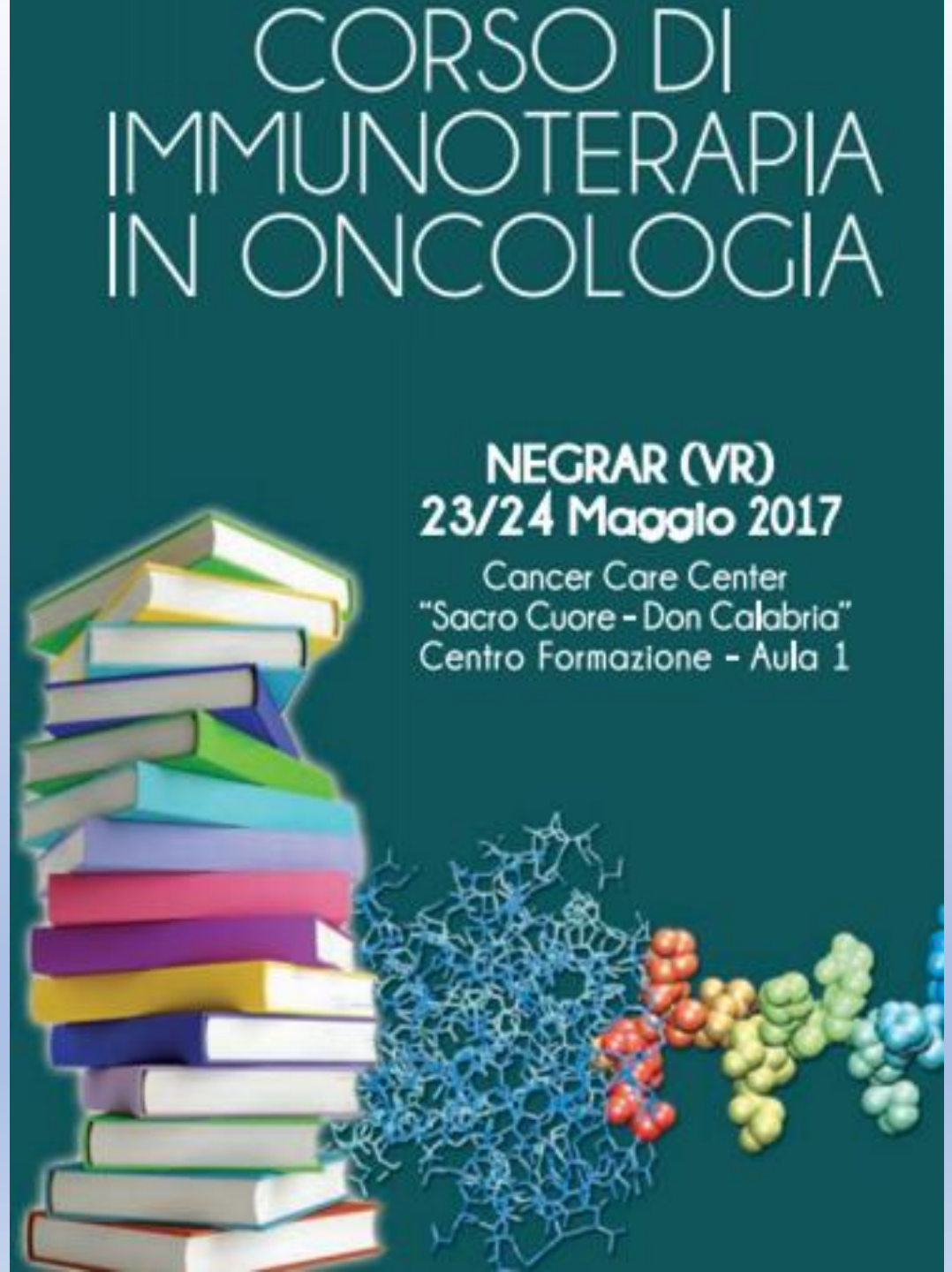
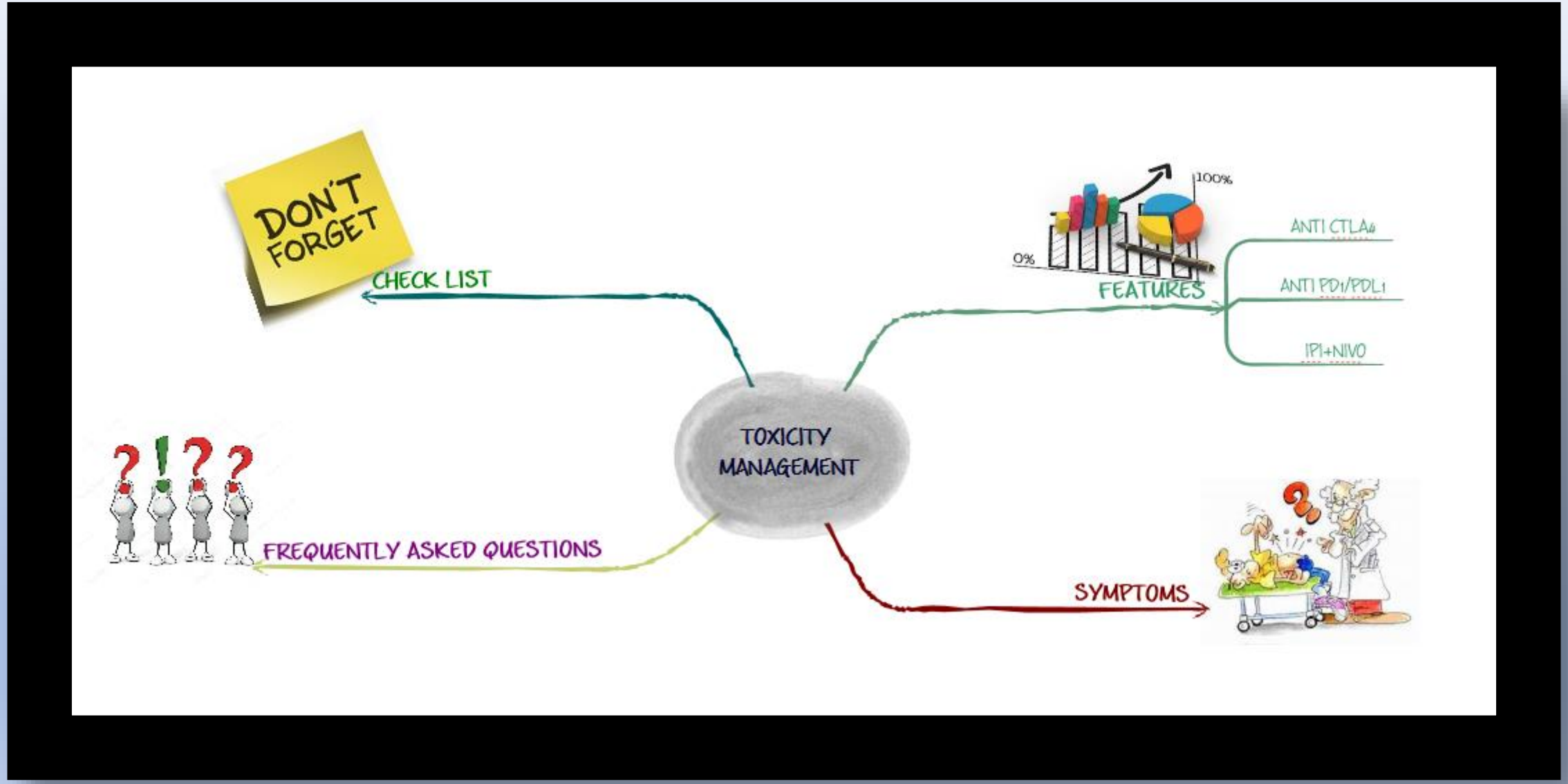


LA GESTIONE DELLA TOSSICITA'

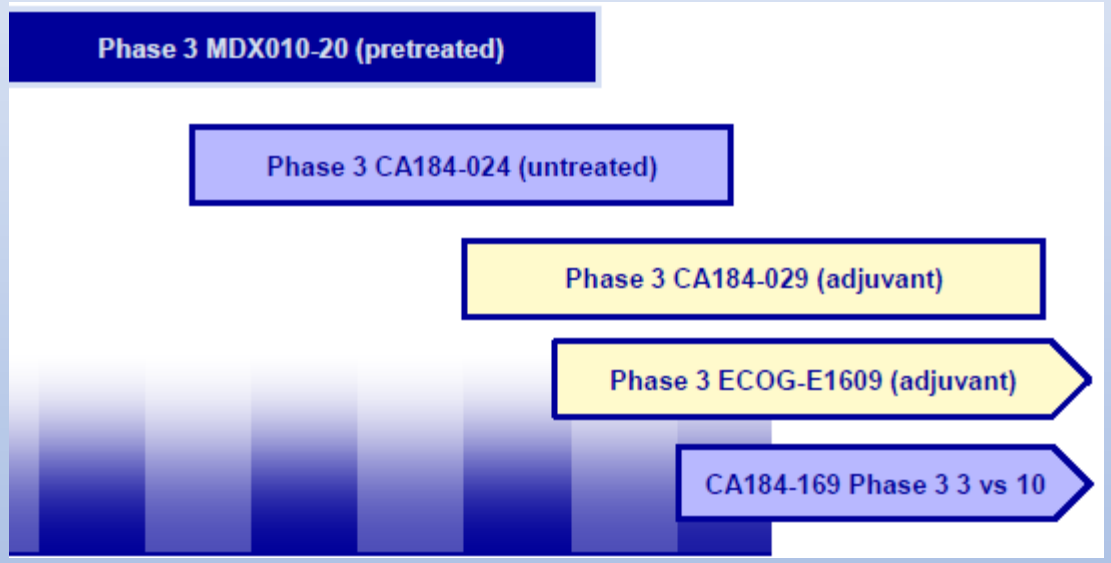
Elisabetta Grego
Oncologia medica
Azienda Ospedaliera Universitaria Integrata – Verona

Agenda


DON'T FORGET
CHECK LIST
100%
0%
FEATURES
ANTI CTLA4
ANTI PD1/PDL1
IPI+NIVO
TOXICITY MANAGEMENT
FREQUENTLY ASKED QUESTIONS
SYMPTOMS

ANTI CTLA4 - IPILIMUMAB

- ✓ Overall incidence of **all grade** irAEs up to **72%**, **high-grade** irAEs was **24%**
- ✓ The risk of developing irAEs was **dosage-dependent**
  (for high-grade RR 3,10 p=0,0008 with IPI 10 mg/kg vs 3 mg/kg)
- ✓ The immune activation can result in a pattern of tissue-specific inflammation that can target **any tissue**
- ✓ Skin and gastrointestinal tract are mostly affected (44% and 35% respectively)
- ✓ Most frequent **high-grade** irAEs: **GI events (11%)**



Hodi FS, Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 363:711-723, 2010
Robert C, Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med 364: 2517-2526, 2011
Bertrand et al, Immune related adverse events associated with anti-CTLA4 antibodies: sy stematic review and meta-analysis, BMC medicine (2015) 13:211

ANTI CTLA4 - IPILIMUMAB

ITALIAN EAP

Ascierto P, Sileni VC, Queirolo P, et al. Journal of Translational Medicine 2014, 12:116

irAE	Patients, n (%)	
	Any grade	Grade 3/4
Total	286 (33)	55 (6)
Pruritus	58 (7)	1 (<1)
Rash	64 (8)	4 (<1)
Diarrhoea	60 (7)	19 (2)
Nausea	47 (6)	2 (<1)
Vomiting	15 (2)	2 (<1)
Constipation	7 (1)	1 (<1)
Abdominal pain	11 (1)	0
Endocrine	7 (1)	1 (<1)
Liver toxicity	19 (2)	15 (2)
Fatigue/asthenia	70 (8)	10 (1)

- Among all 833 treated patients, 399 (**47%**) reported an AE (**any grade**), with grade 3/4 AEs in 100 patients (12%). AEs were considered to be **immune-related in 286 patients (33%**).
- **Most** irAEs were **low grade**, with grade **3/4 irAEs in 55 patients (6%**; most commonly diarrhea, liver toxicity and fatigue/asthenia).
- Baseline **patient characteristics** were **similar** for patients with or without irAEs.
- Median time to resolution was 1.7 weeks (range, 0.1–11.1 weeks) for irAEs of any grade and 1.1 weeks (range, 0.1– 3.4 weeks) for grade 3/4 irAEs.

Memorial Sloan Kettering Cancer Center

Horvat T Z, J Clin Oncol 33 (2015) :3193-3198

irAEs	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Hepatotoxicity	135	23	32	7	0	197
Dermatitis	69	36	18	0	0	123
Diarrhea	25	20	29	12	1	87
Hypophysitis	1	6	10	0	0	17
Uveitis	1	5	1	1	0	8
Other	1	6	8	0	0	15
Total*	232	96	98	20	1	447

Abbreviation: irAEs, immune-related adverse events.
*Patients could have experienced more than one irAE. Therefore, the total number of irAEs is more than the total number of patients.

- Of the 298 patients, 254 (**85%**) experienced **an irAE of any grade**. Grade 3, 4, and 5 irAEs were observed in 91 (31%), 20 (7%), and 1 patient, respectively.
- The **most common irAE of grade 3 or greater** was **diarrhea**, which occurred in 14% of patients and led to discontinuation therapy in 34 patients. Three of the 298 patients (1%) experienced bowel perforation from colitis
- Other irAEs that led to discontinuation of ipilimumab were hepatotoxicity (12 patients), hypophysitis (6 patients), uveitis (2 patients), neurotoxicity (1 patient), and pneumonitis (1 patient).

