CTLA-4 Blockade

Clinical Indications and Management

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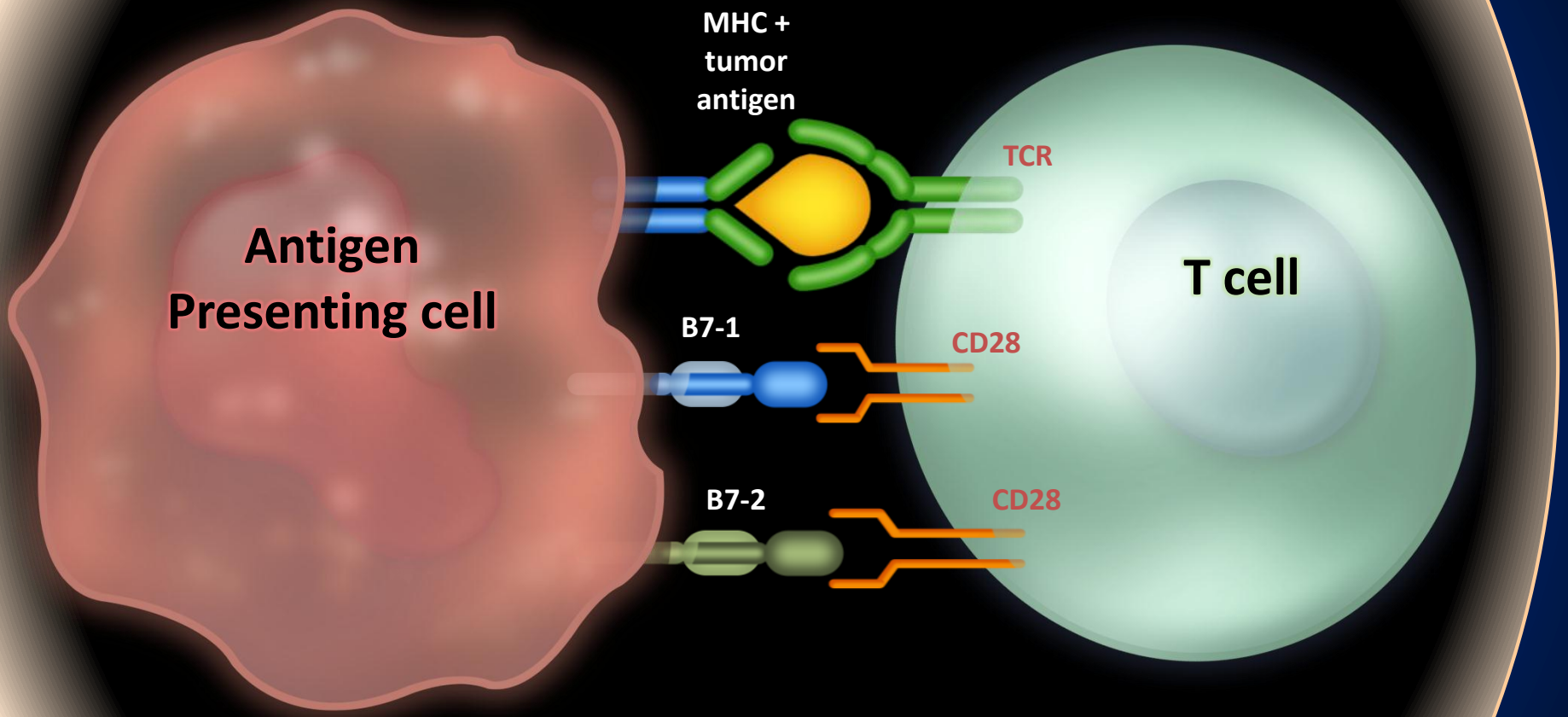
Disclosures

- Received honoraria from BMS for participation in Advisory Board and Speaker’s Bureau
- Participated in BMS, Pfizer sponsored clinical trials

