What's New in Immunotherapy and Targeted Therapy?

18th Focus on Melanoma 2021 Conference

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Abramson Cancer Center

Penn Medicine

Old Model of Cancer Care

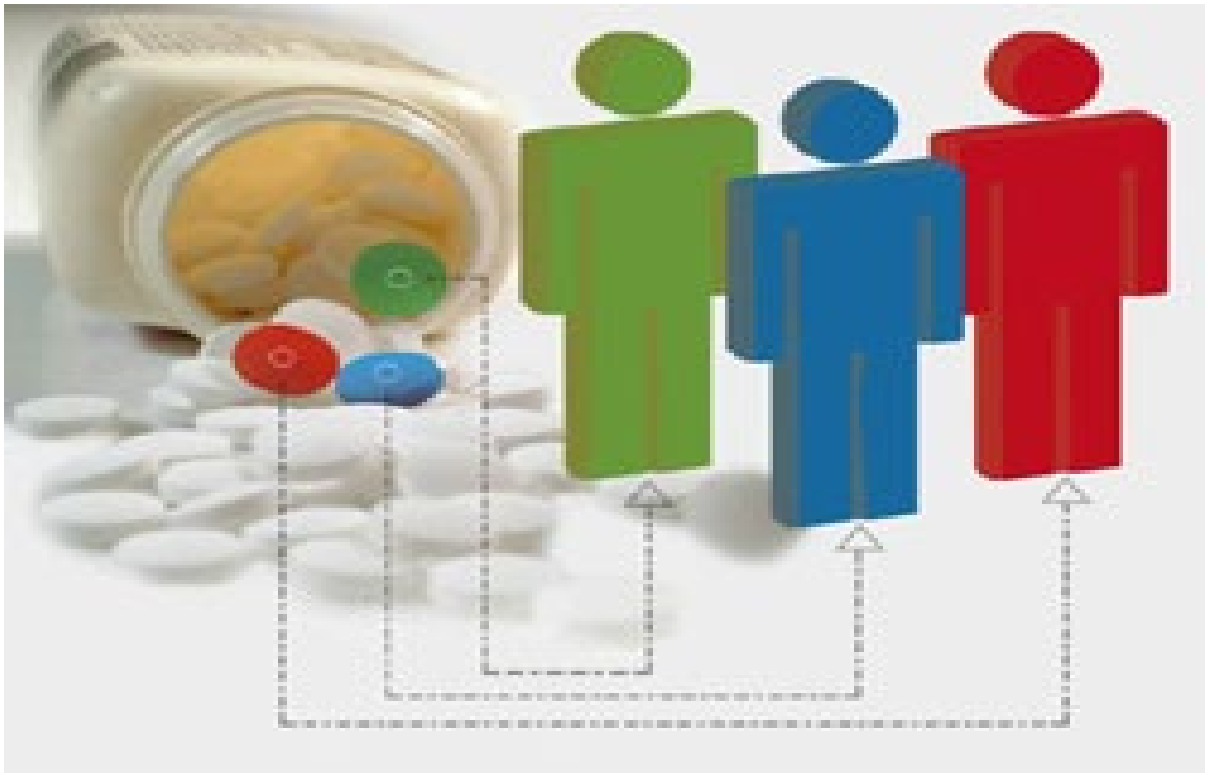
One size fits all

Precision Medicine

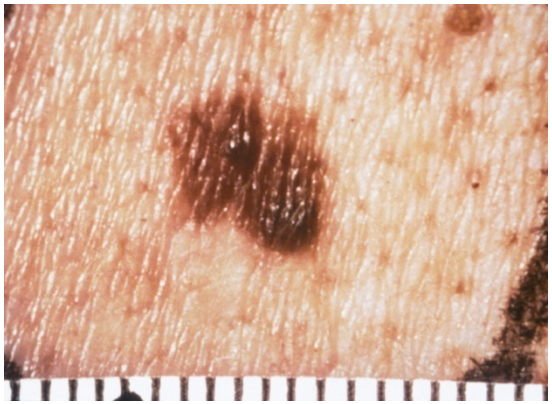
- Precision Medicine
- Personalized Medicine
- Precision Oncology

New approach that takes into account individual variability in genes, environment and lifestyle to allow doctors and researchers to predict more accurately which treatment and prevention strategy will work in which groups of patients.

One Size Does Not Fit All!



Distinct Genetic Changes in Melanoma



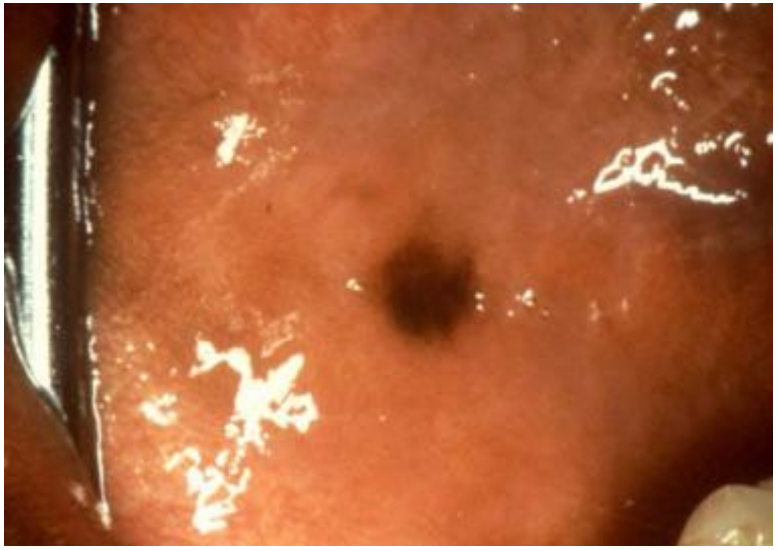
Superficial Spreading Melanoma
Abnormal gene:
BRAF- 50%
NRAS- 20%

