



# CARCINOMA DEL POLMONE NON MICROCITOMA: QUALI NOVITA' PER IL 2016?



## Immunoterapia.

Quadri clinici e gestione della tossicità.

*Evidenze dalla Letteratura Scientifica*



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**Verona, 09 Aprile 2016**

# Disclosures

- Advisory Boards/Honoraria/Speakers' fee/Consultant for:
  - Eli-Lilly, WALCE
- Research Support / Grants from:
  - A.I.R.C. (Associazione Italiana Ricerca sul Cancro)
  - I.A.S.L.C. (International Association for the Study of Lung Cancer)
  - Fondazione *Cariverona*



# What kind of toxicity?

	Nivolumab [Checkmate 017-057]		Pembrolizumab [KEYNOTE-010]		Atezolizumab [POPLAR]	
	All Grade	G3-4	All Grade	G3-4	All Grade	G3-4
<b>All</b>	<b>58-69</b>	<b>7-10</b>	<b>63</b>	<b>10</b>	<b>67</b>	<b>12</b>
<b>Fatigue</b>	<b>16</b>	<b>1</b>	<b>14</b>	<b>1</b>	<b>20</b>	<b>1</b>
<b>Decrease appetite</b>	<b>10-11</b>	<b>1</b>	<b>14</b>	<b>1</b>	<b>17</b>	<b>1</b>
<b>Asthenia</b>	<b>10</b>	<b>0</b>	<b>6</b>	<b>1</b>	<b>6</b>	<b>1</b>
<b>Nausea</b>	<b>9-12</b>	<b>1</b>	<b>11</b>	<b>1</b>	<b>12</b>	<b>1</b>
Diarrhea	8	1	7	1	7	1
Arthralgia	5	0	-	-	-	-
Pyrexia	5	0	-	-	-	-
Pneumonitis	5	2	5	2	-	-
Rash	4	0	9	1	-	-
Myalgia	2	0	1	0	-	1
Anemia	2	0	3	1	-	-

*Brahmer J et al. N Engl J Med 2015*

*Borghaei H et al. N Engl J Med 2015*

*Herbst RS et al. Lancet 2015*

*Fehrenbacher L et al. Lancet 2016*

# And the comparators?

	<b>Nivolumab [Checkmate 017-057]</b>	<b>Pembrolizumab [KEYNOTE-010]</b>	<b>Docetaxel [vs nivo]</b>	<b>Docetaxel Nintedanib</b>	<b>Docetaxel Ramucirumab</b>
<b>All (%)</b>	<b>58-69</b>	<b>63</b>	<b>86-88</b>	<b>93</b>	<b>98</b>
<b>Grade 3-4 (%)</b>	<b>7-10</b>	<b>10</b>	<b>54-55</b>	<b>72</b>	<b>79</b>
<b>Grade 5 (n)</b>	<b>0</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>5</b>

*Brahmer J et al. N Engl J Med 2015*  
*Borghaei H et al. N Engl J Med 2015*  
*Herbst RS et al. Lancet 2015*  
*Fehrenbacher L et al. Lancet 2016*  
*Reck M et al, Lancet Oncol 2014*  
*Garon EB et al, Lancet 2014*

# IMMUNO-RELATED TOXICITIES

## [skin]



### Manifestations:

Rash: 7-16% (G3-4 1-2%)

