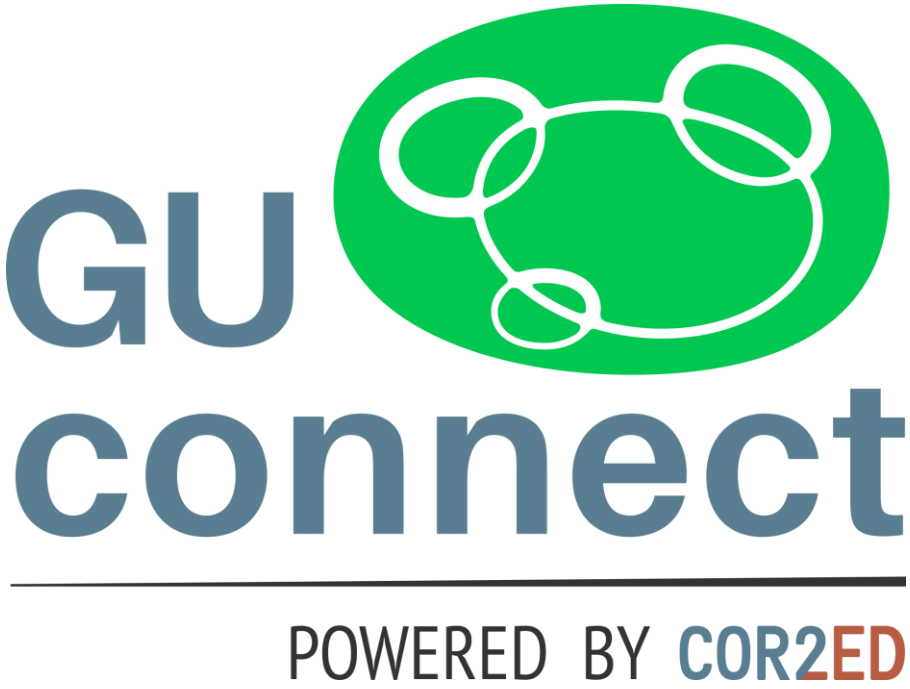
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IMMUNOTHERAPY IN GENITOURINARY TUMORS

By

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INDICATION

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- **Urothelial carcinoma**
  - Atezolizumab (Balar et al. Lancet 2017)
  - Nivolumab (Sharma et al. Lancet Oncol 2016)
  - BCG-Instillation as topical treatment (Lamm et al. J Urol 1980)
- **Prostate cancer**
  - Sipuleucel (Kantoff et al. New Engl. J of Med 2010)
- **Renal cell cancer**
  - Nivolumab (Motzer et al. New Eng. J Med 2015)
  - High-dose IL-2 (Rosenberg et al. Jama 1994)

SIDE EFFECTS OF IMMUNOTHERAPY IN RENAL CELL CANCER

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	IL2 and IFN
Reduced ECOG performance status	30,3%
Fever	25,2%
Hypotension	8,4%
Diarrhoea	7,6%
Vomiting	7,6%
Nausea	5,9%
Cutaneaous signs	5,9%
Neutropenia	4,2%
Pulmonary symptoms	4,2%

Less haematotoxic side effects

Negier et al. 2007 Cancer (110:2468-2477)

IMMUNE ASSOCIATED SIDE EFFECTS

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ENDOCRINE:
Hyper or hypothyroidism
Hypohysitis
Adrenal insufficiency
Diabetes

NEUROLOGIC:
Neuropathy
Guillain Barré
Myelopathy
Meningitis
Encephalitis
Myasthenia