Lentigo Maligna Melanoma
Abnormal gene:
C-kit-2%
BRAF- 10%
NRAS- 10%

Acral Lentiginous Melanoma
Abnormal Gene:
C-kit-15%
BRAF- 15%
NRAS- 15%

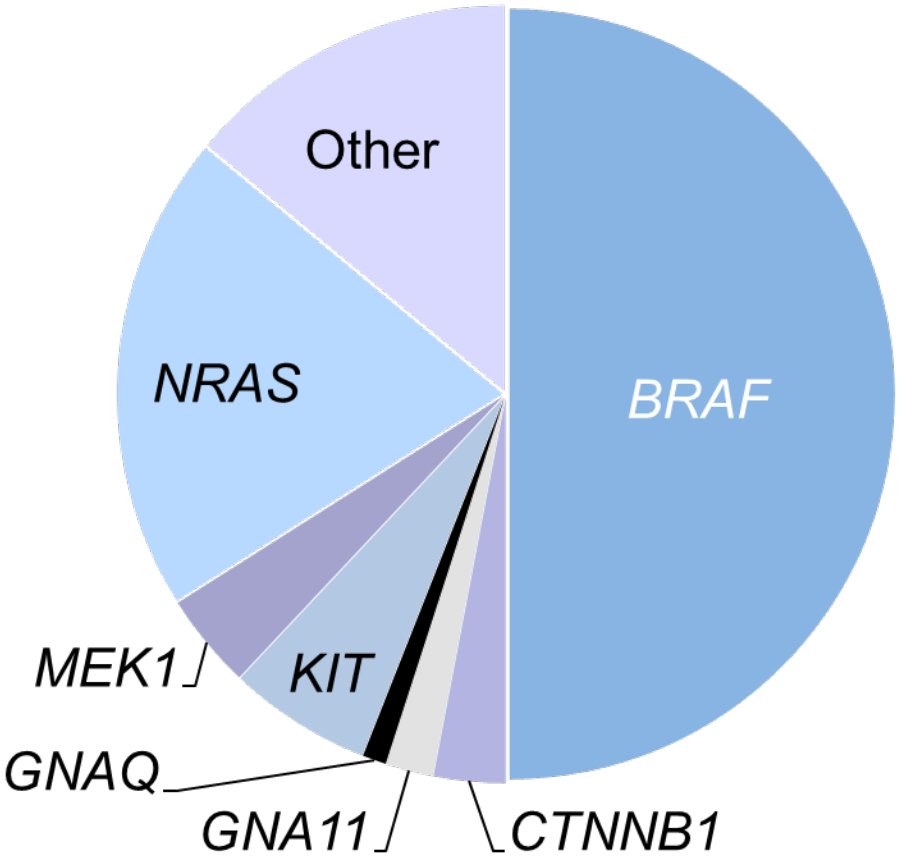
Distinct Genetic Changes in Melanoma

Ocular Melanoma
Abnormal gene:
GNA11- 32%
GNAQ- 50%
BRAF < 1%



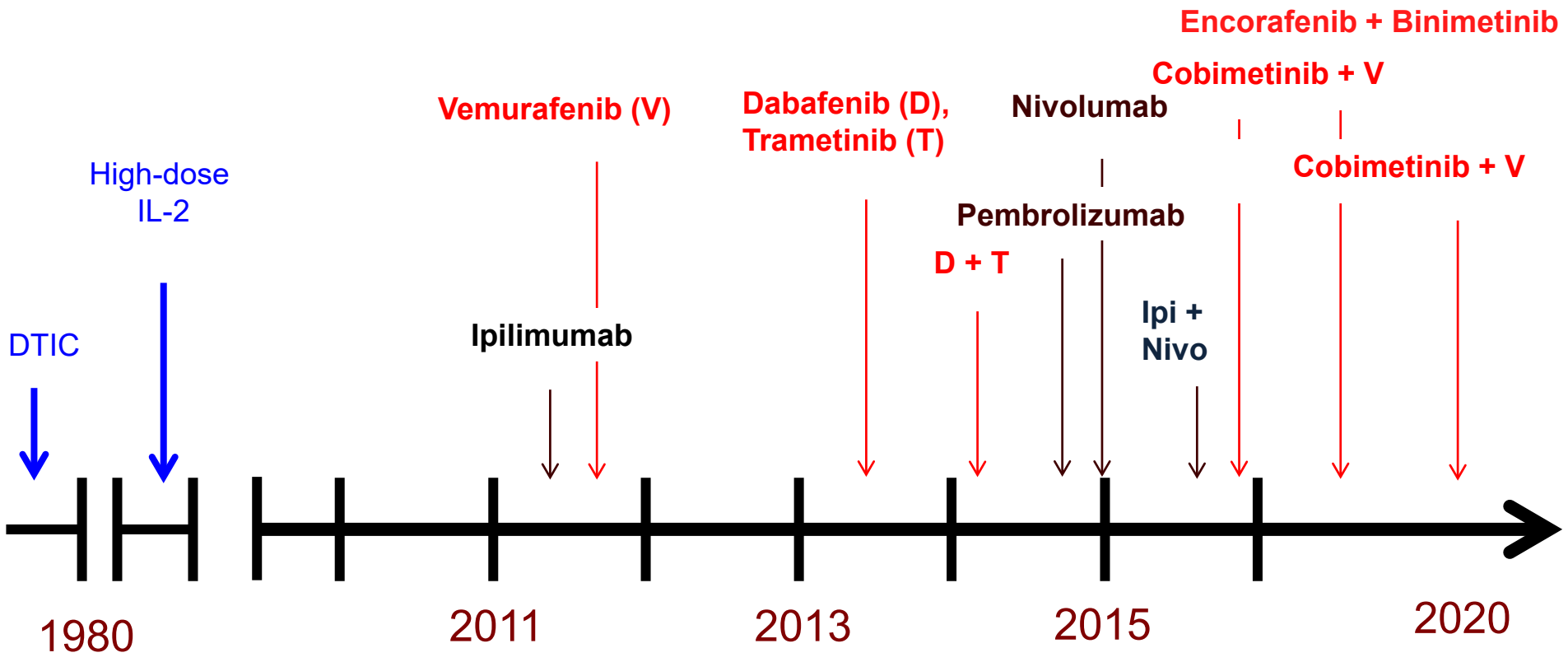
Mucosal Melanoma
Abnormal Gene:
C-kit- 20%
NRAS- 15%
BRAF- 5%

Many mutations in melanoma



- **Difficult to predict which mutations will be present in a particular tumor**
- **Molecular profiling can help clinicians:**
  - Enroll patients in clinical trials
  - Make informed therapeutic choices