Pruritus: 6-10%

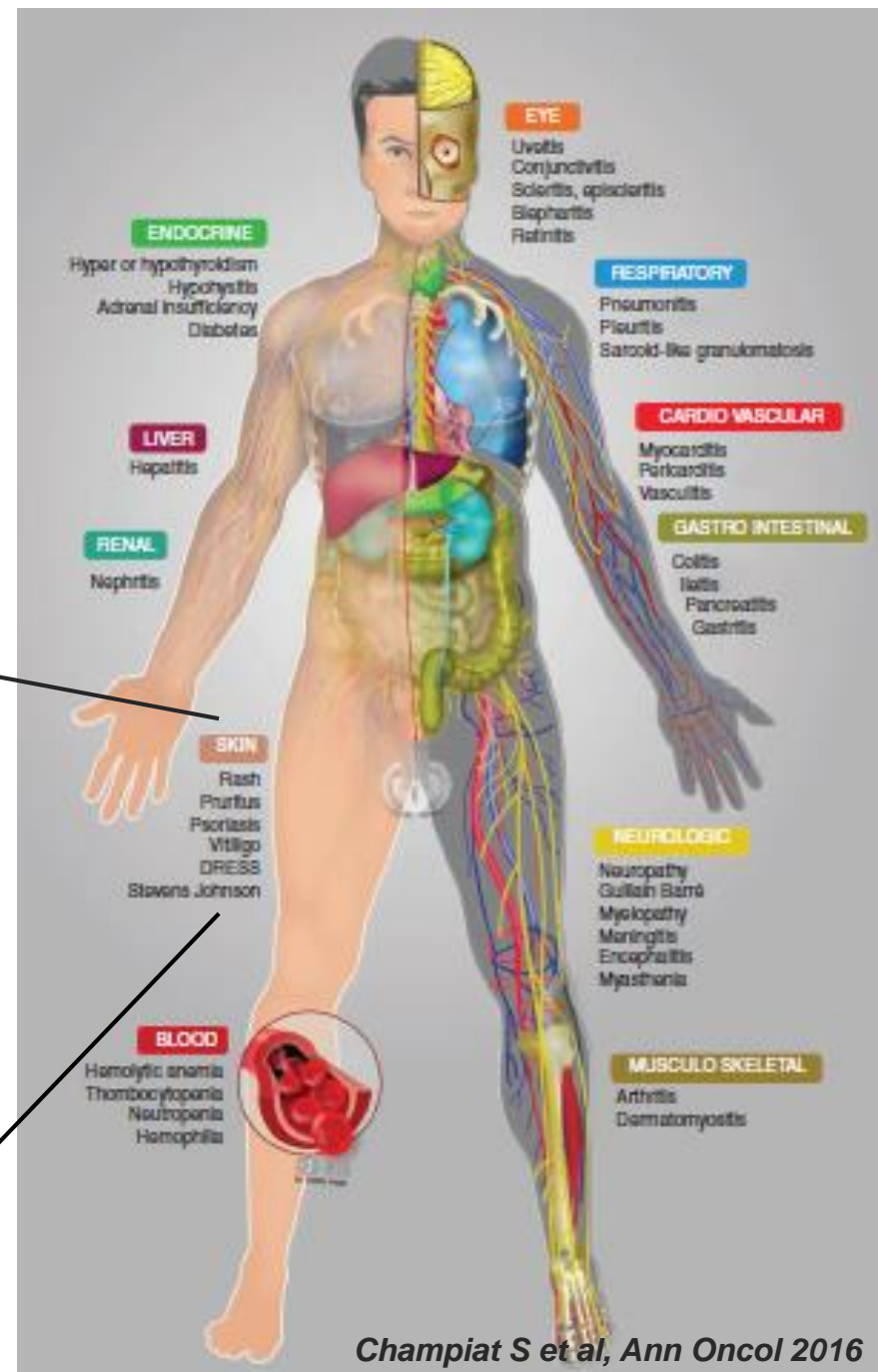
Erythema: 0.4%

Skin exfoliation: 0.4%

Urticaria: 0.4%

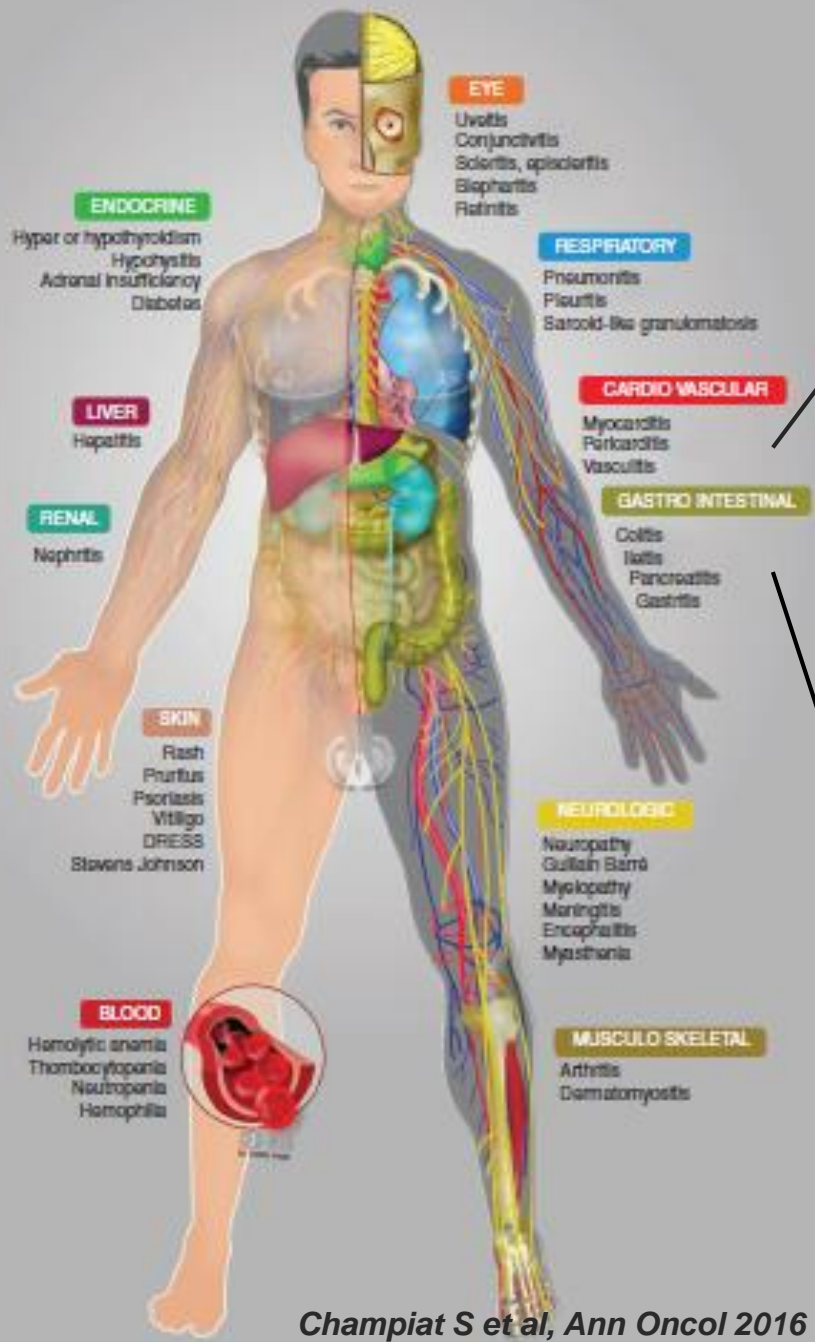
### Treatment:

Observation or topical corticosteroid treatment or oral steroids +/- oral anti-histaminic drugs to improve pruritus





# IMMUNO-RELATED TOXICITIES [gastrointestinal]



## Manifestations:

Diarrhea: 7-12% (G3-4 1-2%)

Colitis (mucosal erythema and ulcerations) is rare

**Diagnosis:** CT abdomen scan, rectosigmoidoscopy or ileocolonoscopy with biopsies

## Treatment:

Most cases of diarrhea are low grade and can be symptomatically treated and dose delay *versus* high grade diarrhea with high dose intravenously steroid therapy

**N.B.** exclusion infectious diarrhea (screening stool samples)

# IMMUNO-RELATED TOXICITIES

## [endocrine]

### Manifestations:

Hypothyroidism: **6-8%** (G3-4 0-1%)

