SASRO Meeting 2018, University of Zurich, Campus Irchel

Neue Substanzen bei Kombinationstherapien

New substances in combinational therapies

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New substances in oncology and their combinations

Topics of our talk

mode of action of new drugs and their combinations

efficacy

adverse effects

Patient counsuling

New substances in the cancer treatment

Immuntherapy (checkpoint inhibitors)

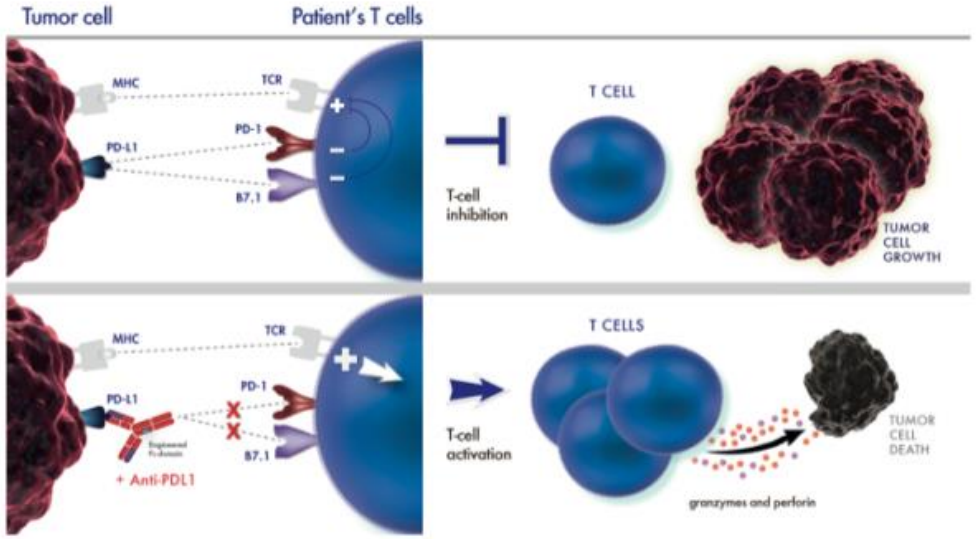
Targeted agents (tyrosine kinase inhibitors)

Immunotherapy: checkpoint inhibitors

Immune cells (T-cell responses) are regulated through a balance of inhibitory and activating signals

Tumors cells can inhibit immune cells -> tumor growth

Mechanism of action of Immune therapy (Checkpoint inhibitors): «releasing the brake» -> immune cells recognize tumor



Checkpoint inhibitors: mechanism of action

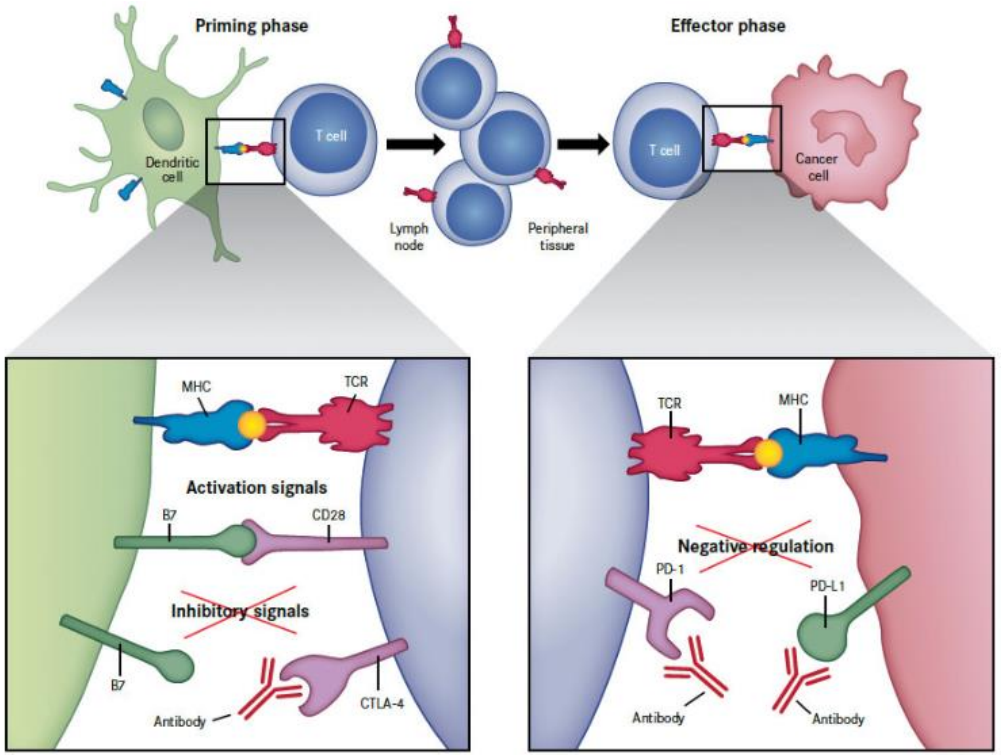
Monoclonal antibodies binding on cell surface proteins (receptors or their ligands)

Anti CTLA 4 (on immune cells): **Ipilimumab**

Anti PD 1 (on immune cell): **Nivolumab, Pembrolizumab**

Anti PD L1 (on tumor cells) **Avelumab, Durvalumab, Atezolizumab**

(LAG3, TIM-3-GAL9)



Approval for Checkpoint inhibitors in Switzerland

Melanoma (Nivo: montherapy or combination with Ipi; adjuvant; pembro; 1st line)

Lung cancer 1st line (nivo: 1st line; pembro: 1st line if PDL1>50%)

Lung cancer 2nd line (pembro)

Head&neck cancer 2nd line (nivo)

Kidney cancer (nivo: 1st line in combinatio withn Ipi, 2nd line motherapy)