ANTI PD1 – NIVOLUMAB, PEMBROLIZUMAB

- ✓ In general grade of irAEs is mild to moderate; **grade 3-4** adverse drug reaction is **<2%**
- ✓ The risk of developing irAEs was **NO dosage-dependent**
- ✓ The rates of any-grade and grade 3 to 4 treatment-related AEs in patients who had received prior anti-CTLA4 are similar to the rates in the naïve population
- ✓ A delayed effect of immune checkpoint antibodies cannot be ruled out, sometimes **up to 1 year after** the start of the anti-PD-1 treatment
- ✓ **Fatigue, rash, pruritus** and **diarrhea** are most frequent events of any grade

MELANOMA,
CHACKMATE 066 naive, 037 pre-treated
KEYNOTE 06

LUNG CANCER,
CHACKMATE 017, 057, 063, 026
KEYNOTE 024, 010

RCC
CHECKMATE 025

H&N, OVARIAN, GLIOBLASTOMA, TNBC, GASTRIC, CRC

Michot et al, Immune-related adverse events with immune checkpoint blockade: a comprehensive review, European Journal of Cancer 54 (2016) 139e148
Boutros et al, Safety profiles of anti-CTLA4 and anti-PD-1 antibodies alone and in combination, Nat Rev Clin Oncol 13 (2016) 473-485
Weber JS et al, Safety Profile of Nivolumab Monotherapy: A Pooled Analysis of Patients With Advanced Melanoma, J Clin Oncol 2017;35(7):785-792

Regardless of type of tumor

MELANOMA, CHACKMATE 066

Robert C, N Engl J Med 2015

Table 3. Adverse Events.*

Event	Nivolumab (N=206)	
	Any Grade	Grade 3 or 4
		no. of patients wit
Any adverse event	192 (93.2)	70 (34.0)
Treatment-related adverse event†	153 (74.3)	24 (11.7)
Fatigue	41 (19.9)	0
Pruritus	35 (17.0)	1 (0.5)
Nausea	34 (16.5)	0
Diarrhea	33 (16.0)	2 (1.0)
Rash	31 (15.0)	1 (0.5)
Vitiligo	22 (10.7)	0
Constipation	22 (10.7)	0
Asthenia	21 (10.2)	0
Vomiting	13 (6.3)	1 (0.5)
Neutropenia	0	0
Thrombocytopenia	0	0
Adverse event leading to discontinuation of treatment	14 (6.8)	12 (5.8)
Serious adverse event		
Any event	64 (31.1)	43 (20.9)
Treatment-related event	19 (9.2)	12 (5.8)

LUNG CANCER, CHACKMATE 017

Brahmer J, N Engl J Med 2015

Table 3. Treatment-Related Adverse Events Reported in at Least 5% of Patier

Event	Nivolumab (N=131)	
	Any Grade	Grade 3 or 4
		number of patients
Any event	76 (58)	9 (7)
Fatigue	21 (16)	1 (1)
Decreased appetite	14 (11)	1 (1)
Asthenia	13 (10)	0
Nausea	12 (9)	0
Diarrhea	10 (8)	0
Arthralgia	7 (5)	0
Pyrexia	6 (5)	0
Pneumonitis	6 (5)	0
Rash	5 (4)	0
Mucosal inflammation	3 (2)	0
Myalgia	2 (2)	0
Anemia	2 (2)	0
Peripheral neuropathy	1 (1)	0
Leukopenia	1 (1)	1 (1)
Neutropenia	1 (1)	0
Febrile neutropenia	0	0
Alopecia	0	0

RCC CHECKMATE 025,

Motzer RJ, et al. N Engl J Med 2015

Table 2. Treatment-Related Adverse Events Reported Treated Patients in Either Group.

Event	Nivolumab Group (N=406)		
	Any Grade	Grade 3 or 4	A
		number of patient	
All events	319 (79)	76 (19)	3
Fatigue	134 (33)	10 (2)	1
Nausea	57 (14)	1 (<1)	
Pruritus	57 (14)	0	
Diarrhea	50 (12)	5 (1)	
Decreased appetite	48 (12)	2 (<1)	
Rash	41 (10)	2 (<1)	
Cough	36 (9)	0	
Anemia	32 (8)	7 (2)	
Dyspnea	30 (7)	3 (1)	
Peripheral edema	17 (4)	0	
Pneumonitis	16 (4)	6 (1)	
Mucosal inflamma-tion	11 (3)	0	
Dysgeusia	11 (3)	0	
Hyperglycemia	9 (2)	5 (1)	
Stomatitis	8 (2)	0	1
Hypertriglyceridemia	5 (1)	0	
Epistaxis	3 (1)	0	

Regardless of dose

MELANOMA,
KEYNOTE 006
Robert C, N Engl J Med 2015

LUNG CANCER,
KEYNOTE 024, 010
Reck M. N Engl J Med 2016, Herbst RS, Lanc Oncol 2016

Table 2. Adverse Events in the As-Treated Population.*

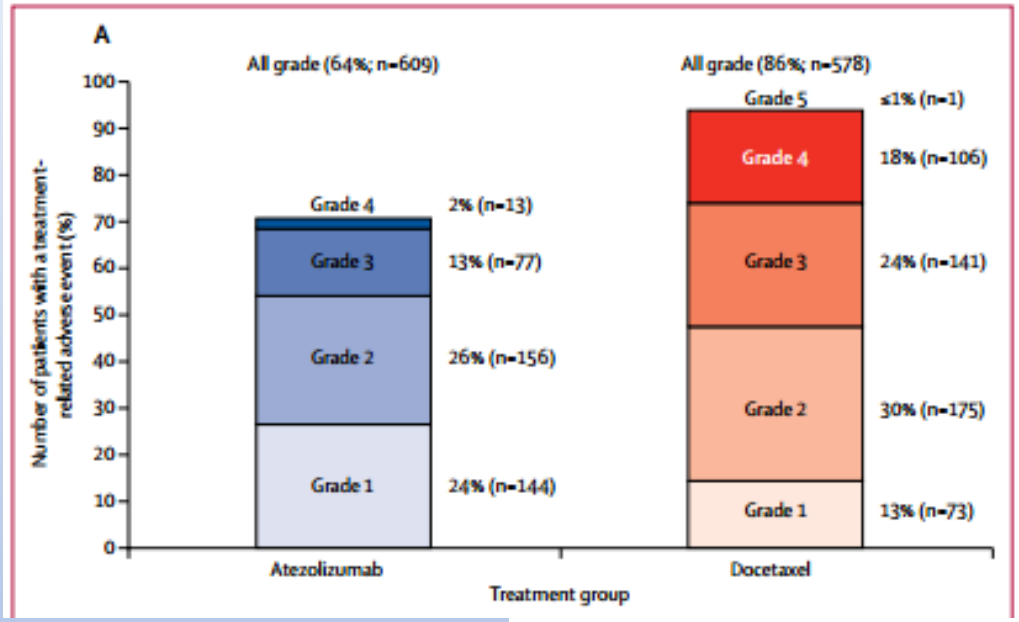
Adverse Event	Pembrolizumab Every 2 Wk (N=278)		Pembrolizumab Every 3 Wk (N=277)	
	Any Grade	Grade 3–5	Any Grade	Grade 3–5
Adverse event of special interest†				
Hypothyroidism	28 (10.1)	1 (0.4)	24 (8.7)	0
Hyperthyroidism	18 (6.5)	0	9 (3.2)	0
Colitis	5 (1.8)	4 (1.4)	10 (3.6)	7 (2.5)
Hepatitis	3 (1.1)	3 (1.1)	5 (1.8)	5 (1.8)
Hypophysitis	1 (0.4)	1 (0.4)	2 (0.7)	1 (0.4)
Pneumonitis	1 (0.4)	0	5 (1.8)	1 (0.4)
Type 1 diabetes mellitus	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)
Uveitis	1 (0.4)	0	3 (1.1)	0
Myositis	0	0	2 (0.7)	0
Nephritis	0	0	1 (0.4)	0

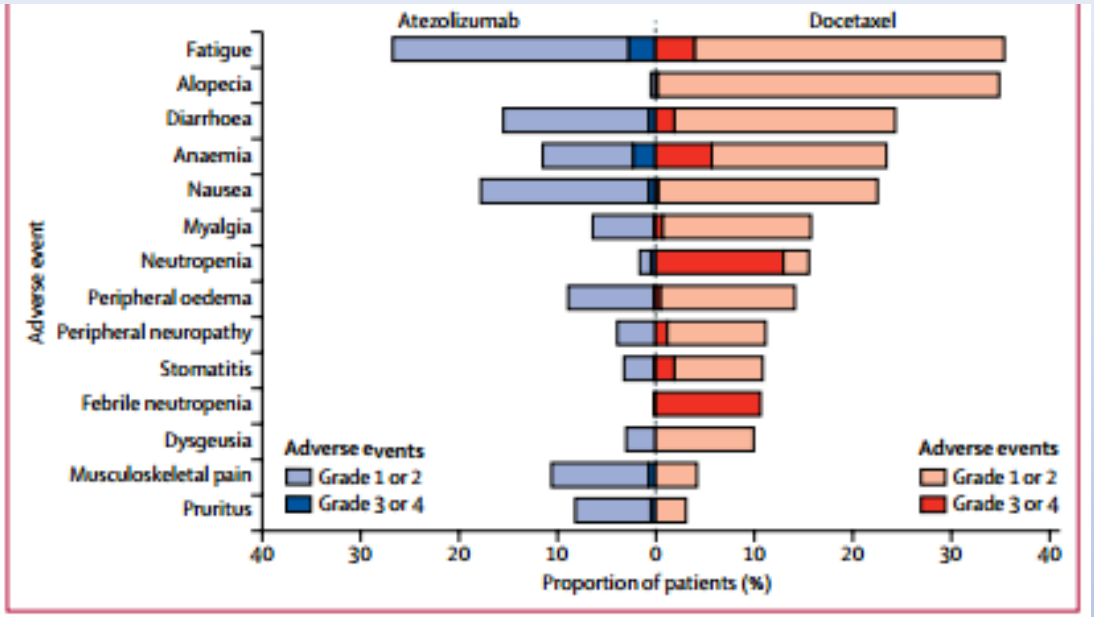
Table 3. Adverse Events in the As-Treated Population.*

Adverse Event	Pembrolizumab Group (N=154)	
	Any Grade	Grade 3, 4, or 5
		number of pa
Immune-mediated§		
Any	45 (29.2)	15 (9.7)
Hypothyroidism	14 (9.1)	0
Hyperthyroidism	12 (7.8)	0
Pneumonitis	9 (5.8)	4 (2.6)
Infusion reaction	7 (4.5)	0
Severe skin reaction	6 (3.9)	6 (3.9)
Thyroiditis	4 (2.6)	0
Colitis	3 (1.9)	2 (1.3)
Myositis	3 (1.9)	0
Hypophysitis	1 (0.6)	1 (0.6)
Nephritis	1 (0.6)	1 (0.6)
Pancreatitis	1 (0.6)	1 (0.6)
Type 1 diabetes mellitus	1 (0.6)	1 (0.6)

	Pembrolizumab 2 mg/kg (n=339)		Pembrolizumab 10 mg/kg (n=343)	
	Any grade	Grade 3–5	Any grade	Grade 3–5
Of special interest occurring in ≥2 patients in the pembrolizumab groups†				
Hypothyroidism	28 (8%)	0 (0%)	28 (8%)	0 (0%)
Pneumonitis‡	16 (5%)	7 (2%)	15 (4%)	7 (2%)
Hyperthyroidism	12 (4%)	0 (0%)	20 (6%)	1 (<1%)
Colitis	4 (1%)	3 (1%)	2 (1%)	1 (<1%)
Severe skin reactions	4 (1%)	3 (1%)	7 (2%)	6 (2%)
Pancreatitis§	3 (1%)	2 (1%)	0 (0%)	0 (0%)
Adrenal insufficiency	2 (1%)	0 (0%)	3 (1%)	1 (<1%)
Myositis	2 (1%)	0 (0%)	1 (<1%)	0 (0%)
Thyroiditis	2 (1%)	0 (0%)	0 (0%)	0 (0%)
Autoimmune hepatitis	1 (<1%)	1 (<1%)	2 (1%)	0 (0%)
Hypophysitis	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)
Type 1 diabetes	1 (<1%)	1 (<1%)	2 (1%)	1 (<1%)