Hyperthyroidism: **2-4%**

Blood TSH decreased

Adrenal insufficiency

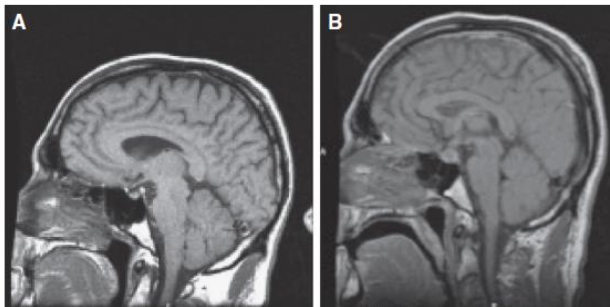
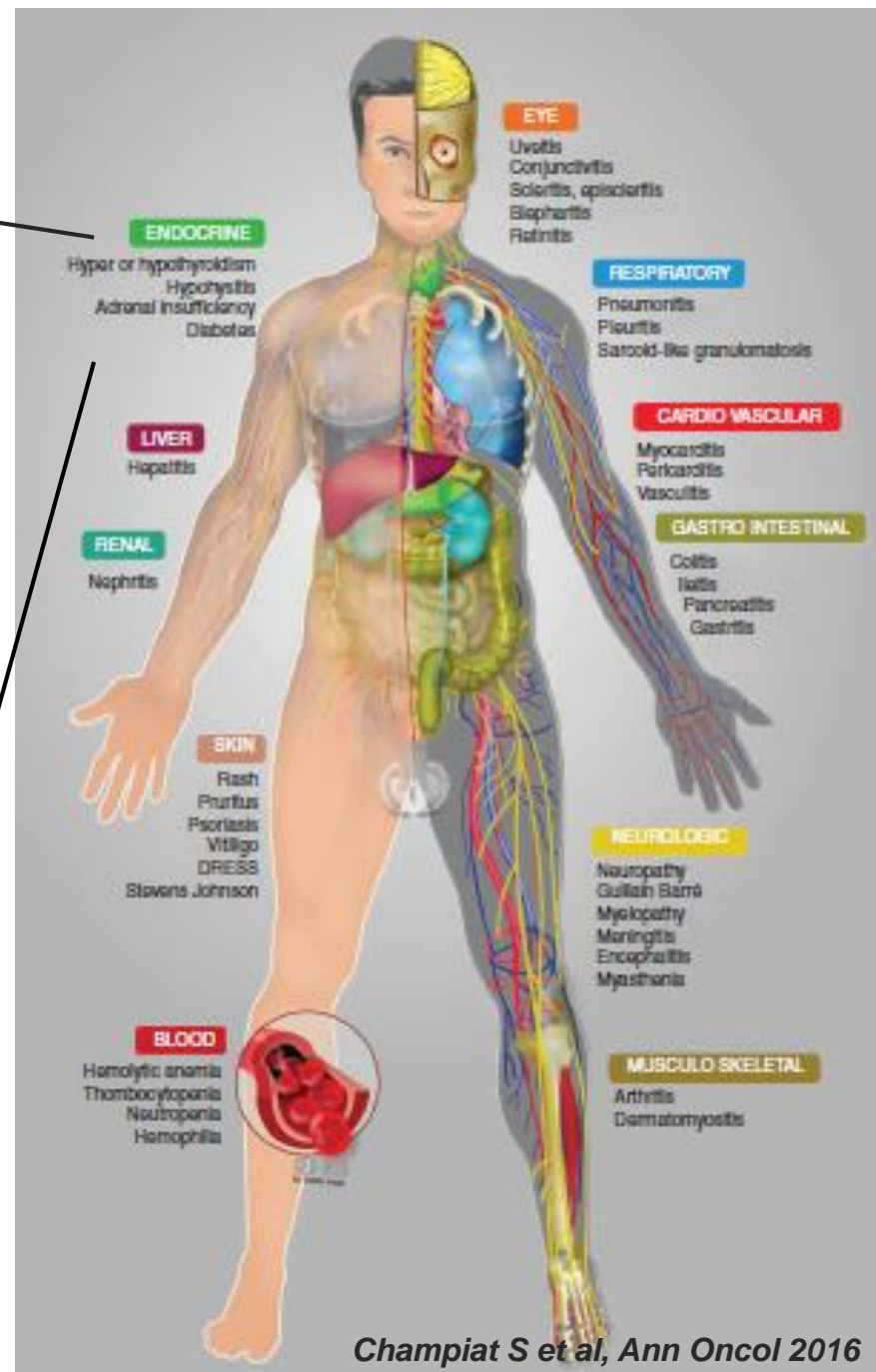
Diabetes

Hypophysitis

Non-specific symptoms: headache, fatigue, weakness, memory loss, impotence, personality changes, and visual-field impairment

