HOT TOPIC

Malattie Neuromuscolari: effetti neurotossici della terapia oncologica di precisione

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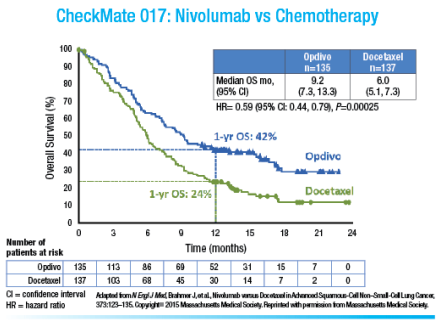
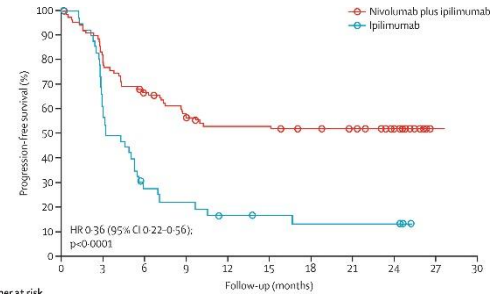
Introduction

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





THE LANCET
Oncology

Combined nivolumab and ipilimumab versus ipilimumab alone in patients with advanced melanoma: 2-year overall survival outcomes in a multicentre, randomised, controlled, phase 2 trial

A Sosa, E Lopez Cadena *et al.*

Table 1. Indications and dates of approval of ICIs by US FDA and EMA updated to January 2018.

ICI and *mechanism of action*	Indication	Approval by US FDA	Approval by EMA
Ipilimumab *Anti-CTLA-4 antibody*	Metastatic melanoma	Mar 2011	Jul 2011
	Adjuvant treatment for stage III resected melanoma	Oct 2015	—
Pembrolizumab *Anti-PD-1 antibody*	Metastatic melanoma	Sep 2014	May 2015
	Advanced non-small cell lung cancer	Oct 2015	Dec 2016
	Recurrent or metastatic head and neck cancer	Aug 2016	—
	Classical Hodgkin lymphoma	Mar 2017	May 2017
	Locally advanced or metastatic urothelial carcinoma	May 2017	Sep 2017
	Any microsatellite instability-high solid tumor	May 2017	—
	Locally advanced or metastatic gastric or gastroesophageal junction cancer	Sep 2017	—
Nivolumab *Anti-PD-1 antibody*	Metastatic melanoma	Dec 2014	Jun 2015
	Advanced non-small cell lung cancer	Mar 2015	Jul 2015
	Metastatic renal cell carcinoma	Nov 2015	Apr 2016
	Classical Hodgkin lymphoma	May 2016	Nov 2017
	Head and neck cancer	Nov 2016	Apr 2017
	Locally advanced or metastatic urothelial carcinoma	Feb 2017	Jun 2017
	Microsatellite instability-high metastatic colorectal cancer	Aug 2017	—
	Hepatocellular carcinoma	Sep 2017	—
	Adjuvant treatment for stage III or IV completely resected melanoma	Dec 2017	—
Ipilimumab + nivolumab	Unresectable or metastatic melanoma	Jan 2016	May 2016
Atezolizumab *Anti-PD-L1 antibody*	Urothelial carcinoma	May 2016	Jul 2017
	Metastatic lung cancer	Oct 2016	Jul 2017
Avelumab *Anti-PD-L1 antibody*	Metastatic Merkel cell carcinoma	Mar 2017	Sep 2017
	Urothelial carcinoma	May 2017	Aug 2017
Durvalumab *Anti-PD-L1 antibody*	Advanced bladder cancer	May 2017	—

EMA, European Medicines Agency; ICI, immune checkpoint inhibitor; US FDA, United States Food and Drug Administration.

