Neuromuscular complications following target therapy in cancer patients

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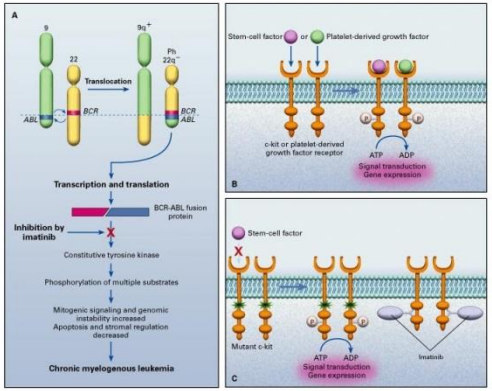
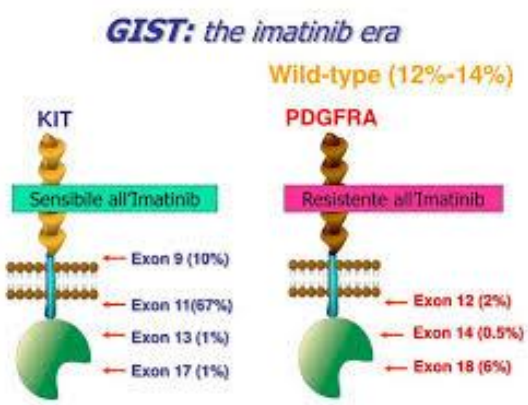
Introduction

- In the last years, many new drugs have been developed targeting different oncology pathways, overall improving both quality of life and survival in several malignancies



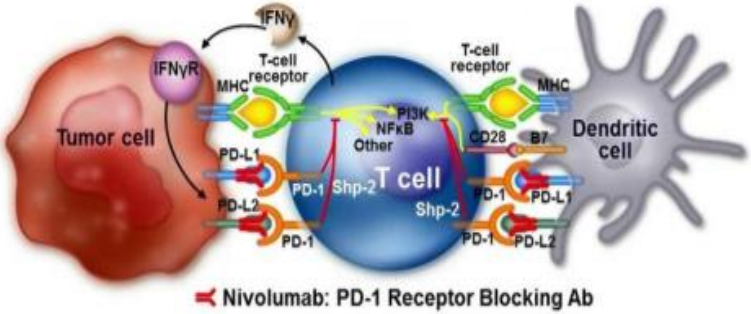
TARGET		APPLICAZIONI
IMATINIB	c-KIT PDGFR	Leucemia mieloide cronica, GIST altri sarcomi
SUNITINIB	VEGFR, PDGFR RET, c-KIT	Carcinoma renale, GIST
SORAFENIB	VEGFR, PDGFR c-RAF	Carcinoma renale, epatocarcinoma
ERLOTINIB	EGFR	Carcinoma polmonare, pancreas
LAPATINIB	EGFR HER-2	Carcinoma mammario



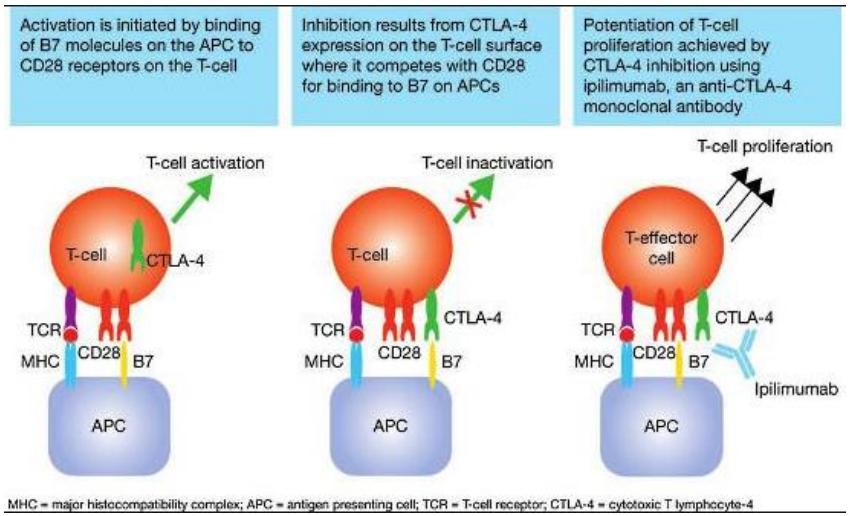
Introduction

Nivolumab Mechanism of Action

- PD-1 expression on tumor-infiltrating lymphocytes is associated with decreased cytokine production and effector function[10]
- Nivolumab binds PD-1 receptors on T cells and disrupts negative signaling triggered by PD-L1/PD-L2 to restore T-cell antitumor function[11–13]