### Treatment:

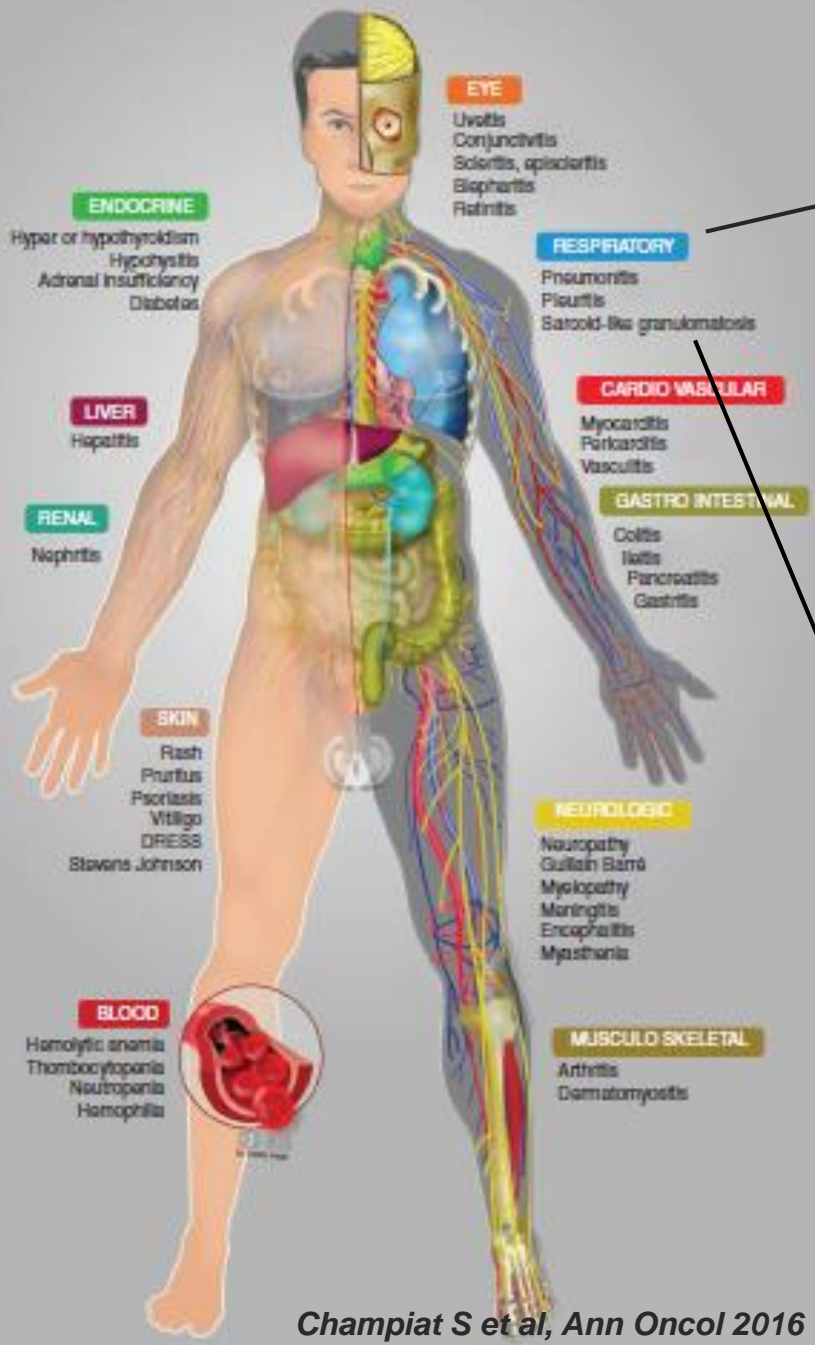
Hormone replacement therapy more than high-dose steroids



6/30/04 - Baseline (4.5 mm)

12/3/04 - Headache/fatigue (10.8 mm)

# IMMUNO-RELATED TOXICITIES [pulmonary]

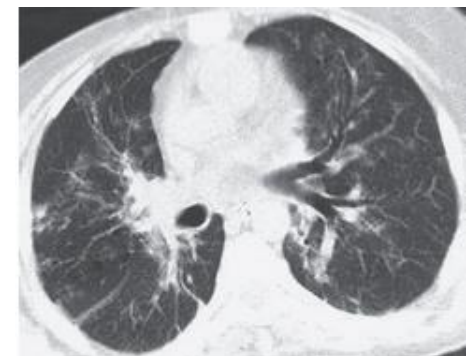
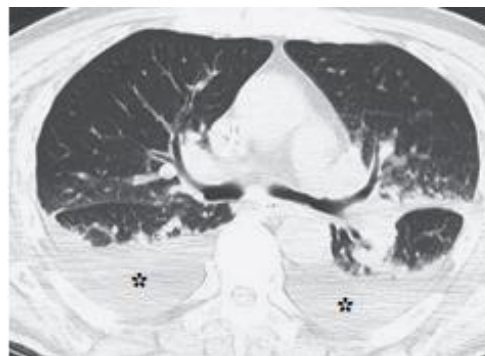


**All grades: 5-6%**  
**Grades 3-4: 2%**

## Manifestations:

From asymptomatic lung infiltrates to a mimic of severe bacterial pneumonia (cough, dyspnea, fever,..)  
Asymptomatic radiographic changes

**Diagnosis:** Pulse oximetry (rest and exertion), CT  
Differential diagnosis: infection, early pulmonary edema, tumor progression (such as lymphangitis), impairment of the cardiopulmonary function