Timeline of approvals



Immunotherapy

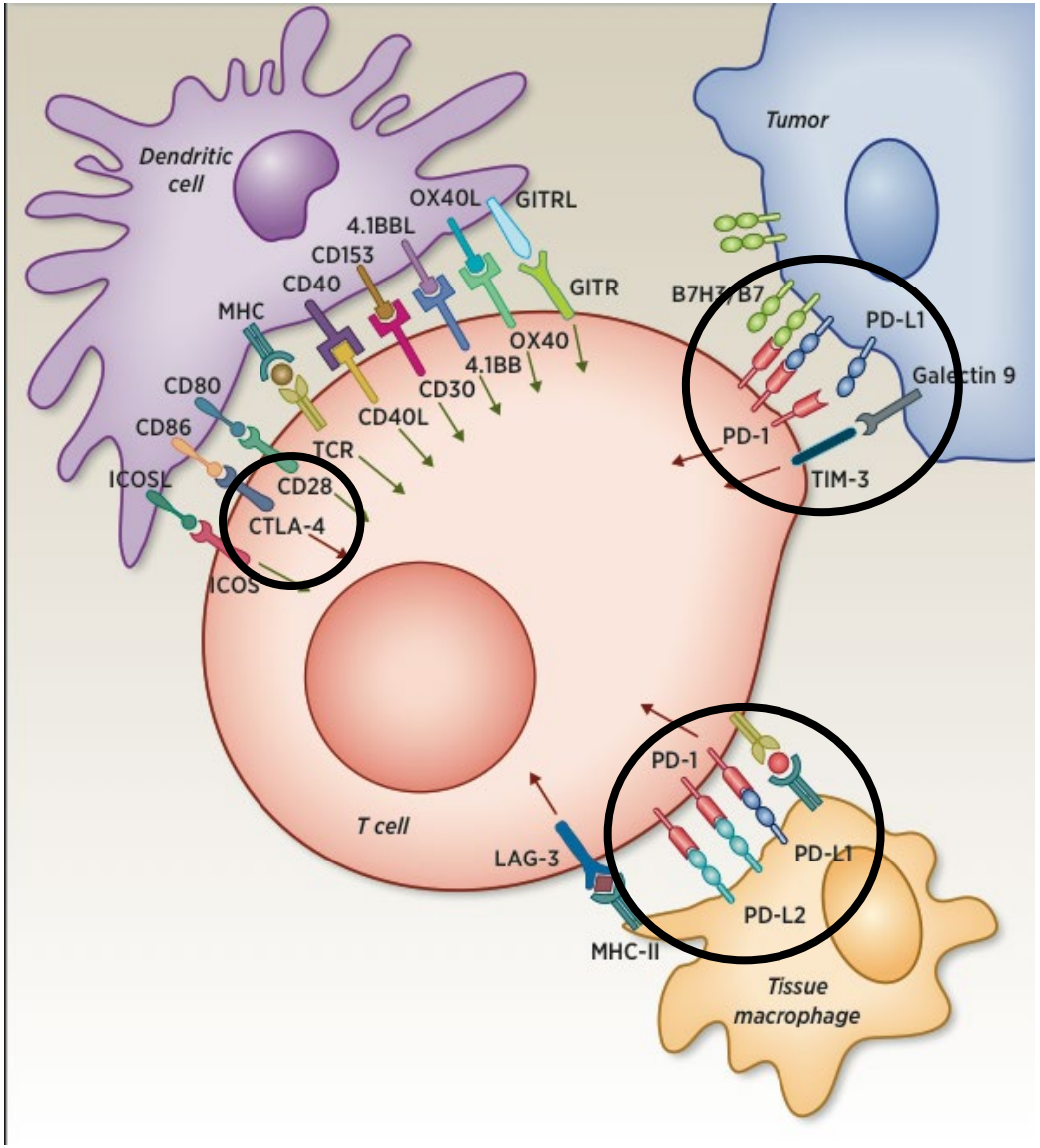
- Interferon
- IL-2
- Ipilimumab (Yervoy)
- Pembrolizumab (Keytruda)
- Nivolumab (Optivo)
- Ipilimumab + Nivolumab
- Talimogene laherparevec, TVEC (imlygic)
- Atezolizumab + Cobimetinib + Vemurafenib

Targeted Therapy

- Dabrafenib (Tafinlar)
- Trametinib (Mekinist)
- Vemurafenib (Zelboraf)
- Cobimetinib (Cotellic)
- Encorafenib (Braftovi)
- Binimetinib (Mektovi)