Urothelial cancer (nivo 2nd line; pembro after platinum)

Hodgkin disease (nivo after HD/ASCT und brenduximab; pembro after 3 line)

CRC MSI high

Merkel cell carcinoma (avelumab)

Combinations of Checkpoint inhibitors

Goal: to achieve better response and prolong survival

Costs: higher rates of adverse effects

two different checkpoint inhibitors (Melanoma, lung, renal cell, trials…)

Immunotherapy and chemotherapy (lung, different trials)

Immunotherapy and radiotherapy (trials, some completed)

Immunotherapy and vaccines (melanoma, trials)

Immunotherapy, chemotherapy and anti-VGEF antibody (published)

Combination of pembrolizumab and chemotherapy in patient with head and neck canc

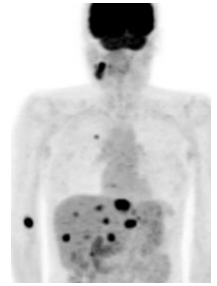
51 year old female patient, heavy smoker; high alcohol consumption

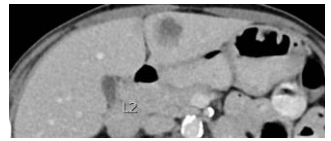
10/2017:

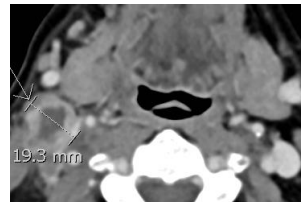
Squamous cell ca of the floor of the mouth

cervical lymphadenopathy

distant metastases (liver, bones)



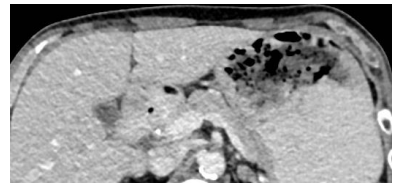


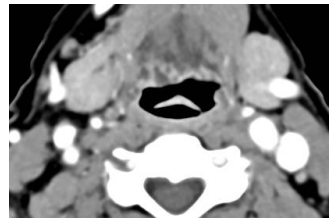


12/17:

<u>Pembrolizumab, carboplatin and 5FU (clinical trial)</u>

followed by pembrolizumab for 2 years



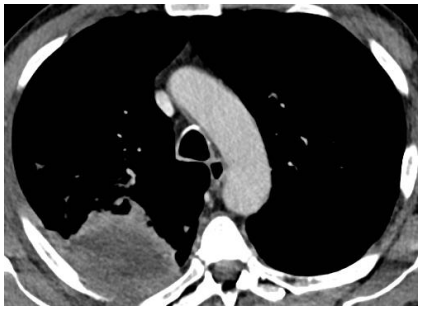


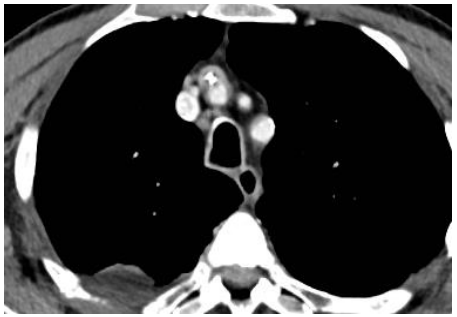
8/18: still in remission

Combination of two checkpoint inhibitors (clinical trial)

68 yo male patient, heavy smoker

1/2016:
Laryngeal cancer pT3 pN0 M0
Radiotherapy with 70 Gy and cisplatin





12/16: Pulmonary metastases

Therapy:

ipilimumab and nivolumab (clinical trial)

After 2 cycles: Partial response

Combination of pembrolizumab and radiotherapy in patient with recurent nasopharyng

2010: chemotherapy (Cis/5FU) followed by RCT (70 Gy); bilateral neck dissection (2011)

2013: diplopia; metastasis of the right occipital condyle and clivus (confirmed)

Chemotherapy (carboplatin, fluorouracil and docetaxel): partial response

2014: progression; infiltration of the cavernous sinus and abducens nerve: stereotactic re-irradiation with CyberKnife, SD

docetaxel and gemcitabine

10/15: progression (skull base, cavernous sinus, Meckel's cave and the internal carotid artery on the right side as well the middle cranial fossa , hypoglossal canal)

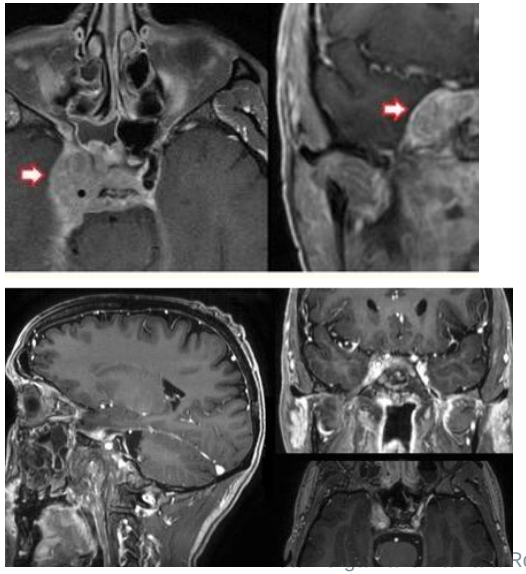
docetaxel and gemcitabine; SD

1/16 **pembrolizumab**; SD

6/2016 **stereotactic re-re-irradiation (45 Gy)**

9/16 **Pembrolizmab**

progression Doxetaxel and pembrolizuab; SD



Combination of immunotherapy and oncolytic virus (clinical trial Talimogene laherparepvec)

51 year old female patient, no risk factors

6/15

Carcinoma of base of the tongue, pT2pN1 (1/15)

Transoral resection; adjuvant radiotherapy (30x2 Gy)

11/15 Relapse (cervical lymphe nodes)