ANTI- PDL1 - ATEZOLIZUMAB



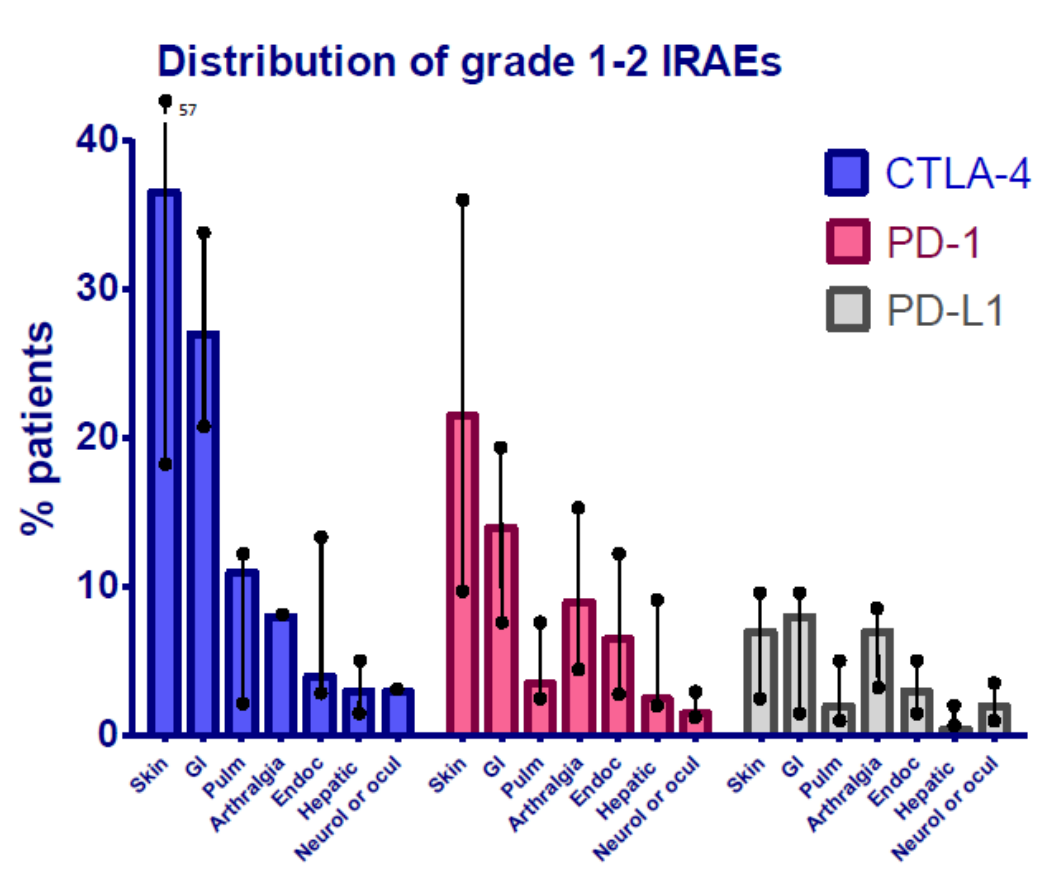


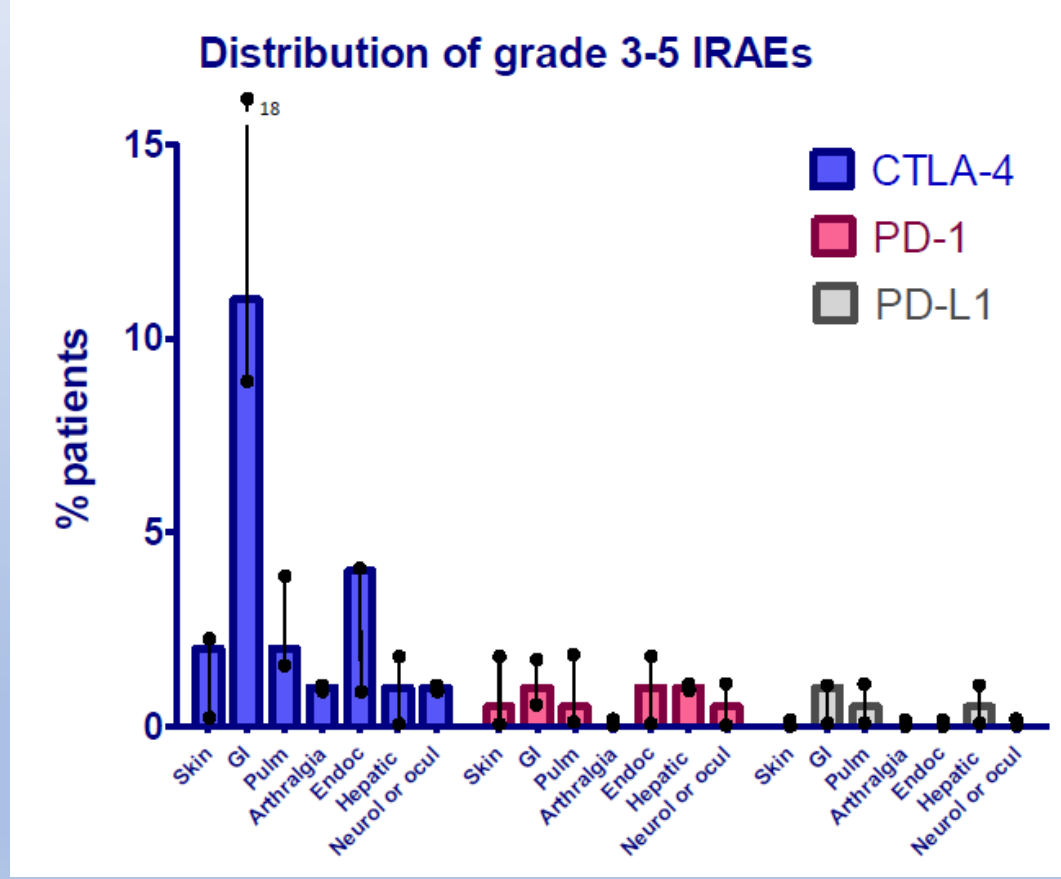
IMMUNE-MEDIATED AEs

	Atezolizumab n = 609	
Selected immune-mediated AEs	All Grade	Grade 3–4
Pneumonitis	1.0%	0.7%
Hepatitis	0.3%	0.3%
Colitis	0.3%	0%

Rittmeyer A, Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK) Lancet 2017; 389: 255–65

ANTI PD1/PDL1 vs antiCTLA4



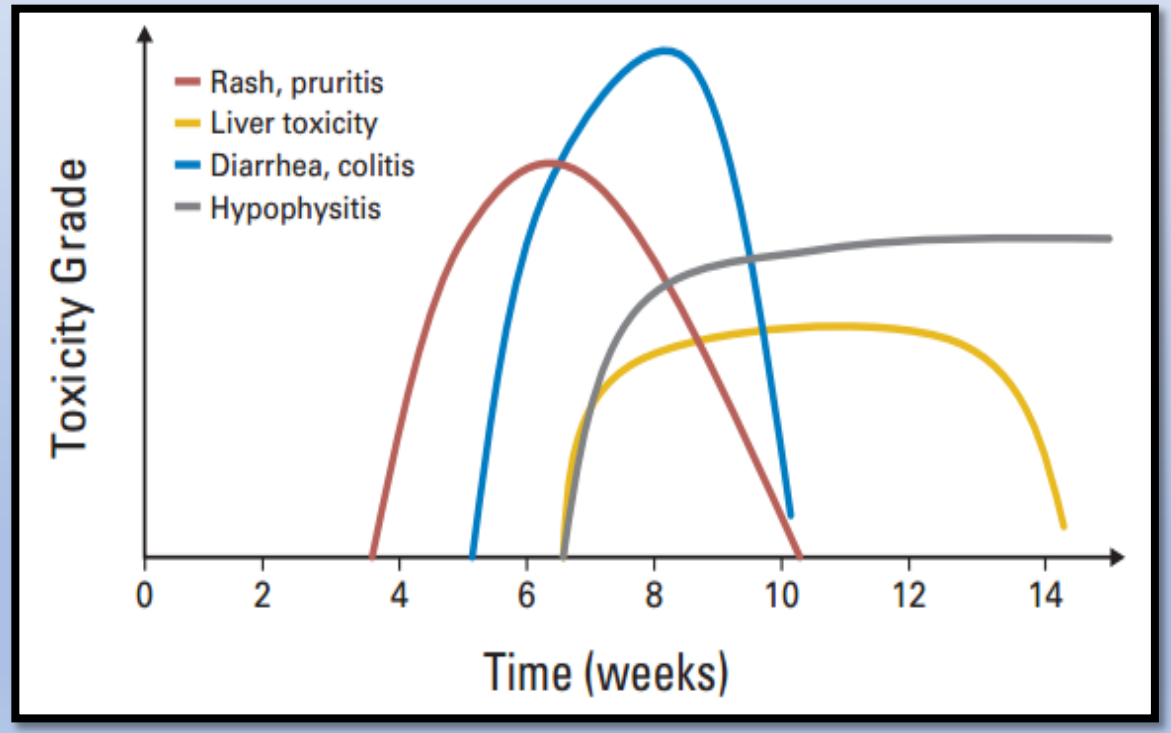


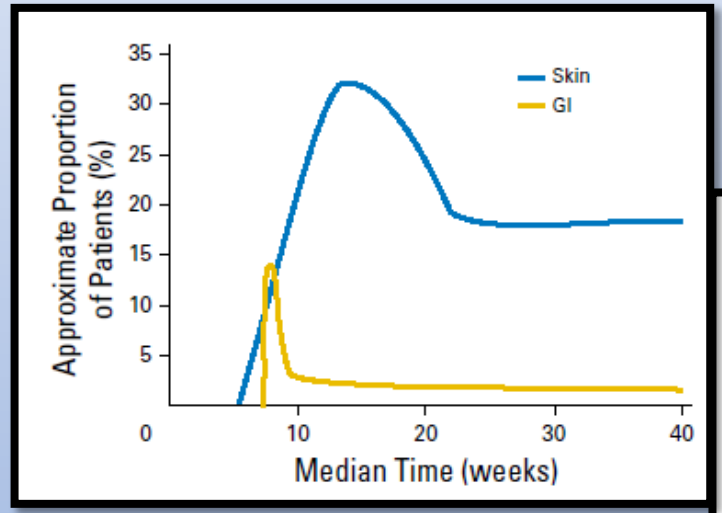
Michot et al, Immune-related adverse events with immune checkpoint blockade: a comprehensive review, European Journal of Cancer 54 (2016) 139e148

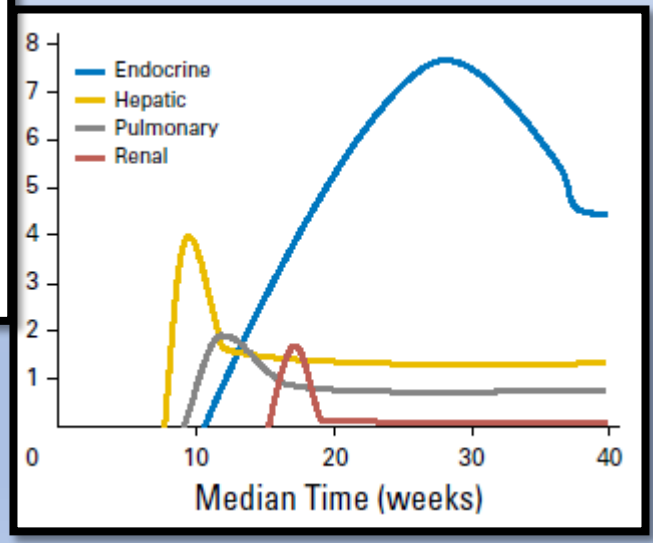
TIMING of OCCURENCE of irAEs

ipilimumab
2-3 weeks after treatment initiation: skin toxicities
6–7 weeks after treatment initiation : gastrointestinal toxicities
9 weeks after treatment initiation : endocrinopathies

nivolumab
skin (5 weeks), GI (7.3 weeks), liver (7.7 weeks), lung (8.9 weeks), endocrine (10.4 weeks) and renal (15.1 weeks)







Weber JS et al, Management of Immune-Related Adverse Events and Kinetics of Response With Ipilimumab J Clin Oncol 2013; 30:2691-2697
Weber JS et al, Safety Profile of Nivolumab Monotherapy: A Pooled Analysis of Patients With Advanced Melanoma, J Clin Oncol 2017;35(7):785-792

COMBO – antiCTLA4 + antiPD1

- ✓ Great impact on OS and PFS, but higher toxicities than monotherapy
- ✓ Overall incidence of **all grade** irAEs **95,8%**, **high-grade** irAEs was **58,5%**
- ✓ Treatment-related AEs tend to occur **earlier** (mostly occur during combination phase)
- ✓ Often **more than one organ** involved
- ✓ **More** patients **discontinued** due to irAEs than with IPI or NIVO
- ✓ **HRQOL maintained** in patients with grade 3/4 AEs
- ✓ irAEs **similar** across **patient subgroups**

MELANOMA,
CHACKMATE 069, 067
KEYNOTE 029

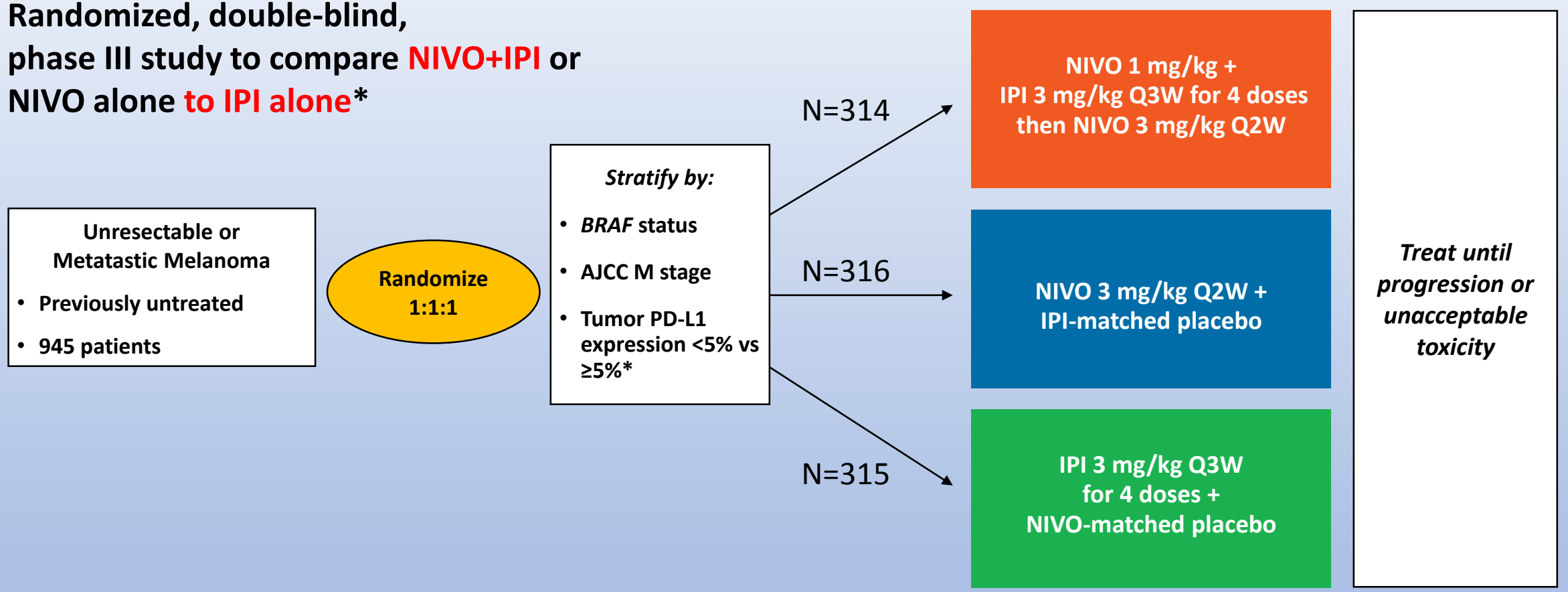
LUNG CANCER,
CHACKMATE 012, 227

RCC
CHECKMATE 016

Larkin J, Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma, N Engl J Med 2015;373:23-34

CHECKMATE-067 - Update AACR 2017

Randomized, double-blind, phase III study to compare NIVO+IPI or NIVO alone to IPI alone*



Database lock: Sept 13, 2016 (median follow-up ~30 months in both NIVO-containing arms)

**The study was not powered for a comparison between NIVO and NIVO+IPI*

HIGHER INCIDENCE

- With an additional 19 months of follow-up, safety was consistent with the initial report

	NIVO+IPI (N=313)		NIVO (N=313)		IPI (N=311)	
Patients reporting event, %	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Treatment-related adverse event (AE)	95.8	58.5	86.3	20.8	86.2	27.7
Treatment-related AE leading to discontinuation	39.6	31.0	11.5	7.7	16.1	14.1
Treatment-related death, n (%)	2 (0.6)[a]		1 (0.3)[b]		1 (0.3)[b]	

- Most select AEs were managed and resolved within 3-4 weeks (85–100% across organ categories)
- ORR was 70.7% for pts who discontinued NIVO+IPI due to AEs, with median OS not reached