How we got here

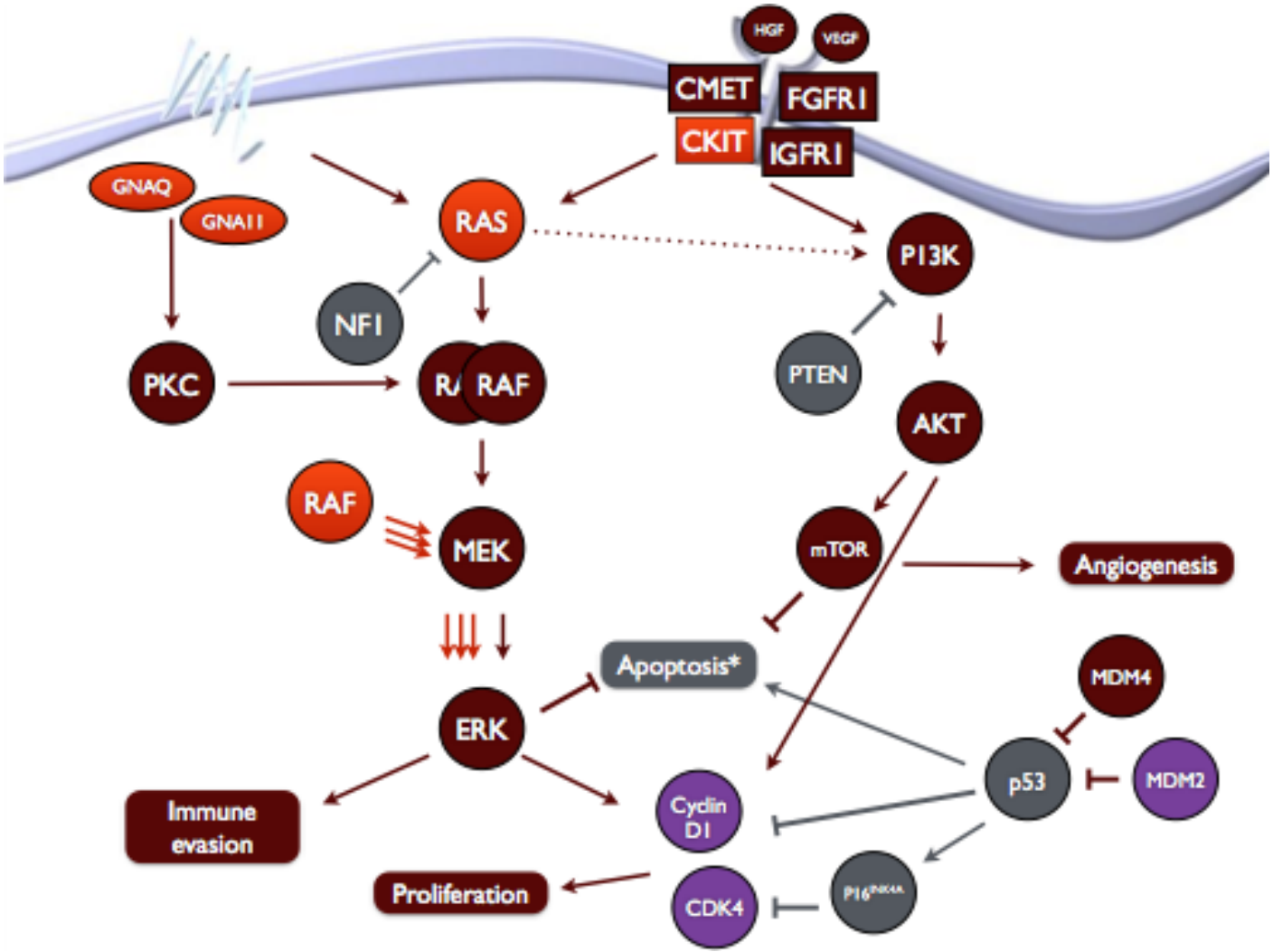
Ipilimumab

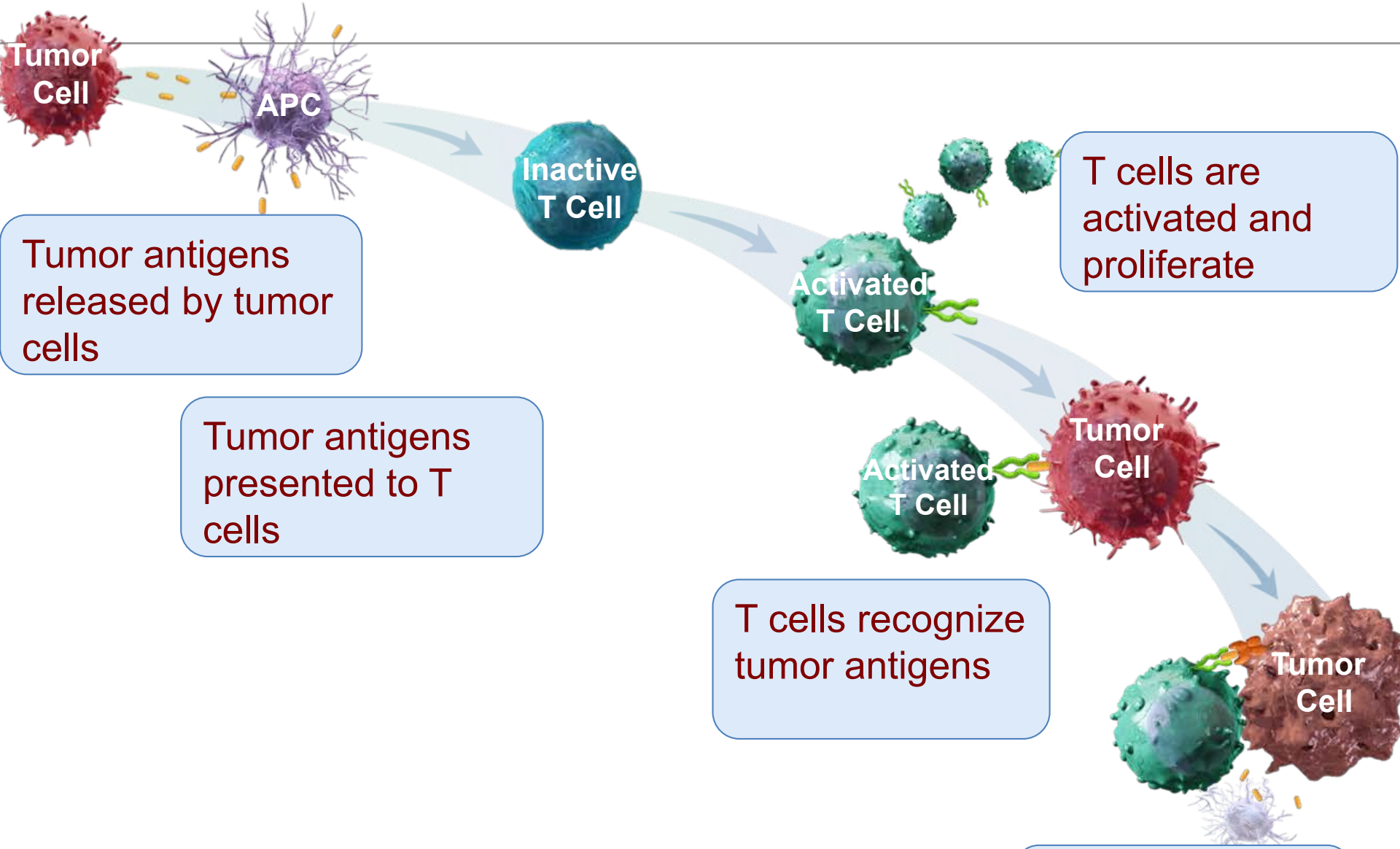


Pembrolizumab
Nivolumab

Atezolizumab

How we got here





Tumor antigens released by tumor cells

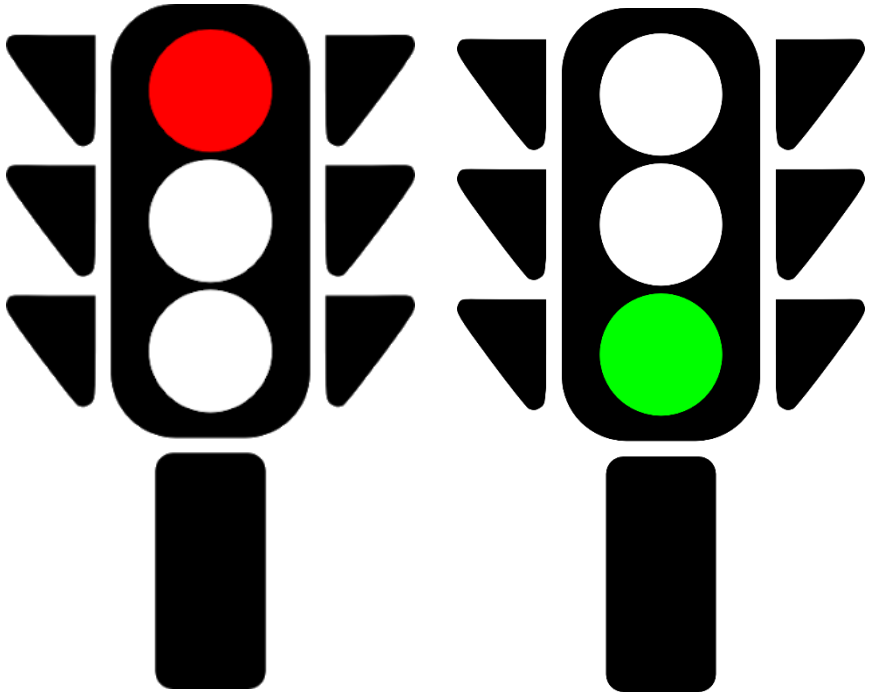
Tumor antigens presented to T cells

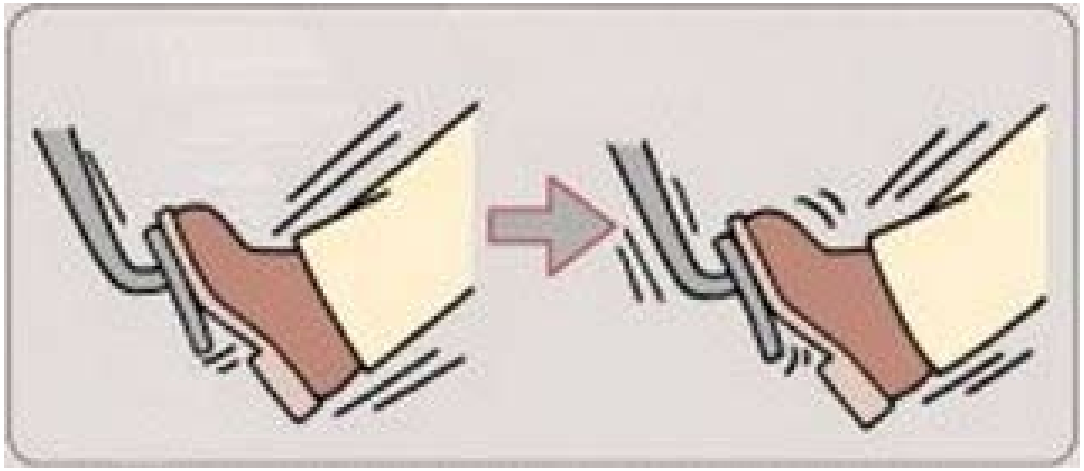
T cells are activated and proliferate