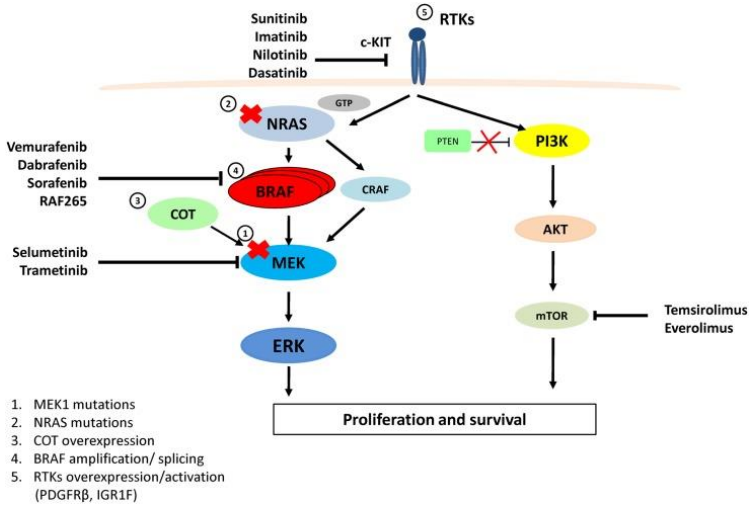
Ipilimumab Mechanism of Action

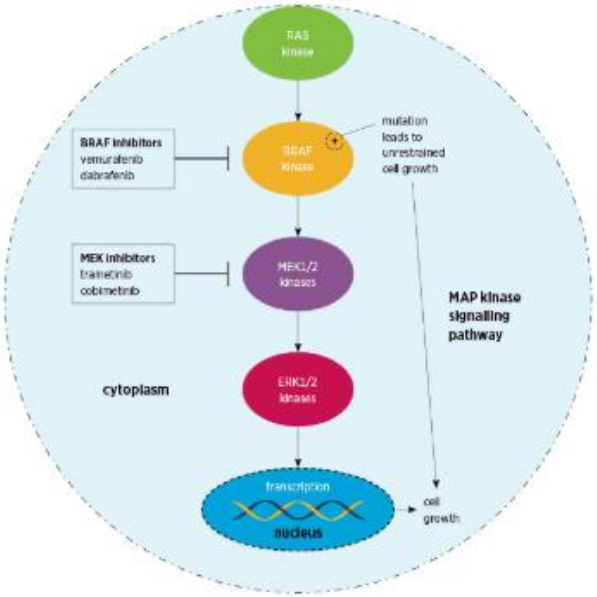


Nivolumab and Ipilimumab are monoclonal antibodies targeting the immune checkpoint molecules programmed cell death-1 (PD1) and cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) respectively. Their role is to restore antitumor immunity

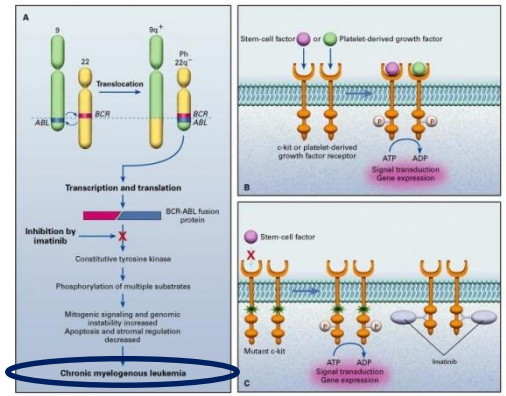
Introduction

Vemurafenib and Cobimetinib Mechanism of Action





Vemurafenib and Cobimetinib are respectively BRAF and MEK inhibitors



Imatinib Mechanism of Action

Imatinib is a tyrosine kinase inhibitor

Introduction

- The increasingly widespread use of these therapies is associated to novel toxicities, mainly immune-related adverse events (irAEs), never observed before

