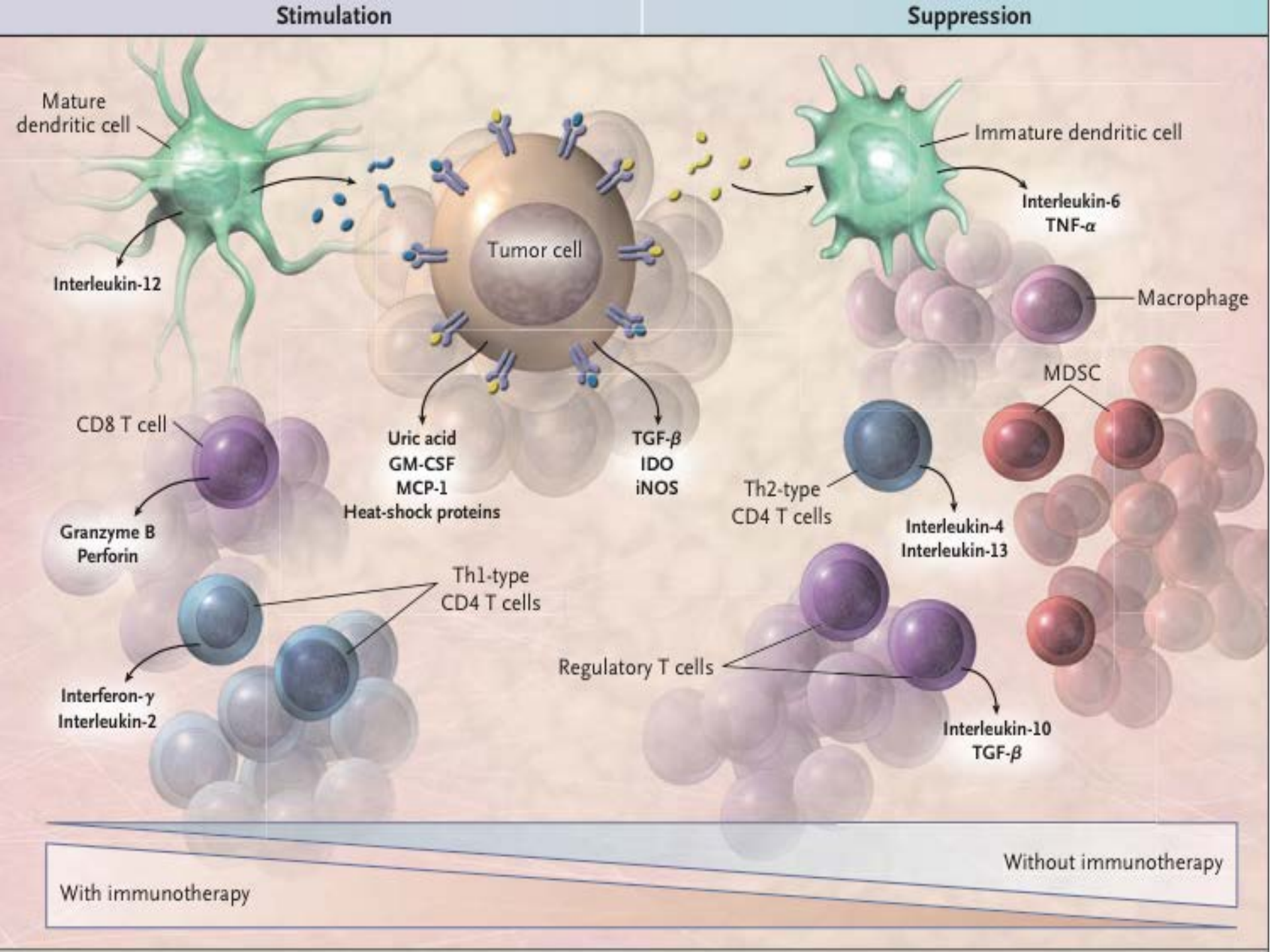
ONKOLOG BAKIŞ AÇISIYLA İMMUNOTERAPİ

Dr Hande Turna
İstanbul Üniversitesi
Cerrahpaşa Tıp Fakültesi
Medikal Onkoloji Bilim Dalı

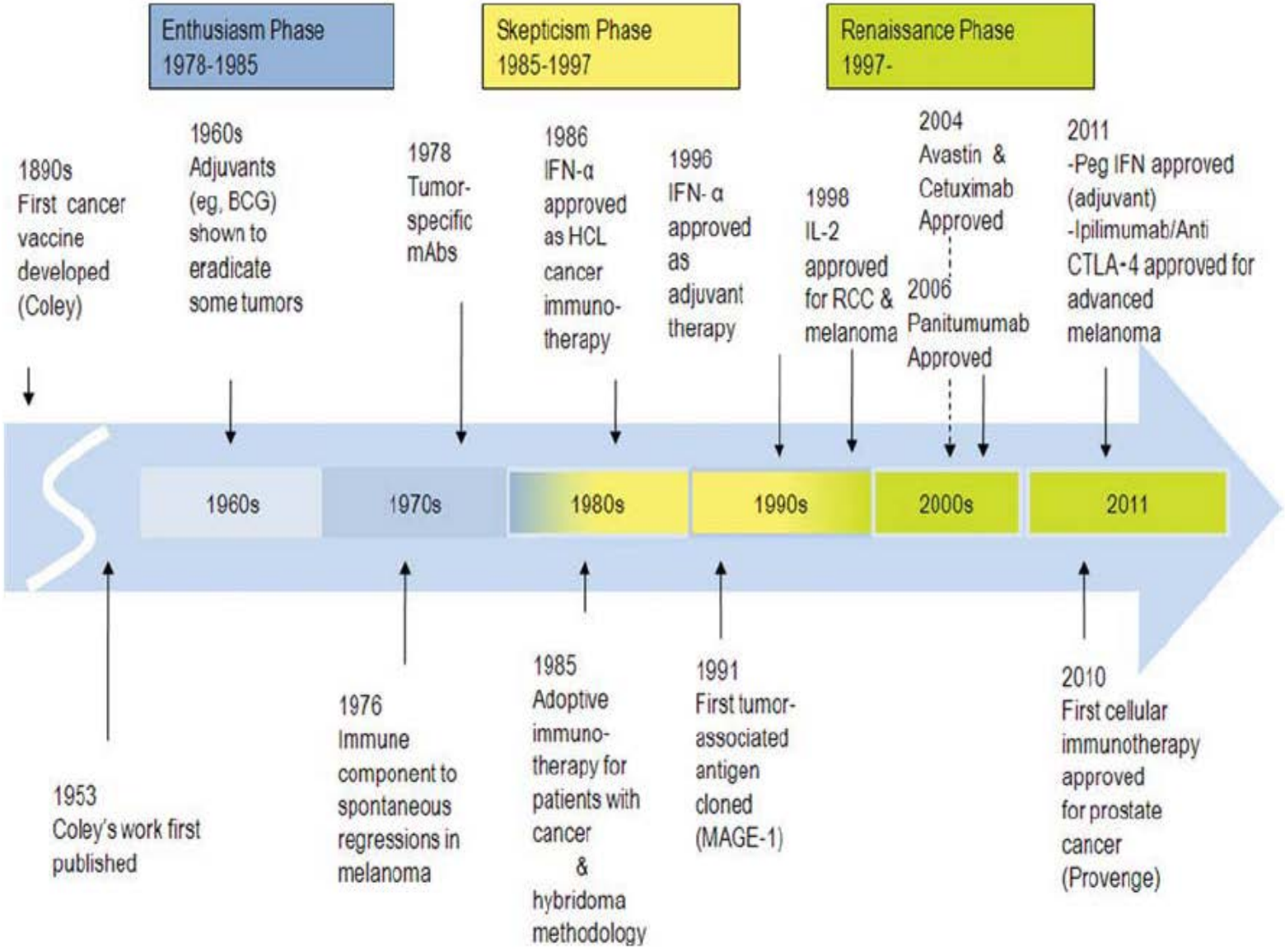

Stimulation
Suppression
Mature dendritic cell
Interleukin-12
Tumor cell
Uric acid
GM-CSF
MCP-1
Heat-shock proteins
TGF-β
IDO
iNOS
Immature dendritic cell
Interleukin-6
TNF-α
Macrophage
MDSC
CD8 T cell
Granzyme B
Perforin
Th2-type
CD4 T cells
Interleukin-4
Interleukin-13
Th1-type
CD4 T cells
Interferon-γ
Interleukin-2
Regulatory T cells
Interleukin-10
TGF-β
With immunotherapy
Without immunotherapy

Photograph by Frans Lanting

National Geographic Best of Wildli

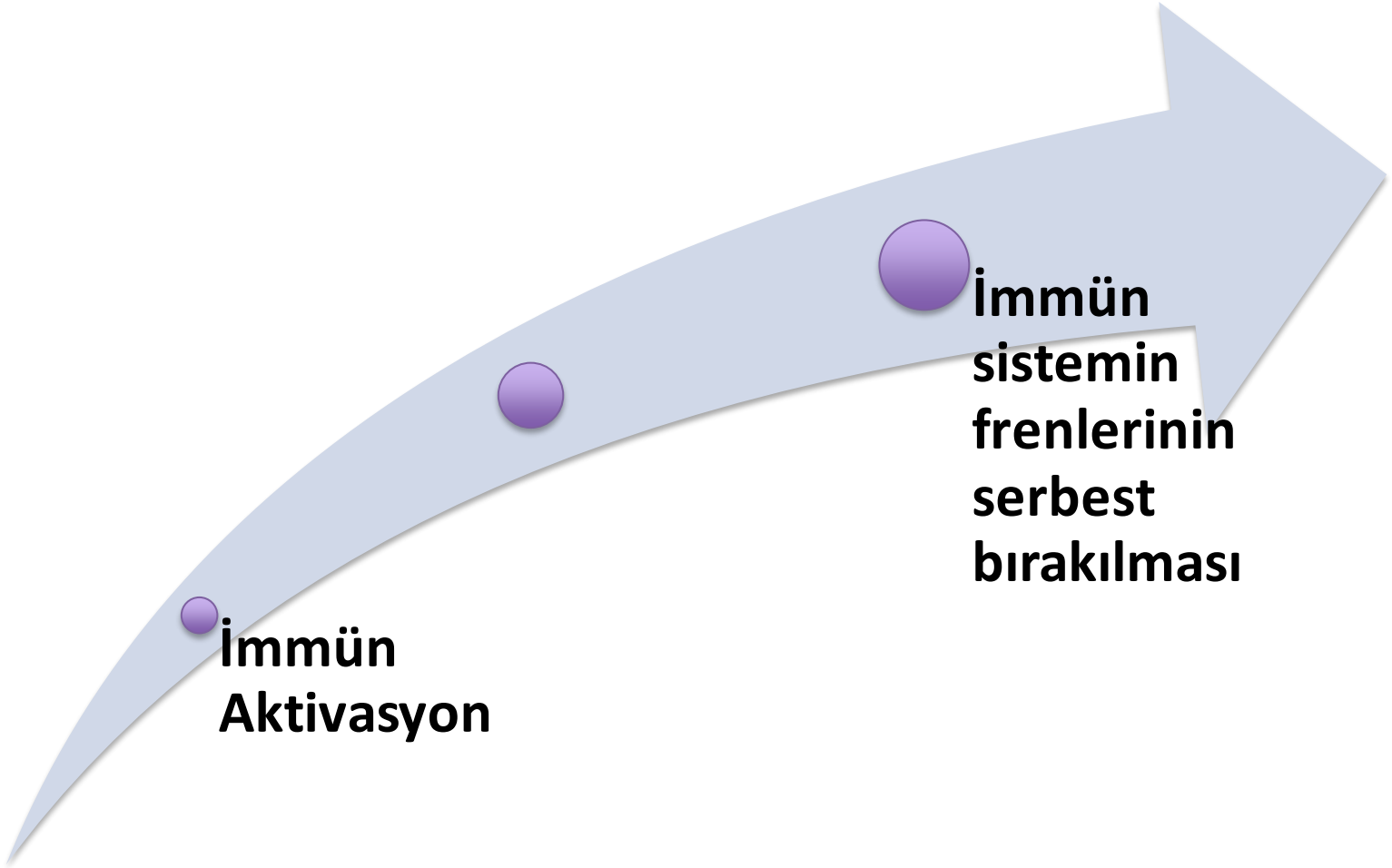
Collector's Edition Vol.

İmmün Sistem

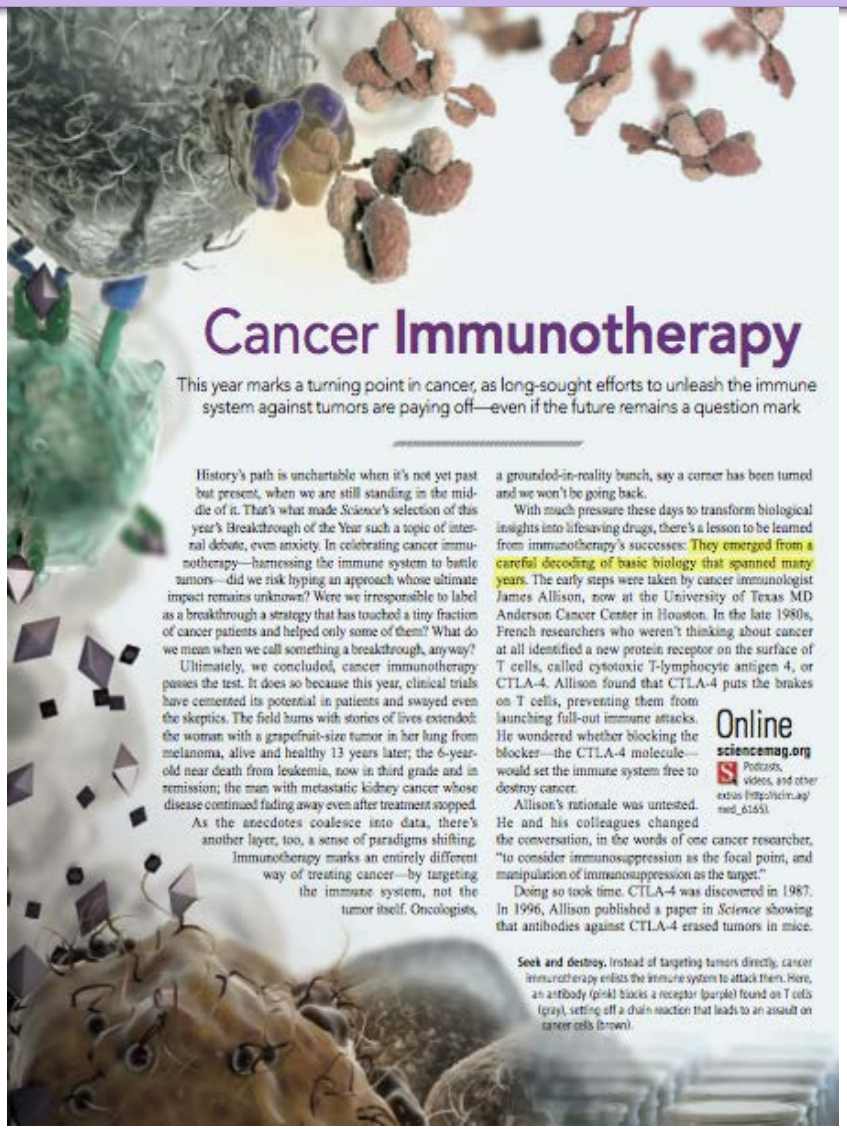


CA Cancer Clin 2012

İmmunoterapide Değişen Yaklaşım
James P Allison



2013-İmmunoonkoloji Yılı



Cancer Immunotherapy

This year marks a turning point in cancer, as long-sought efforts to unleash the immune system against tumors are paying off—even if the future remains a question mark

History's path is unchartable when it's not yet past but present, when we are still standing in the middle of it. That's what made *Science*'s selection of this year's Breakthrough of the Year such a topic of internal debate, even anxiety. In celebrating cancer immunotherapy—harnessing the immune system to battle tumors—did we risk hyping an approach whose ultimate impact remains unknown? Were we irresponsible to label as a breakthrough a strategy that has touched a tiny fraction of cancer patients and helped only some of them? What do we mean when we call something a breakthrough, anyway?

Ultimately, we concluded, cancer immunotherapy passes the test. It does so because this year, clinical trials have cemented its potential in patients and swayed even the skeptics. The field hums with stories of lives extended: the woman with a grapefruit-size tumor in her lung from melanoma, alive and healthy 13 years later; the 6-year-old near death from leukemia, now in third grade and in remission; the man with metastatic kidney cancer whose disease continued fading away even after treatment stopped.

As the anecdotes coalesce into data, there's another layer, too, a sense of paradigms shifting. Immunotherapy marks an entirely different way of treating cancer—by targeting the immune system, not the tumor itself. Oncologists, a grounded-in-reality bunch, say a corner has been turned and we won't be going back.

With much pressure these days to transform biological insights into lifesaving drugs, there's a lesson to be learned from immunotherapy's successes: They emerged from a careful decoding of basic biology that spanned many years. The early steps were taken by cancer immunologist James Allison, now at the University of Texas MD Anderson Cancer Center in Houston. In the late 1980s, French researchers who weren't thinking about cancer at all identified a new protein receptor on the surface of T cells, called cytotoxic T-lymphocyte antigen 4, or CTLA-4. Allison found that CTLA-4 puts the brakes on T cells, preventing them from launching full-out immune attacks. He wondered whether blocking the blocker—the CTLA-4 molecule—would set the immune system free to destroy cancer.

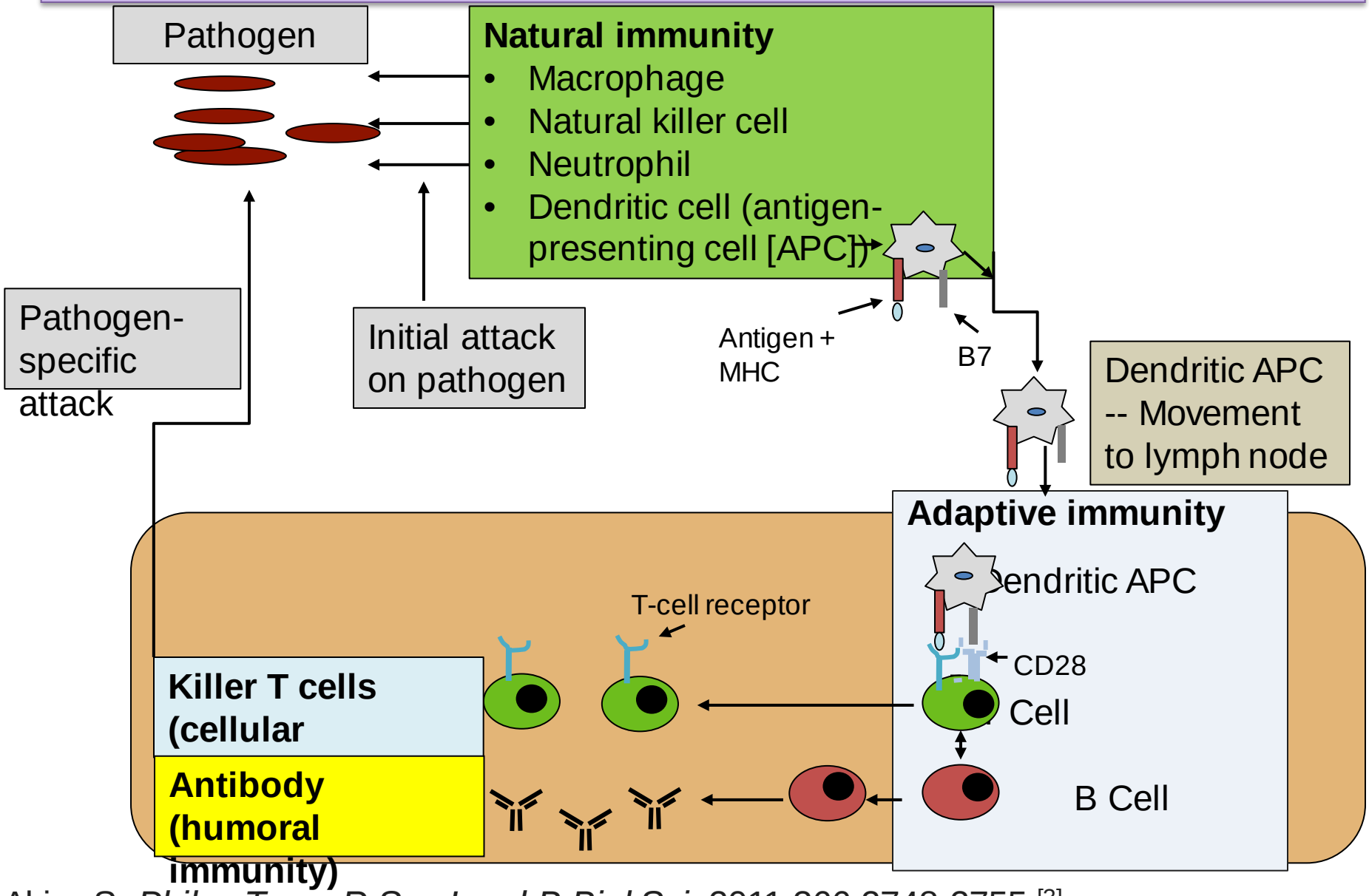
Online
sciencemag.org
Podcasts, videos, and other extras (http://scim.ag/red_6165).

Allison's rationale was untested. He and his colleagues changed the conversation, in the words of one cancer researcher, "to consider immunosuppression as the focal point, and manipulation of immunosuppression as the target."

Doing so took time. CTLA-4 was discovered in 1987. In 1996, Allison published a paper in *Science* showing that antibodies against CTLA-4 erased tumors in mice.