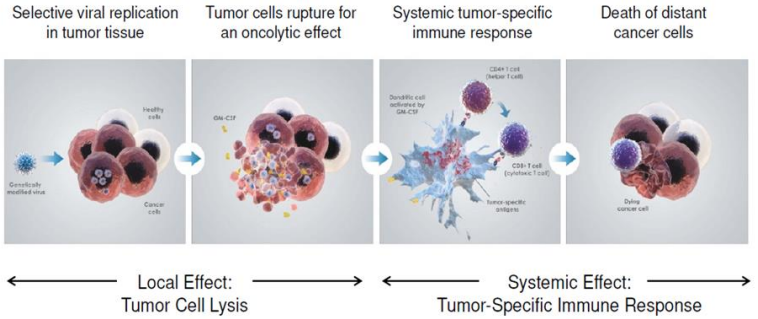
12/15 Chemotherapie (doxetaxel, cisplatin, 5FU)

minor response

1-3/16 Accelerated RT 25x2.5 Gy=50 Gy

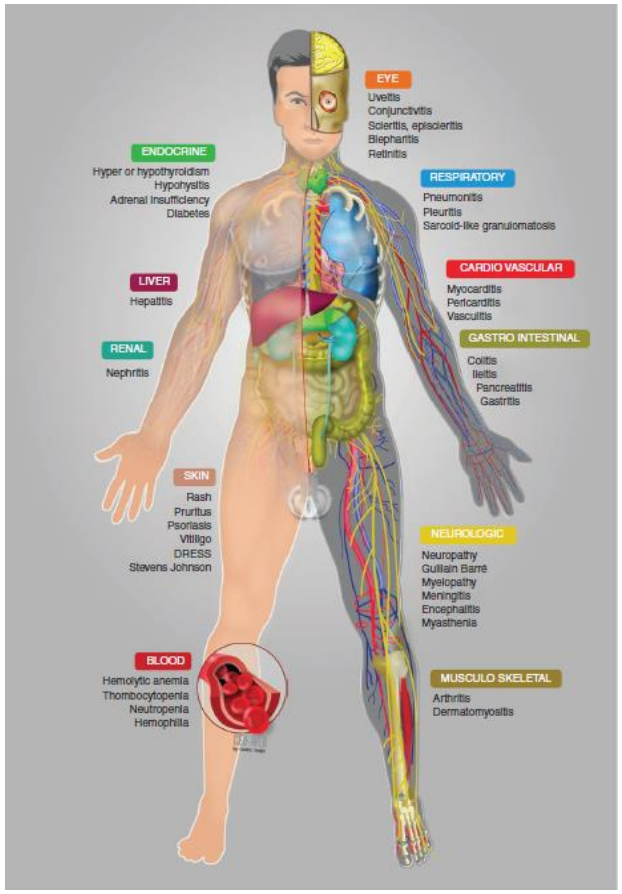
Progression

Clinical trial with checkpoint-inhibitor and vaccine, exitus



UniversityHospital Zürich

Adverse effects of checkpoint inhibitors



Most common AE:
Rash, Pneumonitis, Diarrhoa, Endocrine

Montherapy vs combination:

More active in some trials; no benefit in other trials
-> higher rates of AE

Table 3. Adverse Events.*

Event	Nivolumab (N=313)		Nivolumab plus Ipilimumab (N=313)		Ipilimumab (N=311)	
	Any	Grade 3 or 4	Any	Grade 3 or 4	Any	Grade 3 or 4
	number of patients with event (percent)					
Any adverse event	311 (99.4)	136 (43.5)	312 (99.7)	215 (68.7)	308 (99.0)	173 (55.6)
Treatment-related adverse event†	257 (82.1)	51 (16.3)	299 (95.5)	172 (55.0)	268 (86.2)	85 (27.3)
Diarrhea	60 (19.2)	7 (2.2)	138 (44.1)	29 (9.3)	103 (33.1)	19 (6.1)
Fatigue	107 (34.2)	4 (1.3)	110 (35.1)	13 (4.2)	87 (28.0)	3 (1.0)
Pruritus	59 (18.8)	0	104 (33.2)	6 (1.9)	110 (35.4)	1 (0.3)
Rash	81 (25.9)	2 (0.6)	126 (40.3)	15 (4.8)	102 (32.8)	6 (1.9)
Nausea	41 (13.1)	0	81 (25.9)	7 (2.2)	50 (16.1)	2 (0.6)
Pyrexia	18 (5.8)	0	58 (18.5)	2 (0.6)	21 (6.8)	1 (0.3)
Decreased appetite	34 (10.9)	0	56 (17.9)	4 (1.3)	39 (12.5)	1 (0.3)
Increase in alanine amino-transferase level	12 (3.8)	4 (1.3)	55 (17.6)	26 (8.3)	12 (3.9)	5 (1.6)
Vomiting	20 (6.4)	1 (0.3)	48 (15.3)	8 (2.6)	23 (7.4)	1 (0.3)
Increase in aspartate amino-transferase level	12 (3.8)	3 (1.0)	48 (15.3)	19 (6.1)	11 (3.5)	2 (0.6)
Hypothyroidism	27 (8.6)	0	47 (15.0)	1 (0.3)	13 (4.2)	0
Colitis	4 (1.3)	2 (0.6)	37 (11.8)	24 (7.7)	36 (11.6)	27 (8.7)
Arthralgia	24 (7.7)	0	33 (10.5)	1 (0.3)	19 (6.1)	0
Headache	23 (7.3)	0	32 (10.2)	1 (0.3)	24 (7.7)	1 (0.3)
Dyspnea	14 (4.5)	1 (0.3)	32 (10.2)	2 (0.6)	13 (4.2)	0
Treatment-related adverse event leading to discontinuation	24 (7.7)	16 (5.1)	114 (36.4)	92 (29.4)	46 (14.8)	41 (13.2)