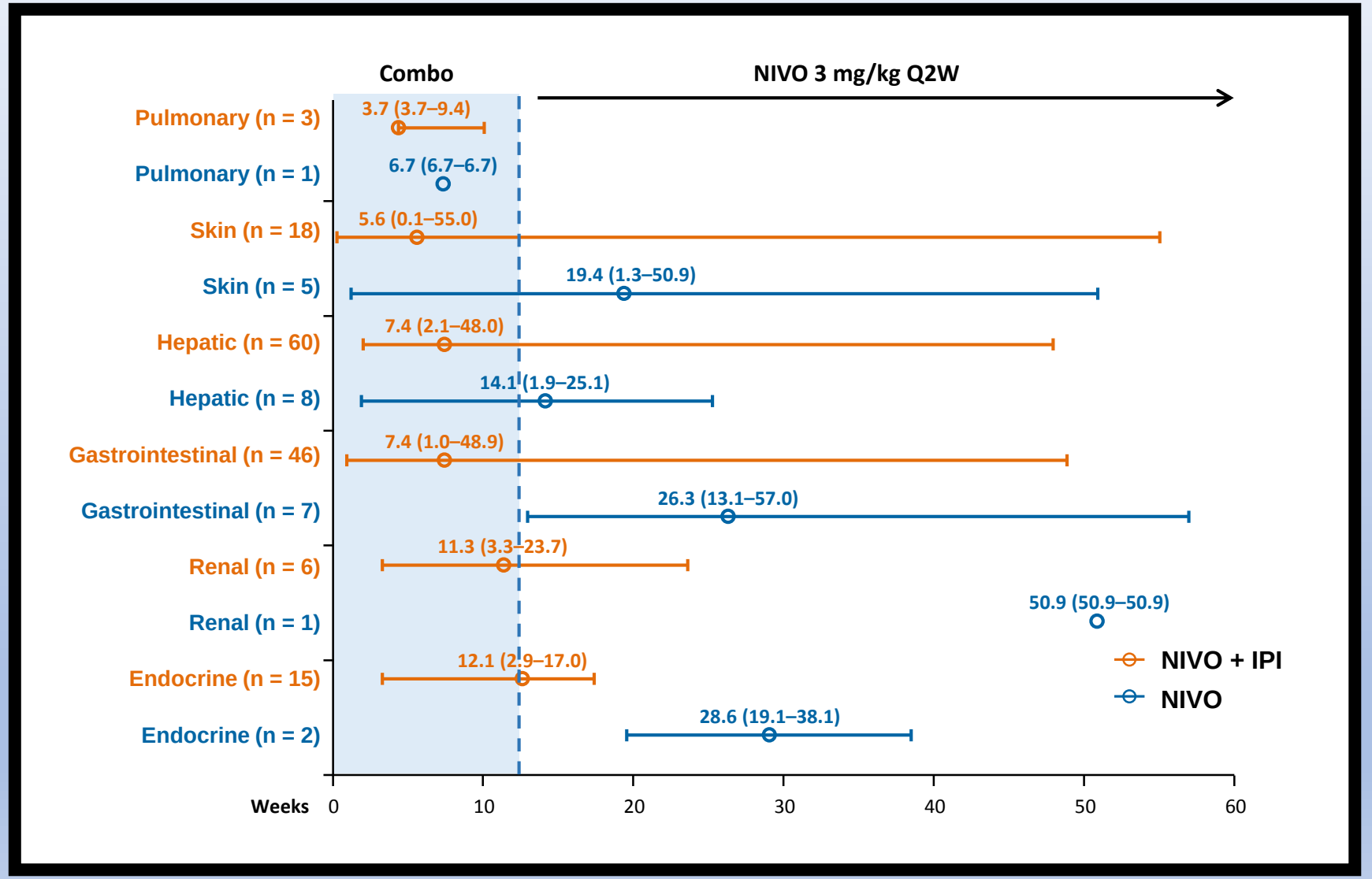
[a]Cardiomyopathy (NIVO+IPI, n=1); Liver necrosis (NIVO+IPI, n=1). Both deaths occurred >100 days after the last treatment.
[b]Neutropenia (NIVO, n=1); colon perforation (IPI, n=1).[1]

Larkin J, et al. *NEJM* 2015;373:23–34.

HIGHER INCIDENCE

Pooled Regimen studies	NIVO+IPI (N = 448)	
Patients reporting ≥1 AEs, %	**Any Grade**	**Grade 3-4**
Any AE	95	55
Skin and subcutaneous tissue disorders	68	8
Pruritus	35	2
Rash	35	4
Maculopapular rash	12	2
Gastrointestinal disorders	60	20
Diarrhea	44	10
Nausea	25	2
Vomiting	14	2
Colitis	13	9
General disorders and administration site conditions	55	5
Fatigue	37	4
Pyrexia	19	1
Investigations	43	23
Increased alanine aminotransferase	18	9
Increased aspartate aminotransferase	17	6
Increased lipase	12	9

ERLIER ONSET



Larkin J, et al. Presented at ECC 2015; abstract 3303.

MORE CATEGORIES INVOLVED

Grade ≥2 Treatment-Related Select AEs Across Organ Categories

Number of organ categories impacted, n (%)[a]	NIVO+IPI	
	Discontinued due to AEs (n = 176)	Did not discontinue due to AEs (n = 231)
0 Category	12 (6.8)	90 (39.0)
1 Category	76 (43.2)	98 (42.4)
2 Categories	70 (39.8)	30 (13.0)
3 Categories	15 (8.5)	10 (4.3)
>3 Categories	3 (1.7)	3 (1.3)

[a]Organ categories: skin, gastrointestinal, endocrine, hepatic, pulmonary, renal.

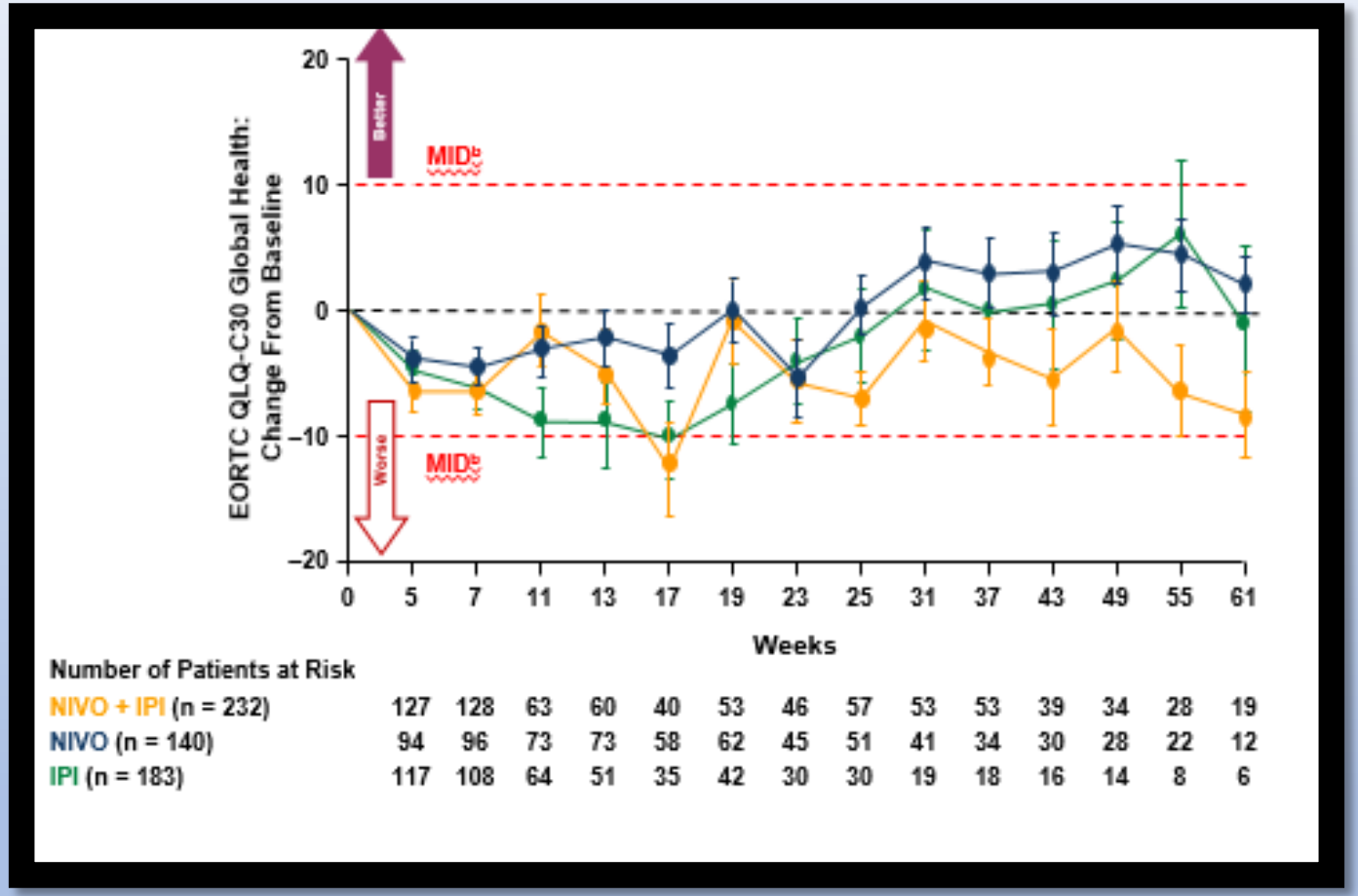
- A higher proportion of patients who received the combination and who discontinued due to AEs experienced at least two grade 2-4 AEs across organ categories during treatment

Schadendorf et al., EADO 2016.

SIMILAR ACROSS SUBGROUPS

Patients Reporting Event, %	NIVO + IPI (n = 313)		NIVO (n = 313)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Treatment-related AE	96	55	82	16
Aged ≥65 and <75 years	95	50	81	22
Aged ≥75 and <85 years	97	48	83	21
M1c disease	94	54	79	14
PD-L1 expression ≥5%	97	53	85	16
Patients with complete response	100	58	93	32

NO DETERIORATION IN QoL

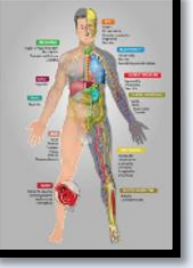


MID considered a change of ≥10 points from baseline.[2]

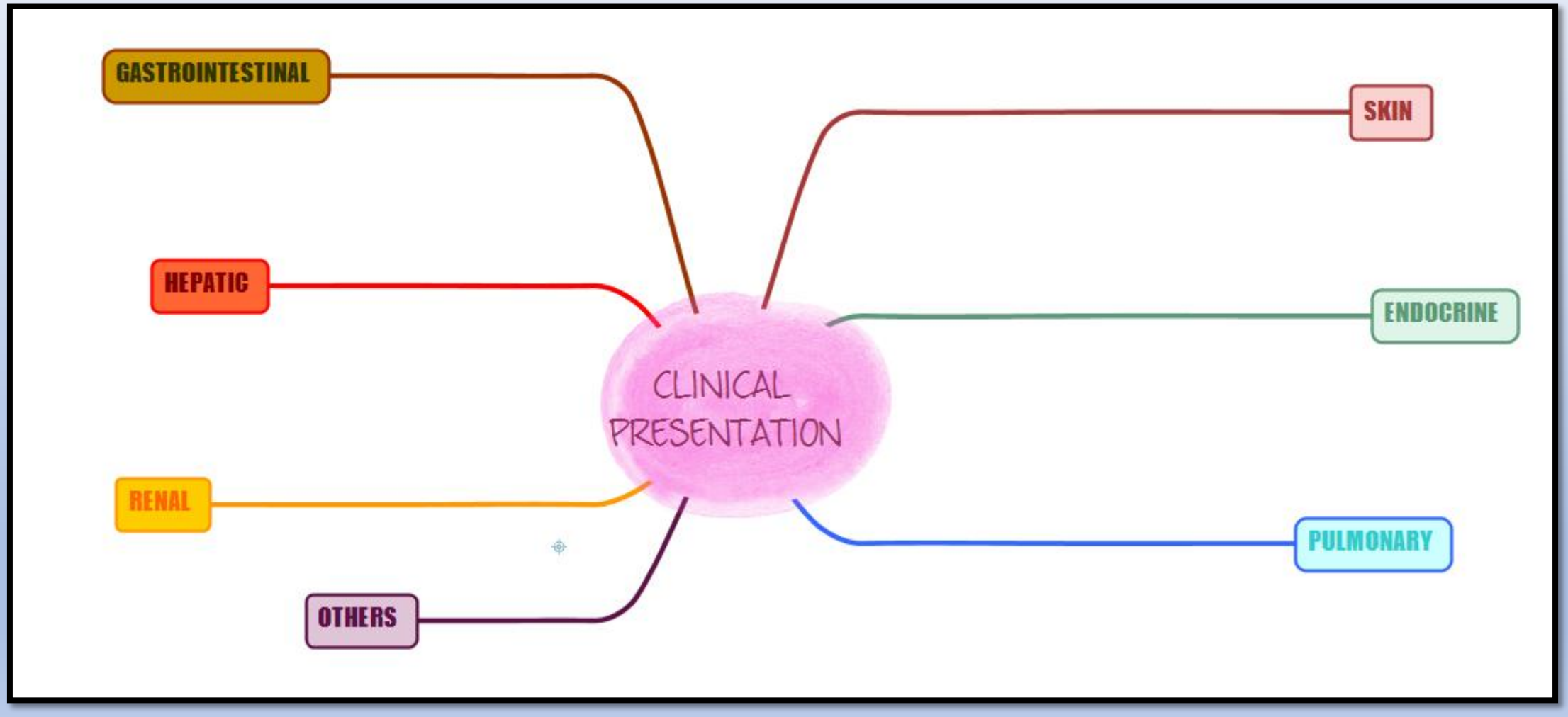
Note: Only time points where data were available for ≥5 patients are plotted on the graph. Patients could enter follow-up visits any time after baseline.

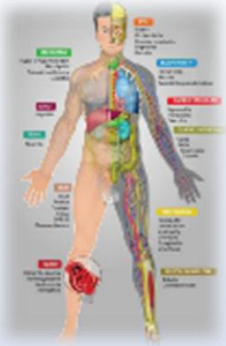
EORTC = European Organisation for Research and Treatment of Cancer; MID = minimum important difference.