T cells recognize tumor antigens

T cells kill tumor cells

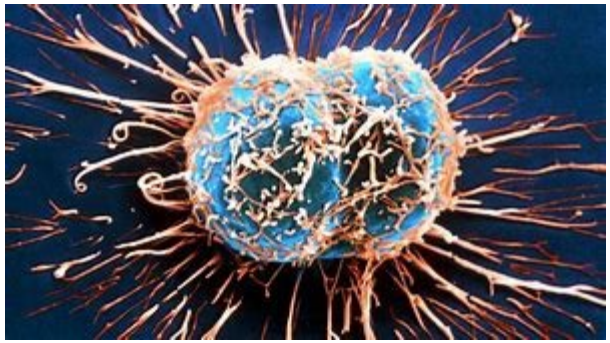
Immunotherapy



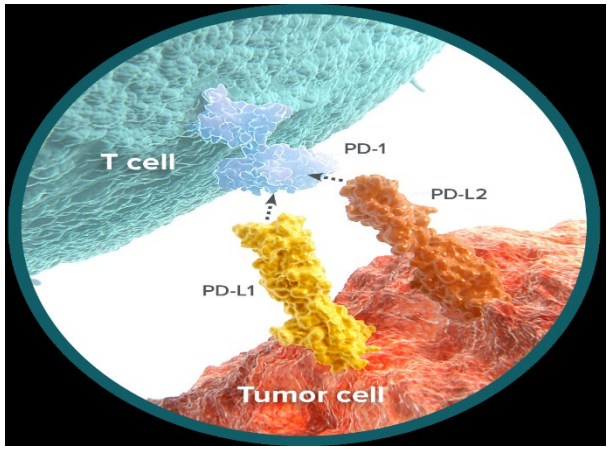


Immune checkpoint inhibitors

Precision Immunotherapy

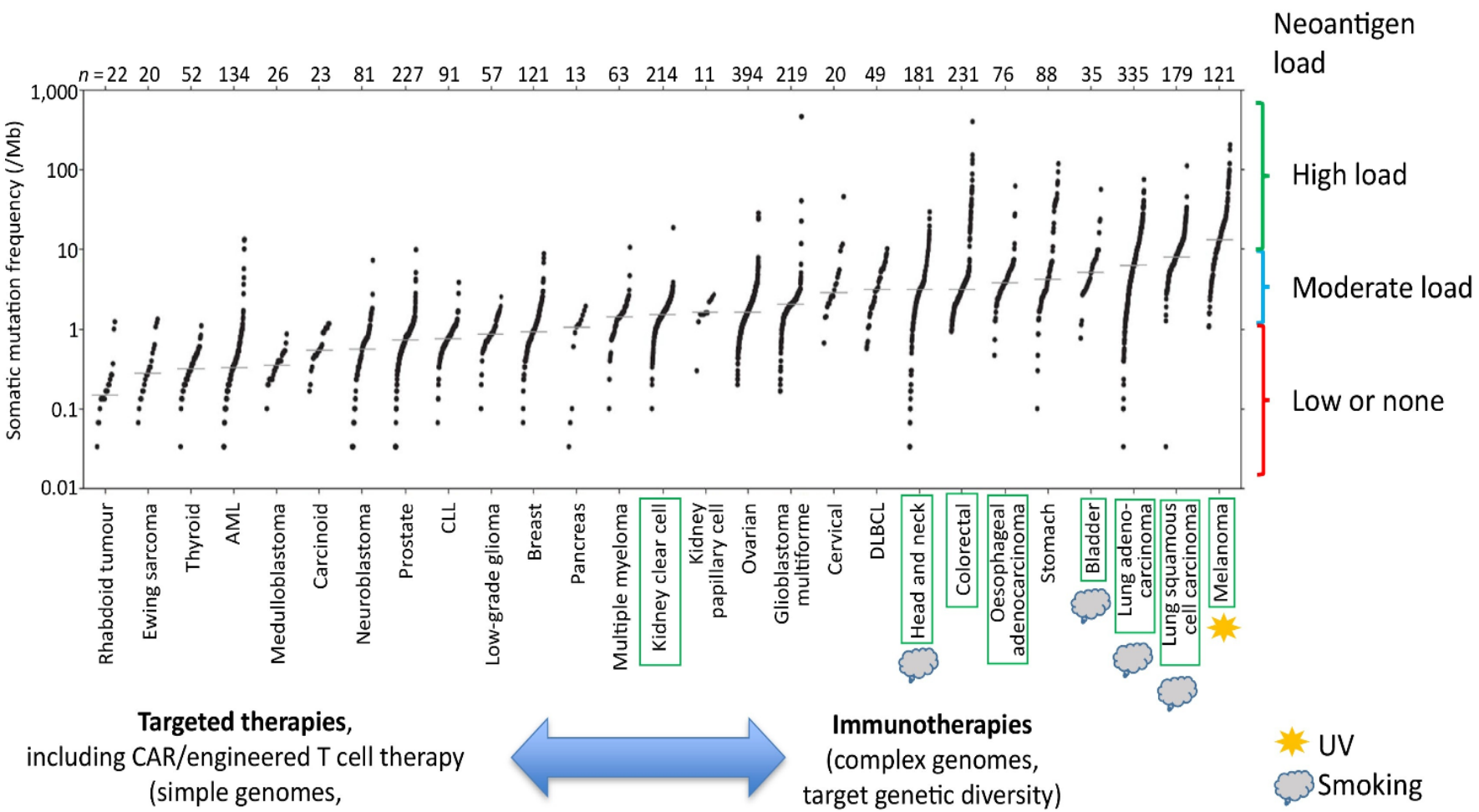


"Mutational Burden"
High numbers of mutations correlate with strong response to immunotherapy