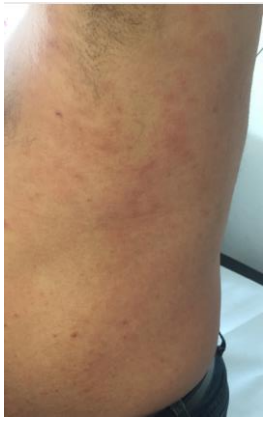
Combined Ipilimumab and Nivolumab or Monotherapy in untreated Melanoma; Larkin et al, NEJM 2015

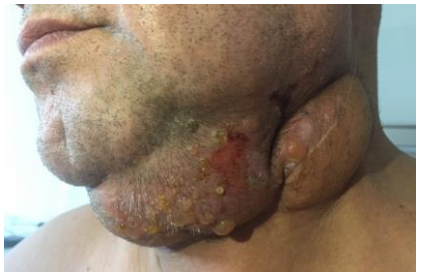
Adverse effects of immunotherapy: Skin

Patient with local relapse of head&neck cancer

1st cycle ipilimumab and nivolumab:
rash and pemphigoid skin
reaction

-> good response to steroids

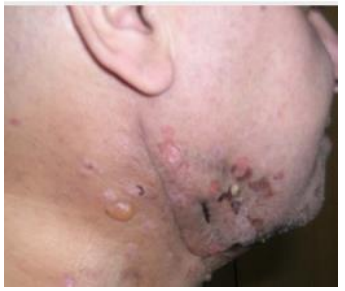


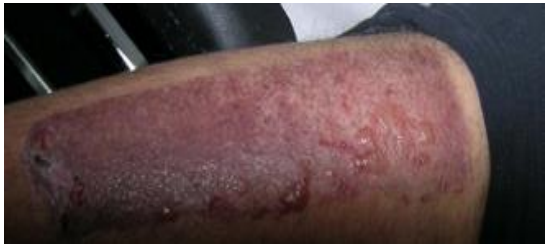


Discontinuation of Immune therapy
(patient's decision)

-> salvalge surgery

Skin reaction (3 months after last
therapy):
response to steroids
Secondary infection





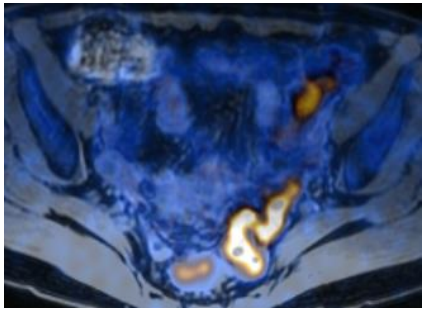
Adverse effects of immune therapy: collitis and pneumonitis

Patient with local relapse of mesopharyx ca

2 cycles with nivolumab monotherapy

Diarrhoa (6-7x day)

-> good response to steroids

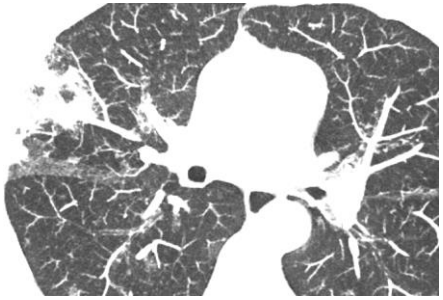


Patient with local relapse of Ca of floor of the mouth

Combination of nivolumab and anti-LAG3 (clinical trial)

Cough -> **pneumonitis**

-> good response to steroids



Management of AE of immunotherapy

JOURNAL OF CLINICAL ONCOLOGY ASCO SPECIAL ARTICLE

Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline

Annals of Oncology 28 (Supplement 4): iv119–iv142, 2017
doi:10.1093/annonc/mdx225

CLINICAL PRACTICE GUIDELINES

Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

Protein Kinase Inhibitors

Tyrosin kinase Inhibitors (TKI):

Inhibition of kinase domains (intracellular part of receptor) -> blocks cell signalling

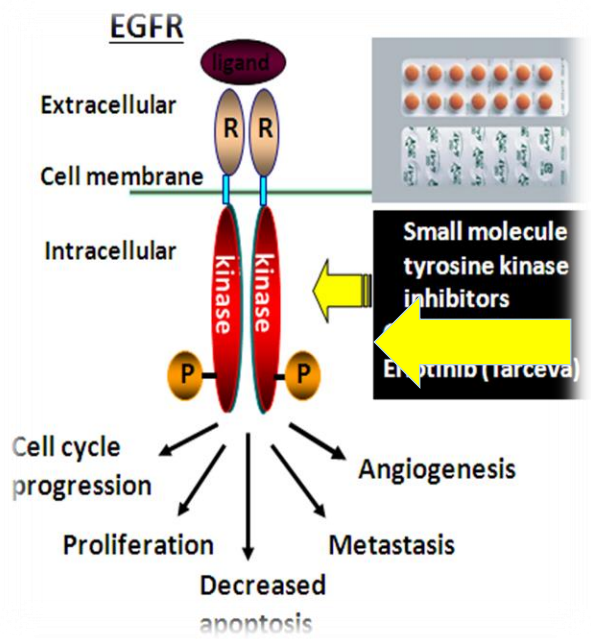
Different receptors: EGFR, HER2..

TKIs: gefinitib, erlotinib, osimertinib, lapatinib

lung ca, renal ca, mama ca, CML..