EYE:
Uveitis
Conjunctivitis
Scleritis, episcletitis
Retinitis

RENAL:
Nephritis

LIVER:
Hepatitis

SKIN:
Rash
Pruritus
Psoriasis
Vitiligo
DRESS
Stevens Johnson

RESPIRATORY:
Pneumonitis
Pleuritis
Sarcoid-like granulomatosis

BLOOD:
Hemolytic anemia
Thrombocytopenia
Neutropenia
Hemophilia

MUSCULOSKELETAL:
Arthritis
Dermatomyositis

CARIOVASCULAR:
Myocarditis
Pericarditis
Vasculitis

GASTROINTESTINAL:
Colitis
Ileitis
Pancreatitis
Gastritis

Modified to Champiat et al. Annals of Oncology 2016

CHECK-POINT INHIBITORS

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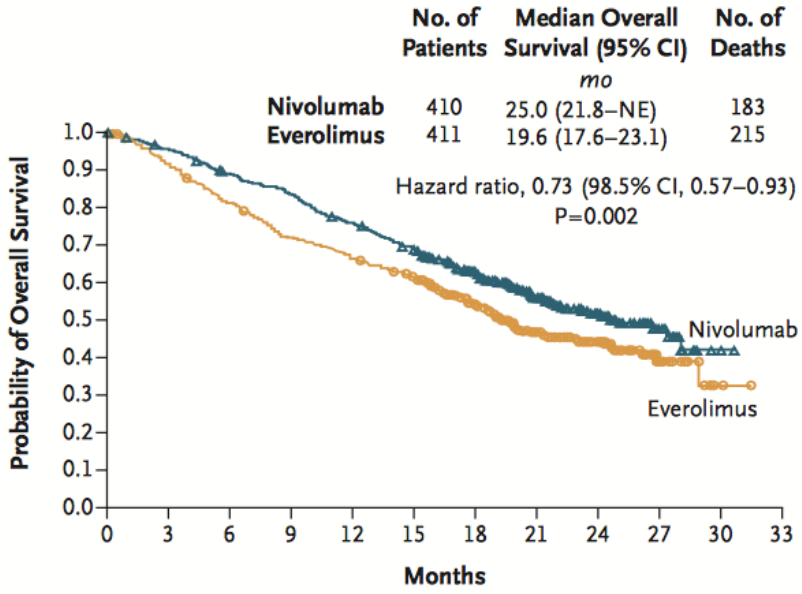
FDA approved

- Nivolumab (PD1 Antibody) (RCC and UCC)
- Atezolizumab (PDL1 Inhibitor) (UCC)

To be expected

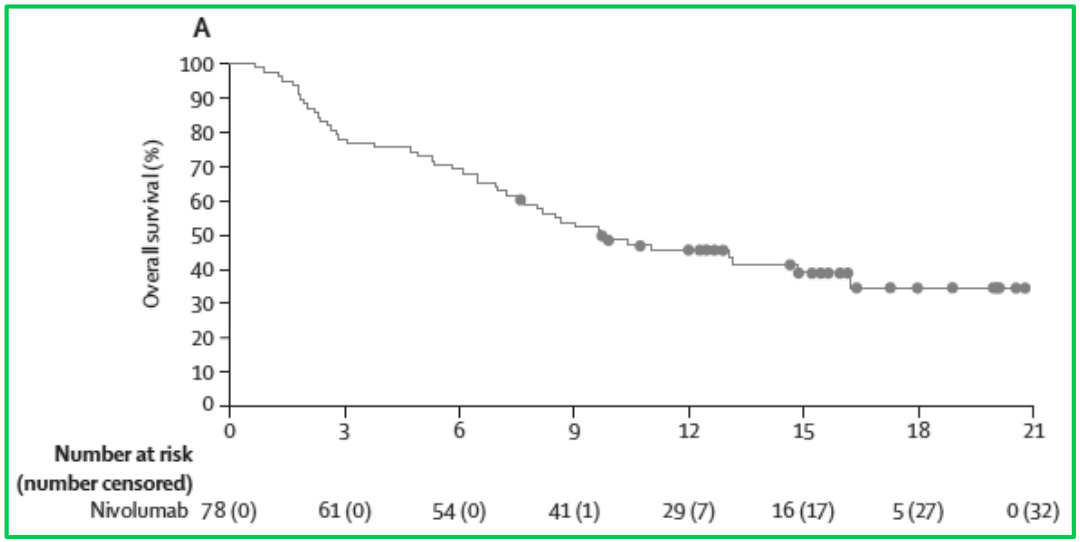
- Pembrolizumab (PD-1 Antibody) (UCC)
- Durvalumab (Anti PDL-1 Antibody) (UCC)

NIVOLUMAB RCC



Event	Nivolumab Group (N=406)		Everolimus Group (N=397)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
All events	319 (79)	76 (19)	349 (88)	145 (37)
Fatigue	134 (33)	10 (2)	134 (34)	11 (3)
Nausea	57 (14)	1 (<1)	66 (17)	3 (1)
Pruritus	57 (14)	0	39 (10)	0
Diarrhea	50 (12)	5 (1)	84 (21)	5 (1)
Decreased appetite	48 (12)	2 (<1)	82 (21)	4 (1)
Rash	41 (10)	2 (<1)	79 (20)	3 (1)
Cough	36 (9)	0	77 (19)	0
Anemia	32 (8)	7 (2)	94 (24)	31 (8)
Dyspnea	30 (7)	3 (1)	51 (13)	2 (1)
Peripheral edema	17 (4)	0	56 (14)	2 (1)
Pneumonitis	16 (4)	6 (1)	58 (15)	11 (3)
Mucosal inflammation	11 (3)	0	75 (19)	12 (3)
Dysgeusia	11 (3)	0	51 (13)	0
Hyperglycemia	9 (2)	5 (1)	46 (12)	15 (4)
Stomatitis	8 (2)	0	117 (29)	17 (4)
Hypertriglyceridemia	5 (1)	0	64 (16)	20 (5)
Epistaxis	3 (1)	0	41 (10)	0