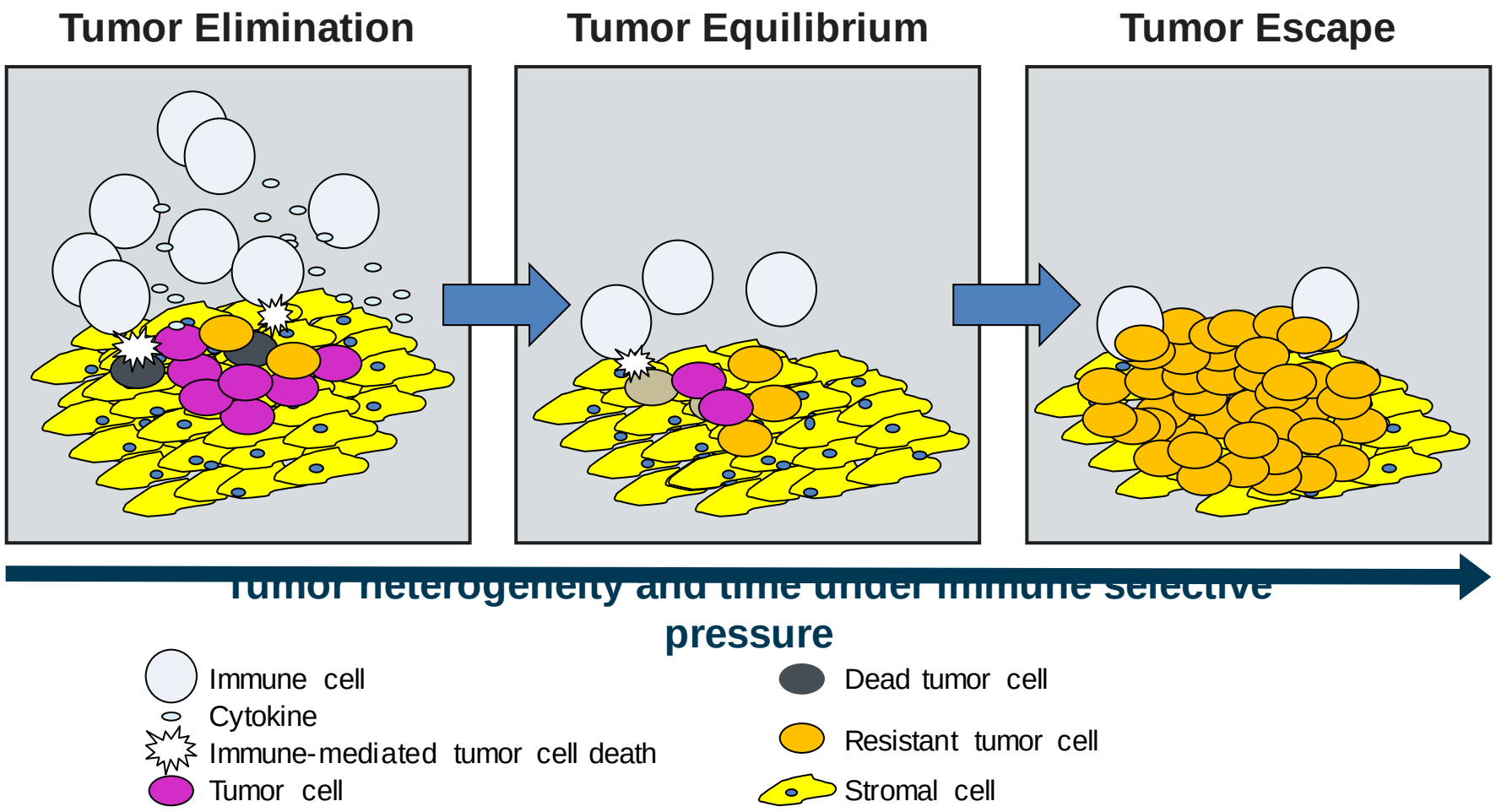
Seek and destroy. Instead of targeting tumors directly, cancer immunotherapy enlists the immune system to attack them. Here, an antibody (pink) blocks a receptor (purple) found on T cells (gray), setting off a chain reaction that leads to an assault on cancer cells (brown).

İmmün Sistem



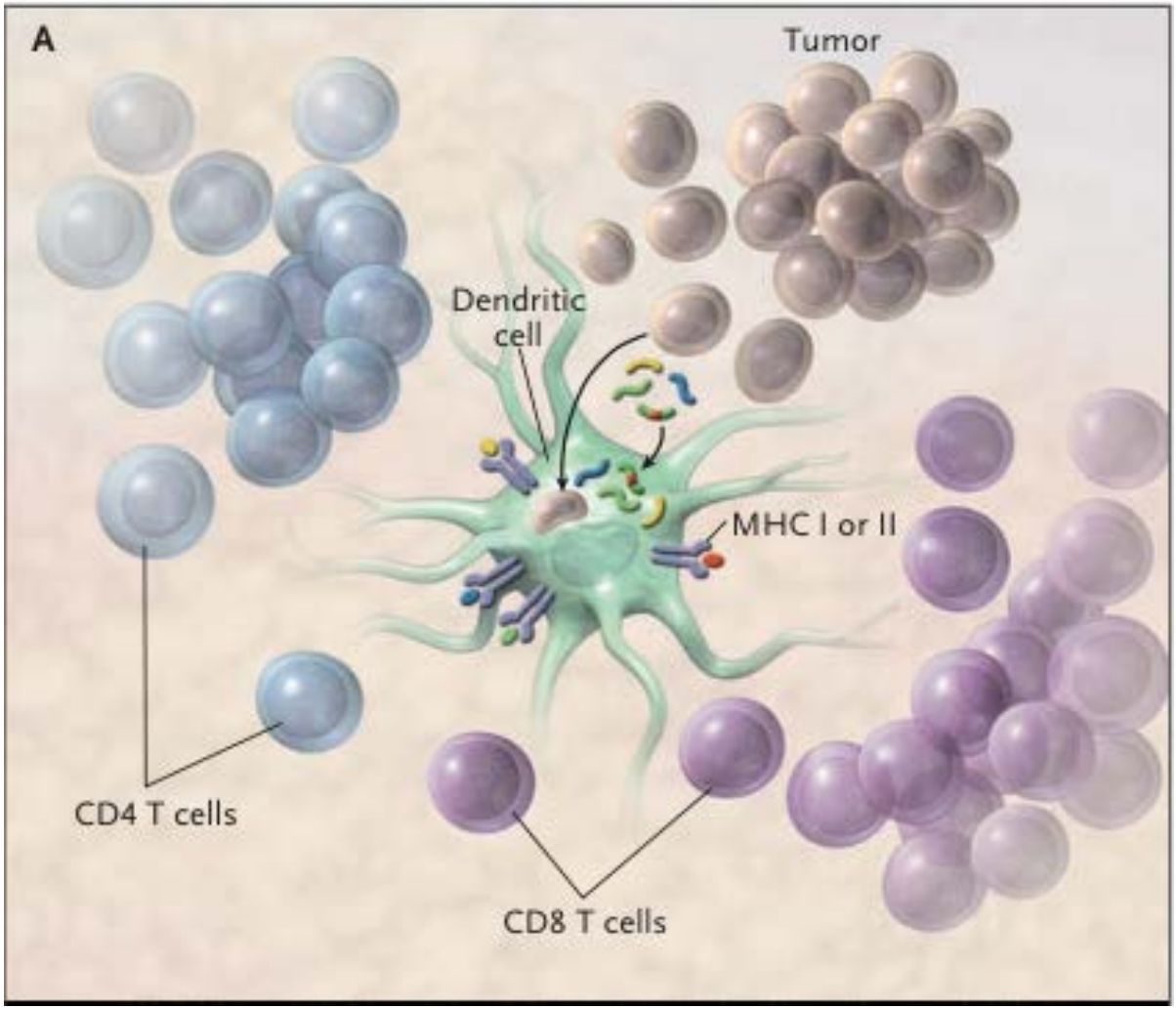
Akira S. *Philos Trans R Soc Lond B Biol Sci.* 2011;366:2748-2755.[3]

İmmün Sistem ve Kanser

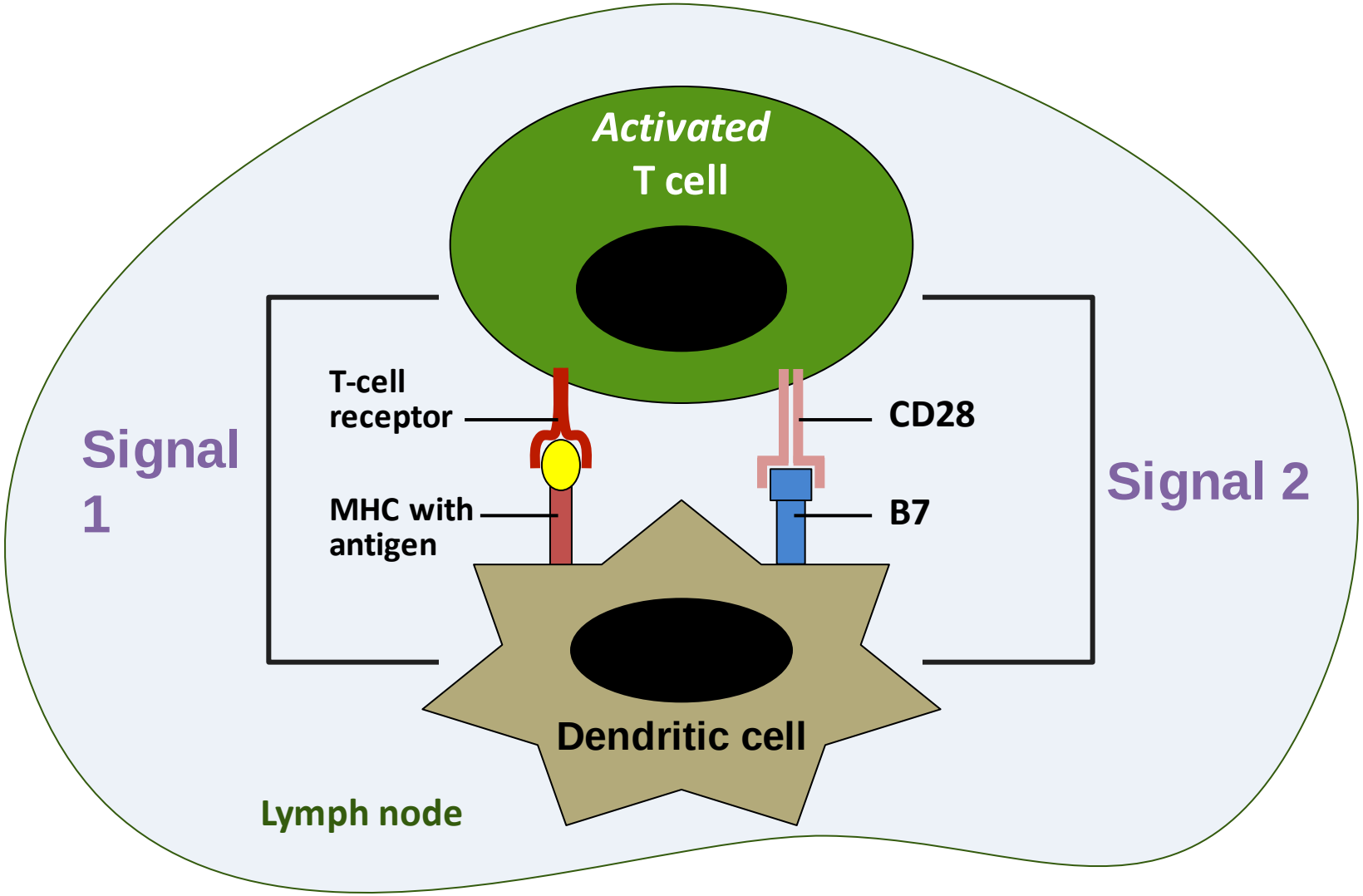


Dunn GP, et al. *Nat Immunol*. 2002;3:991-998[5]; Schreiber R, et al. *Science*. 2011;331:1565-1570[6]; Mittal D, et al. *Curr Opin Immunol*. 2014;27:16-25.[7]

T Hücreleri

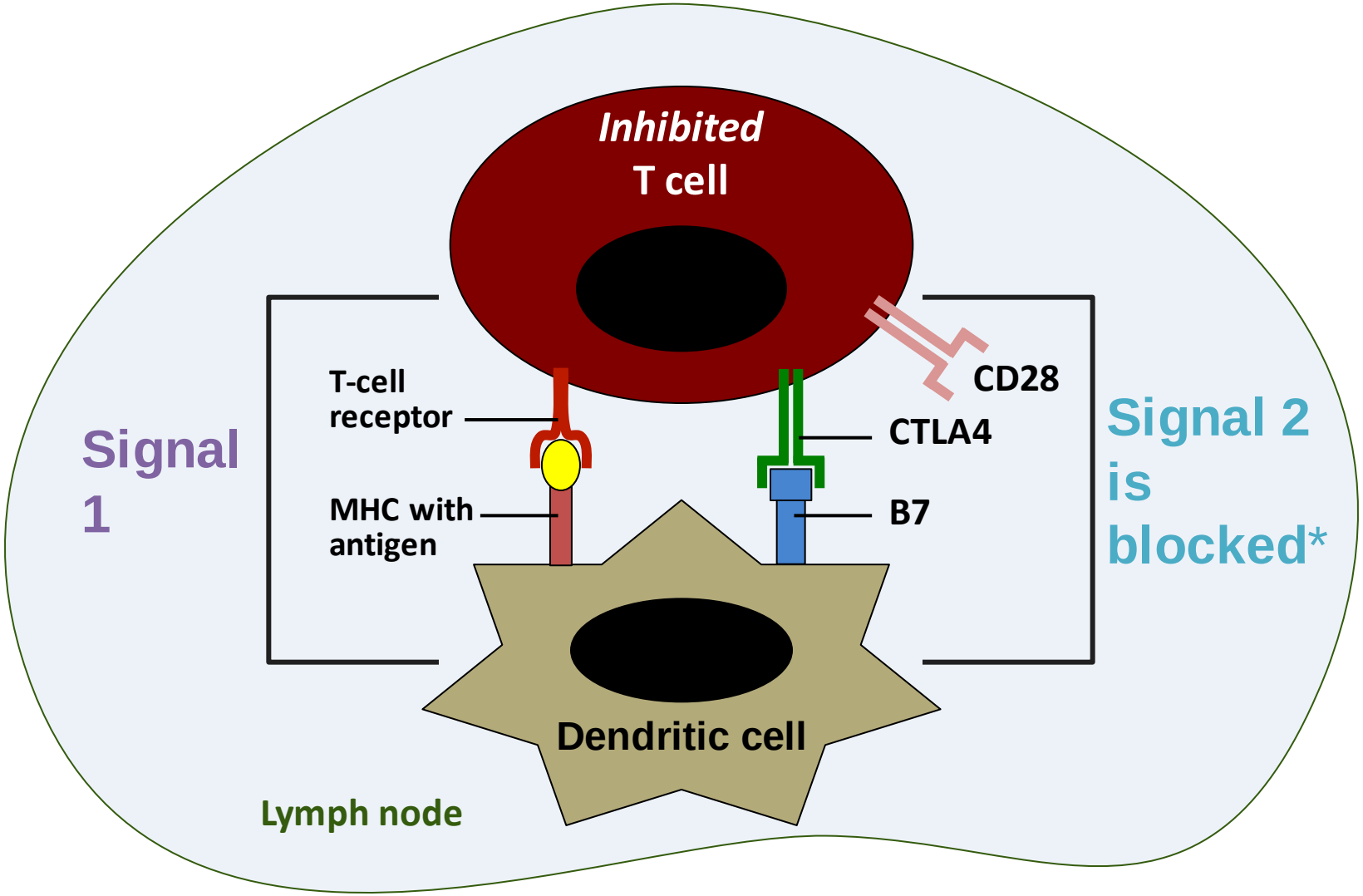


T-Hücre Aktivasyonu



Postow MA, et al. *J Clin Oncol.* 2015 Jan 20. [Epub ahead of print][4]

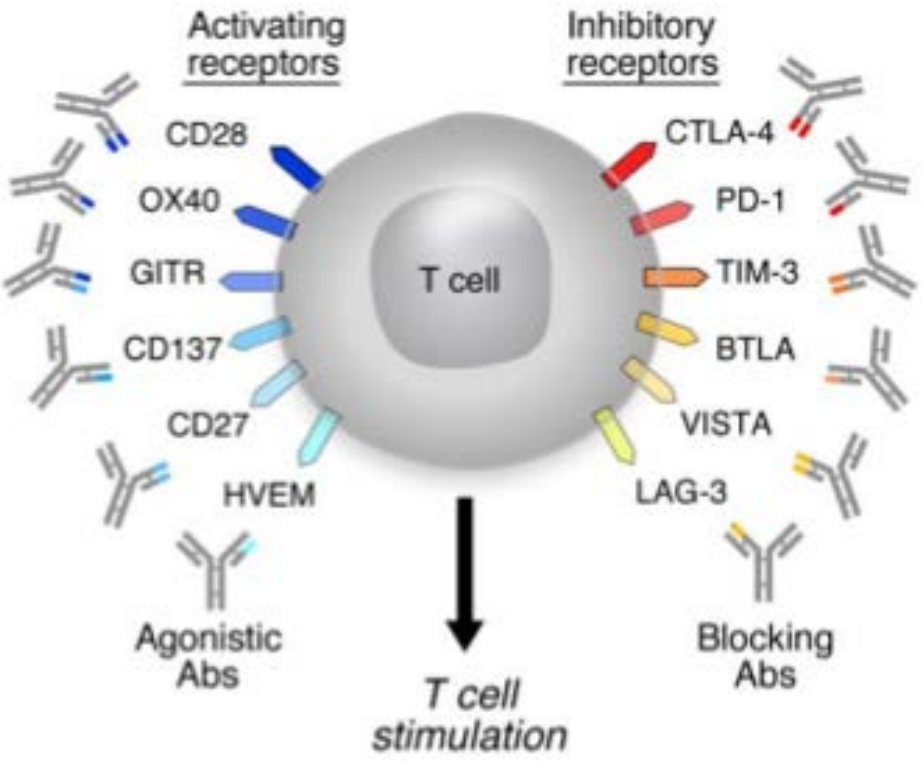
CTLA-4 ile İnhibisyon



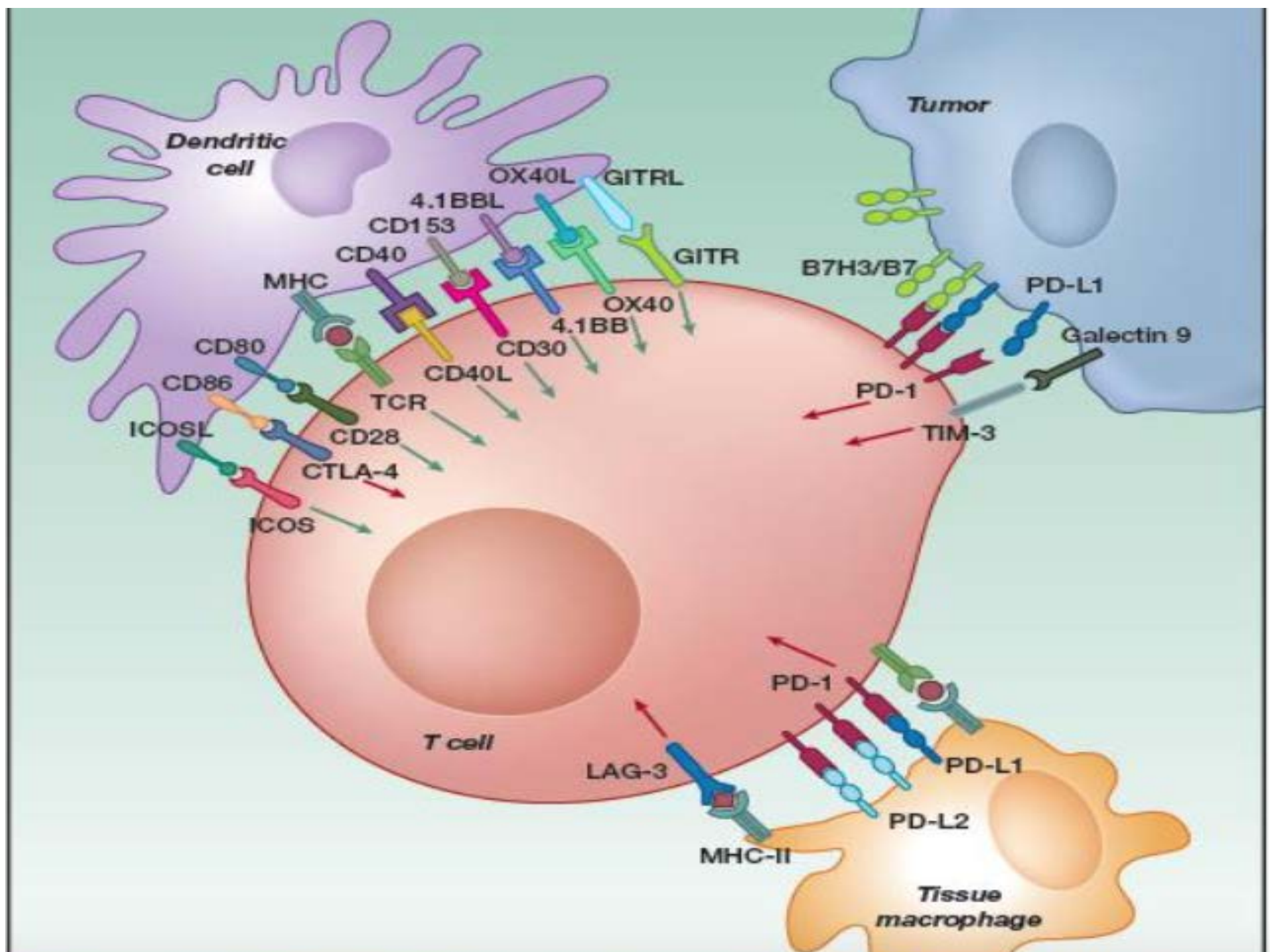
*Antibody to CTLA4 blocks its interaction with B7, restoring the ability of B7 to interact with CD28.