Serine/threonine kinase inhibitors:
(BRAFi, MEKi)

Melanoma, Thyroid ca



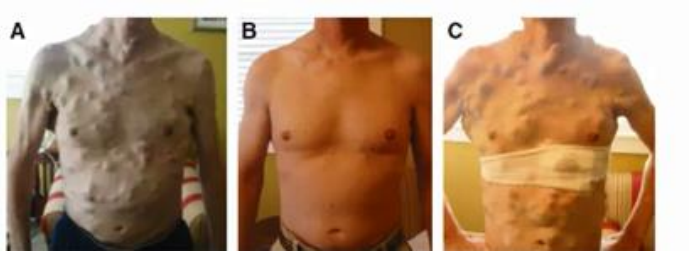
Braf inhibitors (monotherapy)

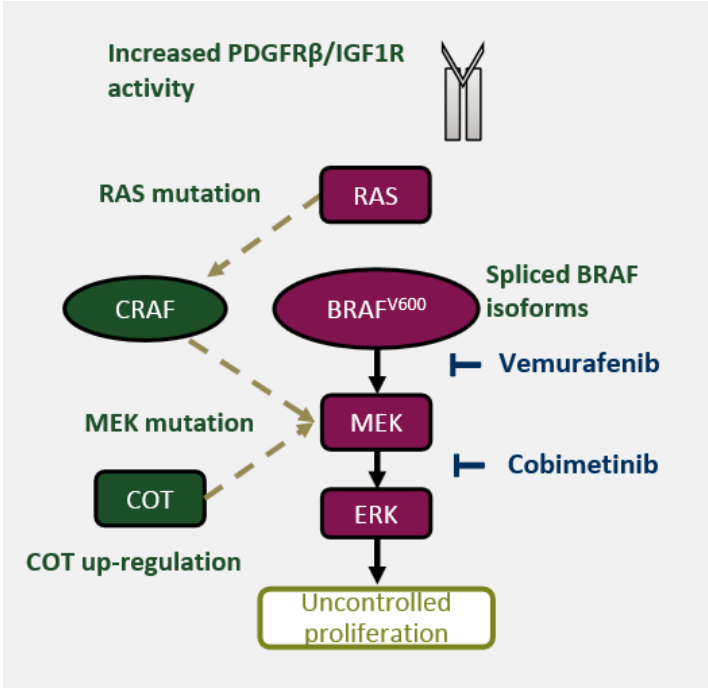
vemurafenib, dabrafenib

Active in melanoma with brafV600 mutations

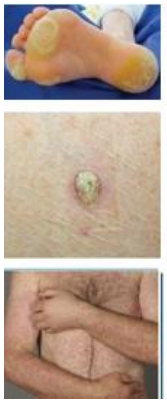
BUT

short remissions





Skin AE



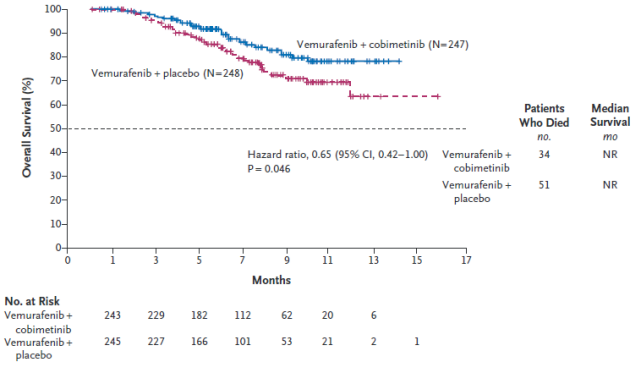
UniversityHospital Zurich

Combination of Braf/mek inhibitors

ESTABLISHED IN 1812 NOVEMBER 13, 2014 VOL. 371 NO. 20

Combined Vemurafenib and Cobimetinib in *BRAF*-Mutated Melanoma

James Larkin, M.D., Ph.D., Paolo A. Ascierto, M.D., Brigitte Dréno, M.D., Ph.D., Victoria Atkinson, M.D., Gabriella Liszkay, M.D., Michele Maio, M.D., Mario Mandalà, M.D., Lev Demidov, M.D., Daniil Stroyakovskiy, M.D., Luc Thomas, M.D., Ph.D., Luis de la Cruz-Merino, M.D., Caroline Dutriaux, M.D., Claus Garbe, M.D., Mika A. Sovak, M.D., Ph.D., Ilsung Chang, Ph.D., Nicholas Choong, M.D., Stephen P. Hack, M.D., Ph.D., Grant A. McArthur, M.B., B.S., Ph.D., and Antoni Ribas, M.D., Ph.D.



Results:

Combination of braf/mek inhibotors compared to monotherapy braf i

- improves response and survival

- Less AE !