1-2%

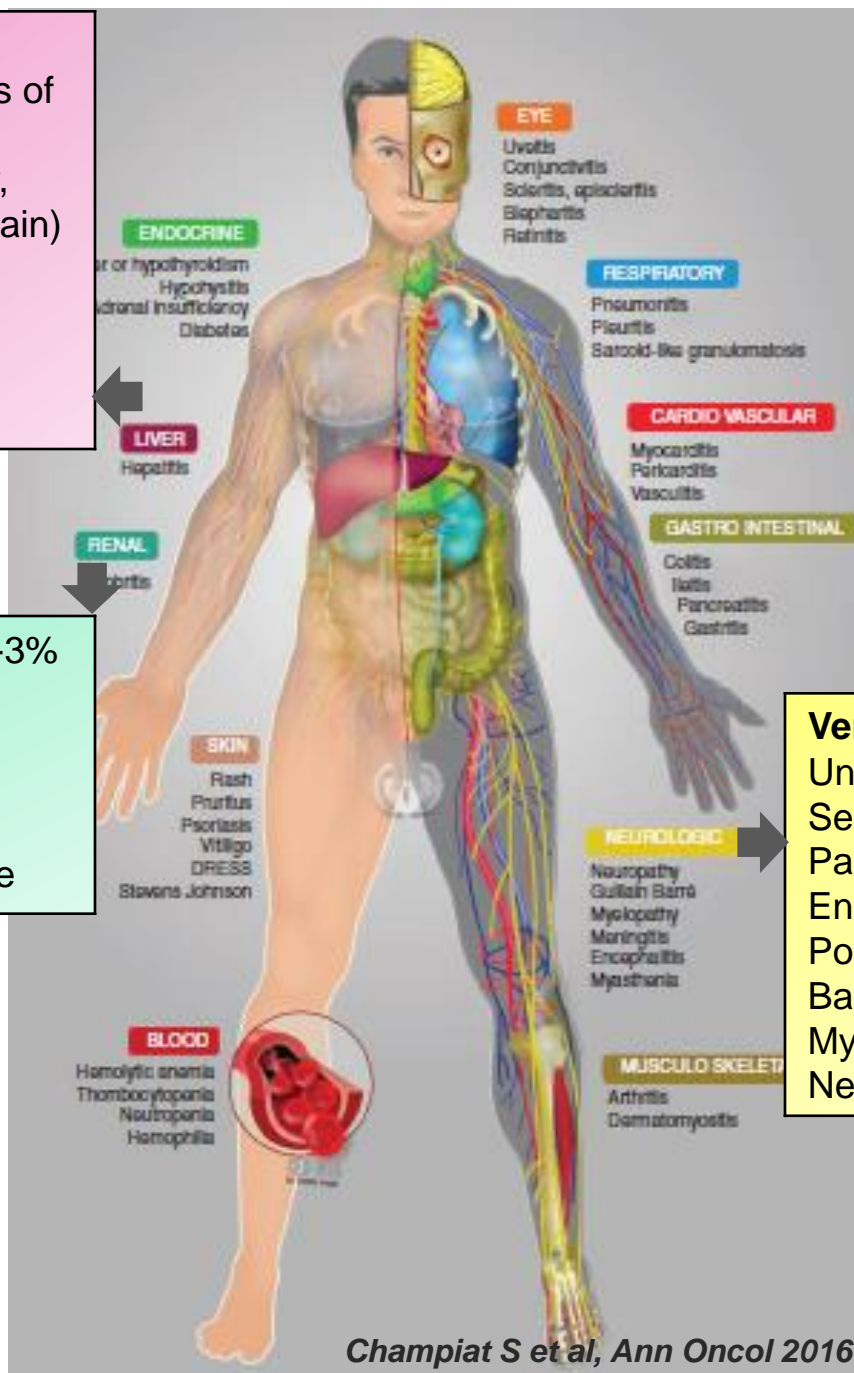
Asymptomatic elevated levels of hepatic transaminases  
Nonspecific symptoms (fever, fatigue, nausea, abdominal pain)

**N.B.:**

Exclusion other etiologies of hepatic injury

Blood creatinine increased 2-3%  
Tubulointerstitial nephritis  
Renal failure

Most commonly present with elevations in serum creatinine



**Very rare**

Unilateral or bilateral weakness  
Sensory alterations  
Paresthesia  
Encephalitis or encephalopathy,  
Polyneuropathy e.g. Guillain-  
Barre Syndrome  
Myasthenic syndromes  
Nerve paralysis

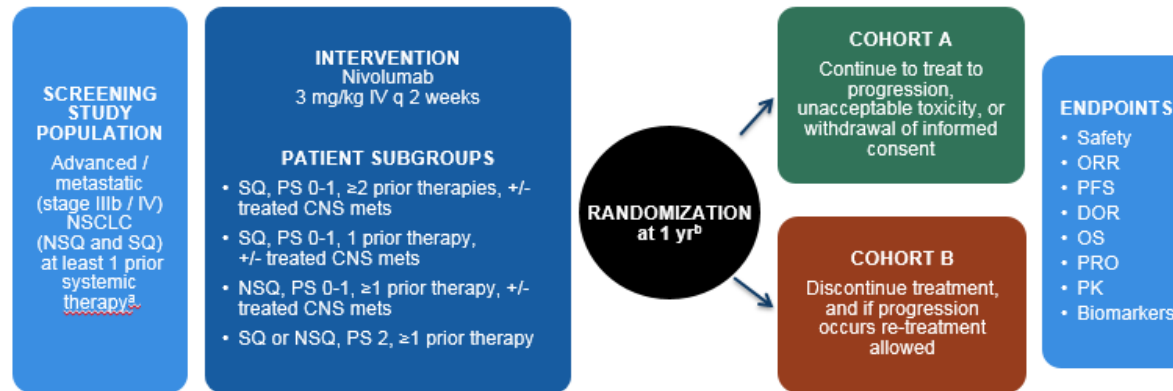
# Real-life Setting?

	<b>Nivolumab</b> Checkmate 017	<b>Nivolumab</b> Checkmate 057	<b>Pembrolizumab</b> KEYNOTE-010	<b>Atezolizumab</b> POPLAR
<b>Median Age</b>	62	61	63	62
<b>&gt; 75 y</b>	8%	7%	N.R.	N.R.
<b>PS 2</b>	N.E.	N.E.	1%	N.E.
<b>Brain Mets</b>	7%	12%	16%	N.R.