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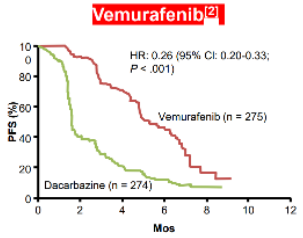
THE LANCET
Oncology

Cobimetinib combined with vemurafenib in advanced *BRAF*^{V600}-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial

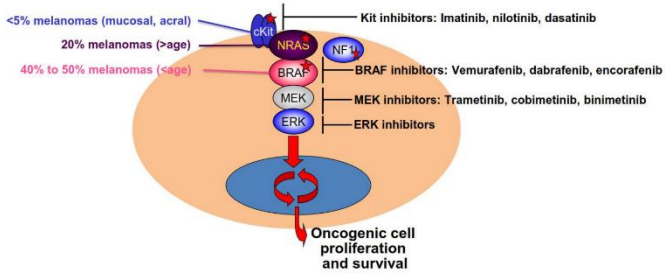
Single-Agent BRAF Inhibition vs Dacarbazine in Advanced Melanoma: PFS



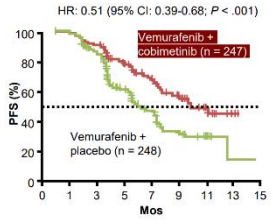
ORR: 48% vs 5% with dacarbazine

Chapman PB, et al. N Engl J Med. 2011;364:2507-2516.

MAPK Pathway As Oncogenic Driver for Melanoma



Combination BRAF/MEK Inhibition vs Single-Agent BRAF Inhibition: **PFS**



coBRIM[2]

2. Larkin J, et al. N Engl J Med. 2014;371:1867-1876.

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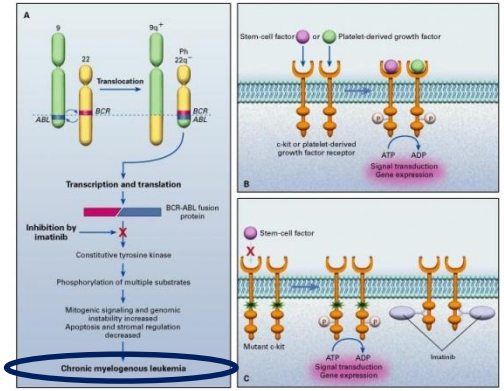
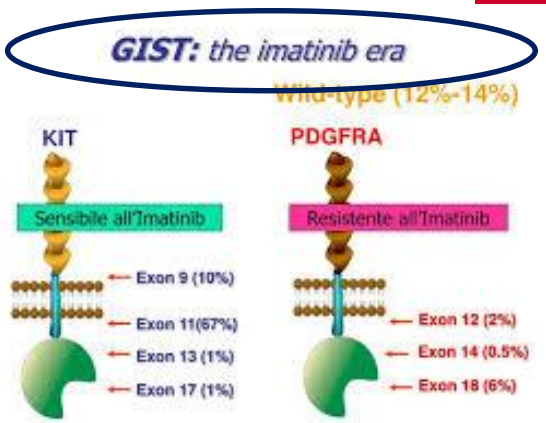


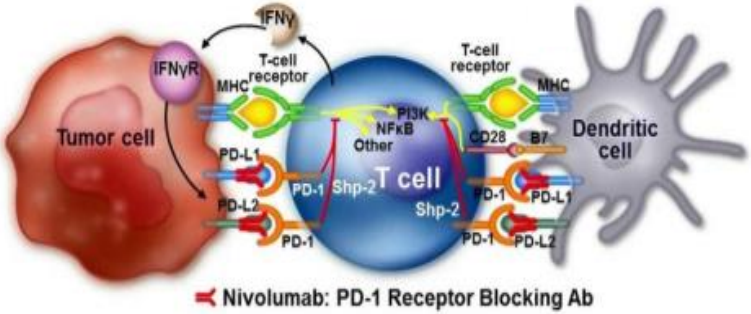
TARGET		APPLICAZIONI
IMATINIB	c-KIT PDGFR	Leucemia mieloide cronica, GIST altri sarcomi
SUNITINIB	VEGFR, PDGFR RET, c-KIT	Carcinoma renale, GIST
SORAFENIB	VEGFR, PDGFR c-RAF	Carcinoma renale, epatocarcinoma
ERLOTINIB	EGFR	Carcinoma polmonare, pancreas
LAPATINIB	EGFR HER-2	Carcinoma mammario