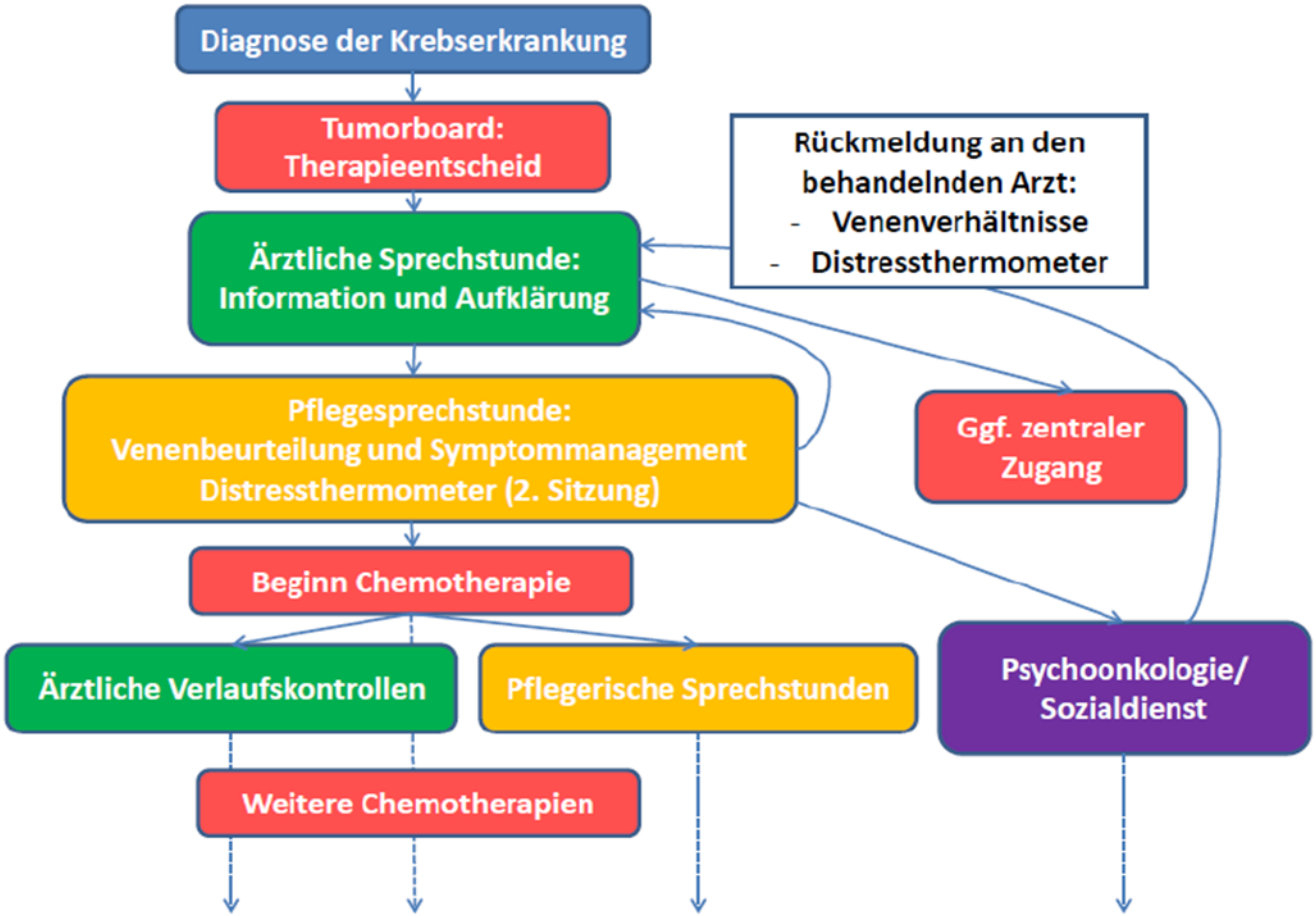
Table 3. Adverse Events.*

Event	Dabrafenib plus Trametinib (N=350)		Vemurafenib (N=349)	
	Any Grade†	Grade 3	Any Grade†	Grade 3
	number of patients (percent)			
Clinically significant adverse events occurring in ≥10% of patients				
Any event	343 (98)	167 (48)	345 (99)	198 (57)
Pyrexia‡	184 (53)	15 (4)	73 (21)	2 (1)
Nausea	121 (35)	1 (<1)	125 (36)	2 (1)
Diarrhea	112 (32)	4 (1)	131 (38)	1 (<1)
Chills	110 (31)	3 (1)	27 (8)	0
Vomiting	101 (29)	4 (1)	53 (15)	3 (1)
Arthralgia	84 (24)	3 (1)	178 (51)	15 (4)
Rash	76 (22)	4 (1)	149 (43)	30 (9)
Alopecia	20 (6)	0	137 (39)	1 (<1)
Hand–foot syndrome§	14 (4)	0	87 (25)	1 (<1)
Hyperkeratosis	15 (4)	0	86 (25)	2 (1)
Skin papilloma	6 (2)	0	80 (23)	2 (1)
Photosensitivity reaction	13 (4)	0	78 (22)	1 (<1)
Adverse events of interest occurring in <10% of patients				
Cutaneous squamous-cell carcinoma (including keratoacanthoma)	5 (1)	5 (1)	63 (18)	60 (17)
Decrease in ejection fraction	29 (8)	13 (4)	0	0
Chorioretinopathy	2 (1)	0	1 (<1)	0
Dermatitis acneiform	22 (6)	0	20 (6)	4 (1)

Concept of nurse consultation at the comprehensive cancer center Zurich (CCCZ)

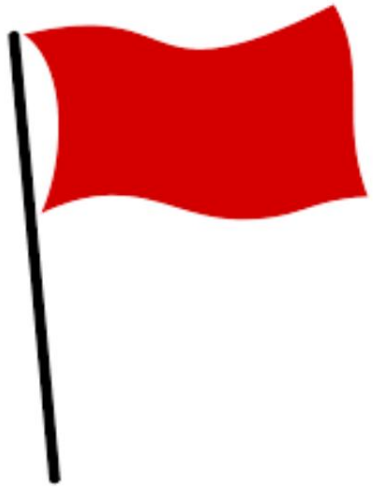
- Start of new treatment or change of treatment: management of possible side effects, schedule, self-care
- Venous access: peripheral access vs central line (peripheral arm assessment)
- Psychological support: distress thermometer, referal to specialists if required
- Basic dietary advice to prevent weight loss
- Referal to the institute of complementary medicine if required and requested

Possible patient pathway



Reference: «Konzept Pflegesprechstunde Onkologie, Medizinbereich Innere Medizin-Onkologie» Kröner, A. et al (2016)

Red flags for patients receiving immunotherapy



Patients need to know when to contact the medical team, as early assessment is crucial:

- Diarrhoea or bowel movements more frequent than usual
- Abdominal pain
- Skin changes such as rash or pruritus
- Shortness of breath
- New or worsening symptoms of cough

->NO SELF-TREATMENT<-

Reference: «Medikamente in der Tumortherapie – Handbuch für die Pflegepraxis» 5. Auflage, Kroner, T. et al (2018)

Dermatological reactions during immunotherapy

Ipilimumab (Yervoy®), CTLA-4 antibody

Very common (≥ 10%):