*Brahmer J et al. N Engl J Med 2015*  
*Borghaei H et al. N Engl J Med 2015*  
*Herbst RS et al. Lancet 2015*  
*Fehrenbacher L et al. Lancet 2016*

# Should Patients be excluded for PS?

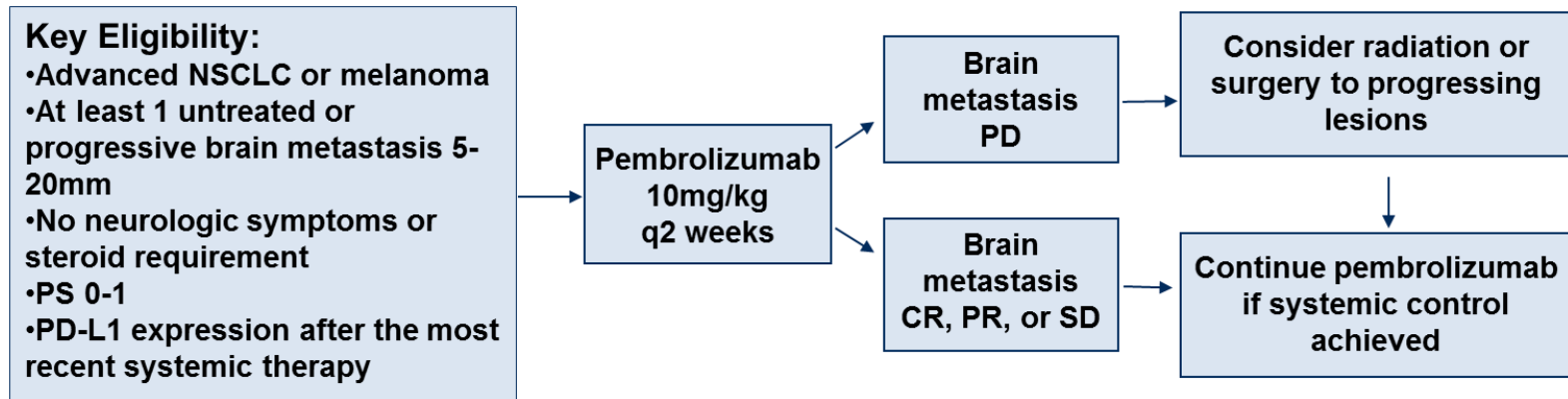
## CA209-153 Study Design



	Nivolumab 3 mg/kg N = 824			Nivolumab 3 mg/kg ECOG PS 0-1 (n = 742)			Nivolumab 3 mg/kg ECOG PS 2 (n = 65)		
	Any Grade n (%)	Grade 3-4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3-4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3-4 n (%)	Grade 5 n (%)
All adverse events	762 (93)	311 (38)	158 (19)	683 (92)	268 (36)	131 (17)	82 (95)	33 (51)	24 (37)
All serious adverse events (SAEs)	309 (38)	223 (27)	158 (19)	257 (35)	185 (25)	131 (17)	42 (65)	29 (45)	24 (37)
All select adverse events	282 (34)	37 (5)	5 (1)	253 (34)	32 (4)	3 (<1)	22 (34)	3 (5)	2 (3)
All treatment-related adverse events	439 (53)	59 (7)	1 (<1)	403 (54)	52 (7)	1 (<1)	27 (42)	4 (6)	0
All treatment-related SAEs	23 (3)	19 (2)	1 (<1)*	18 (2)	14 (2)	1 (<1)	3 (5)	3 (5)	0
All treatment-related select AEs	199 (24)	20 (2)	0	181 (24)	16 (2)	0	14 (22)	2 (3)	0
All AEs leading to discontinuation	87 (11)	53 (6)	34 (4)	69 (9)	42 (6)	27 (4)	16 (25)	9 (14)	7 (11)
All treatment-related SAEs leading to discontinuation	14 (2)	12 (2)	1 (<1)	11 (2)	9 (1)	1 (<1)	2 (3)	2 (3)	0
All treatment-related select AEs leading to discontinuation	12 (2)	11 (1)	0	9 (1)	8 (1)	0	2 (3)	2 (3)	0

# Should Patients with Brain Mets be excluded?

## Phase II Trial of Pembrolizumab for Untreated Brain Metastases



Treatment-related Adverse Event	Any Grade		Grade 3/4		Any Neurologic Adverse Event*	Any Grade		Grade 3/4	
	No.	%	No.	%		No.	%	No.	%
N=18					N=18				
Fatigue	5	28	1	6	Headache	4	22	0	0
Diarrhea/colitis	3	17	1	6	Dizziness	2	11	0	0
Pneumonitis	1	6	1	6	Cognitive dysfunction	1	6	0	0
Hypokalemia	1	6	1	6	Stroke	1	6	0	0
Autoimmune nephritis	1	6	0	0					
Flu-like symptoms	1	6	0	0					
Anorexia	2	11	0	0					
Dermatologic	4	22	0	0					
Endocrine	5	28	0	0					
Hematologic	2	11	0	0					