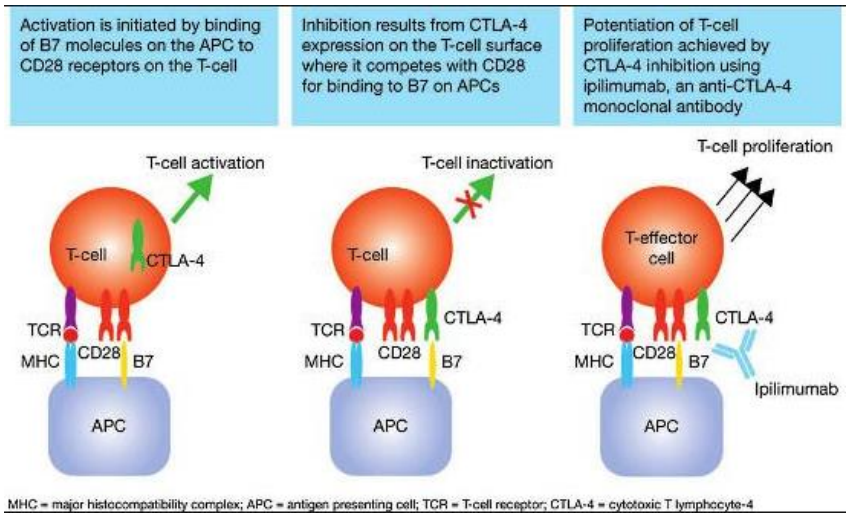
Introduction

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]



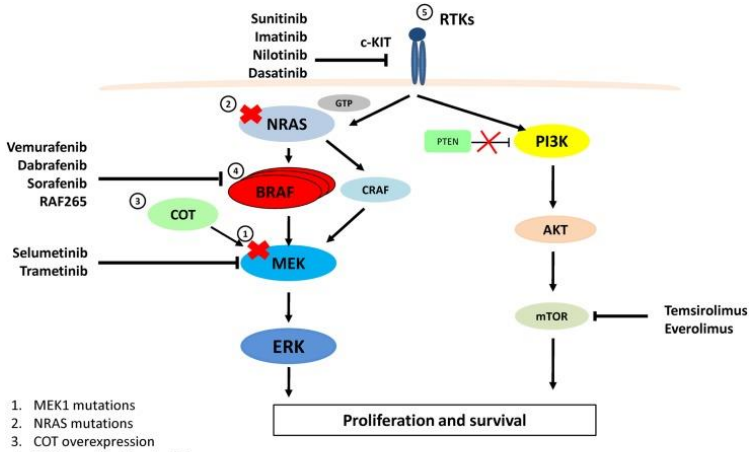
Ipilimumab Mechanism of Action

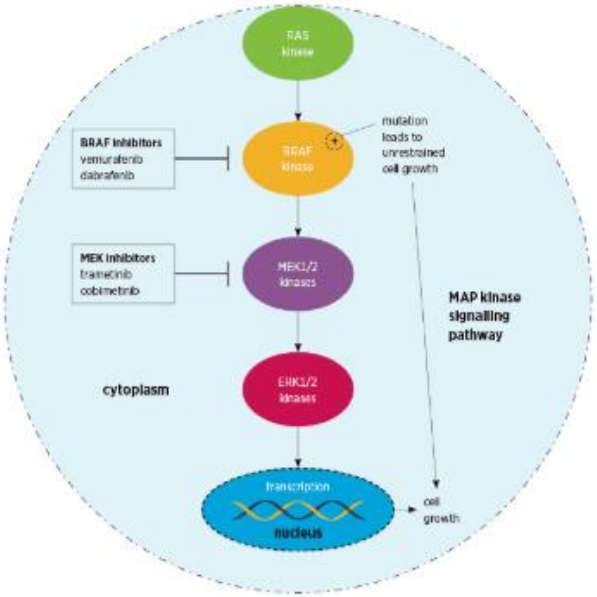


Nivolumab and Ipilimumab are monoclonal antibodies targeting the immune checkpoint molecules programmed cell death-1 (PD1) and cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) respectively. Their role is to restore antitumor immunity

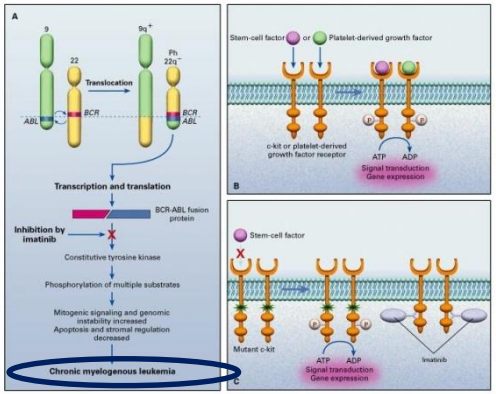
Introduction

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, never observed before

AEs of BRAF/MEK Therapy (cont)