Schadendorf D, et al. Presented at SMR 2015
Osoba D, et al. *J Clin Oncol*. 1998;16:139-144



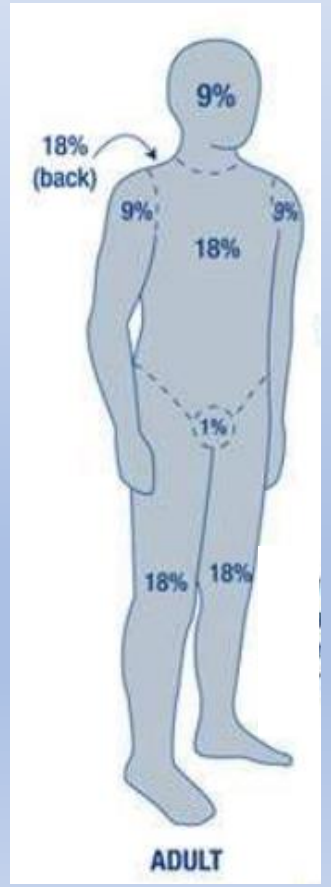
CLINICAL PRESENTATION





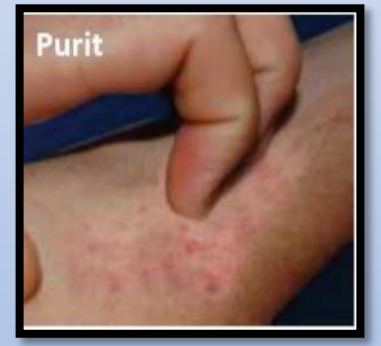
SKIN

(~20-40% Anti-PD1, 60% Ipi+Nivo)

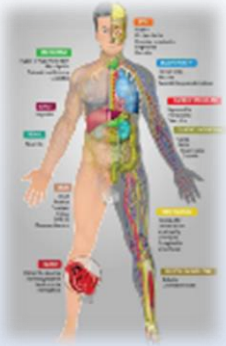


- **Clinical presentations**: **Rash maculopapular/papulopustolar** typically focal occurring on the **trunk**, back, or **extremities;** follicular or urticarial dermatitis; Depigmentation Vitiligo; Some skin reactions occurred in the context of infusion related reaction

- **Severe irAEs**: bullous phemphigoid, Stevens Johnson syndrome, toxic epidermic necrolysis (Lyell's syndrome)



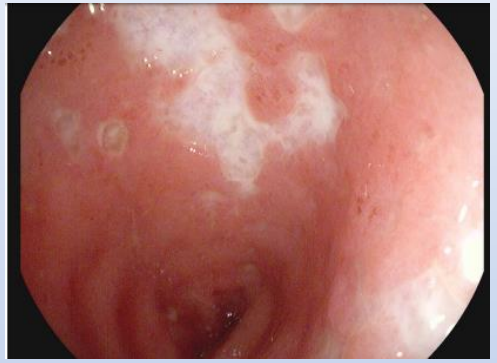
- **Mucosal toxicity**: lichenoide mucositis, oral mucositis, gingivitis, sicca syndrome- like
- **Differential diagnoses**: Infections, exacerbation of pre-existing dermatitis, organ disfunction (liver disease (bilirubin), renal, paraneoplasic)
- **Examinations**: dermal assessment, skin biopsy, kidney and liver function testing, tryptase and IgE.

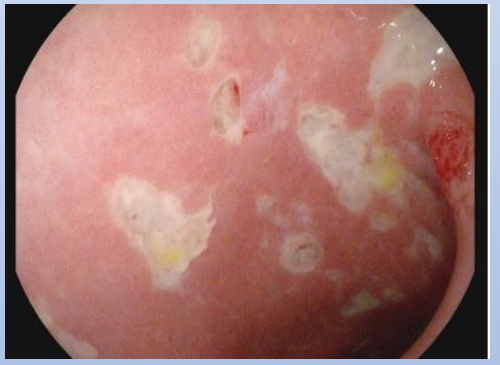


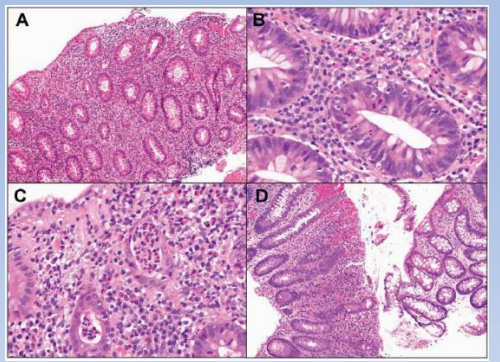
GASTROINTESTINAL TRACT

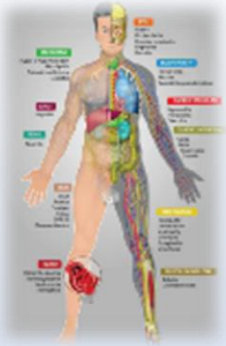
(~17% Anti-PD1, 48% Ipi+Nivo)

- **Clinical presentations**: **Diarrhea** as increased stool frequency; **colitis**: abdominal pain, descending colon is the most common site
- **Severe irAEs**: dehydratation, colonic perforation
- **Mucosal toxicity**: ulcerations with bleeding
- **Differential diagnoses**: infections (bacterial/viral pathogens), *Clostridium difficile*, Cytomegalovirus reactivation
- **Examinations**: Gastroenterologist referral, endoscopy colonoscopy with biopsies; Rule out infection C. Difficile toxin, stool cultures, parasites









ENDOCRINE SYSTEM

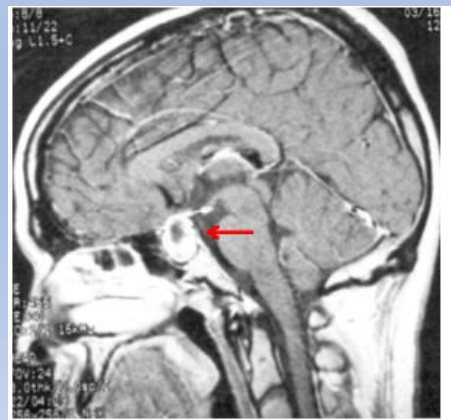
(~ 9% Anti-PD1, 15% Ipi + Nivo)

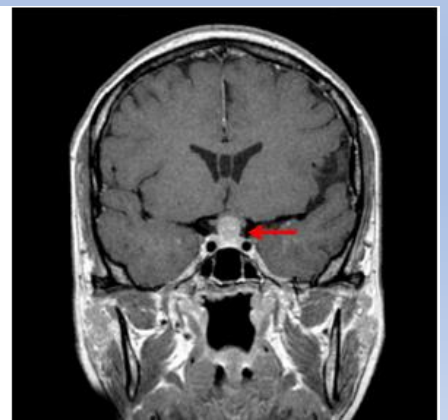
- **Clinical presentations**: fatigue, headache, weakness, nausea, cramps, tachycardia,change in weight, memory loss, impotence, personality changes and visual-field impairment, hypotension, and electrolyte imbalances, other non-specific symptoms

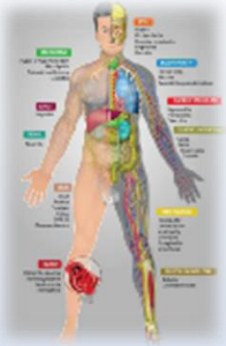
- **Type of endocrinopaties**: hypophysitis, hypothyroidism, hyperthyroidism, thyroiditis, primary adrenal insufficiency

- **Differential diagnoses**: disease progression, brain metastasis

- **Examinations**: Hormonal tests: TSH, free T4, LH, FSH, ACTH, cortisol, for pituitary gland: MRI, anti-thyroglobulin antibodies, anti-thyroid peroxidase antibodies; endocrinology consult



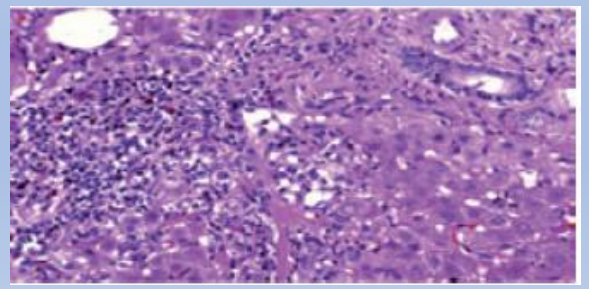


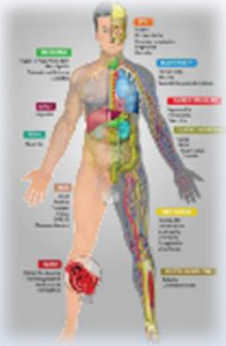


LIVER

(~ 4-7% Anti-PD1, 32% Ipi + Nivo)

- **Clinical presentations**: cholestasis up to jaundice, asymptomatic increase in transaminases, hypochondrial right pain, fatigue
- **Severe irAEs**: severe hepatitis
- **Differential diagnoses**: infections (bacterial/viral/fungal pathogens), progressing liver metastases
- **Examinations**: laboratory tests, virology including rare viruses (EBV, CMV), radiologic assessment (US, CT scan); biopsy





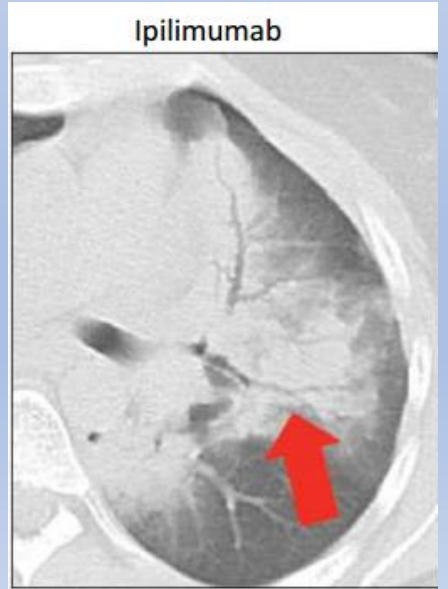
PULMONARY

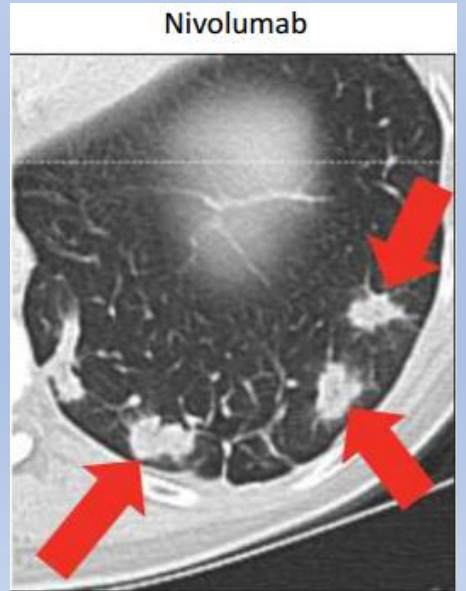
(~2.5% Anti-PD1, 7% Ipi+Nivo)

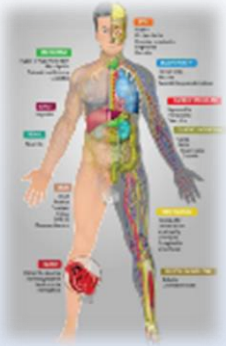
- Clinical presentations: new/worsening dry cough, SOB/Dyspnea (rest or exertion), fever, chest pain, asymptomatic radiographic changes

- **Differential diagnoses**: infections including overt infections (bacterial, viral, fungal pneumonia), malignant lung infiltration, pulmonary embolism, cardiac origin, pericarditis

- **Examinations**: EGA, chest CT scan, bronchoscopy with bronchoalveolar lavage for lymphocytes, infections, lung function tests, cardiac US



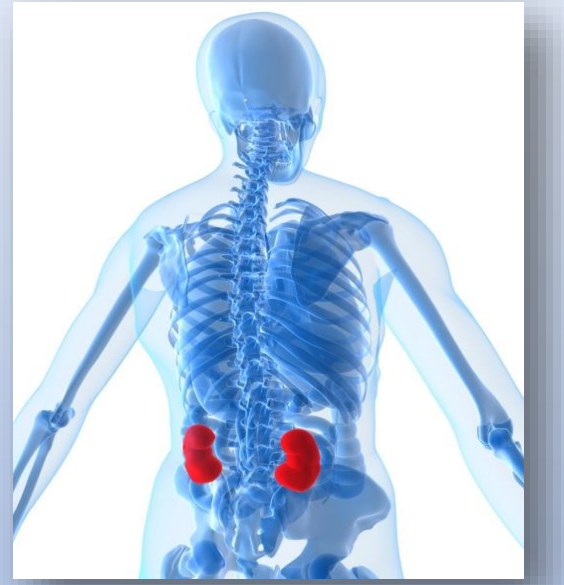


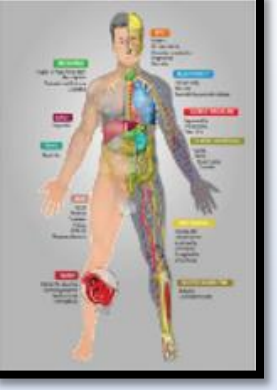


RENAL

(~2% Anti-PD1, 6% Ipi + Nivo)

- **Clinical presentations**: Increase in serum creatinine, decrease in the amount of urine, blood in the urine, swelling, loss of appetite
- **Severe irAEs:** IRA
- **Differential diagnoses**: IVU infections, progressive disease, dehydratation
- **Examinations**: neprhology consult, renal biopsy





OTHERS

- **Hematological syndromes:** hemolytic anemia, thrombocytopenia, neutropenia
- **Ocular Toxicity:** uveitis, retinopathy, episcleritis, conjunctivitis, choroiditis
- **Pancreatic disorders:** amylase and lipase changes, diabetes mellitus
- **Neurological disease:** facial- and abducense nerve paresis, demyelination, polymyalgia rheumatica, Guillain-Barré syndrome, myasthenia syndrome
- **Hypersensitivity/Infusion reactions**

FREQUENTLY ASKED QUESTIONS

- ✓ ***Safety of immune checkpoint inhibitors in special populations (autoimmune diseases, chronic infections, elderly)***
- ✓ ***Does corticosteroid use compromise the effectiveness of therapy?***
- ✓ ***Are irAES predictive of response?***

SAFETY IN SPECIAL POPULATIONS

Ravi *et al. Journal for ImmunoTherapy of Cancer* 2014, **2**:33
http://www.immunotherapyofcancer.org/content/2/1/33

Journal for ImmunoTherapy of Cancer

CASE REPORT Open Access

Ipilimumab administration for advanced melanoma in patients with pre-existing Hepatitis B or C infection: a multicenter, retrospective case series

Sowmya Ravi[1], Kristen Spencer[2], Mary Ruisi[3], Nageatte Ibrahim[4], Jason J Luke[5], John A Thompson[6], Keisuke Shirai[7], David Lawson[8], Heddy Bartell[9], Ragini Kudchadkar[8], Ngoc Thi Gunter[8], Janice M Mehnert[2†] and Evan J Lipson[1*†]

Although this is a small series, the **rate of hepatotoxicity appears similar** to what has been seen in the **general population** treated with ipilimumab, and the ability to administer ipilimumab did not appear to be affected by concomitant hepatitis B or C infection. The **use of ipilimumab** in patients with metastatic melanoma **who have pre-existing hepatitis** can be **considered** among other therapeutic options.