- Exanthema
- Pruritus

Common (≥ 1% to < 10%):

- Xerodermia (skin dryness)
- Hypopigmentation (Melanoma patients)
- Generalised mucositis

Occasional (> 0.1% to < 1%):

- Conjunctivitis
- Intensified lacrimation/inflammation of the lacrimal gland
- Change of hair colour

Reference: «Empfehlungen: dermatologische Reaktionen und unerwünschte Wirkungen unter medikamentöser Antitumortherapie, Prävention und Interventionen», Onkologiepflege Schweiz (2016)

Nivolumab (Opdivo®), PD-1 antibody

Very common (≥ 10%):

- Xerodermia (skin dryness)/Pruritus

Common (≥ 1% to < 10%):

- Exanthema
- Hypopigmentation

Occasional (> 0.1% to < 1%):

- Conjunctivitis

Reference: «Empfehlungen: dermatologische Reaktionen und unerwünschte Wirkungen unter medikamentöser Antitumortherapie, Prävention und Interventionen», Onkologiepflege Schweiz (2016)

Pembrolizumab (Keytruda®), PD-1 antibody

Very common (≥ 10%):

- Pruritus
- Exanthema

Occasional (> 0.1% to < 1%):

- Hypopigmentation (Melanoma patients)
- Conjunctivitis
- Intensified lacrimation/inflammation of the lacrimal gland
- Change of hair colour/depigmentation of eye lashes and hair

Reference: «Empfehlungen: dermatologische Reaktionen und unerwünschte Wirkungen unter medikamentöser Antitumortherapie, Prävention und Interventionen», Onkologiepflege Schweiz (2016)

Atezolizumab (Tecentriq®), PD-L1 antibody

Very common (≥ 10%):

- Exanthema
- Pruritus

Reference: www.compendium.ch

Avelumab (Bavencio®), PD-L1 antibody

Common (≥ 1% to < 10%):

- Exanthema
- Pruritus

Reference: www.compendium.ch

Durvalumab (Imfinzi®), PD-L1 antibody

Very common (≥ 10%):

- Exanthema
- Pruritus

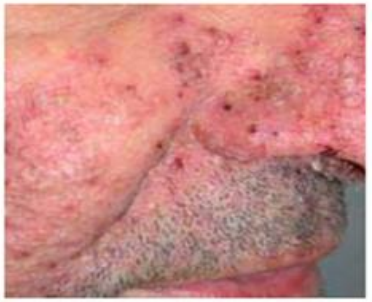
Common (≥ 1% to < 10%):

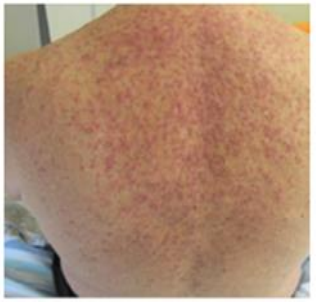
- Oral Mucositis

Reference: www.compendium.ch

Basic care advice

Exanthema



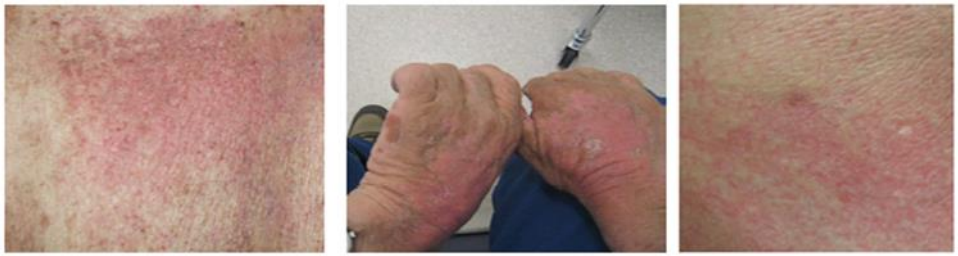


- Early patient education
- Avoiding sun exposure and use of sun protection (SPF > 30)
- Skin cleaning with mild, soap free, pH-neutral wash lotions and wash syndets (e.g. Lubex®, Der-med®, Procutol® or with cleaning oils (e.g. Excipial® Balmandol)
- Face: once a day use of O/W systems (e.g. Excipial® U Hydrolotio)
- Whole body: consequente alcohol and perfume free, moisturising skin care with or without urea (e.g. Excipial® U Lipolotio)
- Careful tapping of the skin after washing
- Avoiding exposure to toxic-irritant substances on the hands
- Lowering the room temperature and increasing air moisture (humidity)
- Face: only dry shave and no use of aftershave

Xerodermia and Pruritus

Skin

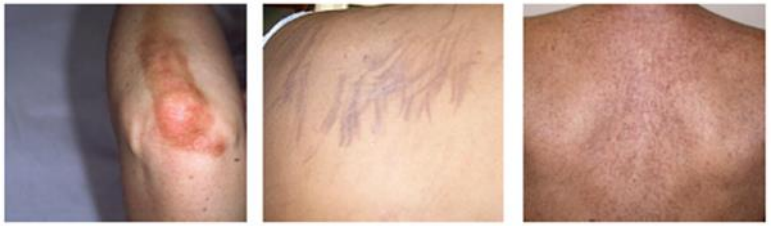
- During the dry phase to use urea-containing lipolotion in an adequate amount (100gr lotion to use within 10 days) after showering or bathing (e.g. Excipial® U Lipolotion, Eucerin® 10% Urea Lotion, Bepanthol® Körperlotion, Antidry® calm Lotion)
- Skin cleaning with mild, soap free, pH-neutral wash lotions and wash syndets or with cleaning oils (see products on previous slide)
- High room humidity
- To apply consequent sun protection