NIVOLUMAB UC



- Neglectable haematotoxicity
- Acute phase reactions

	Grade 1–2	Grade 3	Grade 4
Any event	46 (59%)	17 (22%)	0
Fatigue	26 (33%)	2 (3%)	0
Pruritus	23 (29%)	0	0
Rash, maculopapular	12 (15%)	2 (3%)	0
Lipase elevated	7 (9%)	4 (5%)	0
Nausea	9 (12%)	1 (1%)	0
Arthralgia	9 (12%)	0	0
Anaemia	8 (10%)	0	0
Amylase increased	4 (5%)	3 (4%)	0
Dyspnoea	4 (5%)	1 (1%)	1 (1%)*
Lymphocyte count decreased	3 (4%)	2 (3%)	0
Hyperglycaemia	4 (5%)	1 (1%)	0
Neutrophil count decreased	1 (1%)	2 (3%)	0
White blood cell count decreased	2 (3%)	1 (1%)	0
Hyponatraemia	1 (1%)	1 (1%)	0
Dermatitis acneiform	1 (1%)	1 (1%)	0
Wheezing	1 (1%)	1 (1%)	0
Acute kidney injury	0	1 (1%)	0
Aspartate aminotransferase increased	0	1 (1%)	0
Back pain	0	1 (1%)	0
Colitis	0	1 (1%)	0

ATEZOLIZUMAB UCC

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	Any grade (n=119)	Grade 3–4 (n=119)
Overall	79 (66%)	19 (16%)
Fatigue	36 (30%)	4 (3%)
Diarrhoea	14 (12%)	2 (2%)
Pruritus	13 (11%)	1 (1%)
Decreased appetite	11 (9%)	1 (1%)
Hypothyroidism	8 (7%)	0
Anaemia	6 (5%)	1 (1%)
Chills	6 (5%)	0
Nausea	6 (5%)	0
Pyrexia	6 (5%)	0
Rash	6 (5%)	1 (1%)
Vomiting	6 (5%)	0
Rash, maculopapular	5 (4%)	0
Alanine aminotransferase increased	5 (4%)	4 (3%)
Arthralgia	5 (4%)	0
Aspartate aminotransferase increased	4 (3%)	3 (3%)
Blood alkaline phosphatase increased	4 (3%)	1 (1%)
Blood bilirubin increased	4 (3%)	2 (2%)

	Any grade (n=119)	Grade 3–4 (n=119)
Dyspnoea	4 (3%)	0
Infusion-related reaction	4 (3%)	0
Lymphocyte count decreased	4 (3%)	0
Asthenia	3 (3%)	0
Back pain	3 (3%)	0
Dermatitis acneiform	3 (3%)	0
Dry mouth	3 (3%)	0
Headache	3 (3%)	0
Hypophosphataemia	3 (3%)	2 (2%)
Hypotension	3 (3%)	1 (1%)
Influenza-like illness	3 (3%)	0
Muscle spasms	3 (3%)	0
Thrombocytopenia	3 (3%)	0
Renal failure	2 (2%)	2 (2%)
Autoimmune colitis	1 (1%)	1 (1%)
Liver disorder	1 (1%)	1 (1%)
Hypersensitivity	1 (1%)	1 (1%)
Multiple organ dysfunction syndrome	1 (1%)	1 (1%)
Portal vein thrombosis	1 (1%)	1 (1%)

SWITCH OF SIDE EFFECT SPECTRUM

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- Less problematic side effects concerning haematotoxicity

- Significant increase in endocrine side effects[1]
  - Hypothyroidism HR 8.26 (4,67-14,62) (p<0,0001)
  - Hyperthyroidism HR 5,48 (1,33-22,53) (p=0,02)
  - Hypophysitis HR 22,03 (8,52-56,94) (p<0,00001)
  - Adrenal insufficiency HR 3,87 (1,12-13,41) (p=0,03)

1. Abdel-Rahman Future Oncol 2016

MANAGEMENT OF SIDE EFFECTS (i)

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- Be aware of what you might expect!
- Regular laboratory exams (liver, kidney, endocrine parameters)
- Most side effects are mild, but we have to diagnose them early to avoid severe complications
- Discontinuation does not result in a prompt improvement of the symptoms
- Reintroduction only after completely resolved side effects and end of corticosteroid application
- In case of recurring complications withdrawal of treatment should be discussed