Postow MA, et al. *J Clin Oncol.* 2015 Jan 20. [Epub ahead of print][4]

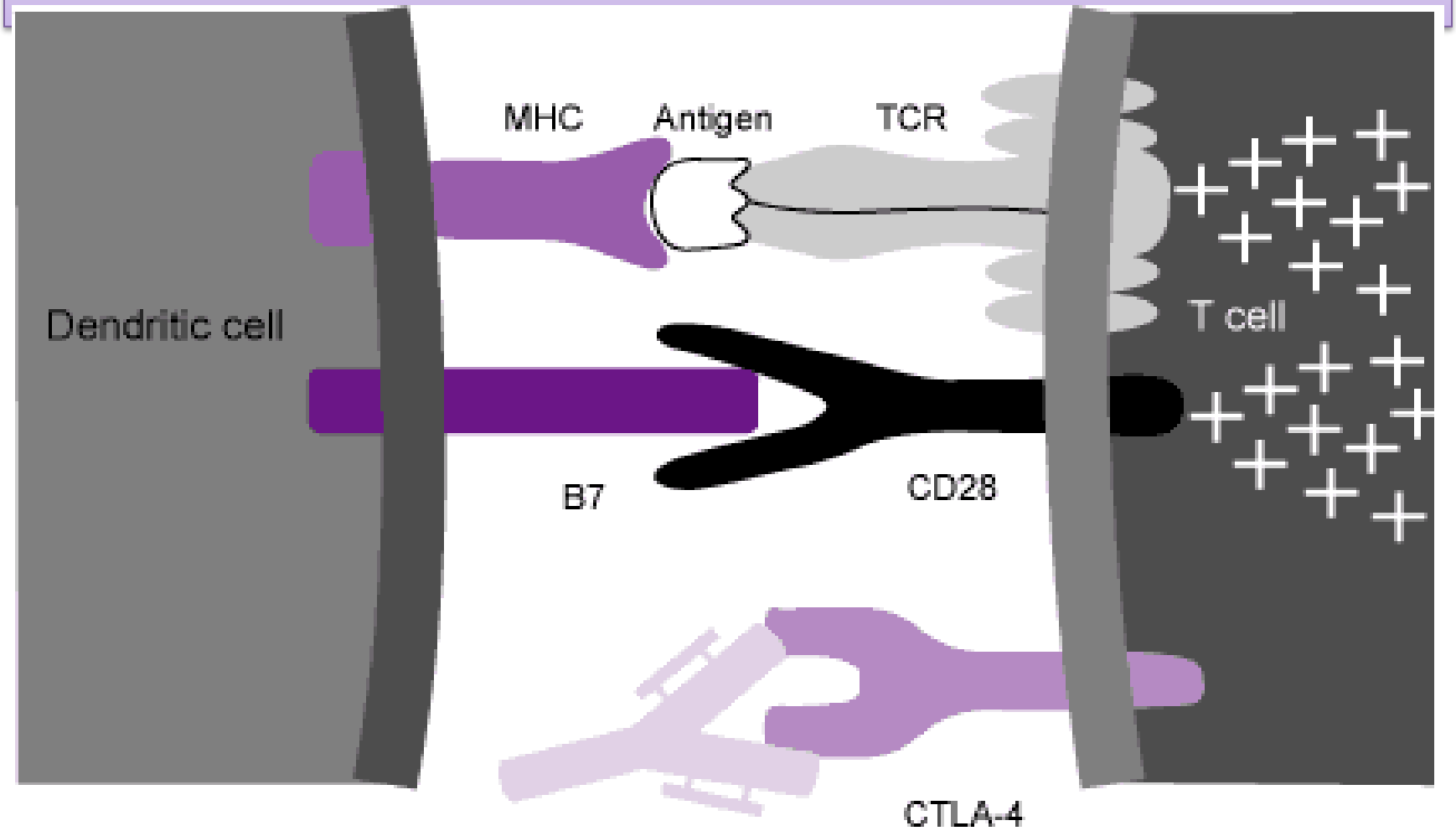
T-Hücrelerindeki Kontrol Noktaları



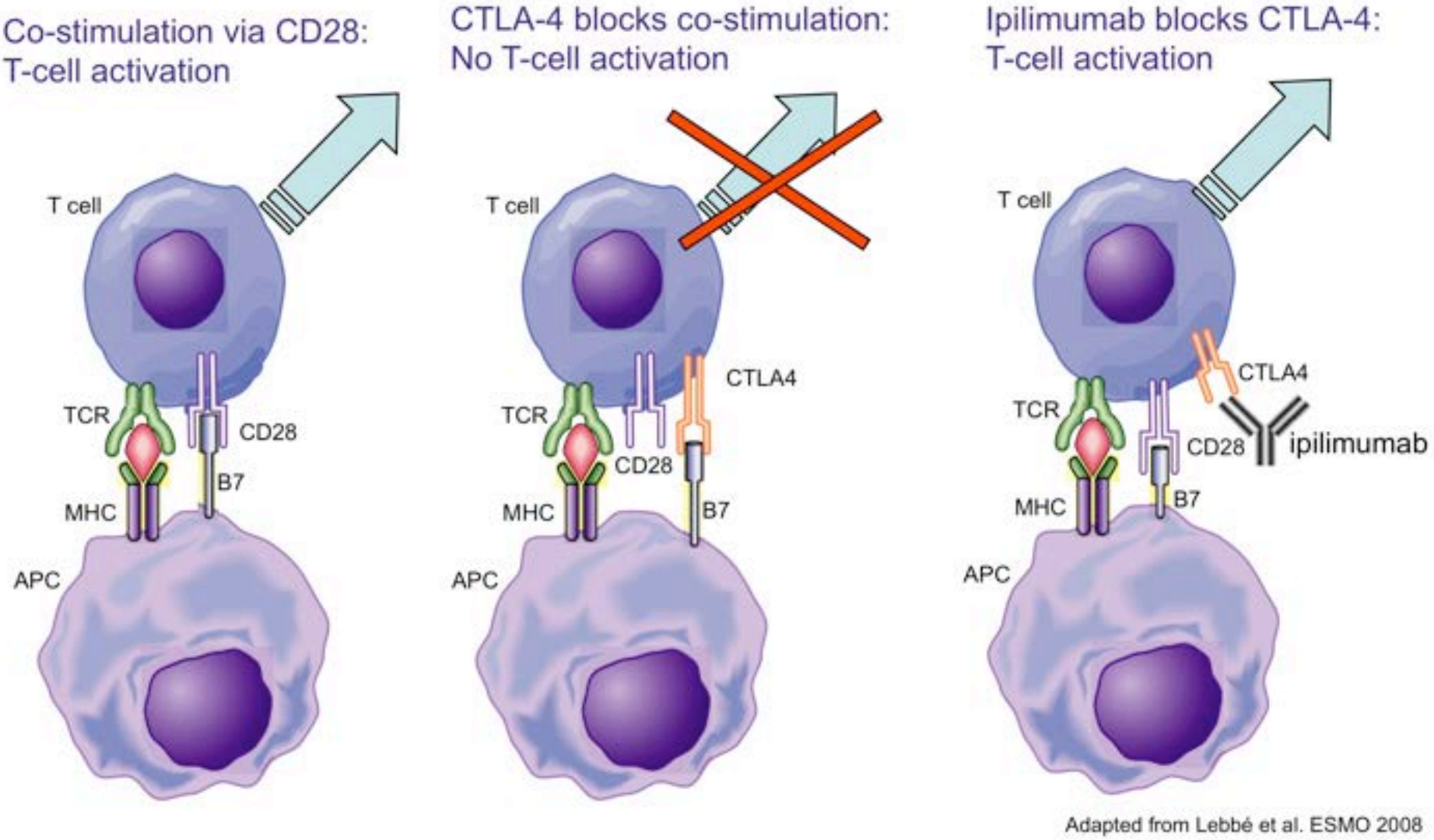
Mellman I, et al. Nature 2011: 480.


Dendritic cell
Tumor
OX40L
GITRL
4.1BBL
CD153
CD40
GITR
MHC
B7H3/B7
PD-L1
OX40
4.1BB
CD30
Galectin 9
CD80
CD40L
CD86
PD-1
TCR
ICOSL
CD28
TIM-3
CTLA-4
ICOS
PD-1
T cell
LAG-3
PD-L1
PD-L2
MHC-II
Tissue macrophage

IPILIMUMAB



Ipilimumab Blocks Negative Signaling From CTLA-4



Adapted from Lebbé et al. ESMO 2008

APC, antigen-presenting cell; CTLA-4, cytotoxic T-lymphocyte antigen-4; MHC, major histocompatibility complex; TCR, T-cell receptor.

The NEW ENGLAND JOURNAL of MEDICINE

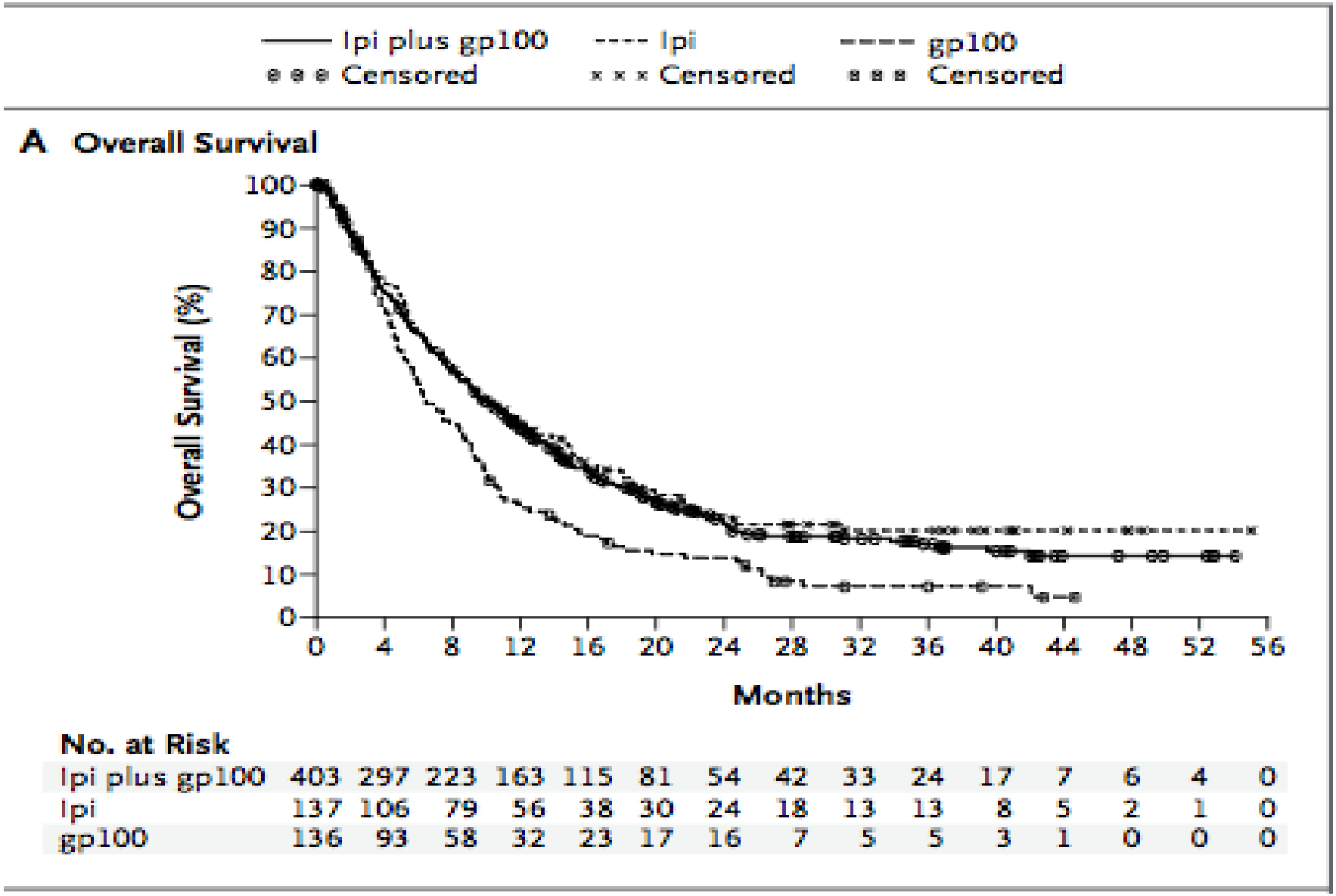
ESTABLISHED IN 1812 AUGUST 19, 2010 VOL. 363 NO. 8

Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

F. Stephen Hodi, M.D., Steven J. O'Day, M.D., David F. McDermott, M.D., Robert W. Weber, M.D., Jeffrey A. Sosman, M.D., John B. Haanen, M.D., Rene Gonzalez, M.D., Caroline Robert, M.D., Ph.D., Dirk Schadendorf, M.D., Jessica C. Hassel, M.D., Wallace Akerley, M.D., Alfons J.M. van den Eertwegh, M.D., Ph.D., Jose Lutzky, M.D., Paul Lorigan, M.D., Julia M. Vaubel, M.D., Gerald P. Linette, M.D., Ph.D., David Hogg, M.D., Christian H. Ottensmeier, M.D., Ph.D., Celeste Lebbé, M.D., Christian Peschel, M.D., Ian Quirt, M.D., Joseph I. Clark, M.D., Jedd D. Wolchok, M.D., Ph.D., Jeffrey S. Weber, M.D., Ph.D., Jason Tian, Ph.D., Michael J. Yellin, M.D., Geoffrey M. Nichol, M.B., Ch.B., Axel Hoos, M.D., Ph.D., and Walter J. Urba, M.D., Ph.D.

676 Evre III-IV Rezeke edilemeyen Malign Melanom

Gp100 **n=403**	• Ortanca SK 6.4ay
Gp100+İpilimumab **n=137**	• Ortanca SK 10 ay • HR 0.68 p<0.001
Ipilimumab **n=136**	• Ortanca SK 10.1ay


Ipi plus gp100
Censored
Ipi
Censored
gp100
Censored
A Overall Survival
Overall Survival (%)
100
90
80
70
60
50
40
30
20
10
0
0 4 8 12 16 20 24 28 32 36 40 44 48 52 56
Months
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

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ipilimumab plus Dacarbazine for Previously Untreated Metastatic Melanoma

Caroline Robert, M.D., Ph.D., Luc Thomas, M.D., Ph.D., Igor Bondarenko, M.D., Ph.D., Steven O'Day, M.D., Jeffrey Weber, M.D., Ph.D., Claus Garbe, M.D., Celeste Lebbe, M.D., Ph.D., Jean-François Baurain, M.D., Ph.D., Alessandro Testori, M.D., Jean-Jacques Grob, M.D., Neville Davidson, M.D., Jon Richards, M.D., Ph.D., Michele Maio, M.D., Ph.D., Axel Hauschild, M.D., Wilson H. Miller, Jr., M.D., Ph.D., Pere Gascon, M.D., Ph.D., Michal Lotem, M.D., Kaan Harmankaya, M.D., Ramy Ibrahim, M.D., Stephen Francis, M.Sc., Tai-Tsang Chen, Ph.D., Rachel Humphrey, M.D., Axel Hoos, M.D., Ph.D., and Jedd D. Wolchok, M.D., Ph.D.

N Engl J Med 2011; 364:2517-2526 | June 30, 2011 | DOI: 10.1056/NEJMoa1104621

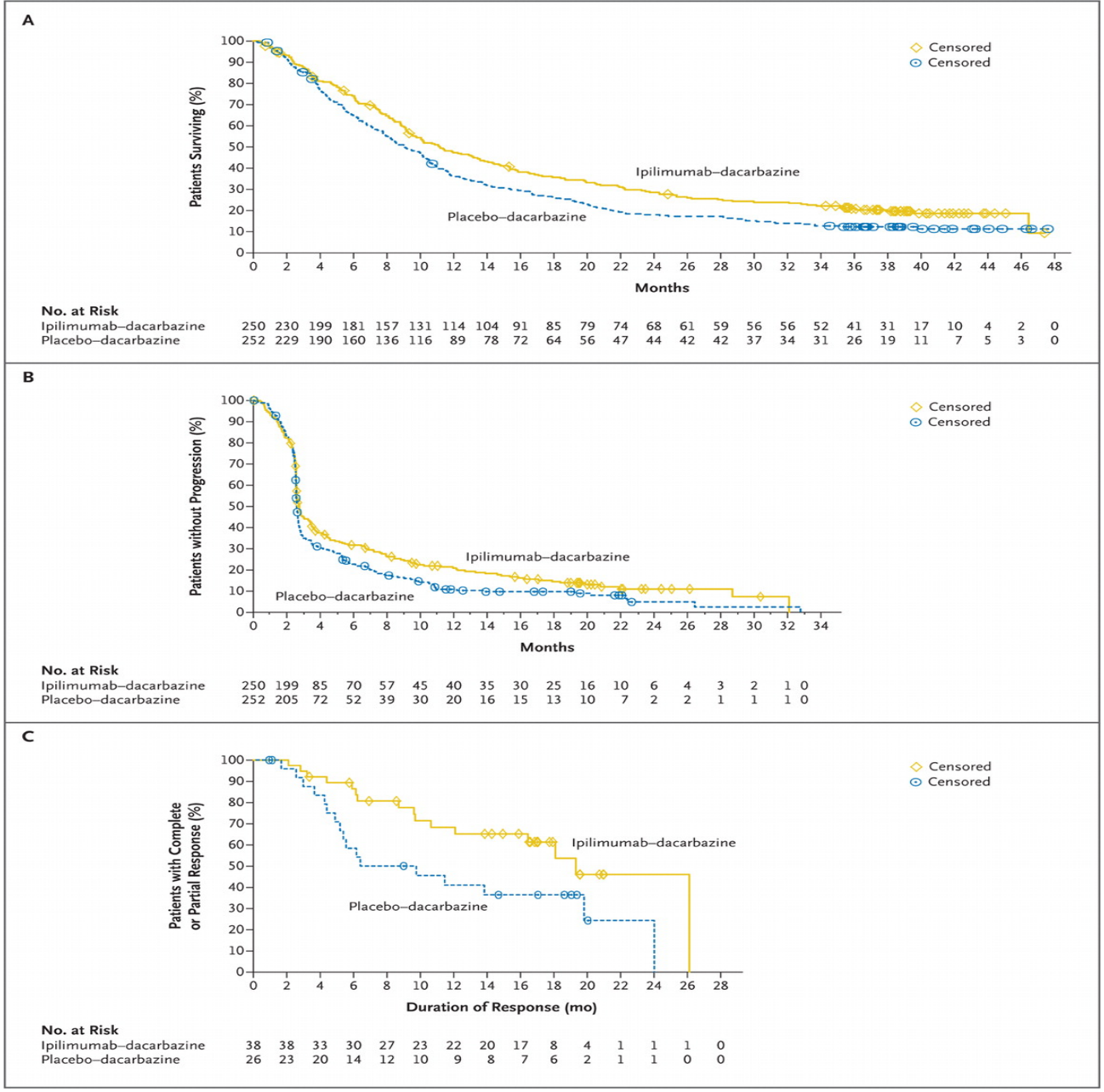
Metastatik Melanom
n=502

Dacarbazine İpilimumab

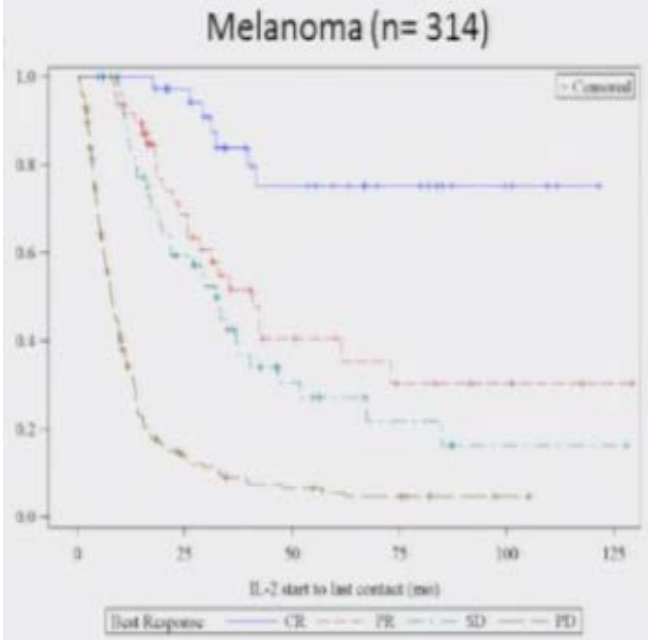
- GSK 11.2ay
- 1 yıllık SK %47.3
- 2 yıllık SK %28.5
- 3 yıllık SK %20.8

Dacarbazine

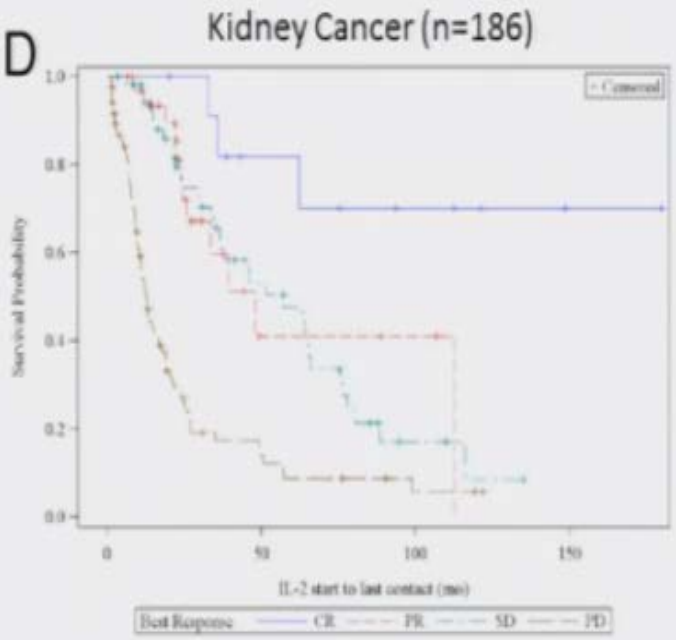
- GSK 9.1ay
- 1 yıllık SK %36.3
- 2 yıllık SK %17.9
- 3 yıllık SK %12.2