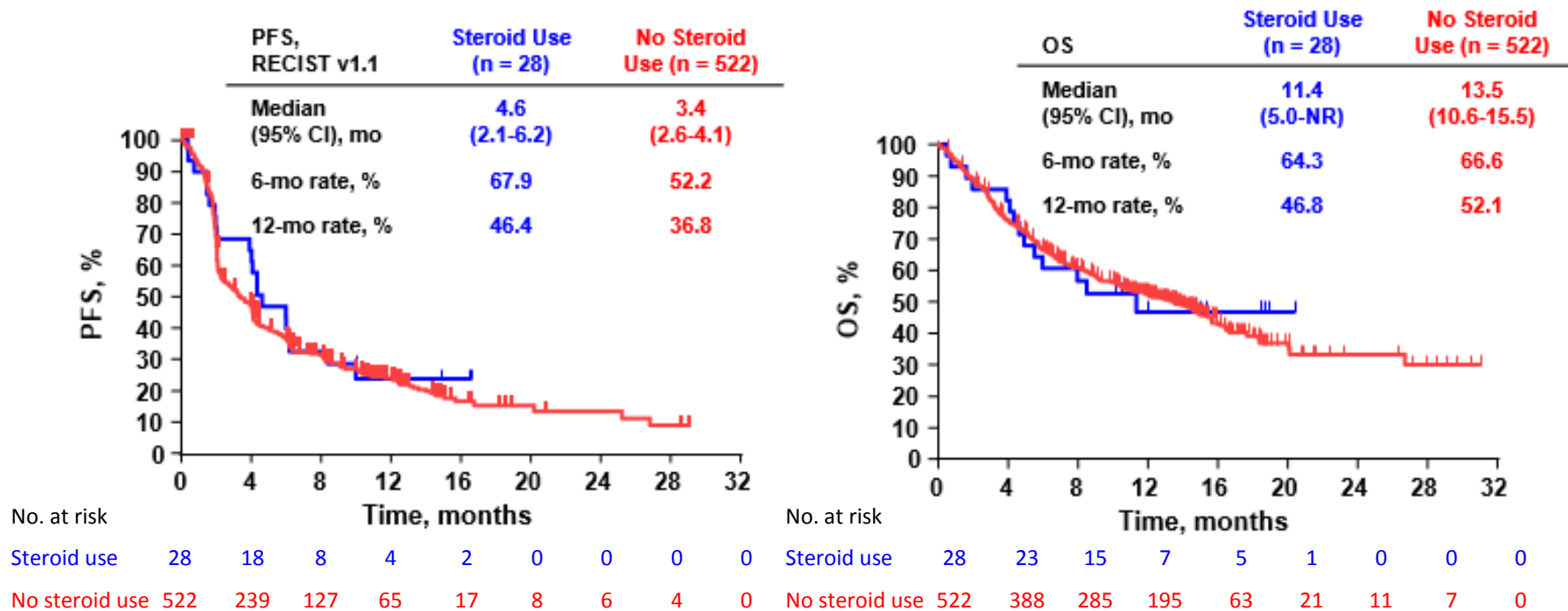
Of 18 treated patients, there were 4 treatment-related AEs grade > 3

**All neurologic adverse events were G1**



# Should Patients receiving steroids be excluded?

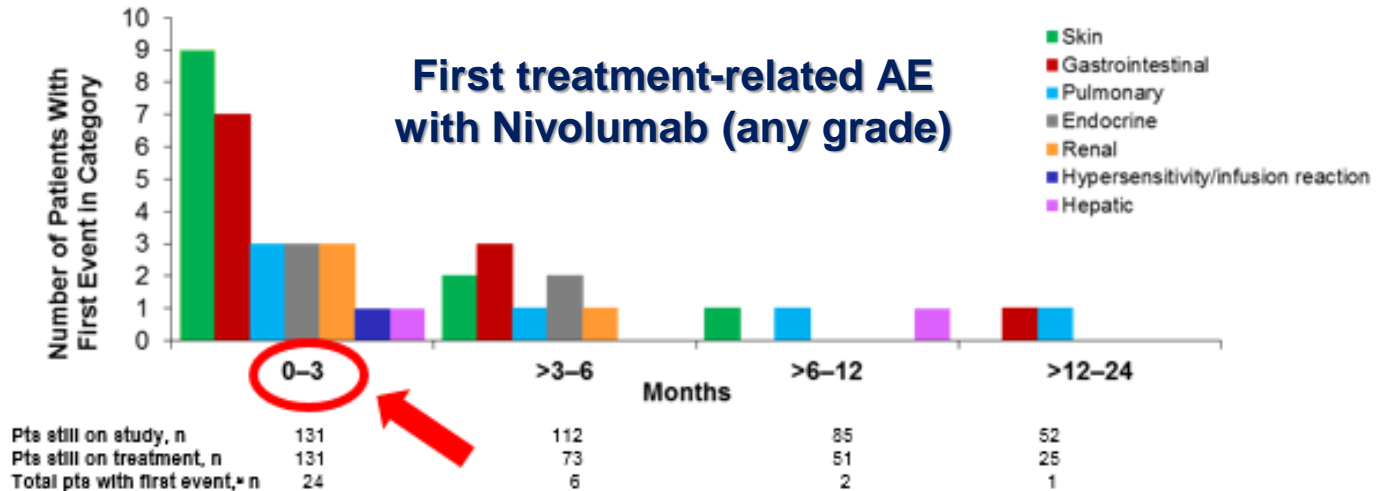
KEYNOTE-001 - NSCLC cohorts n = 550



No clear relationship between steroid use and continued efficacy of pembrolizumab

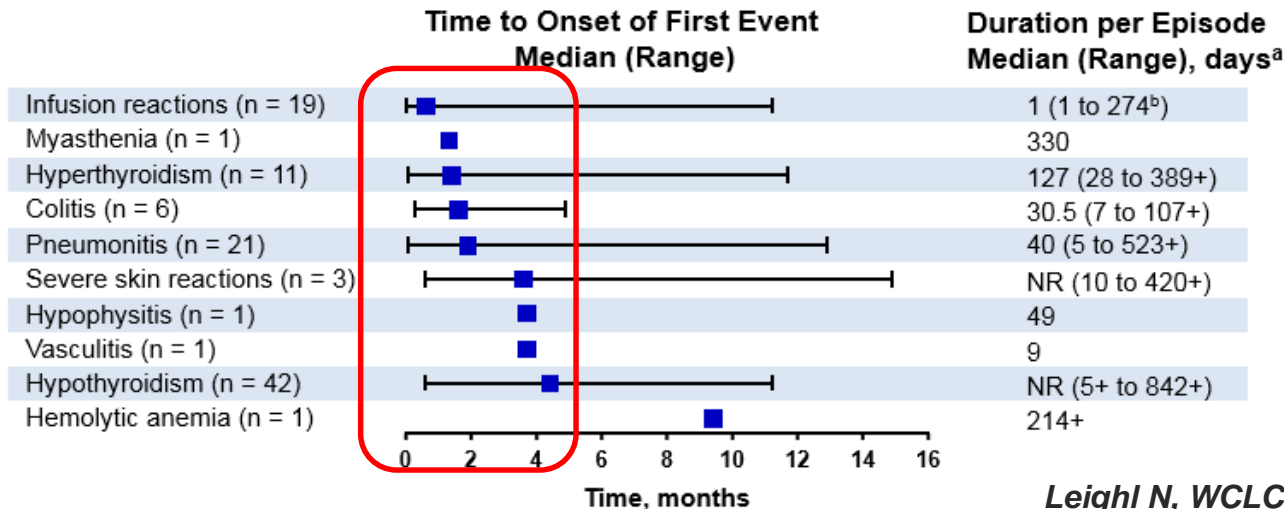
# What else we have to know?