PD-L1 expression on tumor cells

Neoantigens are more likely to occur in highly mutated tumors



Lee et al Trends in Immunology May 2018

Updates in immunotherapy stage IV melanoma

Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study

Caroline Robert, Antoni Ribas, Jacob Schachter, Ana Arance, Jean-Jacques Grob, Laurent Mortier, Adil Daud, Matteo S Carlino, Catriona M McNeil, Michal Lotem, James M G Larkin, Paul Lorigan, Bart Neyns, Christian U Blank, Teresa M Petrella, Omid Hamid, Shu-Chih Su, Clemens Krepler, Nageatte Ibrahim, Georgina V Long

***Lancet Oncol* 2019; 20: 1239–51**

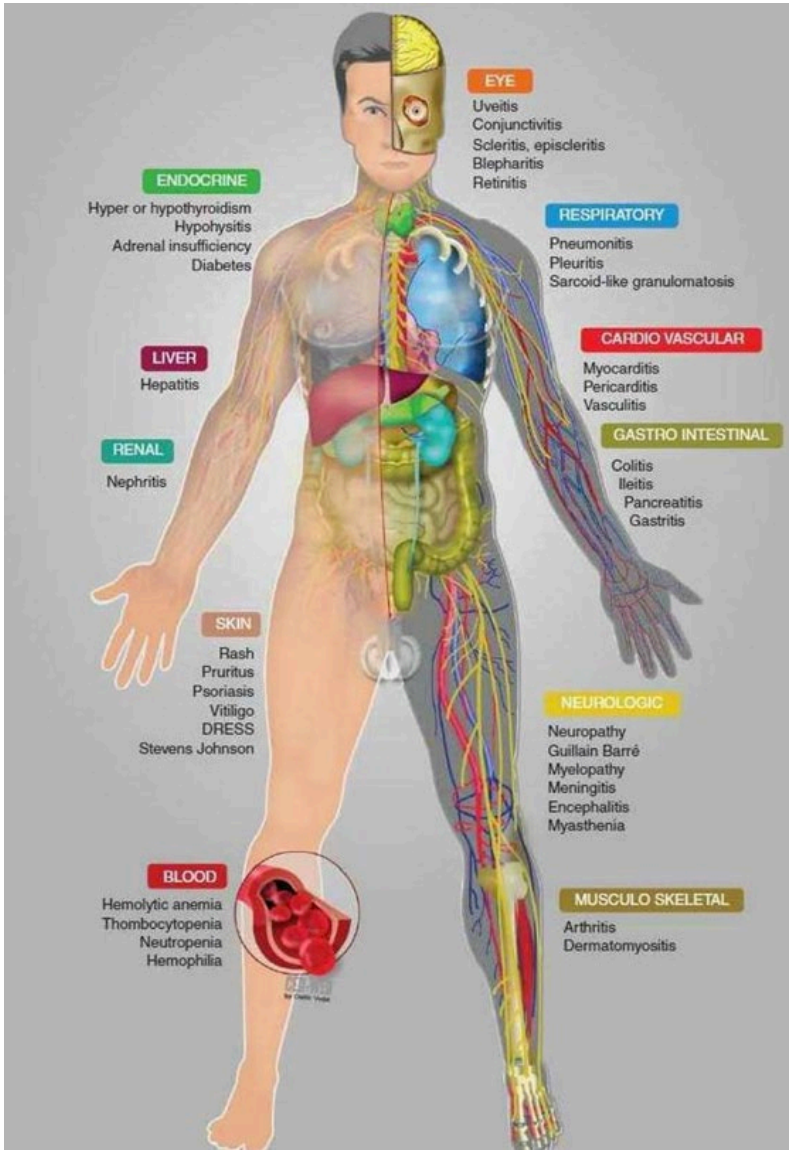
ORIGINAL ARTICLE

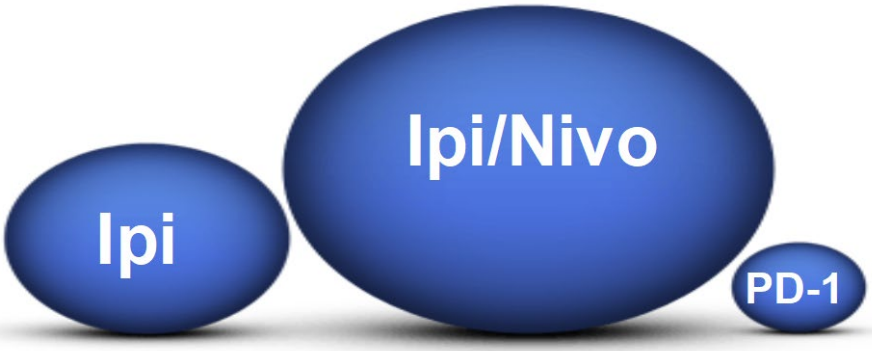
Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma

J. Larkin, V. Chiarion-Sileni, R. Gonzalez, J.-J. Grob, P. Rutkowski, C.D. Lao, C.L. Cowey, D. Schadendorf, J. Wagstaff, R. Dummer, P.F. Ferrucci, M. Smylie, D. Hogg, A. Hill, I. Márquez-Rodas, J. Haanen, M. Guidoboni, M. Maio, P. Schöffski, M.S. Carlino, C. Lebbé, G. McArthur, P.A. Ascierto, G.A. Daniels, G.V. Long, L. Bastholt, J.I. Rizzo, A. Balogh, A. Moshyk, F.S. Hodi, and J.D. Wolchok