MANAGEMENT OF SIDE EFFECTS (ii)

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- Grade 1 toxicity normally surveilled
- Topical or orally taken cortocosteroids in Grade 2 (1-2mg/kg/d Prednison) toxicities stop medication transfer to a specific specialist concerning the side effect
- Grade 3 toxicities stop medication immediate presentation at emergency room 1-2mg/kg/d iv Methylprednisolon till improvement then orally 1-2 mg/kg/d Prednison orally
- Grade 4 toxicities discontinuation of treatment with check point inhibitor emergency room 1-2 mg/kg/d Methylprednisolon, if no additional improvement can be achieved

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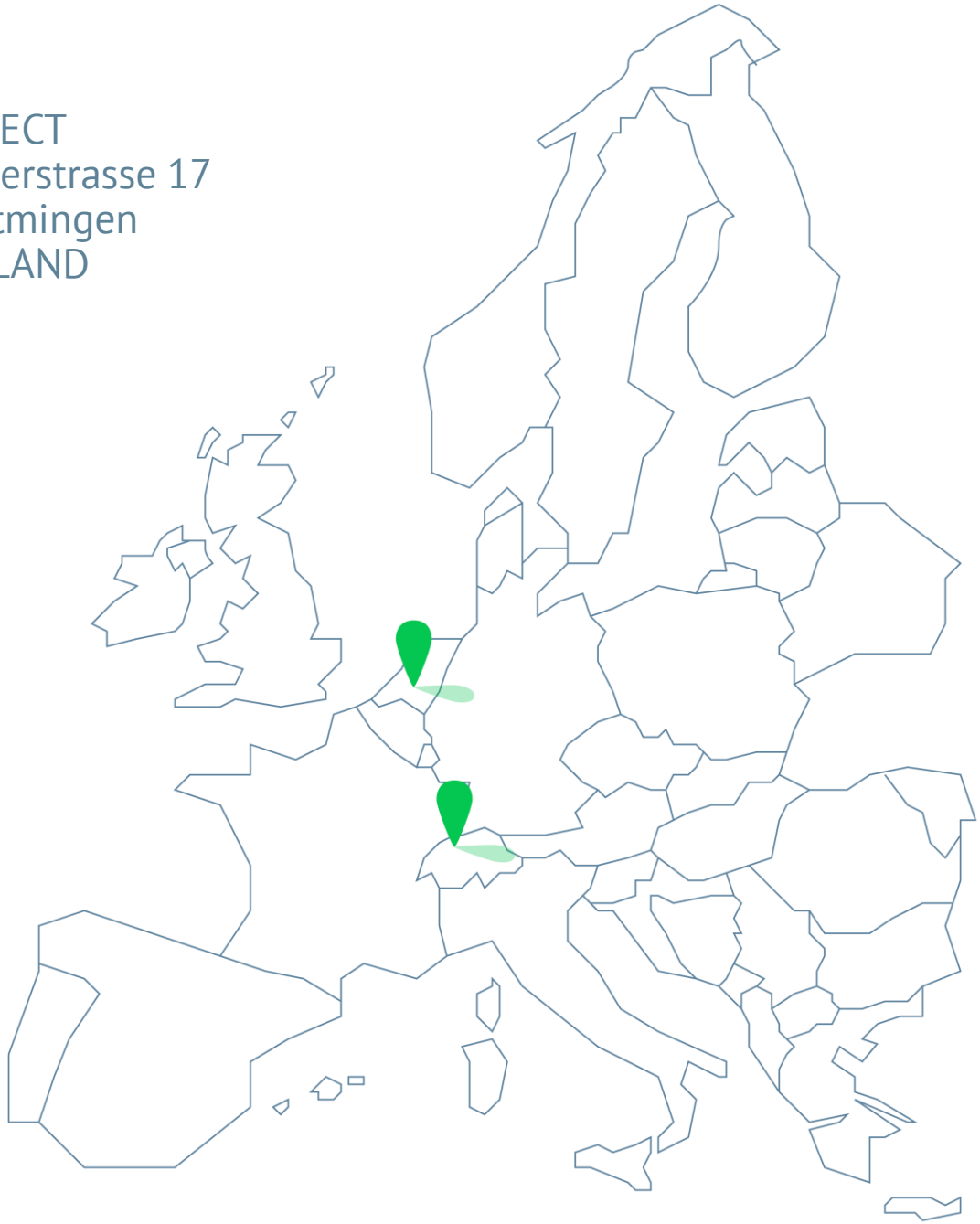

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