A
Patients Surviving (%)
Censored
Censored
Ipilimumab–dacarbazine
Placebo–dacarbazine
Months
No. at Risk
Ipilimumab–dacarbazine 250 230 199 181 157 131 114 104 91 85 79 74 68 61 59 56 56 52 41 31 17 10 4 2 0
Placebo–dacarbazine 252 229 190 160 136 116 89 78 72 64 56 47 44 42 42 37 34 31 26 19 11 7 5 3 0
B
Patients without Progression (%)
Censored
Censored
Ipilimumab–dacarbazine
Placebo–dacarbazine
Months
No. at Risk
Ipilimumab–dacarbazine 250 199 85 70 57 45 40 35 30 25 16 10 6 4 3 2 1 0
Placebo–dacarbazine 252 205 72 52 39 30 20 16 15 13 10 7 2 2 1 1 1 0
C
Patients with Complete or Partial Response (%)
Censored
Censored
Ipilimumab–dacarbazine
Placebo–dacarbazine
Duration of Response (mo)
No. at Risk
Ipilimumab–dacarbazine 38 38 33 30 27 23 22 20 17 8 4 1 1 1 0
Placebo–dacarbazine 26 23 20 14 12 10 9 8 7 6 2 1 1 0 0

Durable clinical responses are seen with IL-2

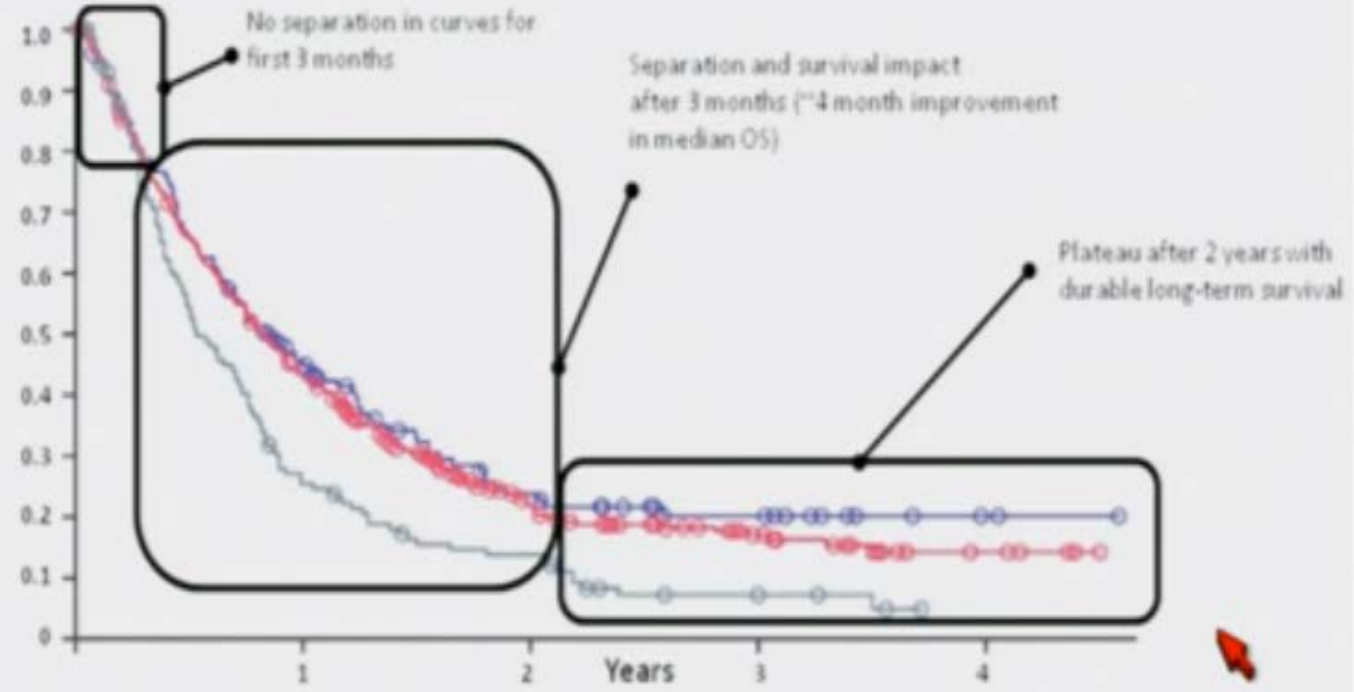


D



(Curti et al. JITC 2014)

Durable clinical responses are seen with anti-CTLA-4 treatment

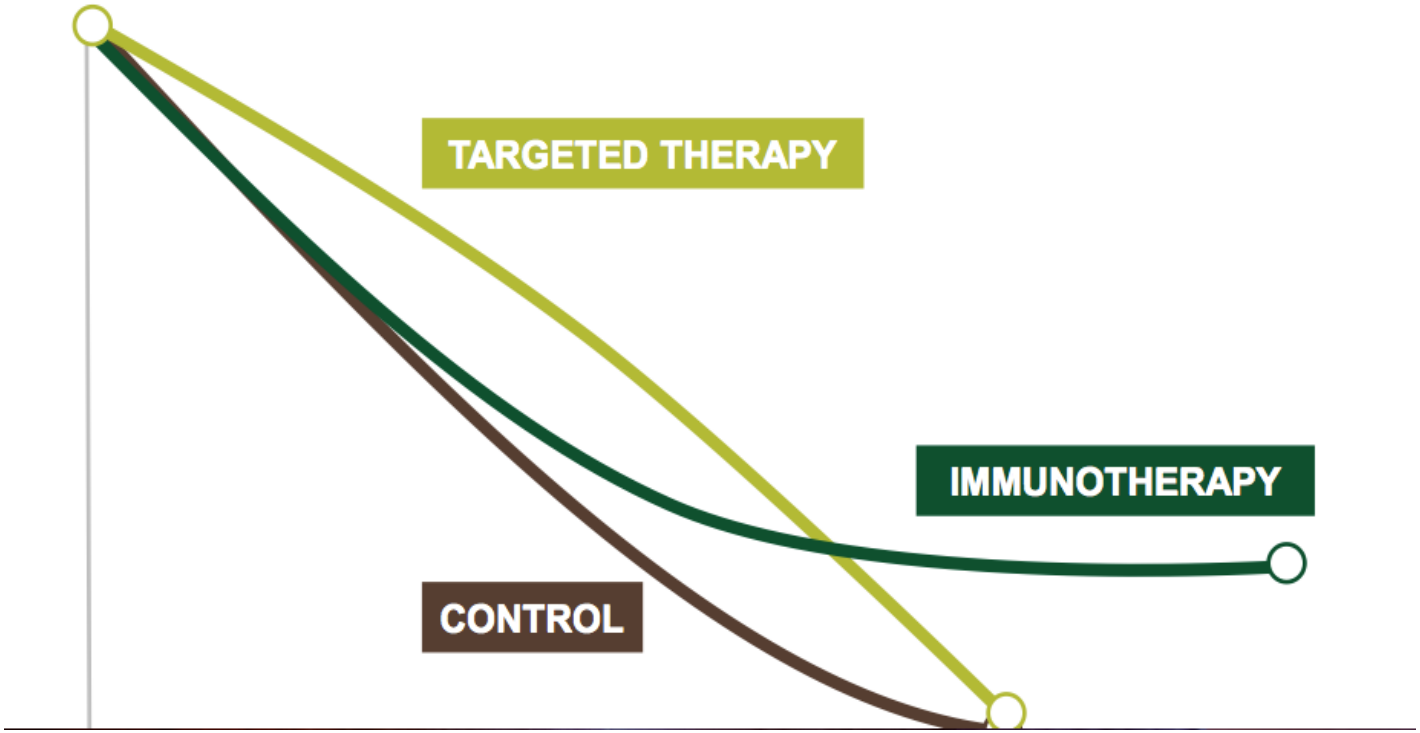


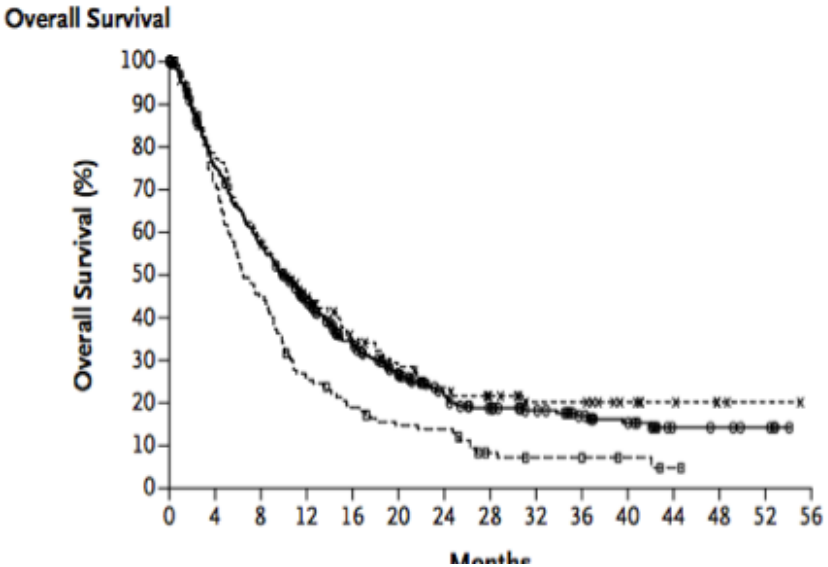
Comparison	HR	P-value
Arms A vs C	0.68	<0.001
Arms B vs C	0.66	0.003

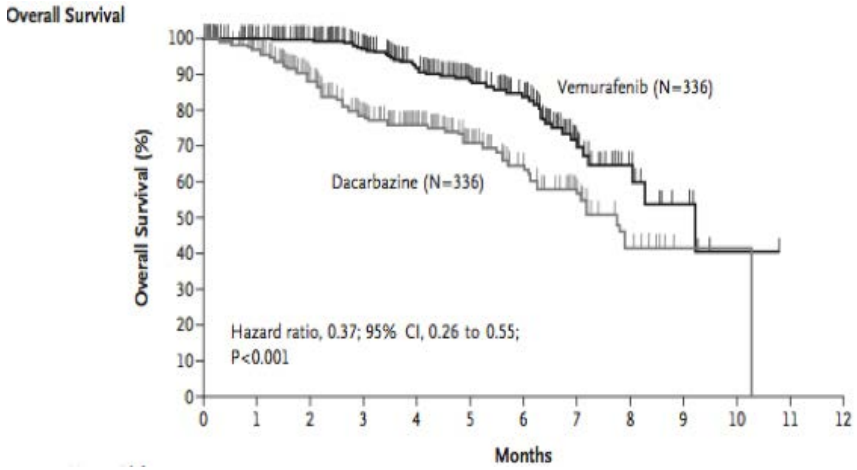
ipilimumab + gp100 (A)
ipilimumab alone (B)
gp100 alone (C)

(Wolchok et al. Ann Acad Sci 2013)

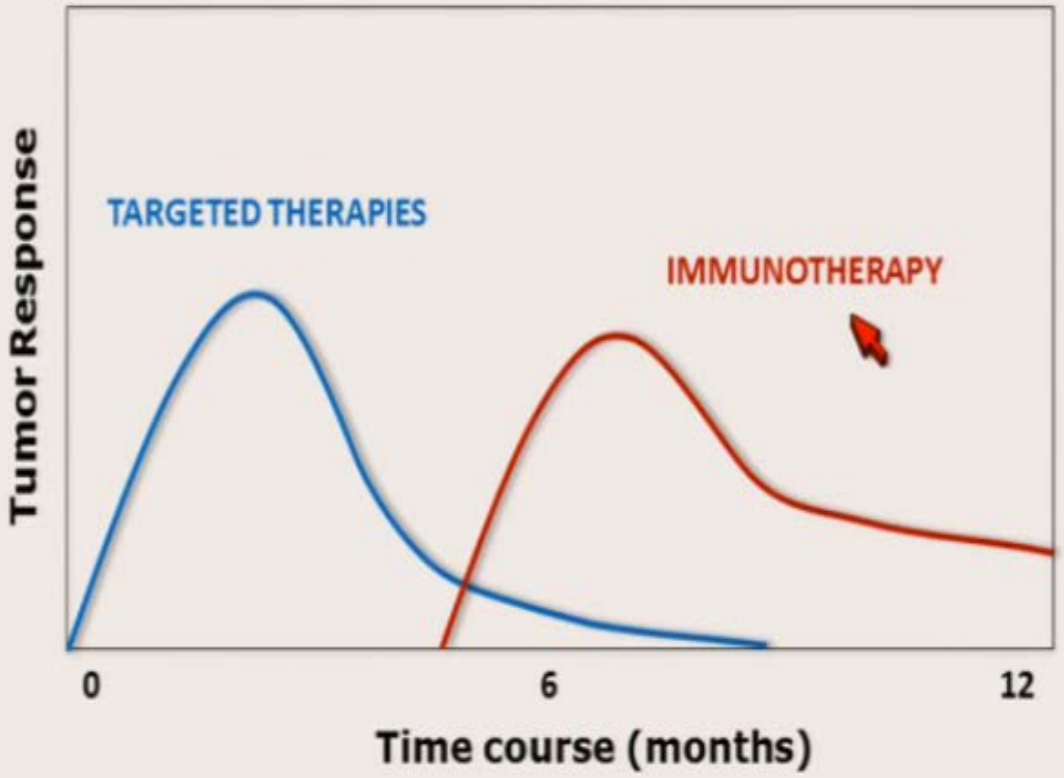
Cancer immunotherapies can improve survival.



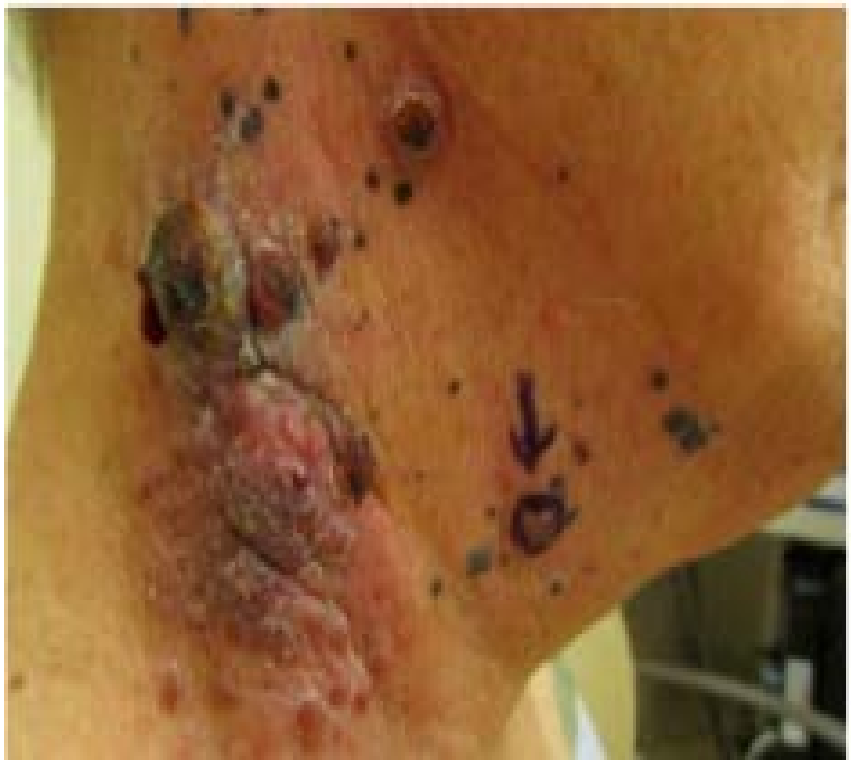

Overall Survival
Overall Survival (%)
100
90
80
70
60
50
40
30
20
10
0
0 4 8 12 16 20 24 28 32 36 40 44 48 52 56


Overall Survival
Overall Survival (%)
Vemurafenib (N=336)
Dacarbazine (N=336)
Hazard ratio, 0.37; 95% CI, 0.26 to 0.55;
P<0.001
0 1 2 3 4 5 6 7 8 9 10 11 12
Months

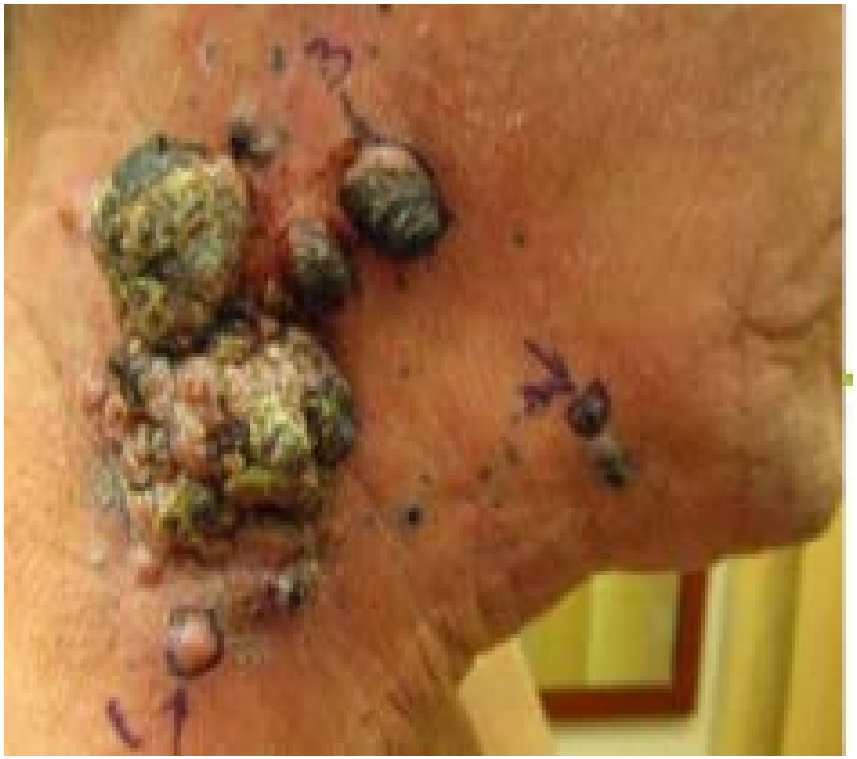
Antitumoral response: Targeted therapies vs. Immunotherapies (CTLA-4 antibodies)



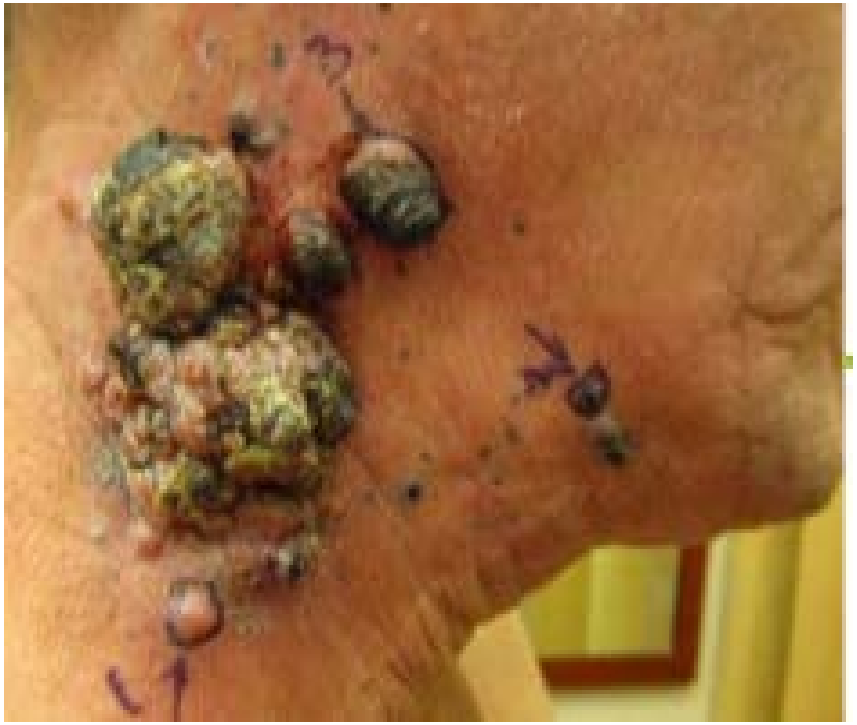
Başlangıç



6.hafta



6.hafta



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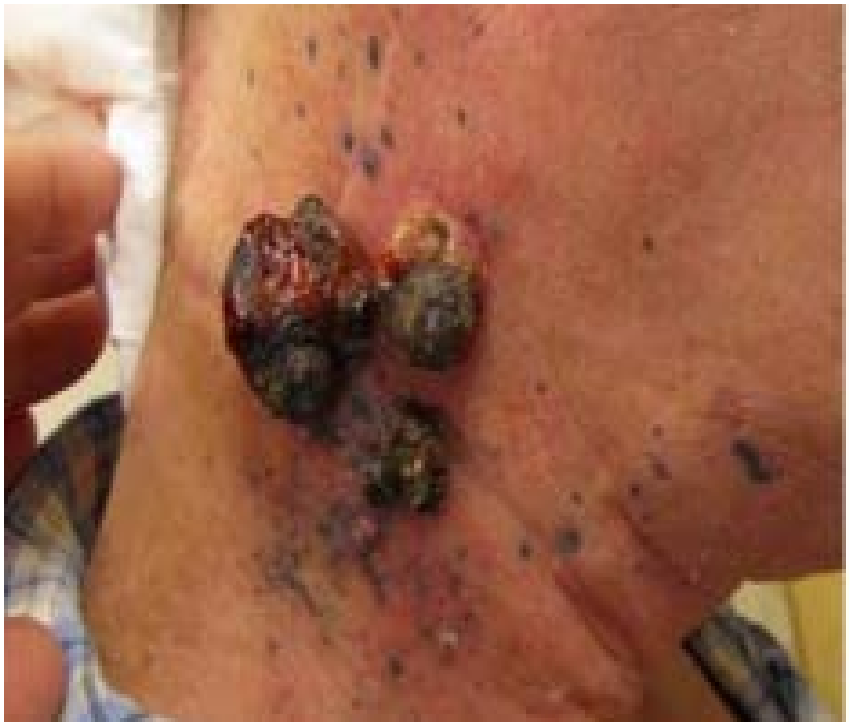
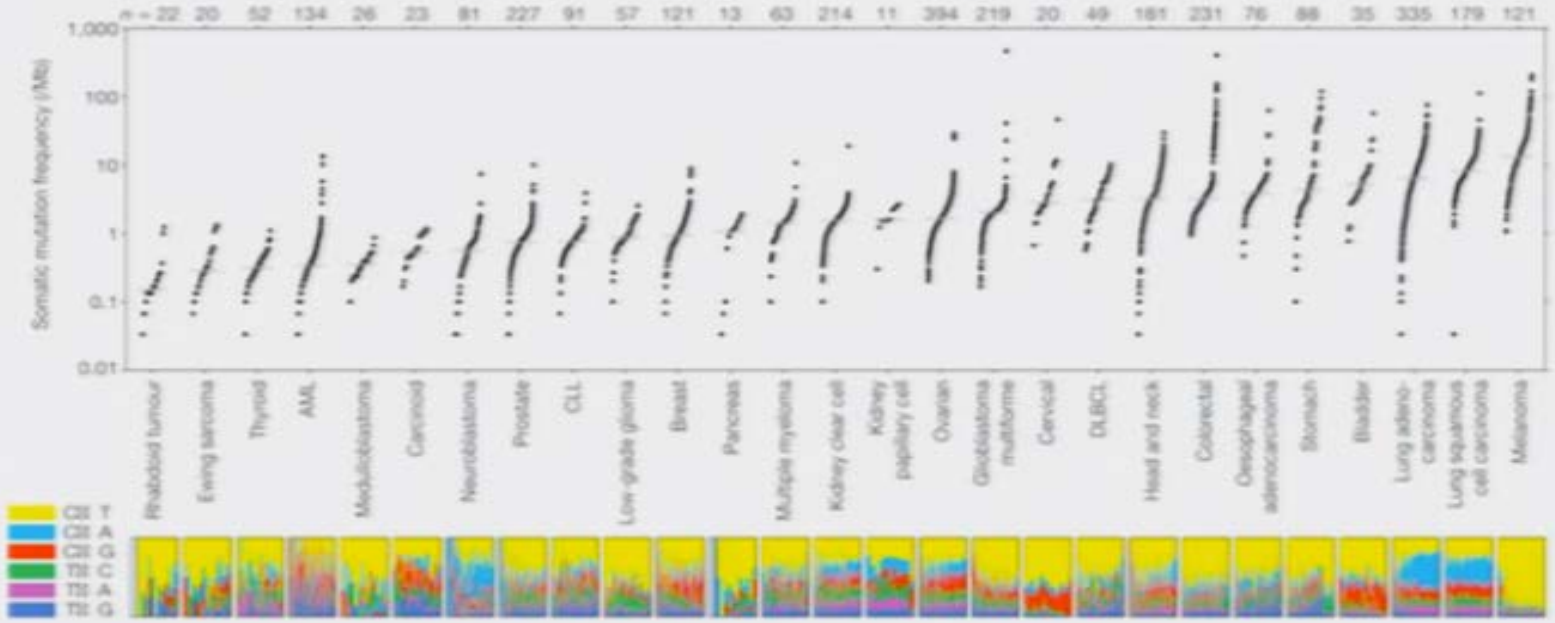