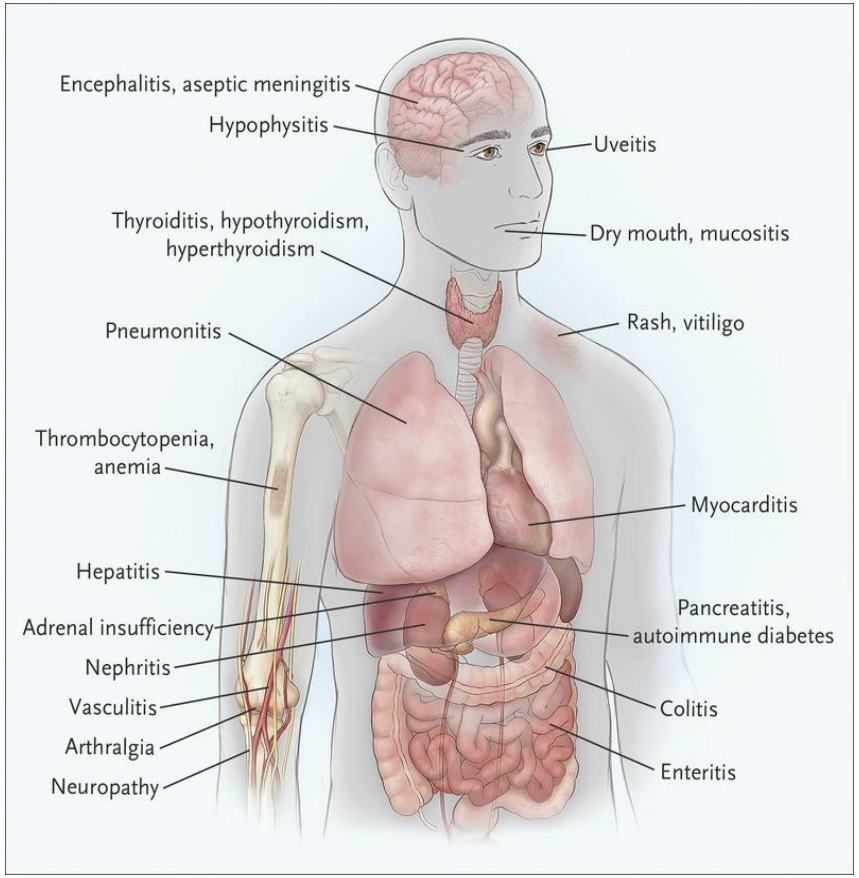
AEs of BRAF/MEK Therapy (cont)

Dabrafenib/Trametinib	Vemurafenib/Cobimetinib
• Pyrexia – most common • Fatigue • Rash • GI (diarrhea, nausea, vomiting) • Increased AST, ALT • Hand-foot syndrome	• Diarrhea – most common • Nausea/vomiting • Rash • Increased AST, ALT • Fatigue • Photosensitivity

Pyrexia is the most common AE; less skin toxicity than vemurafenib/cobimetinib.

Photosensitivity is a major concern; less pyrexia than dabrafenib/trametinib.

NCCN website. 2016; Long GV, et al. *Lancet*. 2015;386:444-451;
Larkin J, et al. *N Engl J Med*. 2014;371:1867-1876.



Immune-related Adverse Events Associated with Immune Checkpoint Blockade. Postow M. et al. 2018 NEJM

IMATINIB

Tossicità: RASH CUTANEO, EDEMA, ESOFAGITE, NAUSEA, CRAMPI MUSCOLARI, DIARREA,TOSSICITA' EPATICA, CARDIOTOSSICITA'

First case report 73 years-old woman

Past medical history: hypertension - partial thyroidectomy in Graves' disease - pulmonary thromboembolism

Present medical history: lung adenocarcinoma diagnosed in 2016 - IV stage

Therapy: Carboplatin + gemcitabine → disease progression → Nivolumab + Ipilimumab in July 2017

Ipilimumab was discontinued after 2 cycles due to subclinical myocarditis → Nivolumab was continued alone for 4 cycles

One month after Ipilimumab withdrawal: the patient sub-acutely developed fatigable diplopia with right eye exotropia, hypertropia and ptosis, mild dysphagia, modest proximal upper limbs weakness → stop Nivolumab

Contrast-enhanced brain MRI - Orbit CT - Thyroid hormonal dosages: negative

Repetitive stimulation test: negative

Acetylcholine receptor antibodies (AChR-Abs): high-titre positivity → Myasthenia Gravis

Treatment: pyridostigmine (stopped due to gastro-enteric side effects) and prednisone (25 mg daily): mild improvement