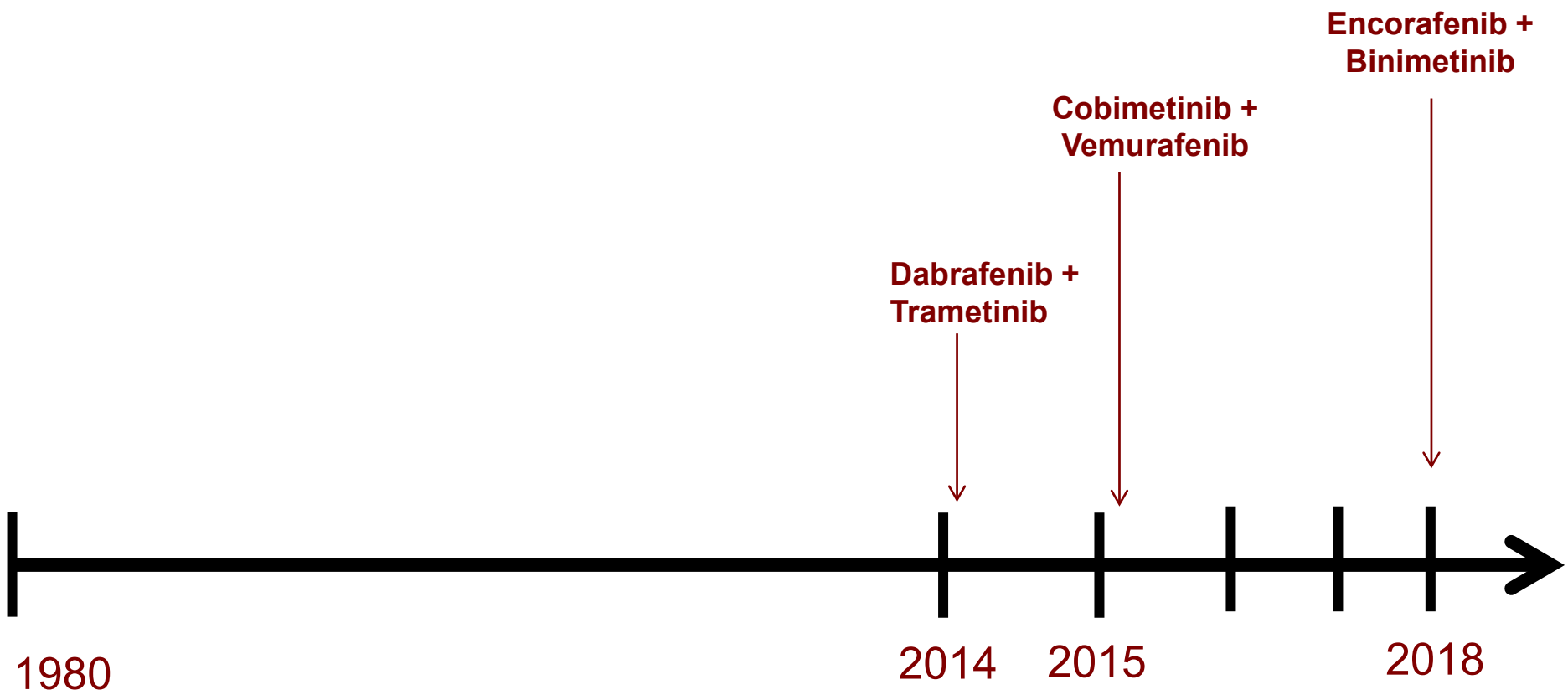
N ENGL J MED 381;16 NEJM.ORG OCTOBER 17, 2019

Toxicity

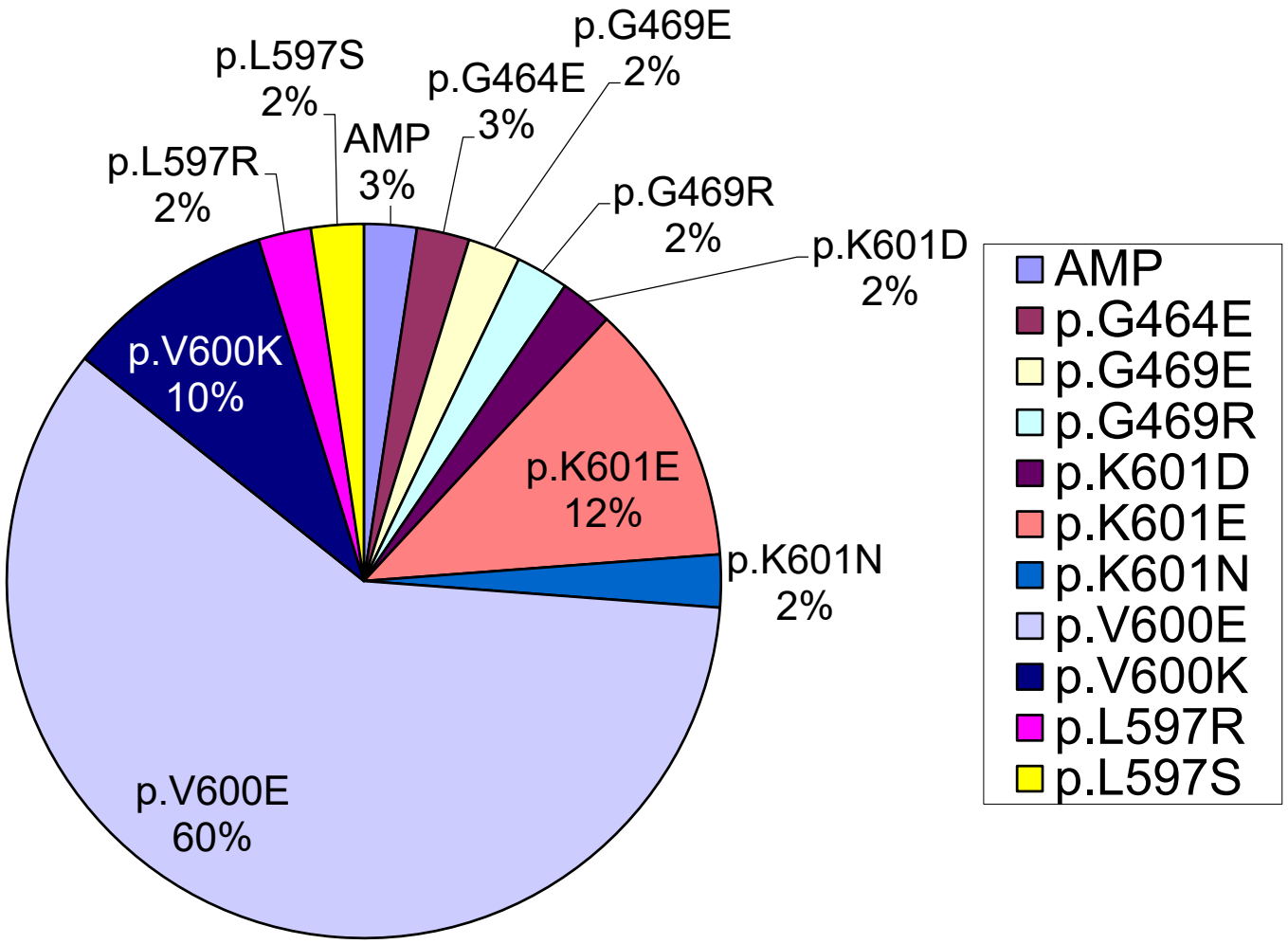

EYE
Uveitis
Conjunctivitis
Scleritis, episcleritis
Blepharitis
Retinitis
ENDOCRINE
Hyper or hypothyroidism
Hypohysitis
Adrenal insufficiency
Diabetes
RESPIRATORY
Pneumonitis
Pleuritis
Sarcoid-like granulomatosis
CARDIO VASCULAR
Myocarditis
Pericarditis
Vasculitis
LIVER
Hepatitis
GASTRO INTESTINAL
Colitis
Ileitis
Pancreatitis
Gastritis
RENAL
Nephritis
SKIN
Rash
Pruritus
Psoriasis
Vitiligo
DRESS
Stevens Johnson
NEUROLOGIC
Neuropathy
Guillain Barré
Myelopathy
Meningitis
Encephalitis
Myasthenia
BLOOD
Hemolytic anemia
Thombocytopenia
Neutropenia
Hemophilia
MUSCULO SKELETAL
Arthritis
Dermatomyositis