İpilimumab Tedavisine Yanıt Şekilleri

- **Klasik Yanıt:**
  - İndeks lezyonlarda gerileme
  - Stabil hastalık veya lezyonlarda çok yavaş gerileme

- **Farklı yanıt şekilleri**:
  - Başlangıçta tümör boyutlarında büyüme bir süre sonra küçülme
  - Yeni lezyonların gelişmesi, zamanla indeks lezyonlar ve yeni gelişen lezyonların gerilemesi

Many of the responsive tumors have a high mutation rate



(Gonzalez-Perez et al, Nat Gen

İpilimumabın Etkisi

- Yanıt oranı %10-15
- Yanıt süresi uzun (medyan 20ay)
- Yanıtın gelişmesi >3ay alabilir.Başlangıçta progresyon görülebilir.
- Cevap elde edilen %20 hastada >2-3 yıl hastalık kontrol altında
- Prediktif iyi bir biyobelirteç yok (lökosit, eozinofil sayısı, immün sistem ilişkili yan etkiler…)

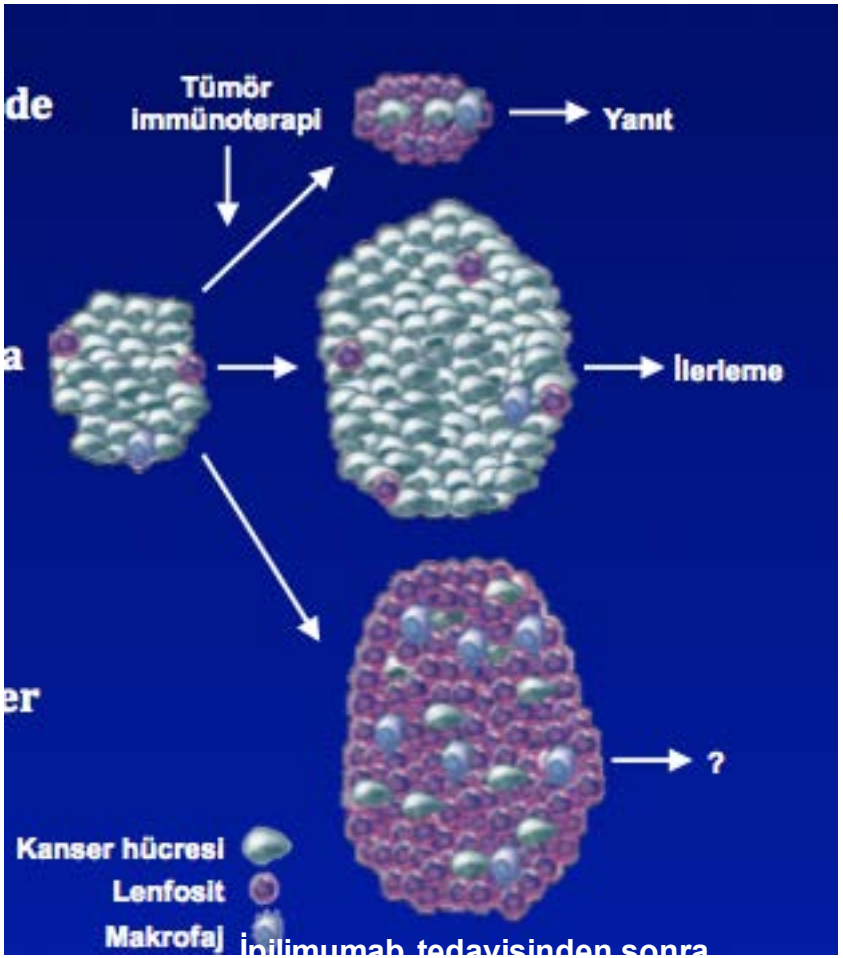
İmmünoterapinin Özellikleri

- Aynı immunoterapi çok farklı tümörlerde işe yarayabilir.
- İmmün sistem yolakları değil tümör antijenlerini hedef alır.
- Tümörde meydana gelen mutasyonlar antijen yapısını değiştirerek immün yanıtı arttırabilir.
- Yanıt elde edilen hastalarda yanıt süresi uzun süreli olur.
- İmmunoterapi tümörü değil hastayı tedavi eder.

İmmünoterapilere yanıt nasıl görülür ?

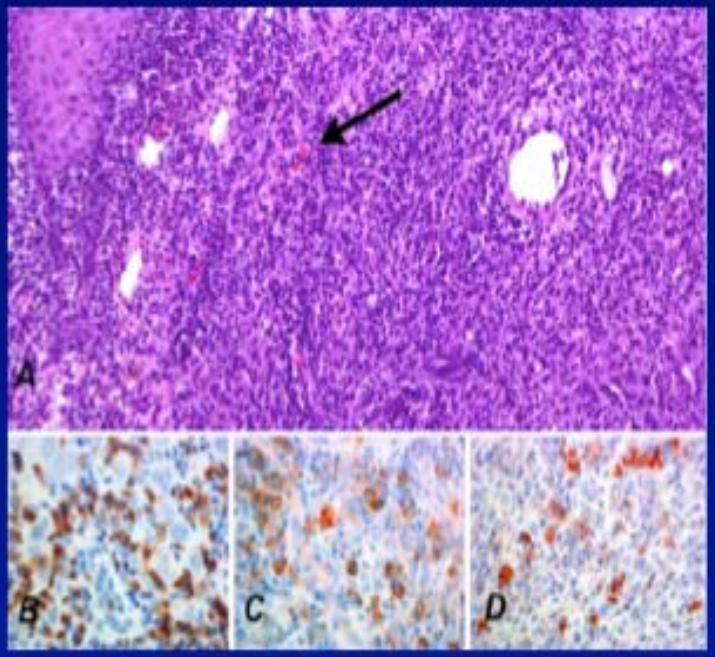
- İpilimumab verilen hastalarda TIL'lere bağlı olarak belirgin intralezyonal ve perilezyonal enflamasyon ve ödem göstermiştir

- İmmunolojik yanıt radyolojik olarak yalancı bir progresyon olarak yorumlanabilir



1. Ribas A, et al. *Clin Cancer Res* 2009;15:7116–7118
2. Hamid O, et al. *J Transl Med*

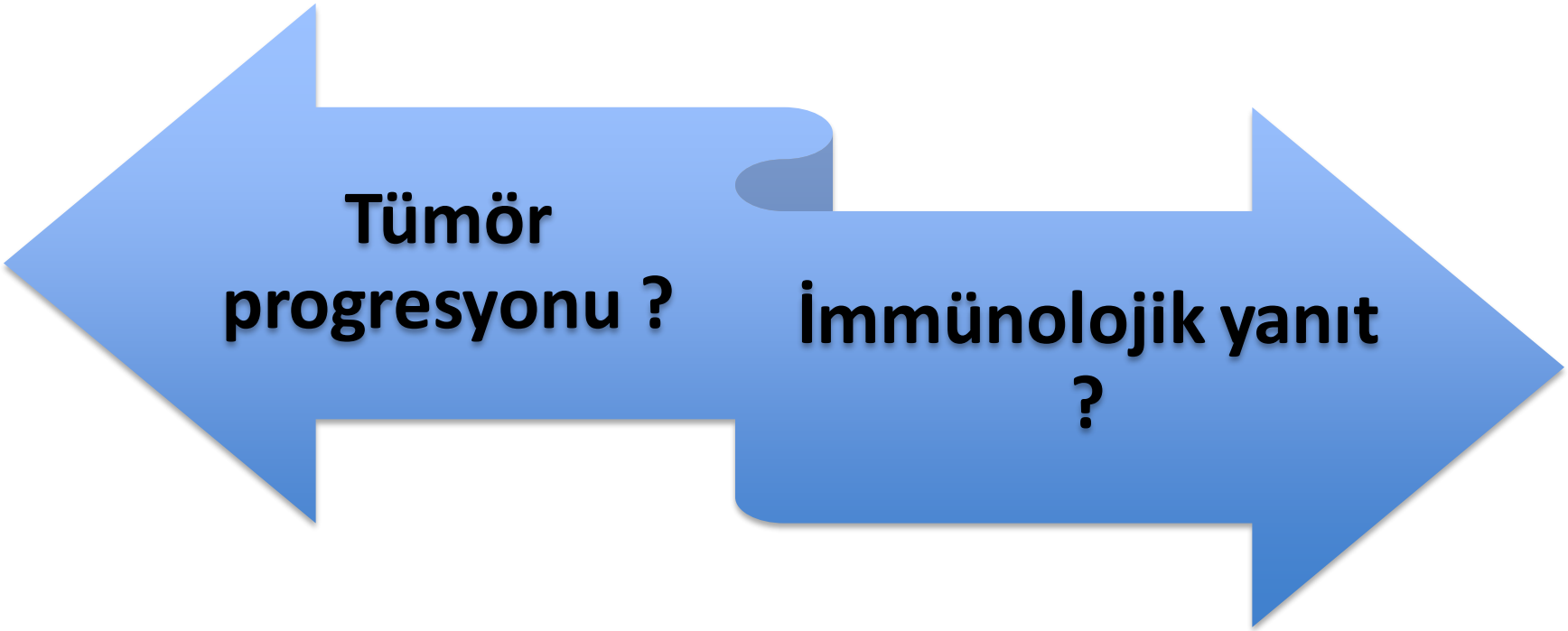
- **Tümör lezyonlarının volümetrik değerlendirmesi tümör lezyonlarında ipilimumabın biyolojik etkilerini yansıtmaz**



- İpilimumab idame tedavisi sırasında bir kütanöz bacak lezyonunda yoğun enflamatuvar infiltrat
- Hastada Hafta 12 ila 16 arasında tümör hacminde %36 artış (WHO kriterlerine göre PD)
- Hafta 20'den itibaren PR
- İpilimumab tedavisine başlandıktan sonra 17+ ay devam etmektedir

=> SD ve PR'ler sitotoksik kemoterapiden çok daha uzun sürelidir

Di Giacomo AM, et al. Cancer Immunol Immunother 2009;58:1297-306


Tümör progresyonu ?
İmmünolojik yanıt ?

RECIST v1.1 vs. Modified RECIST (Immune criteria)

Summary of Changes	RECIST v1.1	Modified RECIST
New lesion after baseline	Define progression	New measurable lesion are added into the total tumor burden and followed
Target lesions	Limited to 5	Limited to 10
Non-target lesions	May contribute to the designation of the overall progression	Contribute only in the assessment of a complete response
Radiographic progression	First instance of ≥ 20% increase in the sum of diameters or unequivocal progression in non-target disease	Determined only on the basis of measurable disease; may be confirmed by a consecutive assessment ≥4 weeks from the date first documented

Modified RECIST:

- **Derived from RECIST v1.1 conventions**
- **Used for assessing disease progression and response to immunotherapy in solid tumors**

GASTROİNTESTİNAL

Aşağıdaki gibi belirtiler ve semptomlar:

- Divare
- Karın ağrısı
- Ateşin eşlik ettiği veya etmediği dışkıda kan veya mukus
- Bağırsak perforasyonu
- Peritoneal belirtiler
- İleus

KARACİĞER

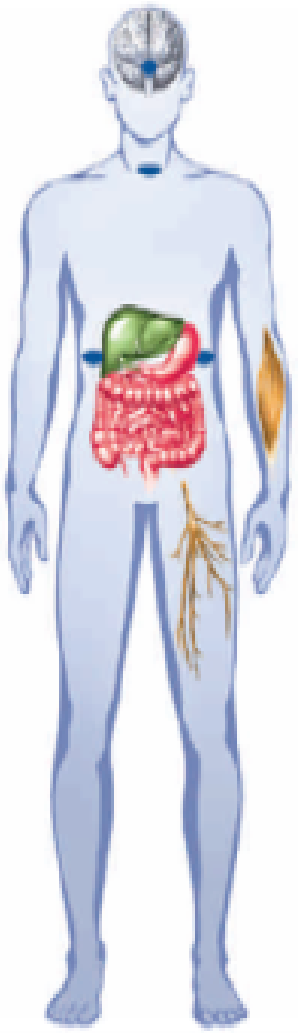
Aşağıdaki gibi belirtiler

- Anormal karaciğer fonksiyon testleri (örn. AST, ALT veya total bilirubin)
- Sarılık
- Karaciğer yetmezliği

CİLT

Aşağıdaki gibi semptomlar

- Prürit
- Deri döküntüsü
- Deride kuruluk
- Dermatit



NÖROLOJİK

Aşağıdaki gibi semptomlar

- Unilateral veya bilateral güçsüzlük
- Duyusal değişiklikler
- Parestezi

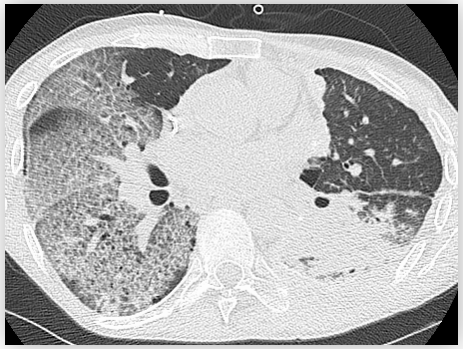
ENDOKRİN

Aşağıdaki gibi belirtiler ve semptomlar:

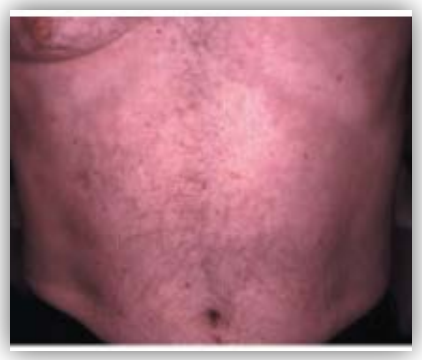
- Yorgunluk
- Baş ağrısı
- Mental durum değişiklikleri
- Karın ağrısı
- Anormal bağırsak alışkanlıkları
- Hipotansiyon
- Anormal tiroit fonksiyon testleri ve/veya serum kimyası

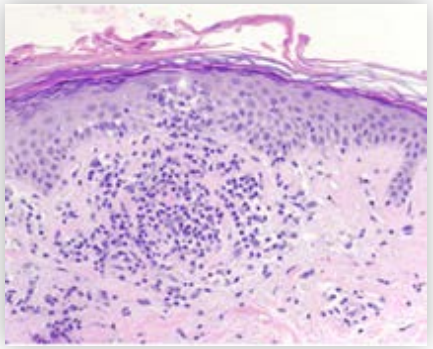
İmmünolojik Yan Etkiler

Pnömonitis(anti-PD-1)

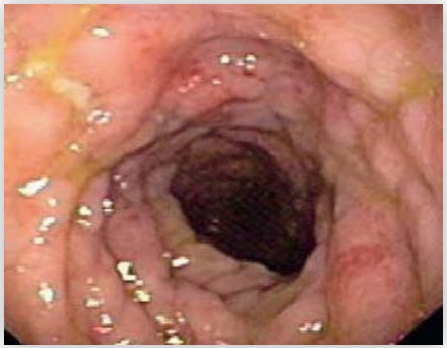


Döküntü (anti-CTLA-4

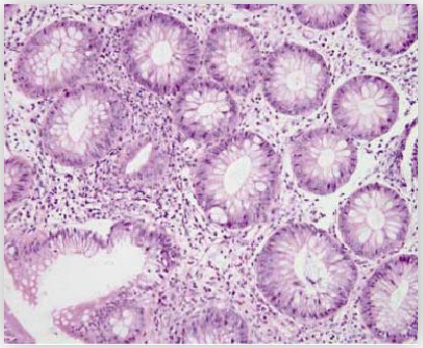


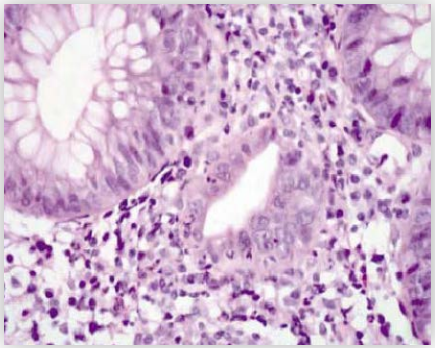


Gastrointestinal yan etkiler (anti-CTLA-4)



Kolonda ülserasyon ve ödem



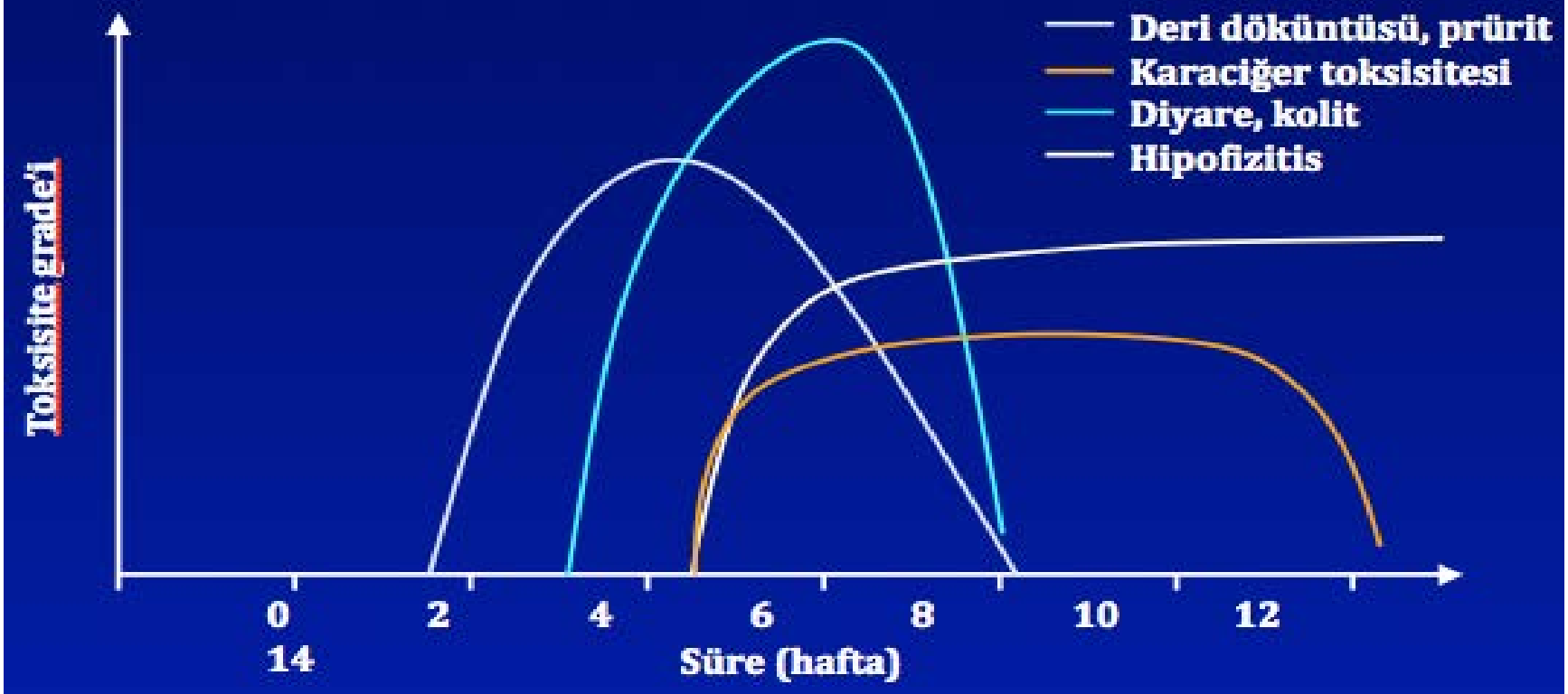


Fokal aktif kolit goblet hücre kaybı ve epitelde nötrofil infiltrasyonu

1Hodi F, et al. *Proc Natl Acad Sci USA.* 2003;100:4712–4717; 2. Maker A, et al. *Ann Surg Oncol.* 2005;12:1005–1016.