→ IVIg (2g/kg) + prednisone 50 mg daily → almost complete resolution of the symptoms

The patient started a third line therapy with vinorelbine

Second case report 73 years-old man

Past history: worked as welder

Present medical history: pleural mesothelioma diagnosed in December 2017

Therapy: first line Nivolumab + Ipilimumab in February 2018

Two weeks after the first infusion he developed myocarditis (TnI 7 µg/l) and myositis (CPK 9000 UI)

Nivolumab and Ipilimumab were discontinued and steroid therapy was administered (methylprednisolone 120 mg/daily)

Two weeks later: he developed dysphagia, dysphonia, progressive respiratory failure that required NIV and dysautonomia

Brain and Chest CT scan: excluded CNS involvement and tumor progression

CSF analysis: protein 0,23 g/L - 0,3 cells/mmc

AChR-Abs - anti-MUSK-Abs - anti-VGCC-Abs – onconeural-Ab - myositis-Ab: negative

Repetitive stimulation test: incremental response to high frequency stimulation → Lambert-Eaton Myasthenic Syndrome

Treatment: methylprednisolone (120 mg/daily) - Plasma Exchange - IVIg (2g/kg - 3 cycles) - Rituximab (2 infusions, 1000 mg each, 15 days apart) - 3,4-diaminopyridine (10 mg tid): only mild benefit (weaning of NIV during daytime)

Third case 51 years-old woman

Past medical history: paroxysmal tachycardia

Present medical history: left leg cutaneous melanoma + inguinal lymph nodes micro-metastases diagnosed in 2014

Therapy: melanoma excision and lymphadenectomy + Vemurafenib in 2014 - Cobimetinib was added in February 2017

Adverse reactions: urticarial in face and chest and headache

One year after the beginning of the combined treatment: she sub-acutely developed forehead corrugator weakness, difficulty in protrude her lips and puffing cheeks, diplopia, drooling

Contrast-enhanced Brain MRI and Total body PET: negative

CSF analysis: protein 1,280 g/L - 10 cells/mmc (lymphocytes)

AChR-Abs - anti-MUSK-Abs - anti-VGCC-Abs - onconeural-Abs - anti-gangliosides-Ab: negative

NCS: axonal motor neuropathy with predominant cranial nerve involvement→Sub-Acute Motor Axonal Neuropathy

Treatment: methylprednisolone (1000 mg x 5 days) with remission

Fourth case 65 years-old man

Past medical history: arterial hypertension

Present medical history: emicolectomy and partial ileal resection for GIST (gastrointestinal stromal tumor) in January 2018

Therapy: KIT exon 11 mutation → adjuvant therapy with Imatinib began in April 2018

Few days after the first administration he developed neck muscles and masticatory weakness: Imatinib was discontinued for 2 days with benefit

Therapy was restarted and 2 days later: right eye ptosis, head drop, dysphagia and respiratory failure that required intubation and ventilation

Brain CT: excluded CNS involvement

AChR-Abs: high-titre positivity → Myasthenia Gravis

Total body CT: no thymoma - no tumor progression

Treatement: pyridostigmine - Plasma Exchange - methylprednisolone (120 mg, tapered): mild benefit

→ IVIg cycle (2g/kg): allowed extubation

Discussion and conclusions

- The exact mechanism of neuromuscular complications is still unclear, but it is strongly thought to be due to autoreactive T-lymphocyte activation
- With regard to immune checkpoint inhibitors:
  - PD-1 is expressed on the surface of autoreactive T lymphocytes
  - PD-1 prevents autoimmunity and maintains immune cell tolerance
  - CTLA-4 is an essential negative regulator of peripheral T cell function
  - CTLA-4 has a crucial role in mediating peripheral T cell tolerance
- The blockade of both PD-1 and CTLA-4 activates autoreactive T cells

- Concerning BRAF and MEK inhibitors:
  - the response to corticosteroids in our patient suggests an immune-mediated effect
  - BRAF inhibitors seem to increase recognition of melanoma cells by a hyperactivated T-cell response
  - Melanocytes and Schwann cells are both derived from neural crest cells and share surface molecules
- Molecular mimicry of surface molecules may result in autoimmune neuropathies

Discussion and conclusions

- To conclude, we strengthen the relevance of neuromuscular complications in patients treated with new target therapies, because they can become life-threatening if not promptly managed