Ipi
Ipi/Nivo
PD-1

BRAF/MEK inhibitor combinations



BRAF mutations differ



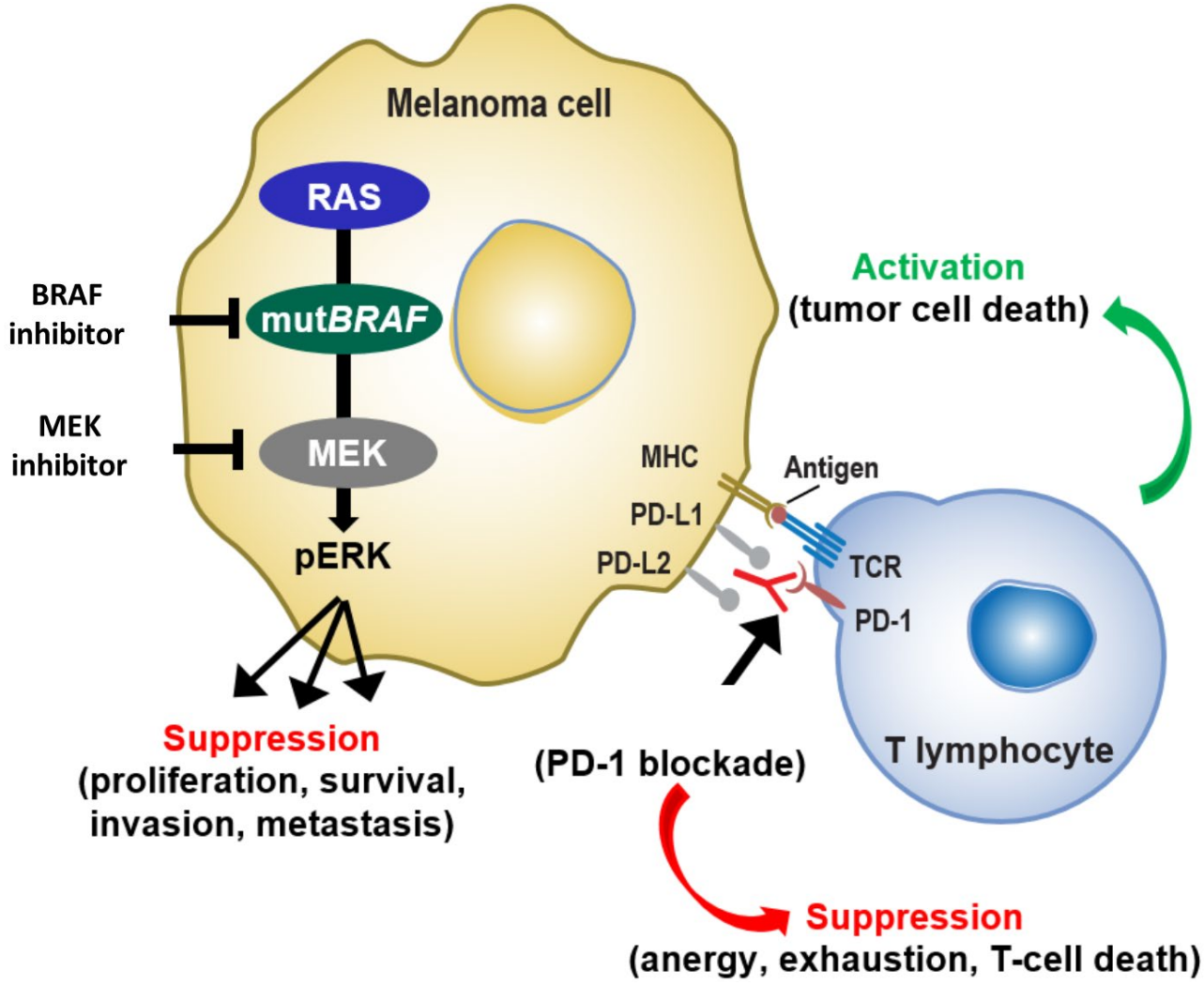
Even mutations in commonly mutated genes vary between individuals

Targeted therapy toxicity

- **Pyrexia**
- **Rash**
- **Photosensitivity**
- **Nausea**
- **Arthralgias**
- **Abnormalities in liver enzymes**
- **Cardiac toxicities**
- **Increase in cuSCCs**

ALL REVERSIBLE!!!

Triplet Therapy



Triplet Therapy Trials

Vem/Cobi/Atezo
vs Vem/Cobi
IMSpire150

Dab/Tram/Pembro
vs Dab/Tram
Keynote-022

Dab/Tram/Sparta
vs Dab/Tram
COMBI-i

What's on the horizon

- **Combination Trials**
  - Combinations with radiation
  - Combinations with hydroxychloroquine
- **New Targets: "Next Generation"**
  - LAG-3, TIM-3, TIGIT
- **Adoptive T Cell Therapy**
- **CAR T Cell Therapy**
- **Cancer Vaccines**

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Bristol Myers Squibb Announces LAG-3-Blocking Antibody Relatlimab and Nivolumab Fixed-Dose Combination Significantly Improves Progression-Free Survival vs. Opdivo (nivolumab) in Patients with Previously Untreated Metastatic or Unresectable Melanoma

MAY 19, 2021

What's on the horizon

- **Combination Trials**
  - Combinations with radiation
  - Combinations with hydroxychloroquine
- **New Targets: "Next Generation"**
  - LAG-3, TIM-3, TIGIT
- **Adoptive T Cell Therapy**
- **CAR T Cell Therapy**
- **Cancer Vaccines**

Penn Trials for Metastatic Melanoma

RADVAX trial	• Ipilimumab, nivolumab and radiation
LIMIT trial	• Nivolumab and hydroxychloroquine
Umbrella trial	• Includes rotating new drugs combined with pembrolizumab (TIGIT, CTLA-4, Lenvatanib)
BAMM trial	• Dabrafenib, trametinib and hydroxychloroquine

In Summary

- **Precision Medicine** approach to cancer treatment
- Clinical Trials
- Biomarker research