Yan Etkiler

- İlk olarak cilt, sonrasında kolit, hipofizitis ve son olarak hepatit

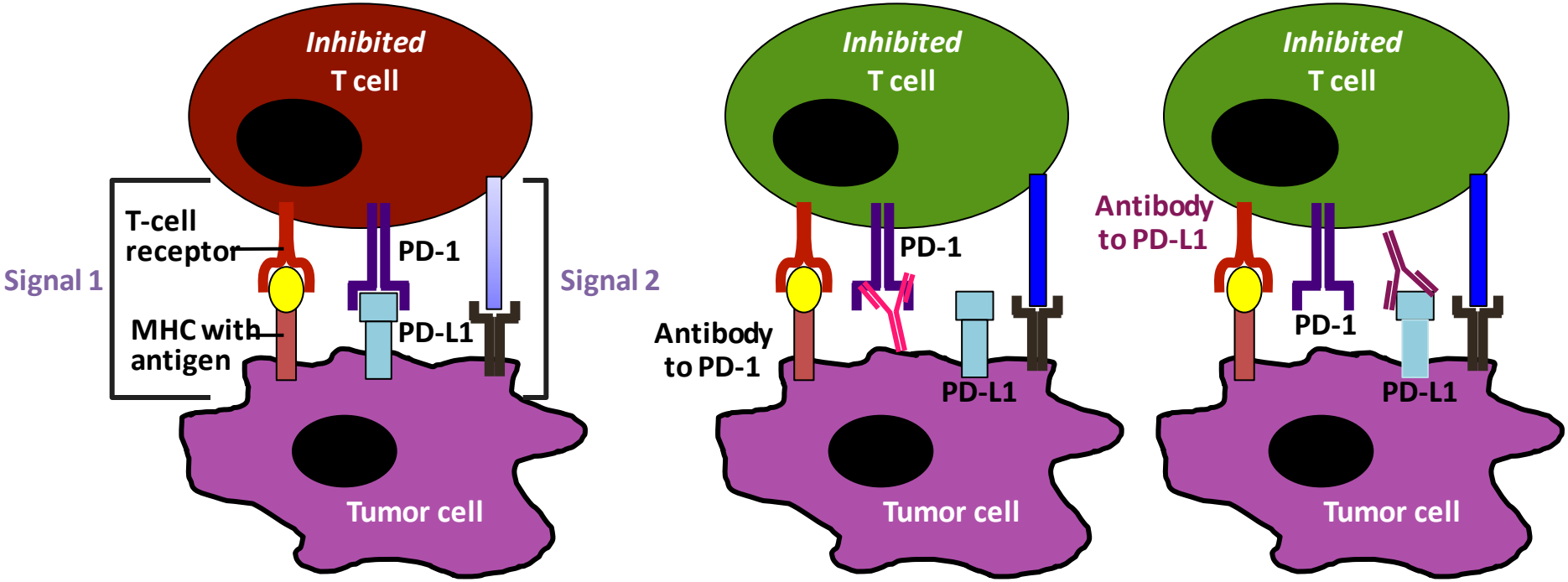


Weber JS, et al. *J Clin Oncol* 2012;30:2691-2697

PD-1/PD-L1

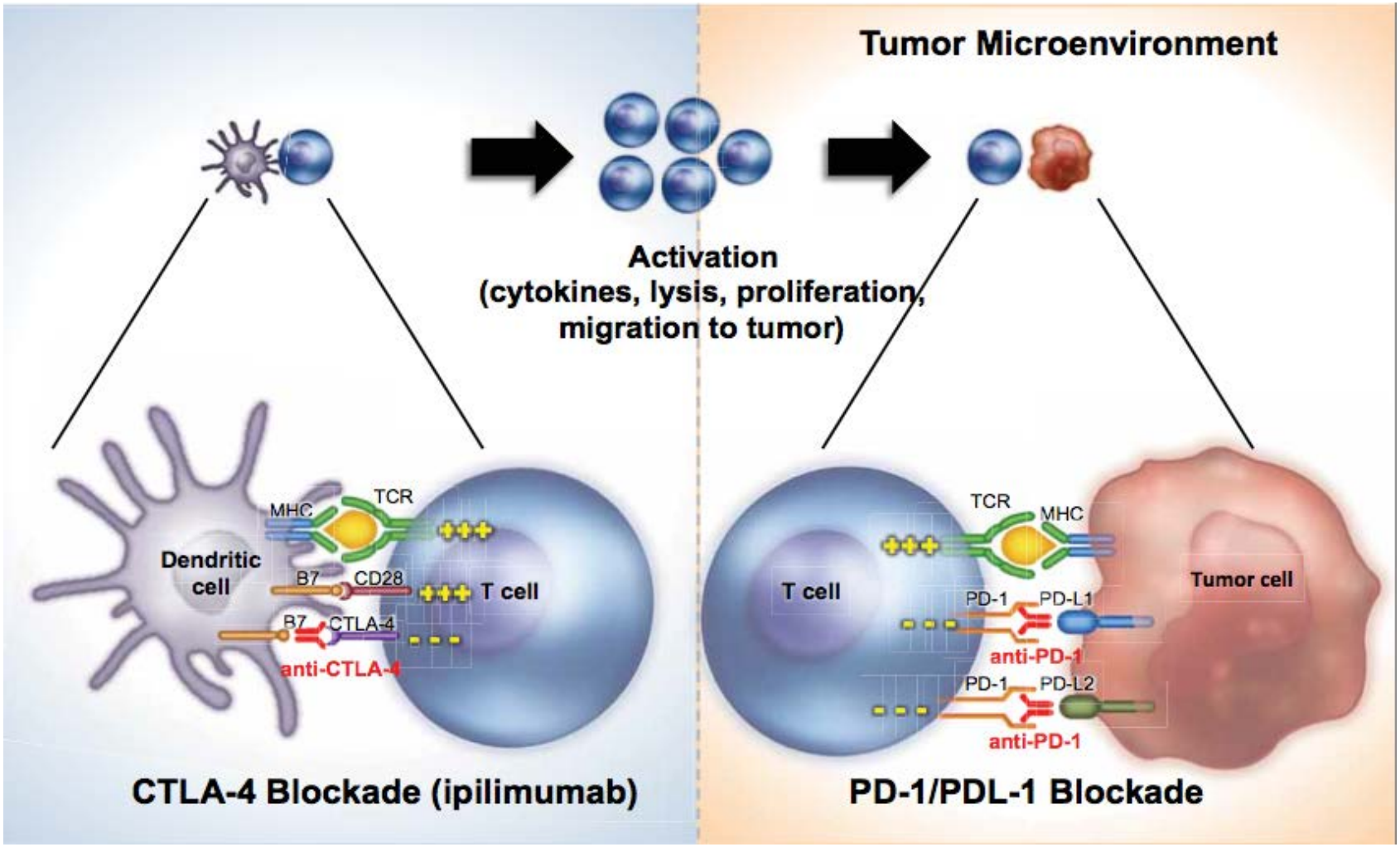
Binding of PD-L1 to PD-1 receptor downregulates T-cell effector functions

Antibody-mediated blockage of the binding of PD-L1 protein to PD-1 receptor restores T-cell effector functions

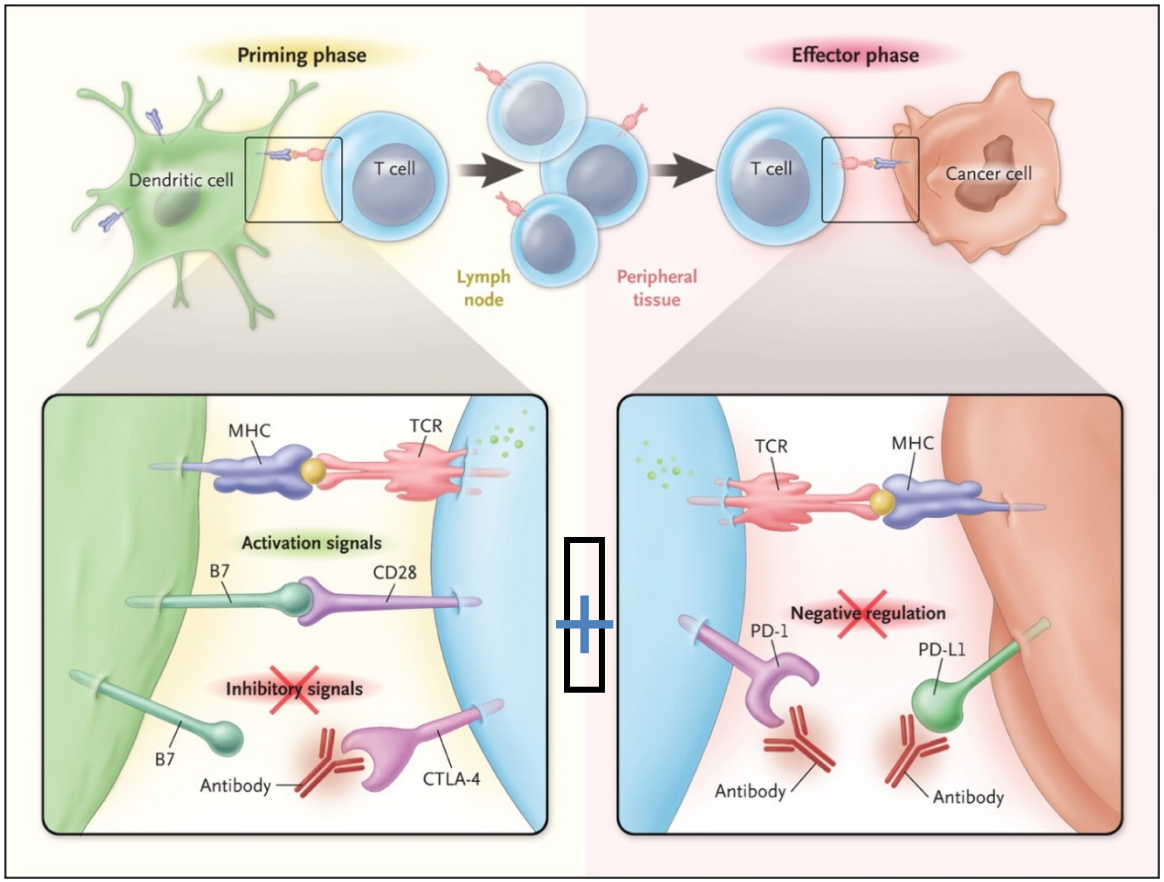


Sznol M, Chen L. *Clin Cancer Res.* 2013;19:1021-1034.[47]

CTLA-4 ve PD-1


Tumor Microenvironment
Activation
(cytokines, lysis, proliferation,
migration to tumor)
Dendritic
cell
MHC
TCR
B7
CD28
T cell
B7
CTLA-4
anti-CTLA-4
CTLA-4 Blockade (ipilimumab)
T cell
TCR
MHC
PD-1
PD-L1
anti-PD-1
Tumor cell
PD-1
PD-L2
anti-PD-1
PD-1/PDL-1 Blockade

CTLA-4 ve PD-1/L1 Kontrol Noktası İnhibitörleri



Ribas A. N Engl J Med. 2012;366:2517-2519. Copyright © 2012 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

	CTLA-4	PD-1
Ekspresyon	T hücreleri	T hücreleri B hücreleri NK hücreleri Dendritik hücreler
Ligandları	Antijen presente eden hücreler B7 ailesi (CD80/86) ▪B7.1 (CD80) ▪B7.2 (CD86	Hemopoetik hücreler Hemopoetik olmayan dokular ve organlar **Tümör Hücreleri** ▪PD-L1 (B7-H1/CD274) ▪PD-L2 (B7-CD/CD273)
Tedavide kullanılan inhibitörler	İpilimumab	Nivolimumab Pembrolizumab

Merelli B, et al. Crit Rev Oncol Hematol. 2014;89:140-165.

Anti-CTLA-4	Anti-PD1	Anti-PD-L1
İpilimumab Bristol- Myers Squibb IgG1	Nivolimumab Bristol-Myers Squibb IgG4	Atezolizumab MPDL3280A- Roche-Genentech IgG1
Tremilumumab Medimmün-Astra- Zeneca IgG2	Pembrolizumab (MK-3475) Merck Humanize IgG4	Medi-4736 Medimmün-Astra Zeneca IgG1
	Pidilizumab Cure Tech Humanize IgG1	Amp-514 Medimmün –Astra Zeneca
	Amp-224 Medimmün-Asta Zeneca PD1/B7 Fc fusion protein	MDX-1105/BMS936559 Bristol-Myers Squibb

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 28, 2012 VOL. 366 NO. 26

Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer

Suzanne L. Topalian, M.D., F. Stephen Hodi, M.D., Julie R. Brahmer, M.D., Scott N. Gettinger, M.D., David C. Smith, M.D., David F. McDermott, M.D., John D. Powderly, M.D., Richard D. Carvajal, M.D., Jeffrey A. Sosman, M.D., Michael B. Atkins, M.D., Philip D. Leming, M.D., David R. Spigel, M.D., Scott J. Antonia, M.D., Ph.D., Leora Horn, M.D., Charles G. Drake, M.D., Ph.D., Drew M. Pardoll, M.D., Ph.D., Lieping Chen, M.D., Ph.D., William H. Sharfman, M.D., Robert A. Anders, M.D., Ph.D., Janis M. Taube, M.D., Tracee L. McMiller, M.S., Haiying Xu, B.A., Alan J. Korman, Ph.D., Maria Jure-Kunkel, Ph.D., Shruti Agrawal, Ph.D., Daniel McDonald, M.B.A., Georgia D. Kollia, Ph.D., Ashok Gupta, M.D., Ph.D., Jon M. Wigginton, M.D., and Mario Sznol, M.D.

- 296 olgu
- Yanıt Oranı (236 olguda)
  - KHDAK %18
  - Melanom %28
  - Renal Hücreli karsinom %27
- Grade 3-4 yan etki % 14
- İmmunohistokimyasal PD-L1 incelemesi
  - Negatif ise yanıt yok
  - Pozitif ise %36

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Safety and Activity of Anti–PD-L1 Antibody in Patients with Advanced Cancer

Julie R. Brahmer, M.D., Scott S. Tykodi, M.D., Ph.D., Laura Q.M. Chow, M.D., Wen-Jen Hwu, M.D., Ph.D., Suzanne L. Topalian, M.D., Patrick Hwu, M.D., Charles G. Drake, M.D., Ph.D., Luis H. Camacho, M.D., M.P.H., John Kauh, M.D., Kunle Odunsi, M.D., Ph.D., Henry C. Pitot, M.D., Omid Hamid, M.D., Shailender Bhatia, M.D., Renato Martins, M.D., M.P.H., Keith Eaton, M.D., Ph.D., Shuming Chen, Ph.D., Theresa M. Salay, M.S., Suresh Alaparthy, Ph.D., Joseph F. Grosso, Ph.D., Alan J. Korman, Ph.D., Susan M. Parker, Ph.D., Shruti Agrawal, Ph.D., Stacie M. Goldberg, M.D., Drew M. Pardoll, M.D., Ph.D., Ashok Gupta, M.D., Ph.D., and Jon M. Wigginton, M.D.

N Engl J Med 366,26;2012

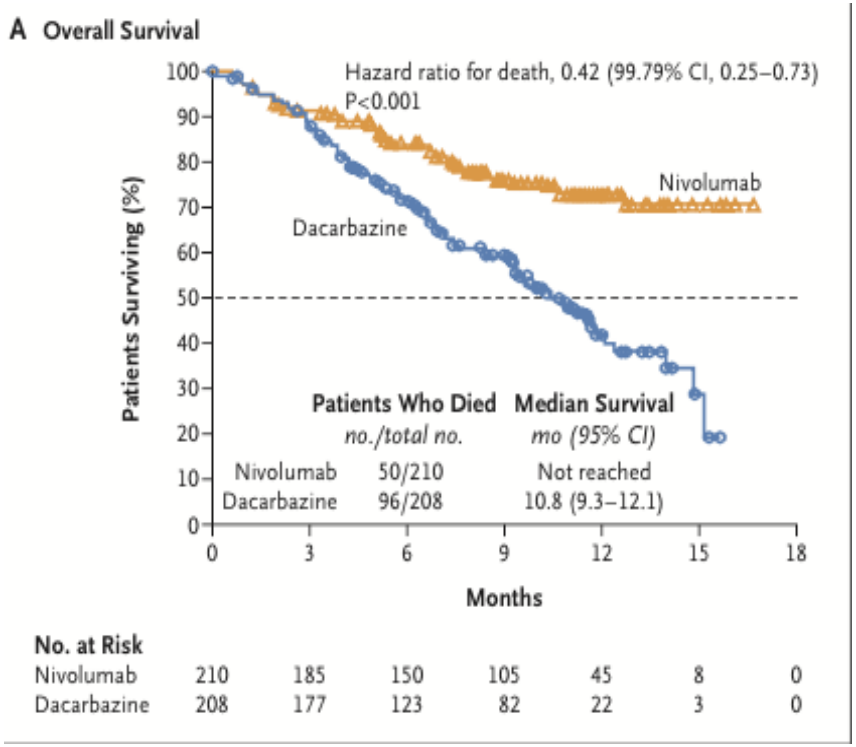
Anti-PDL1 Antikoru Faz I Çalışma
N Engl J Med 366; 2012

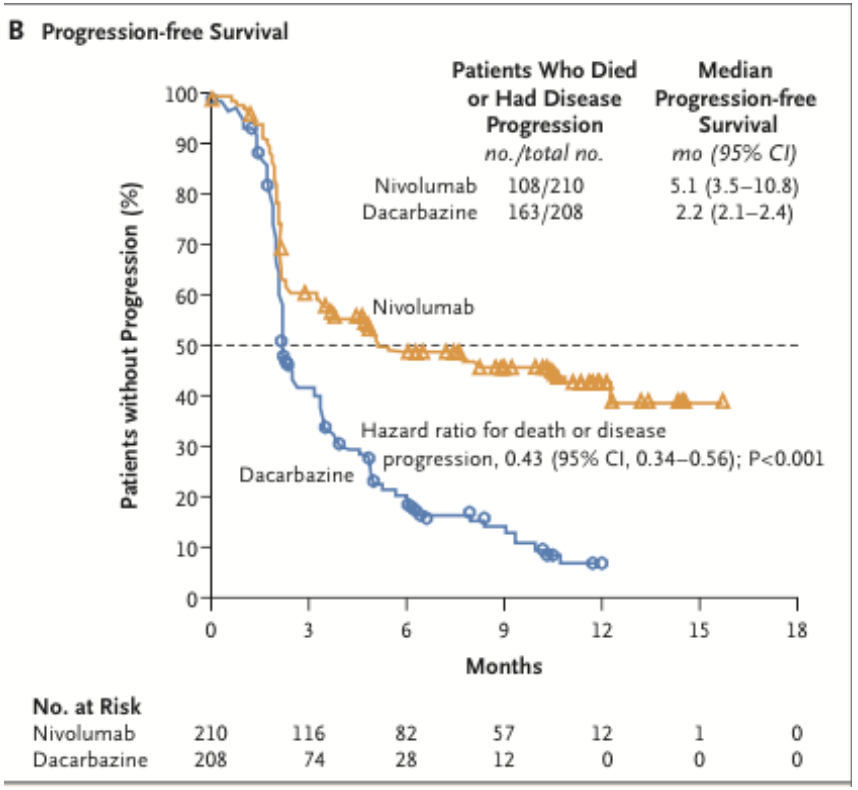
- 207 olgu
  - 75 KHDAK (5/49)
  - 55 malign melanom (9/52)
  - 18 kolorektal kanser
  - 17 renal cell (2/17)
  - 17 0ver kanseri
  - 14 pankreas kanseri
  - 7 mide kanseri
  - 4 meme kanseri
- Objektif yanıt oranı %6-17
- Stabilizasyon %12-41
- Yan etki %9

Anti-PD-1 ve anti-PD1L1

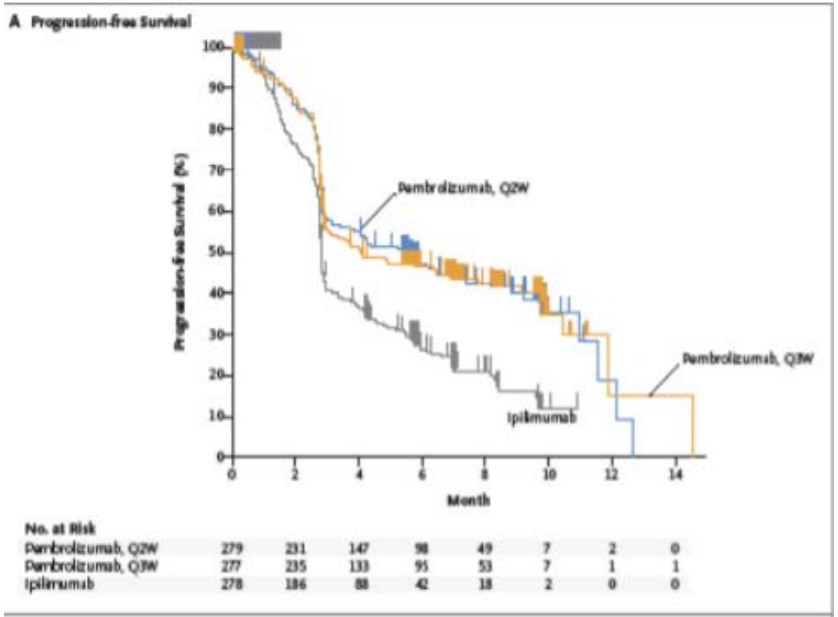
- Melanom
- RCC
- KHDAK
- Mesane
- Baş Boyun
- Lenfoma
- Glioblastoma multiforme
- Diğer tm ???