SAFETY IN SPECIAL POPULATIONS

Underlying Autoimmune Disease Is Not a Contraindication to the Use of Ipilimumab

Mary L. Disis, MD

The use of immune
ticancer agents with
ing existing tumor-s

Related article page 234

fects observed with
fied in patients with
would have an exac
tory condition. This
number of patients
mune checkpoint in
lifetime risk of develo
matic disease is esti
for men.[1] Data on the
disease who have
therapy are needed.

In this issue of J
our knowledge, the
with preexisting autoimmune disease who have been treated with ipilimumab to date. These patients had a diversity of autoimmune disease ranging from rheumatoid arthritis and psoriasis to more serious conditions such as ulcerative colitis and multiple sclerosis. Only a minority of patients (8 [27%]) had an exacerbation of their disease with ipilimumab therapy. All flares could be medically treated and usually were observed within 3 to 6 weeks of initiating therapy. Typical immune-related adverse events (irAEs) (grade 3-5) occurred in 10 (33%) of the patients. A recent meta-analysis of ipilimumab-mediated irAEs in 1265 patients from 22 clinical trials reported an incidence of 25% of higher-grade irAEs with treatment. At 33%, these types of adverse events may be more common in patients with underlying autoimmune disease.[3] Fifteen patients (50%) with autoimmune disease experienced neither a flare of their underlying condition nor an irAE. The clinical response rate in this cohort was 20%, typical for ipilimumab, with 5 partial and 1 complete response.

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vented with vigilance to identify symptoms at an early stage in evolution. The same approach would be used with patients having concurrent autoimmune disease, as has been demonstrated by Johnson et al,[2] to ensure patient safety.

Johnson DB, Sullivan RJ, Ott PA, et al. Ipilimumab therapy in patients with advanced melanoma and preexisting autoimmune disorders. JAMA Oncol. 2016;2(2):234-240.

SAFETY IN SPECIAL POPULATIONS

Programmed cell death protein-1 (PD-1) inhibitor therapy in patients with advanced melanoma and preexisting autoimmunity or ipilimumab-triggered autoimmunity

Ralf Gutzmer [a,*], Anika Koop [a], Friedegund Meier [b], Jessica C. Hassel [c], Patrick Terheyden [d], Lisa Zimmer [e], Lucie Heinzerling [f], Selma Ugurel [e], Claudia Pföhler [g], Anja Gesierich [h], Elisabeth Livingstone [e], Imke Satzger [a], Katharina C. Kähler [i], for the German Dermatooncology Group (DeCOG)

European Journal of Cancer 75 (2017) 24e32

Conclusion: While preexisting autoimmunity commonly showed a flare during PD-1i therapy, a flare of ipilimumab-triggered irAE was rare. Response rates were above 30% and unrelated to irAE. PD-1i therapy can be considered in patients with autoimmune disorders depending on severity and activity of autoimmunity.

SAFETY IN SPECIAL POPULATIONS

Chiarion Sileni *et al. Journal of Experimental & Clinical Cancer Research* 2014, **33**:30
http://www.jeccr.com/content/33/1/30

Journal of Experimental & Clinical Cancer Research

RESEARCH Open Access

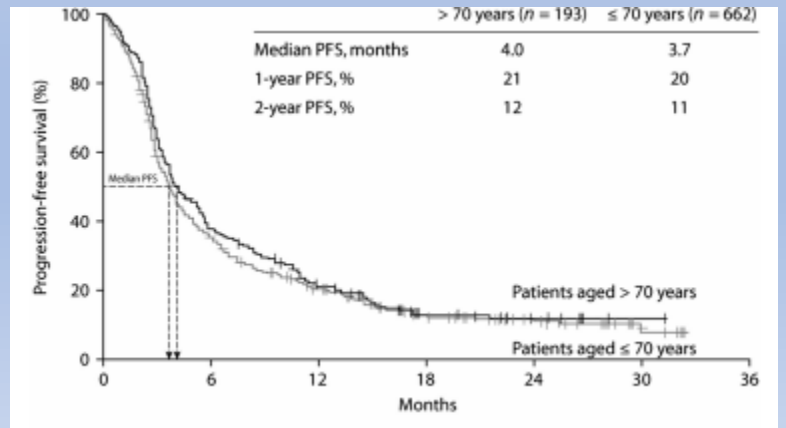
Efficacy and safety of ipilimumab in elderly patients with pretreated advanced melanoma treated at Italian centres through the expanded access programme

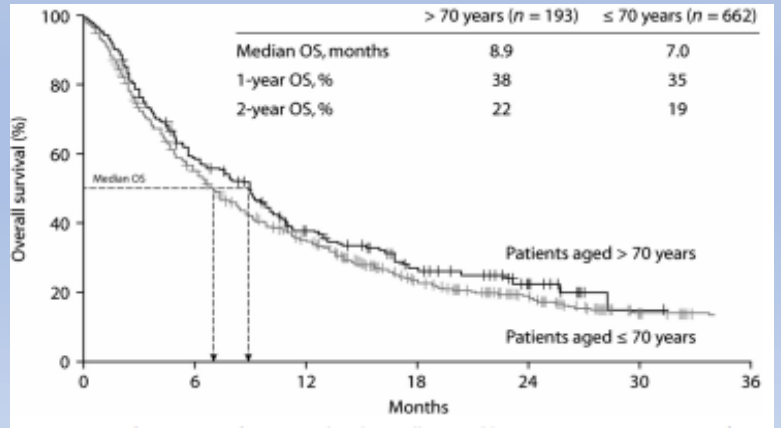
Vanna Chiarion Sileni[1*], Jacopo Pigozzo[1], Paolo Antonio Ascierto[2], Antonio Maria Grimaldi[2], Michele Maio[3], Lorenza Di Guardo[4], Paolo Marchetti[5,6], Francesco de Rosa[7], Carmen Nuzzo[8], Alessandro Testori[9], Emilia Cocorocchio[10], Maria Grazia Bernengo[11], Michele Guida[12], Riccardo Marconcini[13], Barbara Merelli[14], Giorgio Parmiani[15], Gaetana Rinaldi[16], Massimo Aglietta[17,18], Marco Grosso[19] and Paola Queirolo[19]

Table 3 Treatment-related AEs experienced by at least 2% of patients aged > 70 or ≤ 70 years

Treatment-related AEs experienced by at least 2% of patients	Patients aged > 70 years ($n = 193$), n (%)		Patients aged ≤ 70 years ($n = 662$), n (%)	
	Any grade	Grade III–IV	Any grade	Grade III–IV
Pruritus	11 (6)	0	47 (7)	1 (<1)
Rash	19 (10)	1 (<1)	45 (7)	3 (<1)
Diarrhoea	9 (5)	2 (1)	51 (8)	17 (3)
Nausea	5 (3)	0	42 (6)	2 (<1)
Liver toxicity	3 (2)	2 (1)	16 (2)	13 (2)

AEs, adverse events.

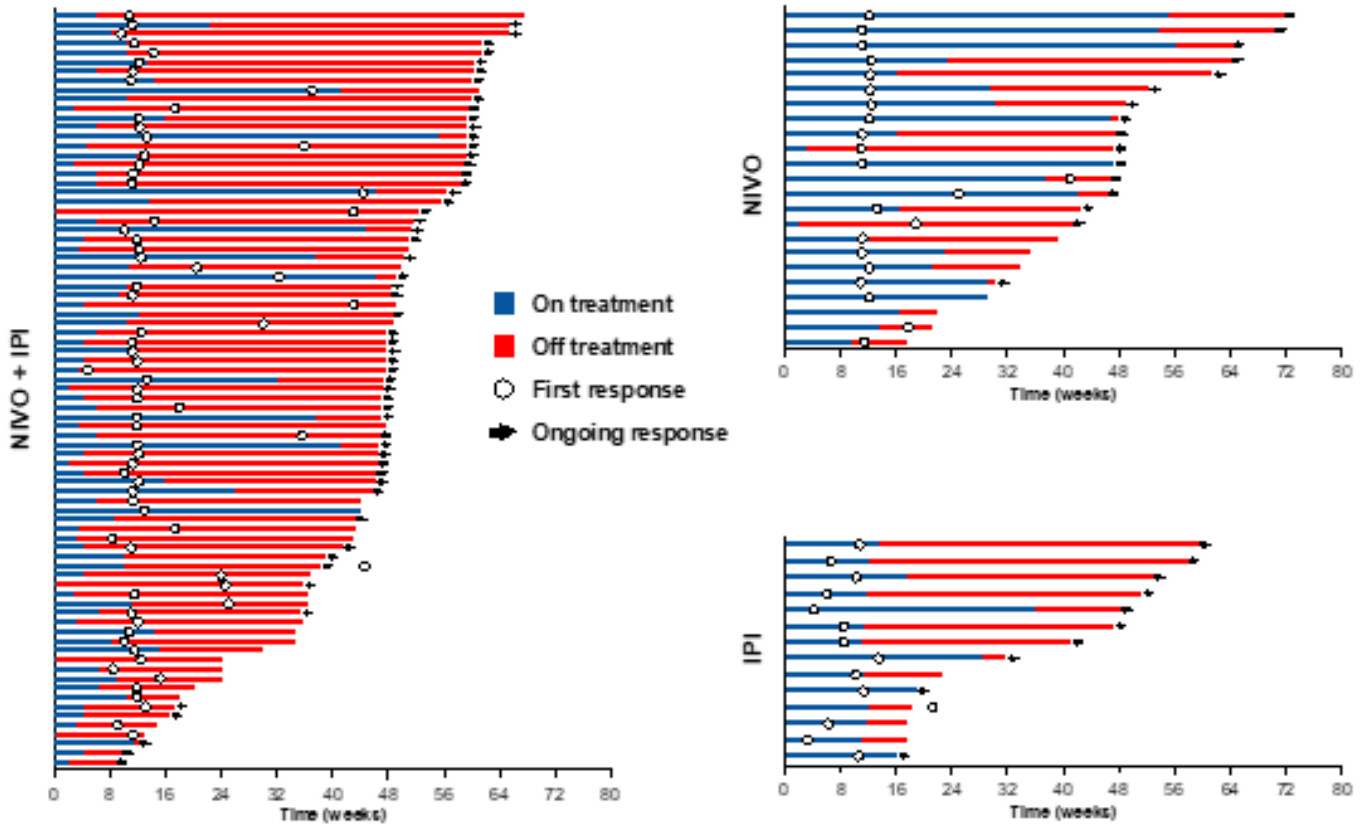




DOES STEROID USE AFFECT THE OUTCOMES?

Response, Time to Response, and Response Durability in Patients Who *Discontinued* Regimen Due to Toxicity (CheckMate 067)[1]

- 68% (81/120), 85% (23/27), and 30% (14/47) of patients who discontinued the NIVO + IPI regimen, NIVO, and IPI, respectively, due to drug-related toxicity experienced a complete or partial response



1. Larkin J, et al. Presented at ECC 2015; abstract 3303.

DOES STEROID USE AFFECT THE OUTCOMES?

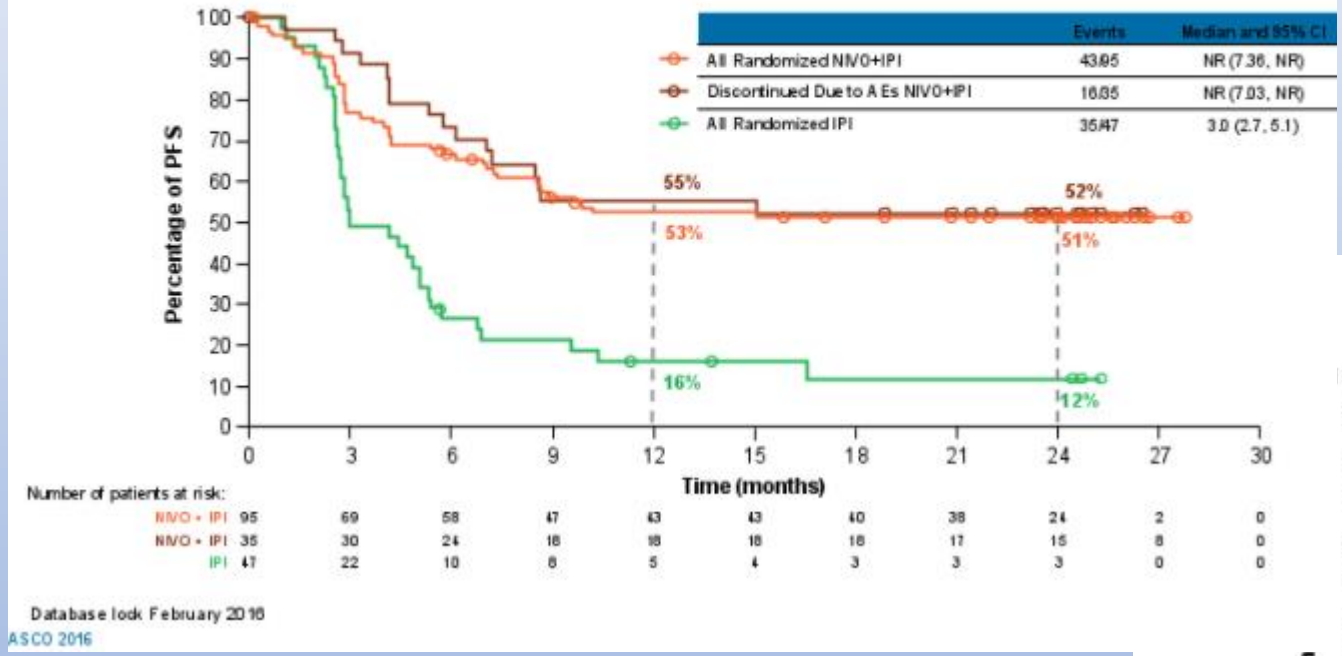
Overall Survival in Patients With Advanced Melanoma (MEL) Who Discontinued Treatment With Nivolumab (NIVO) Plus Ipilimumab (IPI) Due to Toxicity in a Phase II Trial (CheckMate 069)

F. Stephen Hodi,[1] Michael A. Postow,[2] Jason Chesney,[3] Anna C. Pavlick,[4] Caroline Robert,[5] Kenneth Grossmann,[6] David McDermott,[7] Gerald Linette,[8] Nicolas Meyer,[9] Jeffrey Giguere,[10] Sanjiv S. Agarwala,[11] Montaser Shaheen,[12] Marc S. Ernstoff,[13] David R. Minor,[14] April Salama,[15] Matthew H. Taylor,[16] Patrick A. Ott,[1] Joel Jiang,[17] Paul Gagnier,[17] Jedd D. Wolchok[2]

[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [3]University of Louisville, Louisville, KY, USA; [4]New York University, New York, NY, USA; [5]Gustave Roussy, Villejuif-Paris-Sud, France; [6]Huntsman Cancer Institute, Salt Lake City, UT, USA; [7]Beth Israel Deaconess Medical Center, Boston, MA, USA; [8]Washington University, St Louis, MO, USA; [9]Institut Universitaire du Cancer, Toulouse, France; [10]Greenville Health System, Greenville, SC, USA; [11]St Luke's Cancer Center and Temple University, Bethlehem, PA, USA; [12]University of New Mexico, Albuquerque, NM, USA; [13]Dartmouth Hitchcock Medical Center, Lebanon, NH, USA; [14]California Pacific Center for Melanoma Research, San Francisco, CA, USA; [15]Duke University, Durham, NC, USA; [16]Oregon Health & Science University, Portland, OR, USA; [17]Bristol-Myers Squibb, Princeton, NJ, USA

DOES STEROID USE AFFECT THE OUTCOMES?

