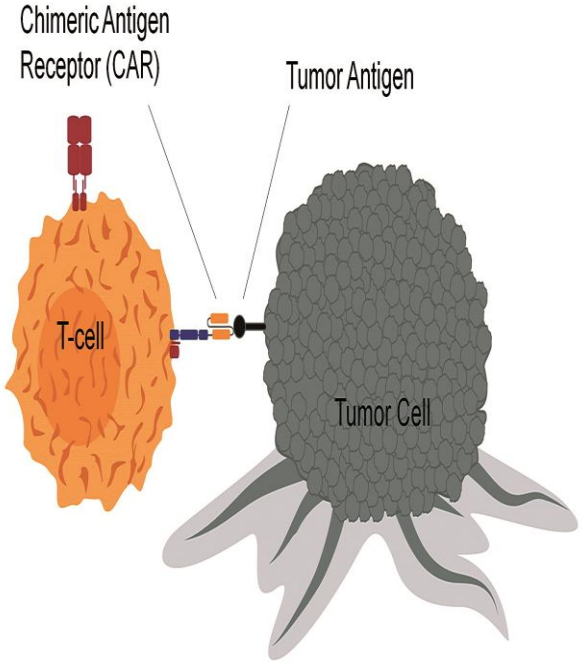
ONCOLYTIC VIRUSES

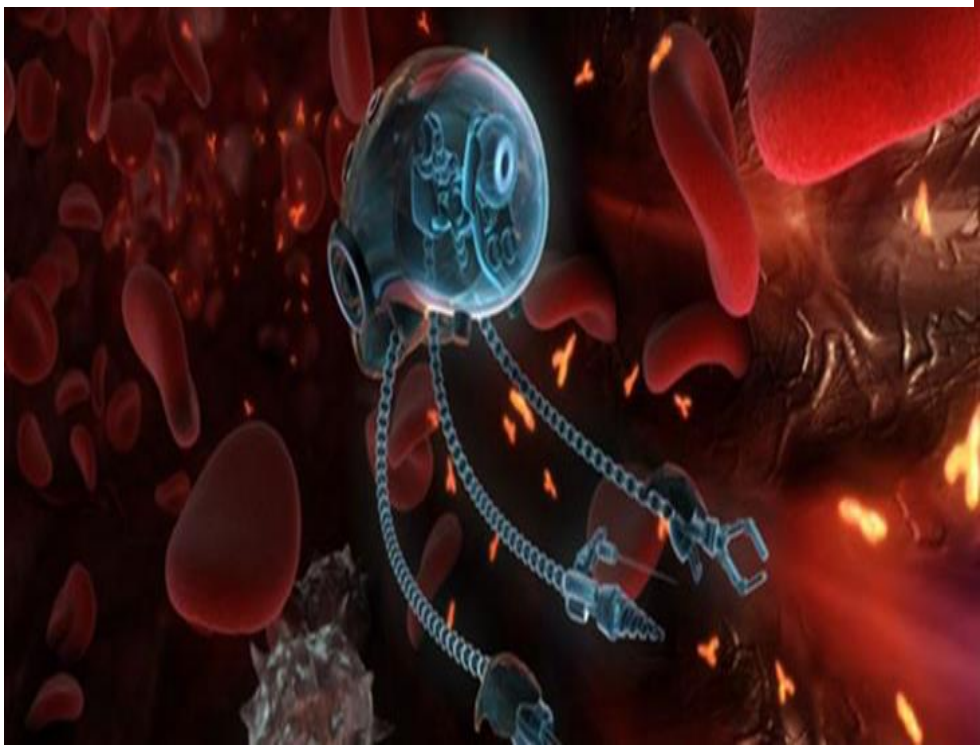


BIOTHERAPEUTICS AGAIN

CAR: Modular Design



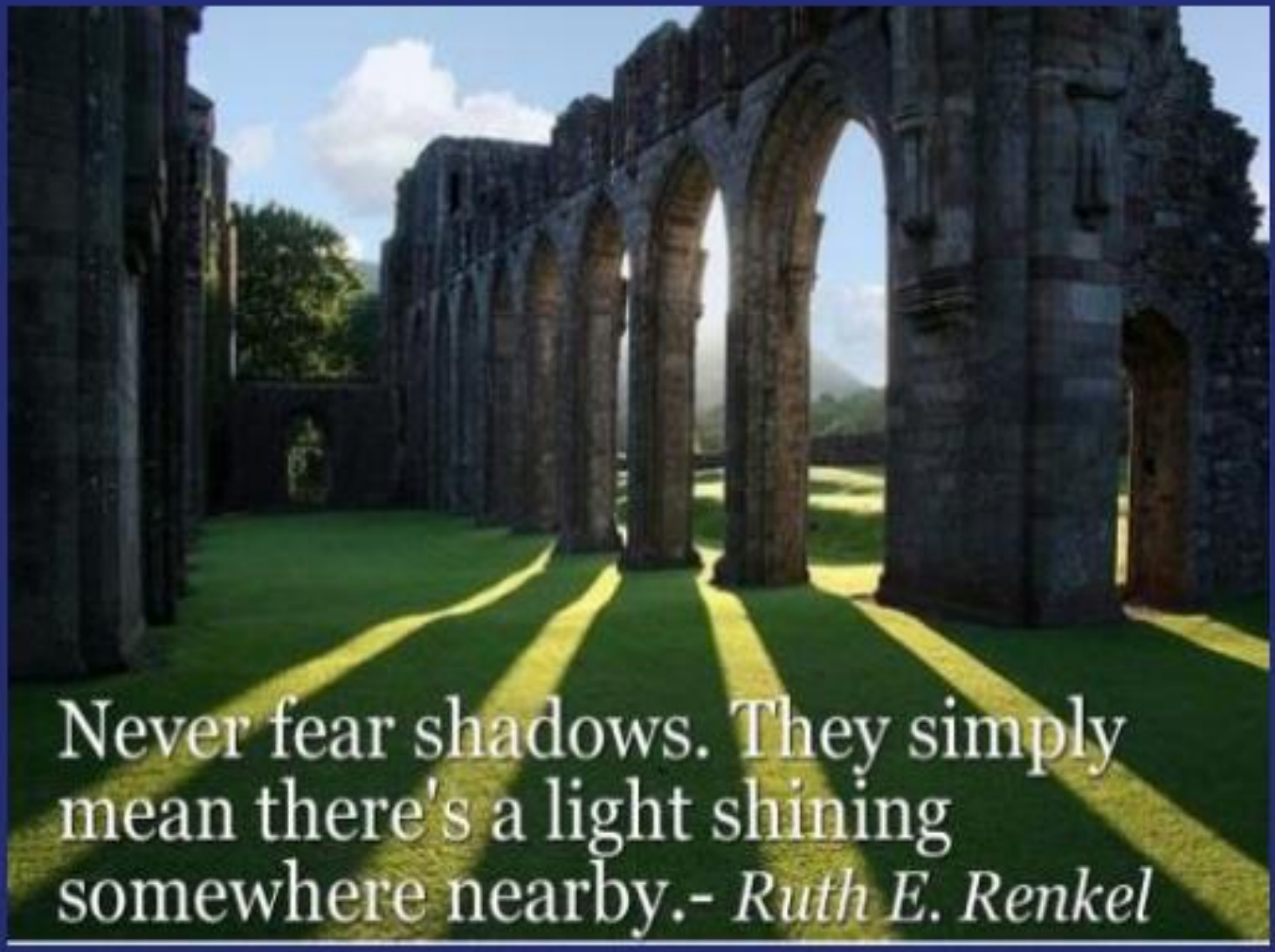




Sonuç olarak, Bizi cezbetti

- Devam eden cevaplar %20-30
- İmmun ilişkili yan etkiler
- Atipik klinik yanıt paternleri (psödoprogresyon, atipik yanıt)
- Açık sağ kalım oranları
- Bir eksik alanda elimiz güçlendi
- Ancak kür için daha fazlası gerek

How to bring light into the shadow



-
- Teşekkürler

BAŞKENT ÜNİVERSİTESİ

Kanserde Destek Tedaviler ve

Palyatif Bakım Sempozyumu

Sheraton Hotel Adana

12-13 Mayıs 2018