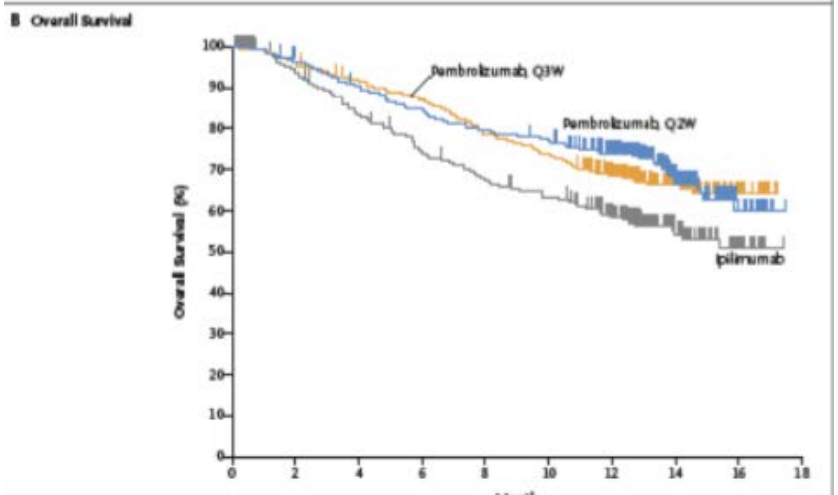
Nivolumab- Melanom



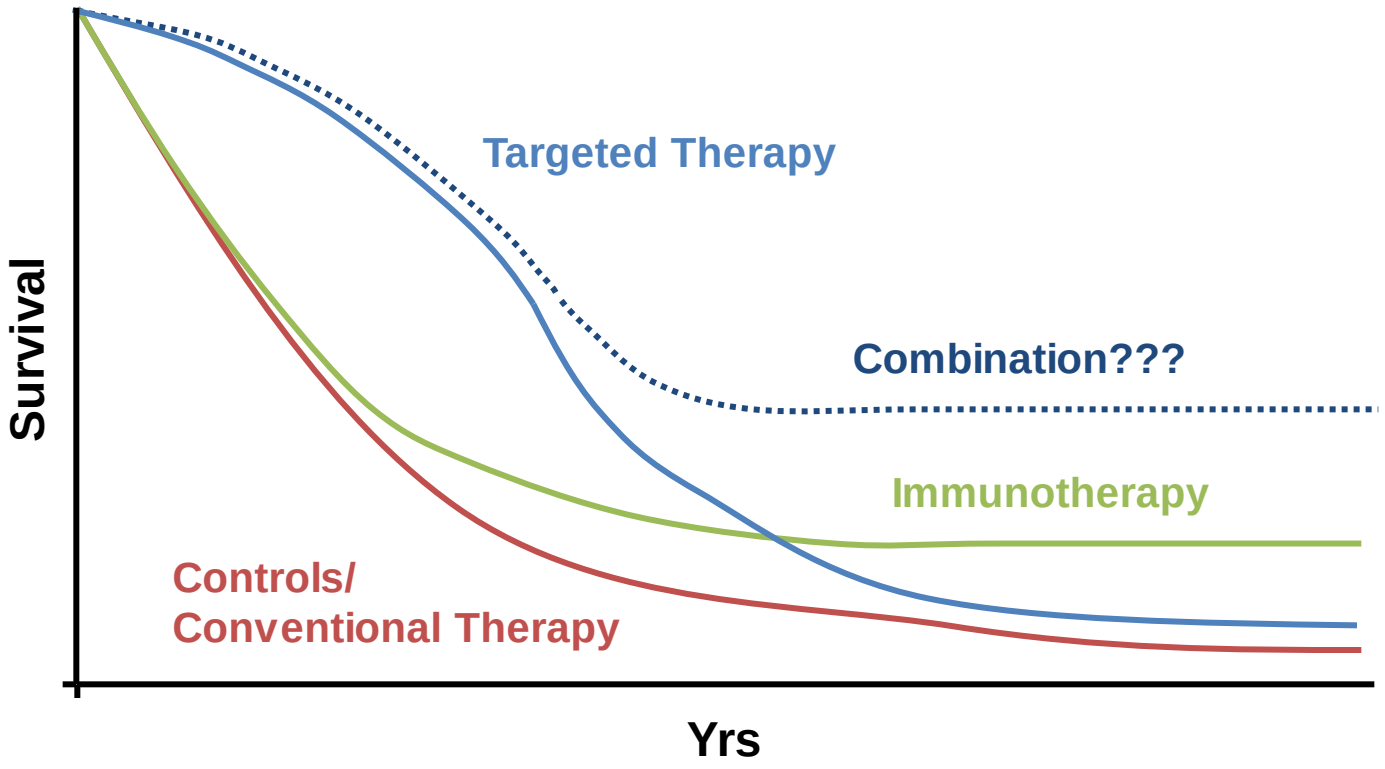


Pembrolizumab versus Ipilimumab in Advanced Melanoma





KOMBİNE TEDAVİ?

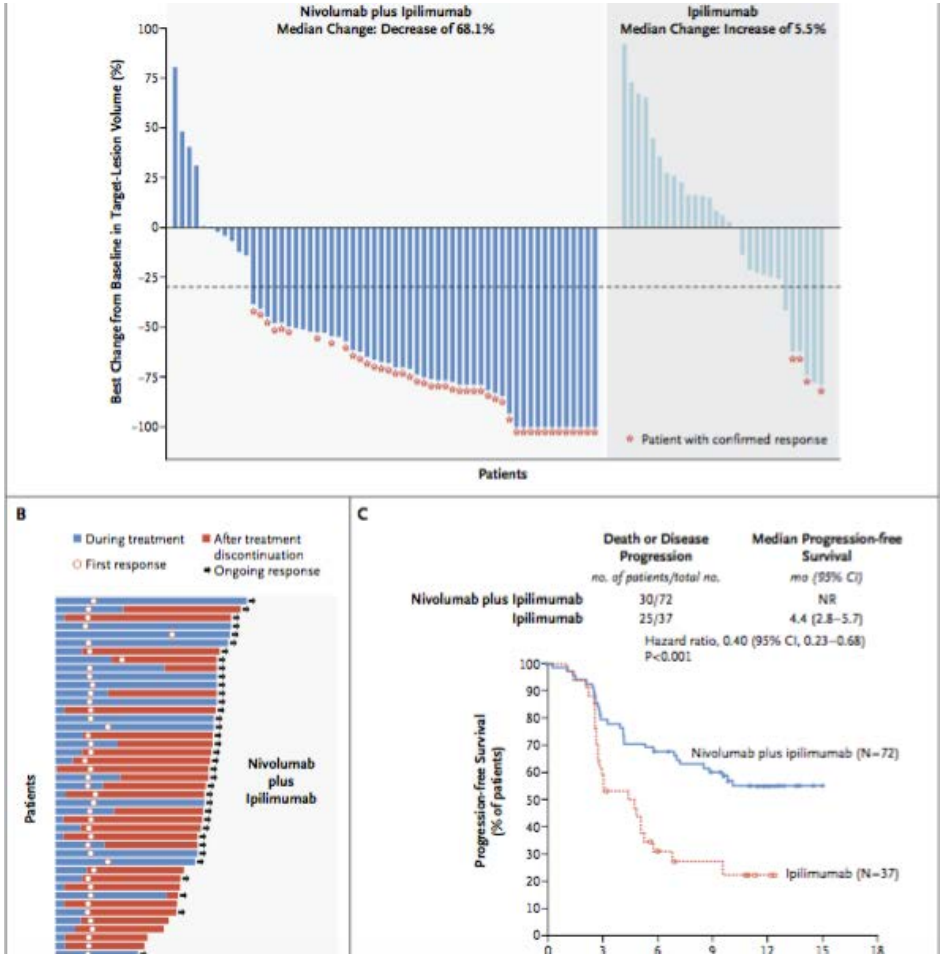


Adapted from Ribas A, et al. Clin Cancer Res. 2012;18:336-341

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab and Ipilimumab versus Ipilimumab in Untreated Melanoma

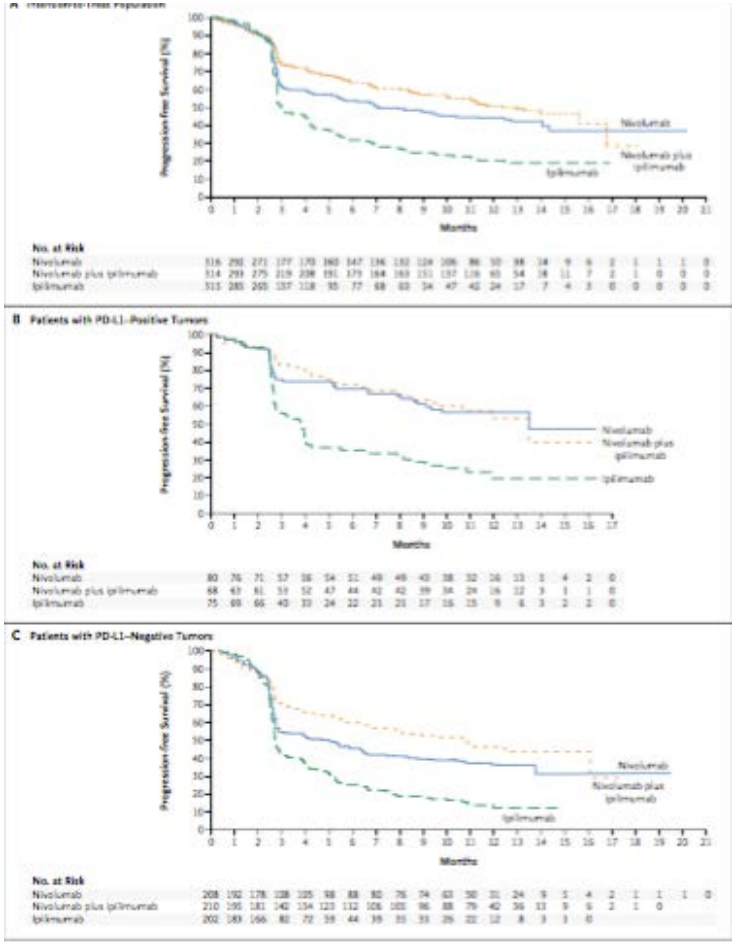


N engl j med 372;21; 2015

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma

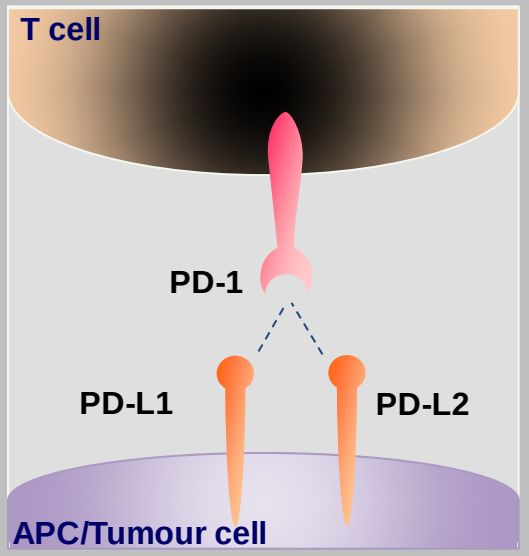


İmmunolojik Ajanlar İçin Prediktör

Biyobelirteç Var mı?

PD-L1
-BİYOBELİRTEÇ OLARAK-

- Tümör hücreleri ve antjen sunan immün sistem hücrelerinde bulunabiliyor.
- Dinamik bir şekilde eksprese ediliyor.



Adapted from McDermott and Atkins 2013 and Ceeraz et al 2013[1,5]

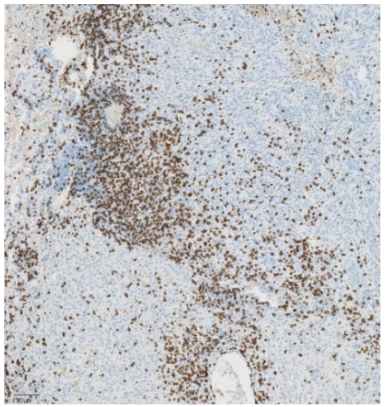
Ligation results in decreased proliferation, cytokine secretion, and cytotoxicity

PD-L1 Ekspresyonu Dinamik

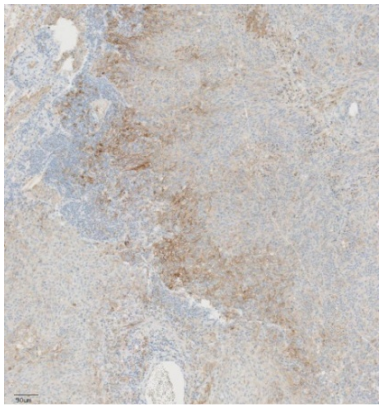
Baseline

On-treatment

CD8 T cells

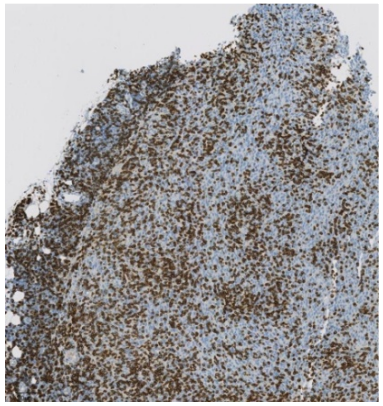


PD-L1

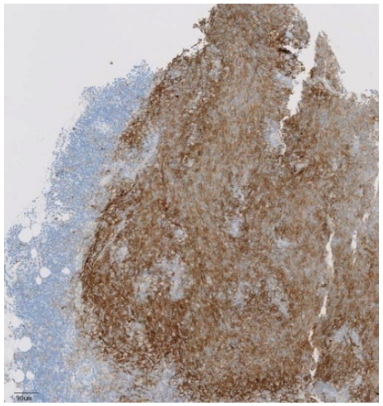


MPDL3280A (PD-L1 inhibitor)

CD8 T cells



PD-L1



T cells and tumour cells expressing PD-L1

Powderly J, et al. Oral presentation at ASCO 2013 (abstr. 3001).

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pembrolizumab for the Treatment of Non–Small-Cell Lung Cancer

Edward B. Garon, M.D., Naiyer A. Rizvi, M.D., Rina Hui, M.B., B.S., Natasha Leighl, M.D., Ani S. Balmanoukian, M.D., Joseph Paul Eder, M.D., Amita Patnaik, M.D., Charu Aggarwal, M.D., Matthew Gubens, M.D., Leora Horn, M.D., Enric Carcereny, M.D., Myung-Ju Ahn, M.D., Enriqueta Felip, M.D., Jong-Seok Lee, M.D., Matthew D. Hellmann, M.D., Omid Hamid, M.D., Jonathan W. Goldman, M.D., Jean-Charles Soria, M.D., Marisa Dolled-Filhart, Ph.D., Ruth Z. Rutledge, M.B.A., Jin Zhang, Ph.D., Jared K. Lunceford, Ph.D., Reshma Rangwala, M.D., Gregory M. Lubiniecki, M.D., Charlotte Roach, B.S., Kenneth Emancipator, M.D., and Leena Gandhi, M.D., for the KEYNOTE-001 Investigators*

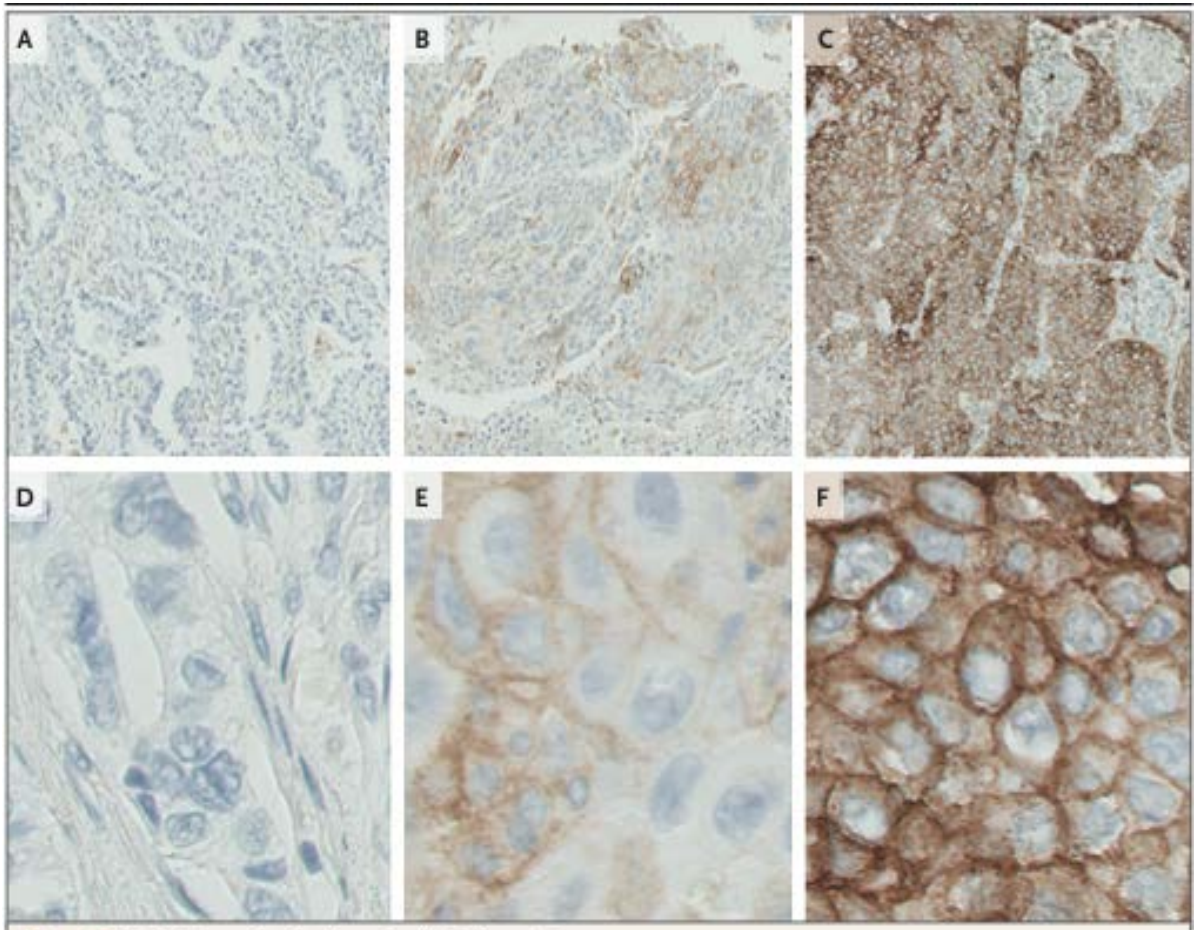
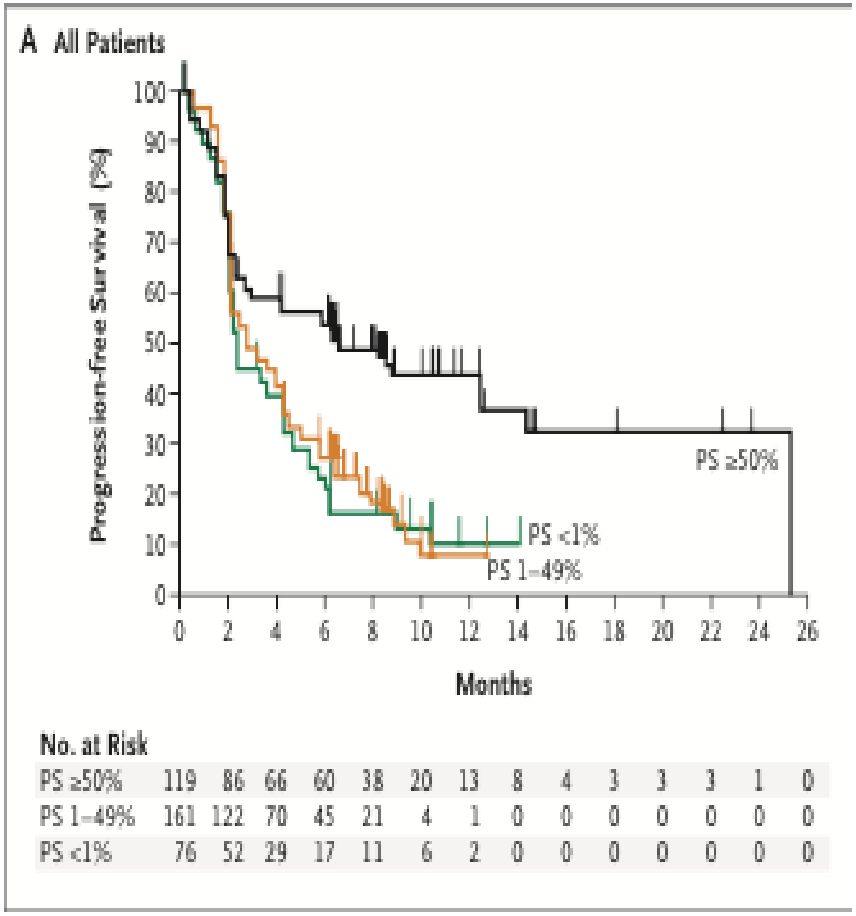
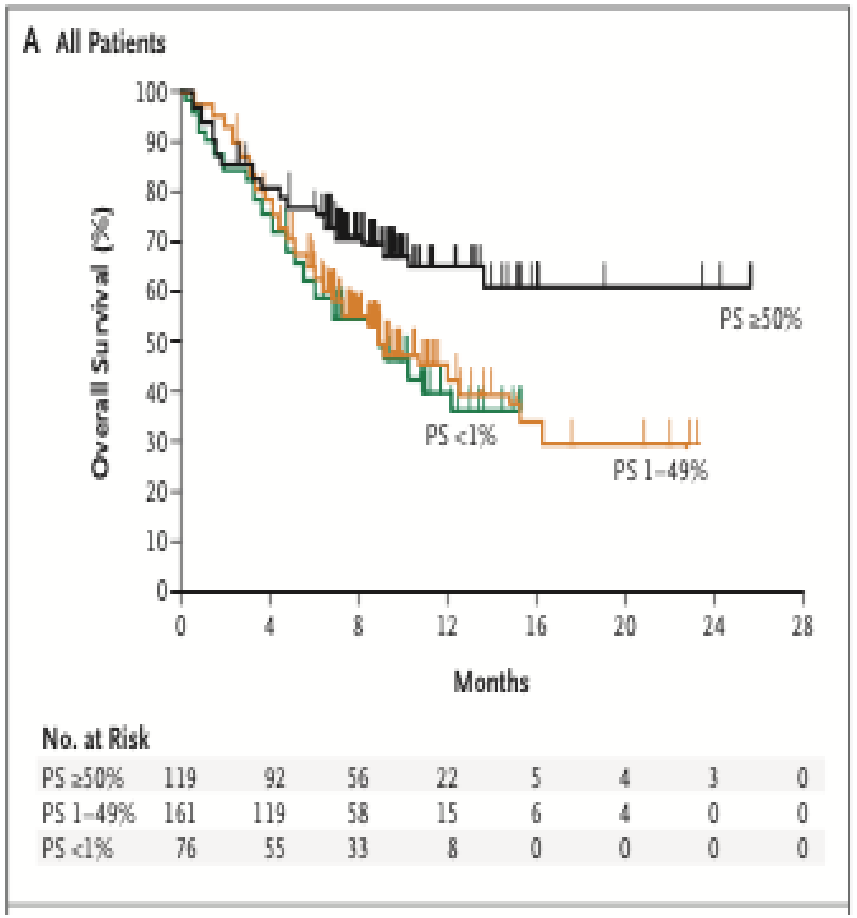


Figure 1. PD-L1 Expression in Non–Small-Cell Lung Cancers.