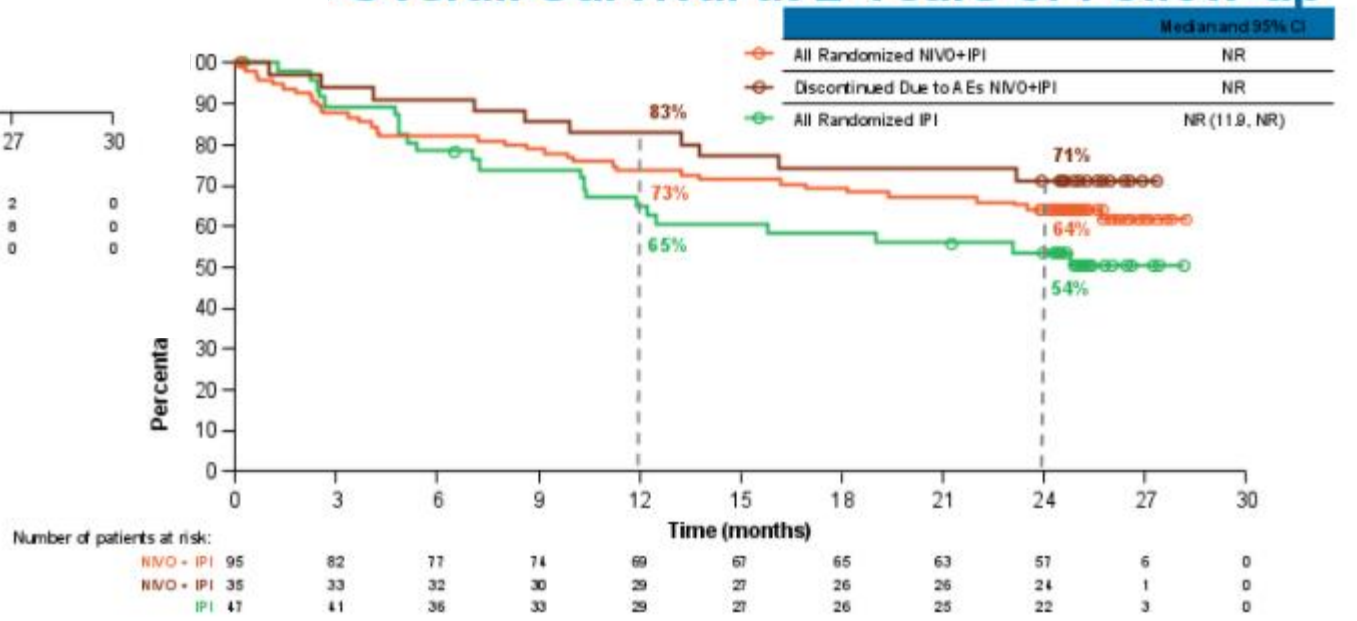
Progression-Free Survival at 2 Years of Follow-up



Database lock February 2016

ASCO 2016

Overall Survival at 2 Years of Follow-up



Database lock February 2016

ASCO 2016

Do steroids impact the efficacy of PD1/PDL1 antibodies? Pembrolizumab as one example

Antitumor response and corticosteroid use

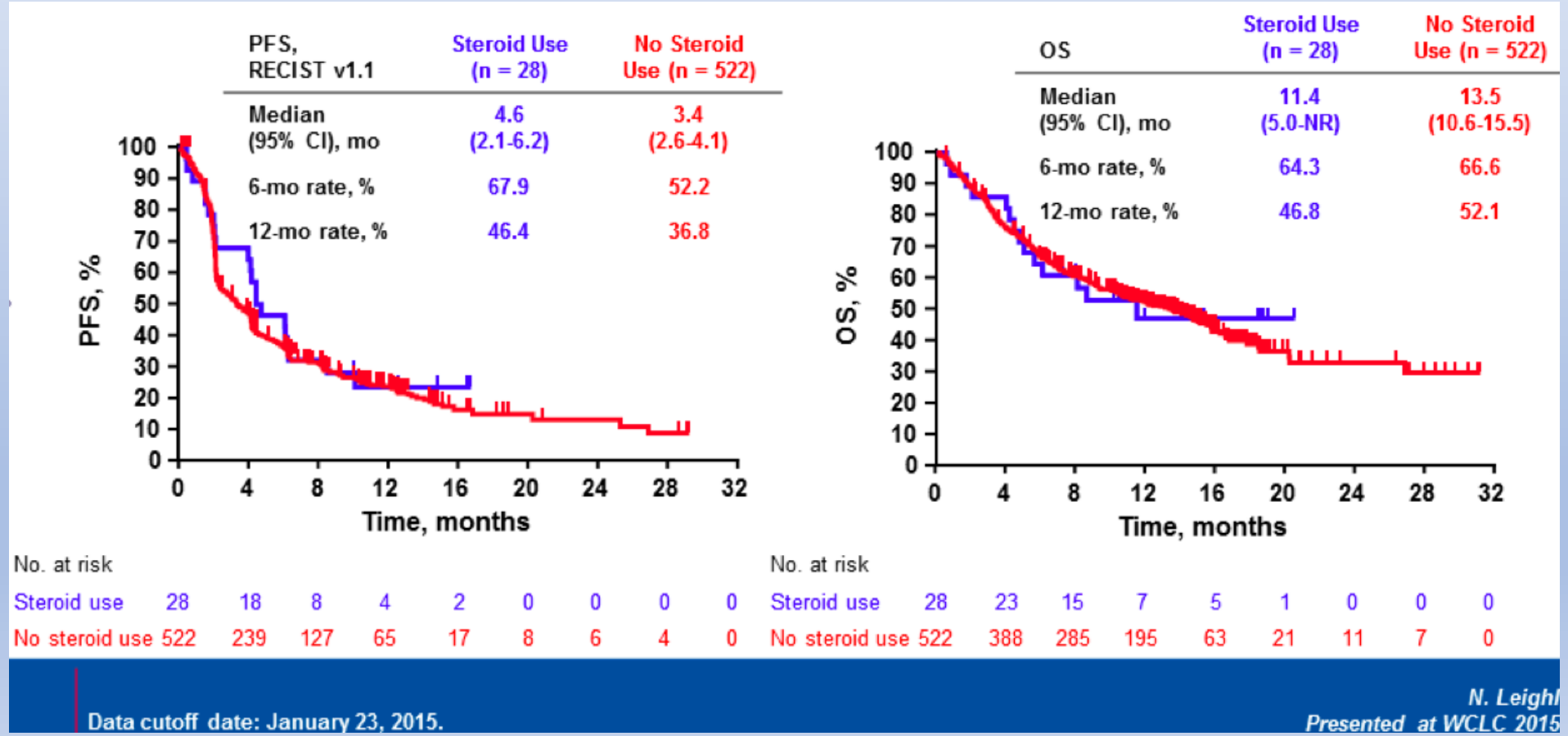
	Steroid Use (n = 28)	No Steroid Use (n = 522)
CR,[a] % (95% CI)	0.0 (0.0-12.3)	0.8 (0.2-2.0)
ORR,[a] % (95% CI)	32.1 (15.9-52.4)	19.5 (16.2-23.2)
DCR,[a] % (95% CI)	64.3 (44.1-81.4)	49.6 (45.2-54.0)
Time to response, median (range), months	2.0 (1.8-3.9)	2.1 (1.4-19.4)
Duration of response, median (range), months	NR (4.2-14.5+)	23.3 (1.0+-23.3)

[a]Assessed per RECIST v1.1 by central review.
Data cutoff date: January 23, 2015.

N. Leighl
Presented at WCLC 2015

Do steroids impact the efficacy of PD1/PDL1 antibodies? Pembrolizumab as one example

Survival and corticosteroid use



irAEs AS MARKERS OF RESPONSE

Grimaldi *et al. Journal for ImmunoTherapy of Cancer* 2015, **3**(Suppl 2):P186
http://www.immunotherapyofcancer.org/content/3/S2/P186

Journal for ImmunoTherapy of Cancer

POSTER PRESENTATION **Open Access**

Correlation between immune-related adverse events and response to pembrolizumab in advanced melanoma patients

Antonio Maria Grimaldi[1], Ester Simeone[2], Lucia Festino[2], Diana Giannarelli[3], Marco Palla[1], Corrado Caracò[4], Marcello Curvietto[2], Assunta Esposito[2], Maria Chiara Grimaldi[5], Nicola Mozzillo[4], Paolo A Ascierto[6*]

Conclusions

OR and DCR with pembrolizumab are similarly observed among pts who develop irAEs or not. Thus, pts who do not experience an irAE have the same probability to reach clinical benefit with pembrolizumab than those who experienced irAEs

Grimaldi AM, Simeone E, Festino L, et al. Correlation between immune-related adverse events and response to pembrolizumab in advanced melanoma patients. J Immunother Cancer. 2015;3(Suppl 2):186.

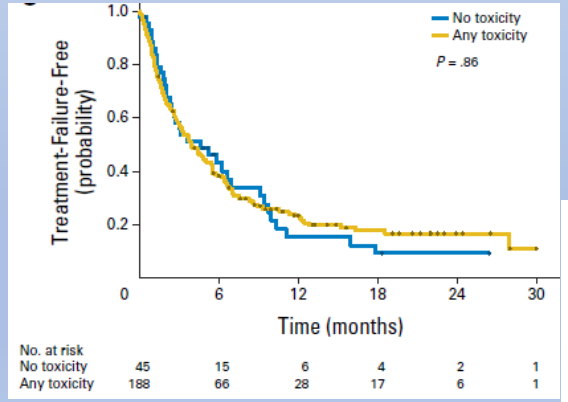
irAEs AS MARKERS OF RESPONSE

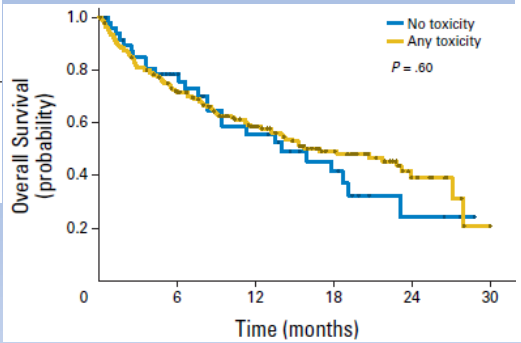
RESEARCH Open Access

Clinical experience with ipilimumab 3 mg/kg: real-world efficacy and safety data from an expanded access programme cohort

Paolo A Ascierto[1,18*], Ester Simeone[1], Vanna Chiarion Sileni[2], Jacopo Pigozzo[2], Michele Maio[3], Maresa Altomonte[3], Michele Del Vecchio[4], Lorenza Di Guardo[4], Paolo Marchetti[5,6], Ruggero Ridolfi[7], Francesco Cognetti[8], Alessandro Testori[9], Maria Grazia Bernengo[10], Michele Guida[11], Riccardo Marconcini[12], Mario Mandalà[13], Carolina Cimminiello[14], Gaetana Rinaldi[15], Massimo Aglietta[16] and Paola Queirolo[17]

Response according to irRC	Total (*N* = 833)	Any irAE (*n* = 278)	No irAE (*n* = 555)
irCR	29 (3)	10 (4)	19 (3)
irPR	82 (10)	31 (11)	51 (9)
irSD	175 (21)	57 (21)	118 (21)
irPD	547 (66)	180 (65)	367 (66)
irDCR	286 (34)	98 (35)	188 (34)





VOLUME 33 · NUMBER 28 · OCTOBER 1 2015

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Immune-Related Adverse Events, Need for Systemic Immunosuppression, and Effects on Survival and Time to Treatment Failure in Patients With Melanoma Treated With Ipilimumab at Memorial Sloan Kettering Cancer Center