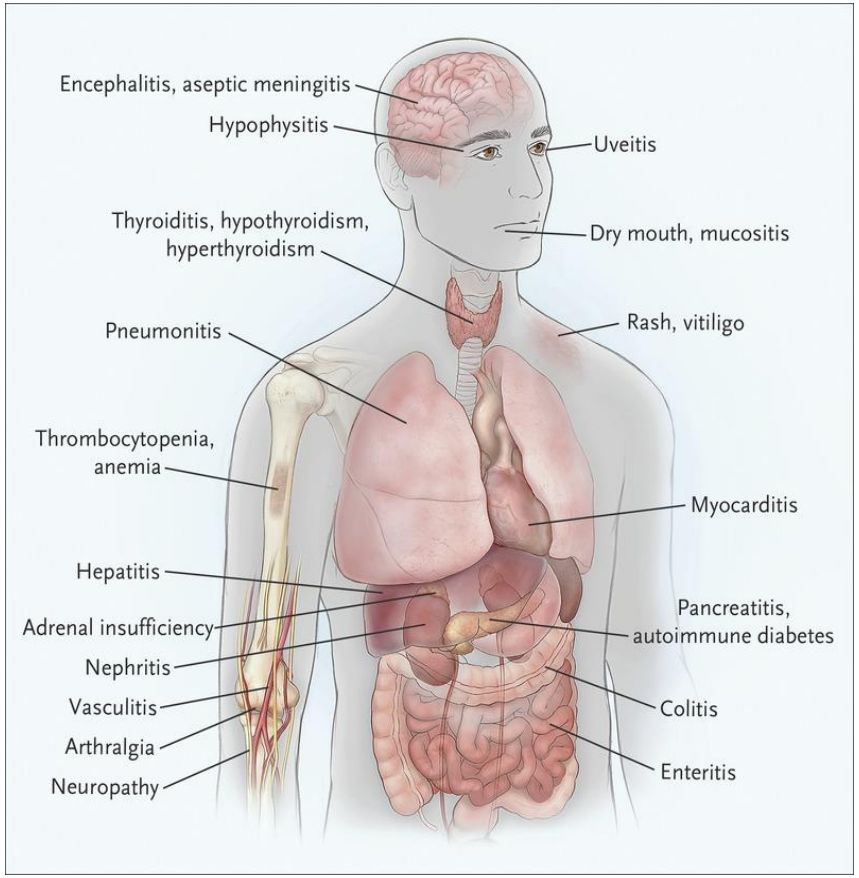
Dabrafenib/Trametinib
- Pyrexia – most common
- Fatigue
- Rash
- GI (diarrhea, nausea, vomiting)
- Increased AST, ALT
- Hand-foot syndrome

Vemurafenib/Cobimetinib
- 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
  - After the beginning of BRAF inhibitor therapy it has been demonstrated an increase in tumour infiltrating lymphocytes in samples from patients and the extent of infiltration correlates with tumour response
  - It is believed that this treatment leads to a suppression of the release of immunosuppressive factors from melanoma cells and increases antigen expression leading to more effective T-cell recognition
  - 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

- Concerning Imatinib:
  - To our knowledge this is the first case of Myasthenia Gravis associated with Imatinib treatment
  - TKI show a broad spectrum of immunomodulatory, “off-target”, effects, which allow long-term therapeutic efficacy that in many patients persists beyond treatment cessation
  - It has been demonstrated that Imatinib inhibits tumour-infiltrating Treg lymphocytes, which have immunosuppressive functions, allowing cytotoxic T-cell relative expansion and anti-tumour suppression
  - Treg cells are essential for maintaining peripheral tolerance against self-antigens, and are implicated in the pathogenesis of different autoimmune diseases.
  - In patients with MG a decreased production of Treg cells has been described in thymoma along with Treg cells subpopulations imbalance in respect to healthy controls.
  - A local disequilibrium of Treg and Teffector cells might be relevant for disease pathogenesis
- In these terms, we can hypothesize that a Treg cells dysfunction is involved in development of MG related to Imatinib treatment.

Discussion and conclusions

- To conclude, we strengthen the relevance of neuromuscular complications in patients treated not only with the latest ICPi, but also with “older” and apparently better-known targeted therapies.
- Also in the latter cases, immune “off-target” mechanisms are involved, and consequences can be life-threatening if not promptly diagnosed and appropriately managed.