Results were reported as the percentage of neoplastic cells showing membranous staining of programmed cell death ligand 1 (PD-L1) (proportion score). Shown are tumor samples obtained from patients with a proportion score of less than 1% (Panel A), a score of 1 to 49% (Panel B), and a score of at least 50% (Panel C) (all at low magnification). Tumor samples with the corresponding proportion scores are shown at a higher magnification in Panels D through F. PD-L1 staining is shown by the presence of the brown chromogen. The blue color is the hematoxylin counterstain.


A All Patients
Progression-free Survival (%)
100
90
80
70
60
50
40
30
20
10
0
0 2 4 6 8 10 12 14 16 18 20 22 24 26
Months
PS ≥50%
PS <1%
PS 1–49%
No. at Risk
PS ≥50% 119 86 66 60 38 20 13 8 4 3 3 3 1 0
PS 1–49% 161 122 70 45 21 4 1 0 0 0 0 0 0 0
PS <1% 76 52 29 17 11 6 2 0 0 0 0 0 0 0

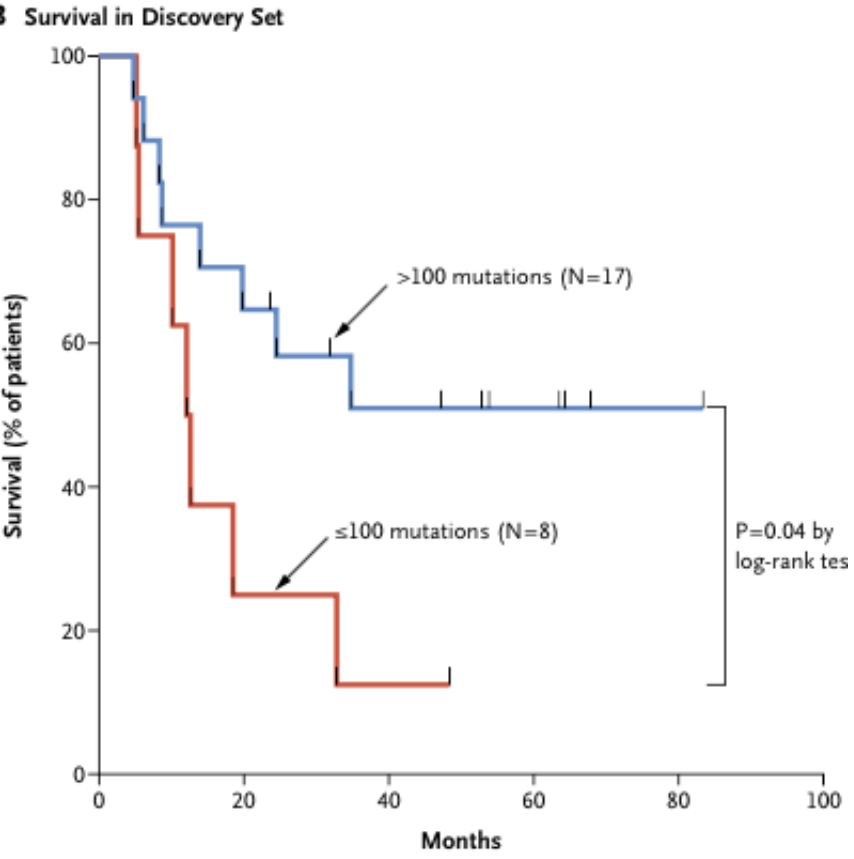

A All Patients
Overall Survival (%)
100
90
80
70
60
50
40
30
20
10
0
0 4 8 12 16 20 24 28
Months
PS ≥50%
PS <1%
PS 1–49%
No. at Risk
PS ≥50% 119 92 56 22 5 4 3 0
PS 1–49% 161 119 58 15 6 4 0 0
PS <1% 76 55 33 8 0 0 0 0

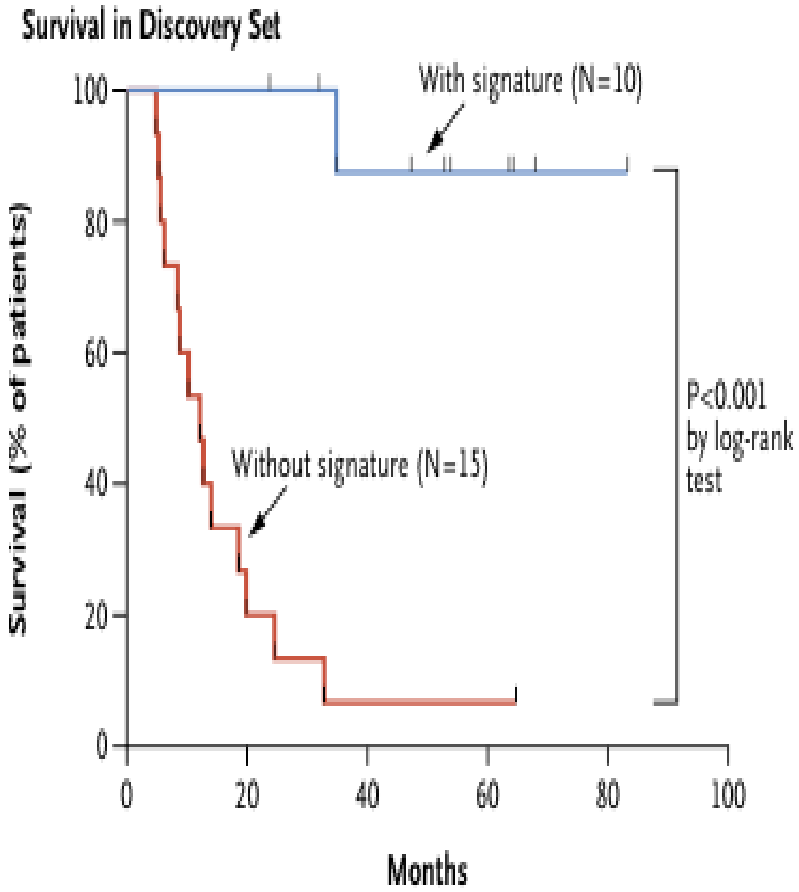
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

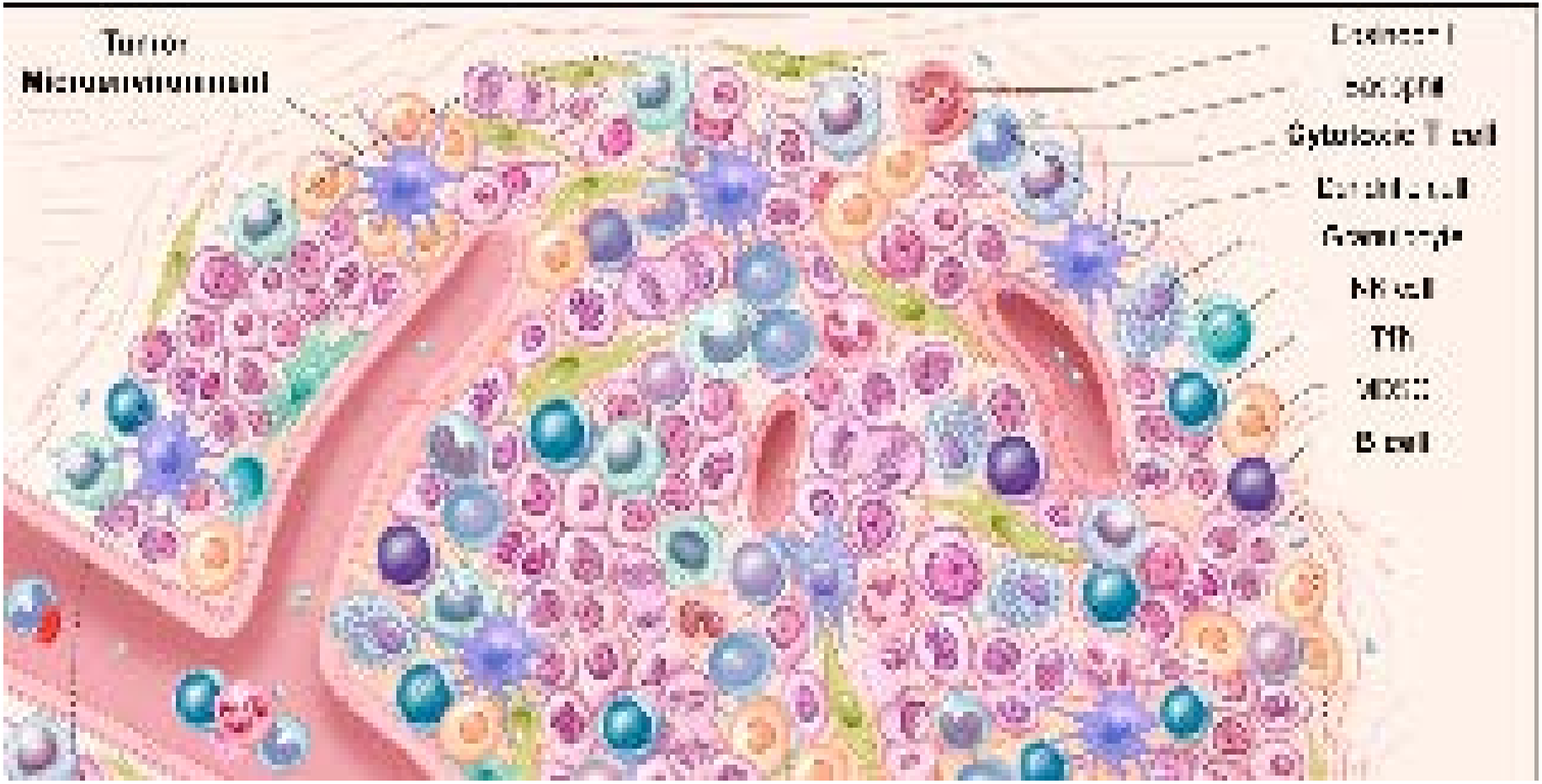
Genetic Basis for Clinical Response to CTLA-4 Blockade in Melanoma

Alexandra Snyder, M.D., Vladimir Makarov, M.D., Taha Merghoub, Ph.D., Jianda Yuan, M.D., Ph.D., Jesse M. Zaretsky, B.S., Alexis Desrichard, Ph.D., Logan A. Walsh, Ph.D., Michael A. Postow, M.D., Phillip Wong, Ph.D., Teresa S. Ho, B.S., Travis J. Hollmann, M.D., Ph.D., Cameron Bruggeman, M.A., Kasthuri Kannan, Ph.D., Yanyun Li, M.D., Ph.D., Ceyhan Elipenahli, B.S., Cailian Liu, M.D., Christopher T. Harbison, Ph.D., Lisu Wang, M.D., Antoni Ribas, M.D., Ph.D., Jedd D. Wolchok, M.D., Ph.D., and Timothy A. Chan, M.D., Ph.D.


B Survival in Discovery Set
Survival (% of patients)
100
80
60
40
20
0
0
20
40
60
80
100
Months
>100 mutations (N=17)
≤100 mutations (N=8)
P=0.04 by
log-rank tes


Survival in Discovery Set
Survival (% of patients)
100
80
60
40
20
0
0
20
40
60
80
100
Months
With signature (N=10)
Without signature (N=15)
P<0.001
by log-rank
test

İmmünom



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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.

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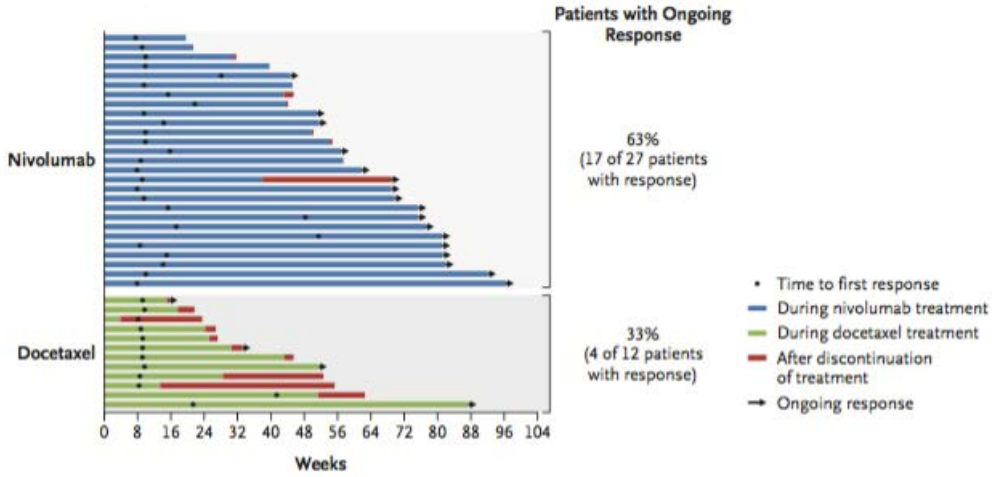
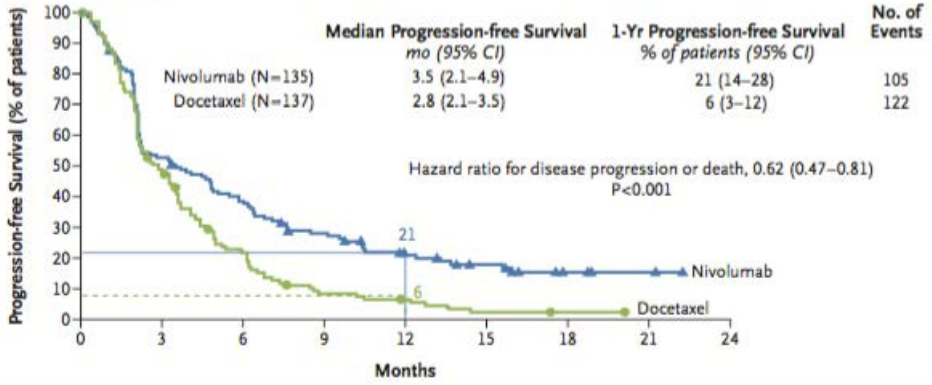
ORIGINAL ARTICLE

Nivolumab versus Docetaxel in Advanced Squamous-Cell Non–Small-Cell Lung Cancer

A Duration of Response



B Progression-free Survival



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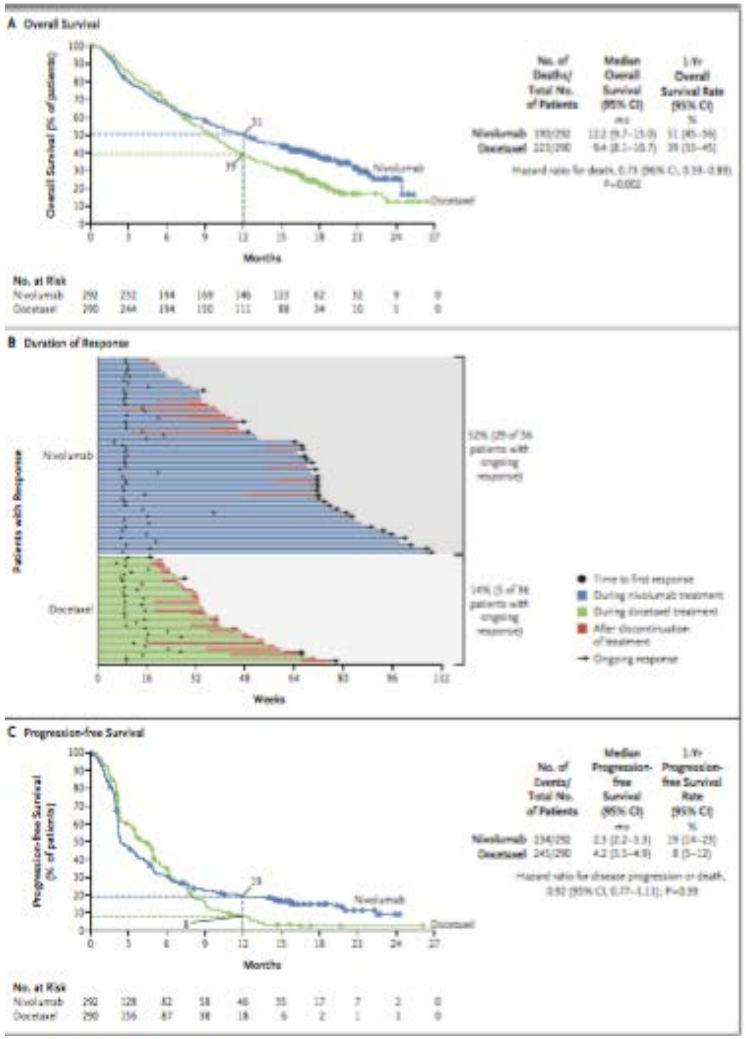
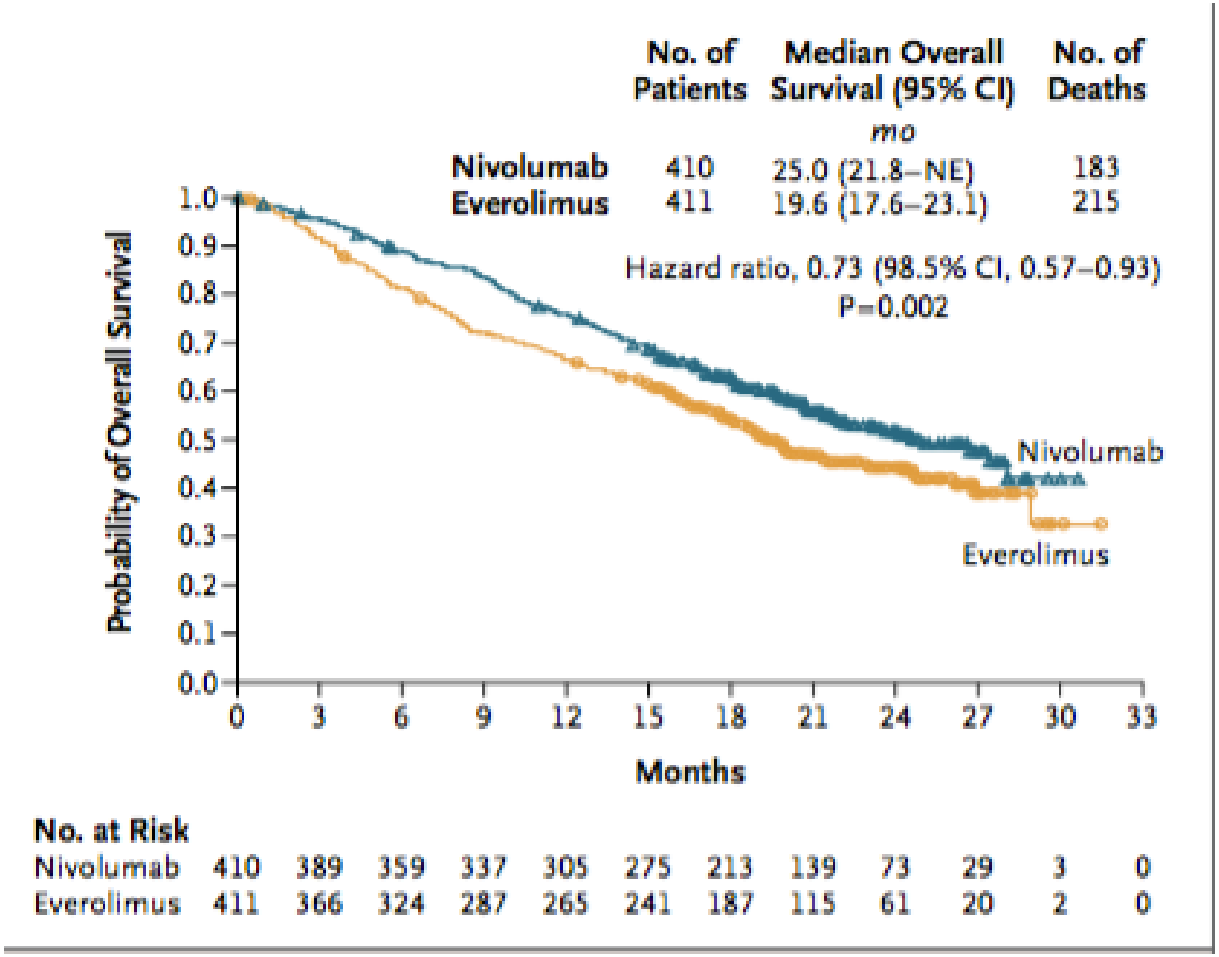


Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma



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