Scalp

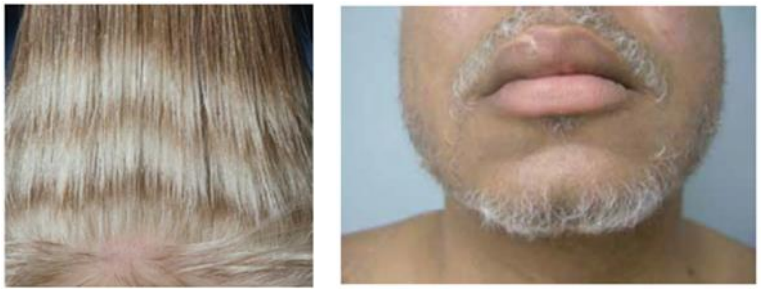
- Lotions can as well be used for the scalp to treat itchyness (e.g. Excipial® U Hydrolotion)
- Hair care with mild shampoos (e.g. Johnsons® Baby Shampoo, Lubex hair®, Crimanex® Shampoo)
- To blow dry hair with cold or room temperature air
- To apply consequent sun protection

Changes of the skin pigmentation and photosensitivity



- Early patient education
- To avoid sun and sun beds to exposed skin areas (i.e. face, ears, neck, arms and hands), to wear thickly woven clothes, if required to use UV-impermeable foils on windows
- Sun protection products against UV-A and UV-B rays with high sun protection factor (> 30)
- To avoid dry skin, itchyness and scratch marks or pressure marks on the skin (e.g. from wearing rucksacks or bras)
- Good skin moisturising

Hair depigmentation



- No prevention possible
- Early patient education
- To use gentle hair tint from the hair dresser if the depigmentation is cosmetically disturbing

Intensified lacrimation/inflammation of the lacrimal gland

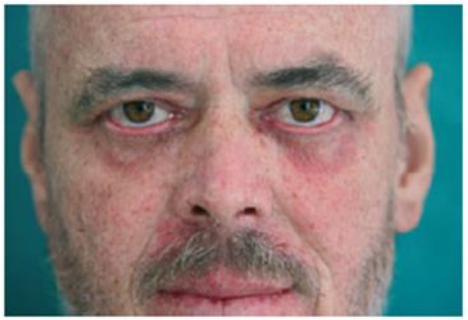
Basic care

- Initial eye assessment
- Eye hygiene
- To avoid mechanical and cosmetical eye irritation
- Sun glasses during sun exposure
- To treat conjunctivitis

Interventions

- Reassessment
- Continuation of the basic care
- Referal to ophthalmologist (in case of inflammation urgent referal required)

Conjunctivitis



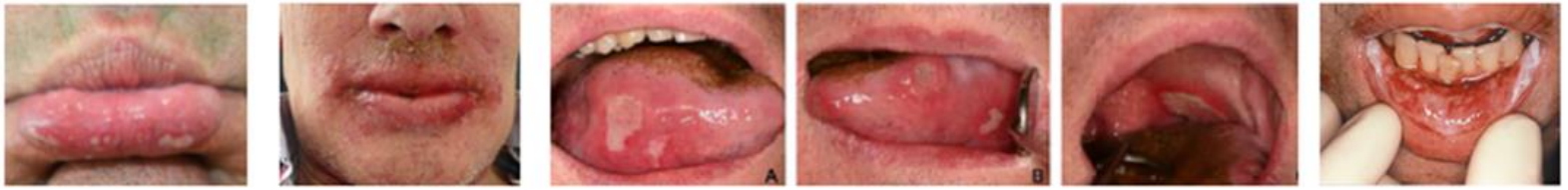
Basic care

- Initial eye assessment
- To avoid exposure to other patients with conjunctivits (avoid contamination)
- To avoid allergens
- To avoid eye drops with potential surface-toxic properties (preservatives, especially benzalkonium chloride)
- To avoid using moisturising eye drops over the expiration date)

Interventions

- Reassessment
- Continuation of the basic care
- To use moisturising eye drops/gels in incomplex cases
- Referal to ophthalmologist in purulent cases, sticky coated eyes, treatment refractory or prolonged cases

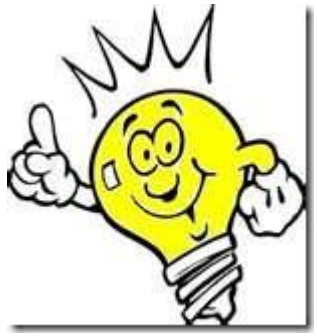
Oral mucositis



- Early patient education with regards to symptoms and management
- To clean teeth at least twice daily during 2 minutes with a soft tooth brush
- Electrical or ultrasound tooth brush is allowed if the patient is used to it
- The use of dental floss is allowed if the thrombocytes or neutrophil granulocytes are within range
- To rinse the mouth at least 4 times daily with water or salt water (1 tea spoon of salt in 1 litre of water)
- To moisturise the lips (e.g. Bepanthen® Nasensalbe)
- To drink at least 1.5 – 2 litres daily to avoid dry mucosa and lips
- To refrain from alcohol and tabacco as they both irritate the oral mucosa additionally
- To avoid sour, spicy and crusty foods which could potentially damage to mucosa
- To avoid mouth washes from the pharmacy or drug store, since they normally contain alcohol which can dry out the mouth additionally

Reference: «Empfehlungen: dermatologische Reaktionen und unerwünschte Wirkungen unter medikamentöser Antitumortherapie, Prävention und Interventionen», Onkologiepflege Schweiz (2016)

Good to know



Onkologiepflege Schweiz (OPS) have created a patient information leaflet called «changes to skin, mucosa, hair and nails during medical anticancer treatment» (Original: «Veränderungen an Haut, Schleimhäuten, Haaren und Nägeln während der Krebsbehandlung mit Medikamenten»).

This leaflet gives an overview about possible dermatological side effects and recommendations to prevent these.

Thank you for your attention

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Any questions?