## Time of onset



- The majority of patients who experienced treatment-related select AEs with nivolumab experienced their first event within the first 3 months of treatment

*Reckamp K, WCLC 2015 [Checkmate 017]*



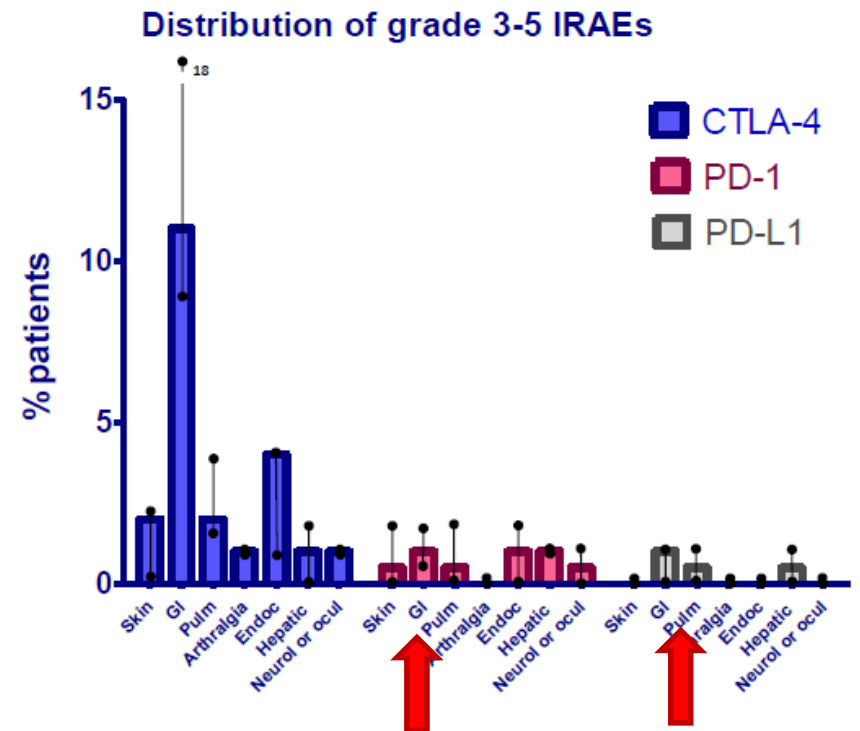
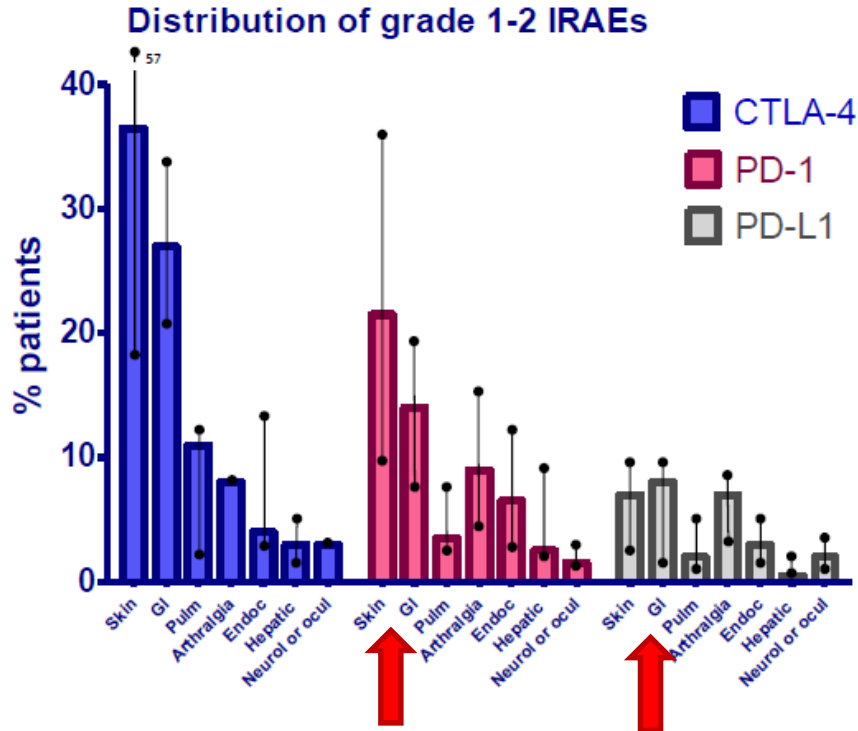
**Pembrolizumab  
KEYNOTE-001**

*Leighl N, WCLC 2015*

# What else we have to know?

## Type of toxicity

Distribution of grade I-II and grade III-V IRAEs for all tumor types in the main clinical trials with anti-CTLA4, anti-PD-1 or anti-PD-L1 antibodies as single therapies.



# How to choose the right candidate? [for an appropriate toxicity prevention]



- Careful familiar and personal history [autoimmune diseases]
- Age, Performance Status, necessity to take steroids
- Physical examination
- Lab tests (including basal TSH, T4, cortisol and ACTH, virology)
- Imaging (extension and disease localizations)

**[with implications for appropriate use of the resources]**

***...Remembering that...***



TERAPIA A BERSAGLIO MOLECOLARE E IMMUNOTERAPIA



*Gestione pratica dei più comuni effetti collaterali*



# ***Patient Education Makes the Difference..***

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