Troy Z. Horvat, Nelly G. Adel, Thu-Oanh Dang, Parisa Momtaz, Michael A. Postow, Margaret K. Callahan, Richard D. Carvajal, Mark A. Dickson, Sandra P. D'Angelo, Kaitlin M. Woo, Katherine S. Panageas, Jedd D. Wolchok, and Paul B. Chapman

irAEs AS MARKERS OF RESPONSE

Published OnlineFirst October 7, 2015; DOI: 10.1158/1078-0432.CCR-15-1136

Cancer Therapy: Clinical

Clinical Cancer Research

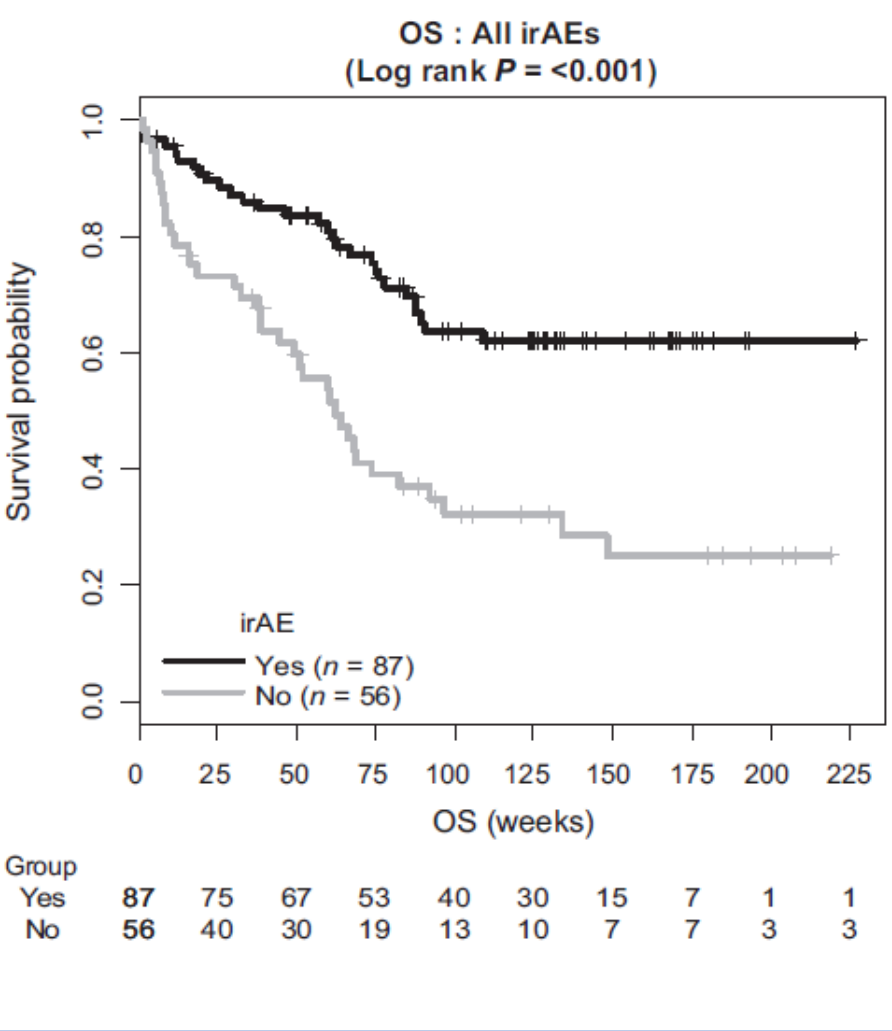
Nivolumab in Resected and Unresectable Metastatic Melanoma: Characteristics of Immune-Related Adverse Events and Association with Outcomes

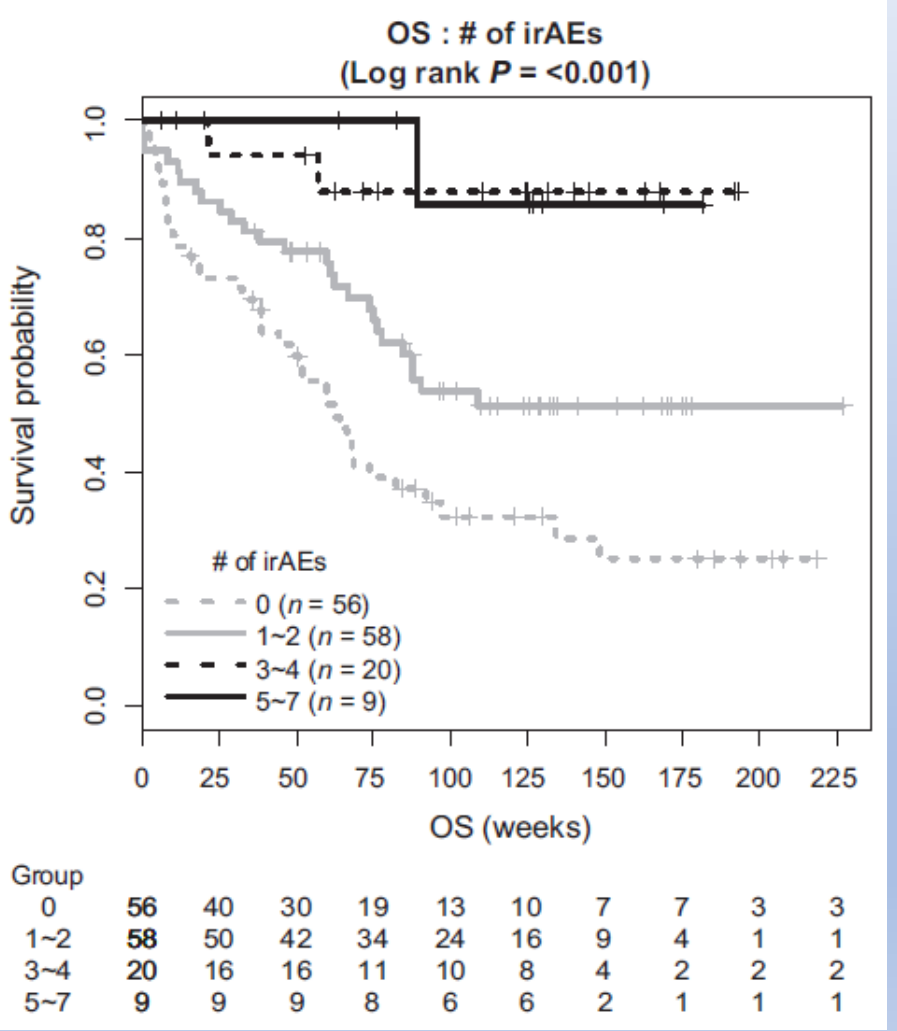
Morganna Freeman-Keller[1], Youngchul Kim[2], Heather Cronin[3], Allison Richards[3], Geoffrey Gibney[4], and Jeffrey S. Weber[5]

Experimental Design: Data were pooled from 148 patients treated with nivolumab plus peptide vaccine or nivolumab alone in two Phase 1 studies (NCT01176474; NCT01176461)

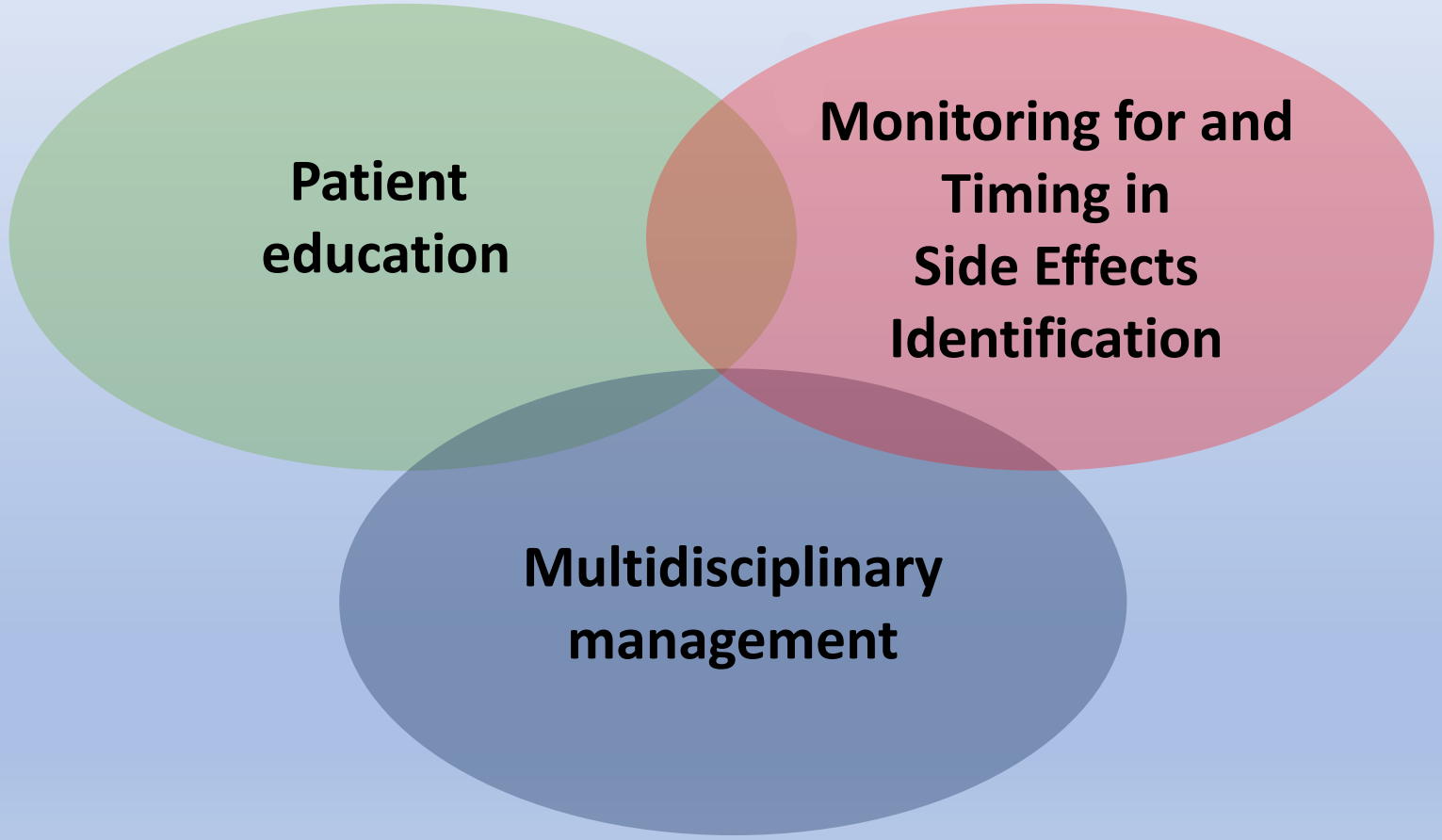
irAE	*n* (%)	Median weeks to onset	Median weeks to resolution	Systemic steroid therapy	Median weeks of steroid therapy
Elevated amylase/lipase	7 (4.7)	2	16	—	—
Elevated ALT/AST	1 (0.7)	2	6	—	—
Diarrhea/enteritis	48 (32.4)	4.2	1.3	Yes	5
Colitis	2 (1.4)	5.3	4	Yes	5
Rash	64 (43.2)	5.6	6.4	—	—
Vitiligo	19 (12.8)	5.4	—	—	—
Hyperthyroidism[a]	2 (1.4)	9.1	11.3	—	—
Hypophysitis	1 (0.7)	20.3	13.8	—	—
Mucositis	9 (6.1)	9.7	4	—	—
Hypothyroidism[a]	16 (10.8)	10.7	17.6	—	—
Pneumonitis	3 (2.6)	10.9	14.9	Yes	4

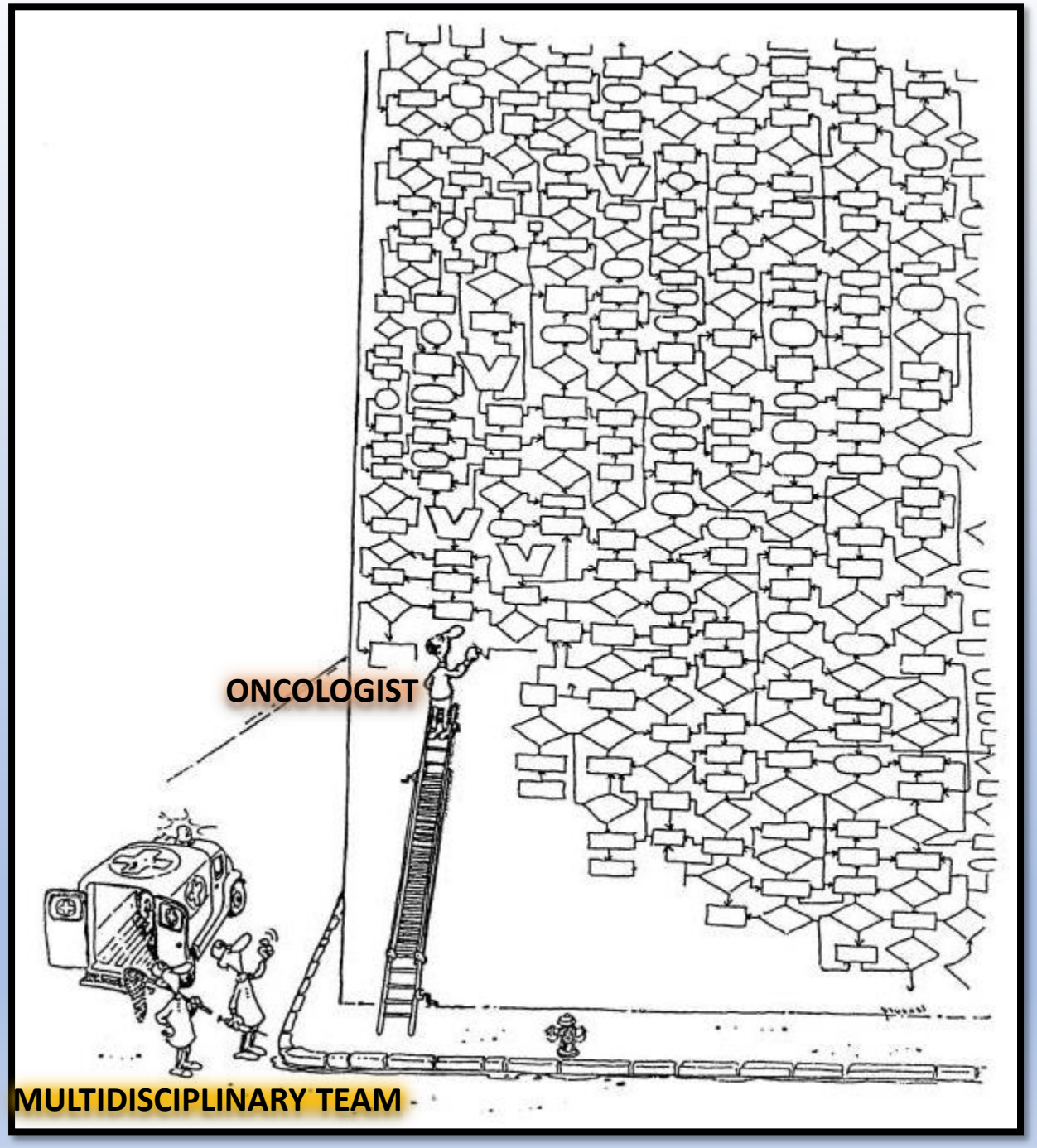
A statistically significant OS difference was noted among patients experiencing any irAE versus those who did not, with greater OS benefit in patients reporting 3 or more events





KEY PRINCIPLES IN IMMUNONCOLOGY





Grazie per l'attenzione