T cell Response – CD28 Co-stimulation



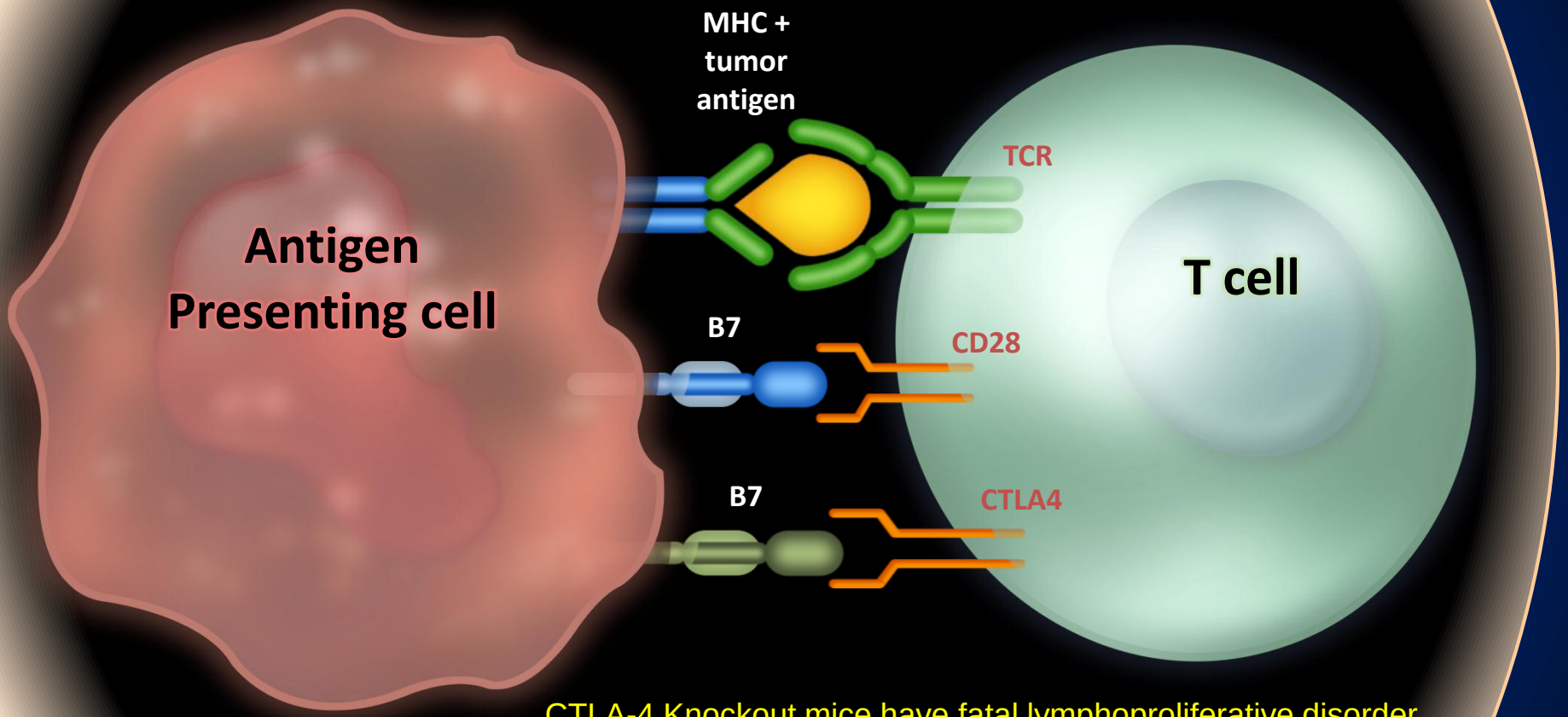
Antibodies to B7 blocked T cell response
CD28 knockout mice have impaired T cell response
B7 knockout mice have no T cell response
CD28 has critical role in T cell activation

T cell Response – Co-stimulation

- TCR engagement insufficient for T cell activation
- APC surface molecule regulates IL-2 prodcution
- CD28 delivers co-stimulatory signal for IL-2 production
- CD28 mediated signaling prevents T cell anergy
- B7-CD28 interaction co-stimulates T cell

Mueller DL, Jenkins MK, Schwartz RH. Annu. Rev. Immunol 1989;7:445-80
Martin PJ et al. J Immunol 1986;136:3282-87
Jenkins MK et al. J Immunol 1991;147:2461-66
Harding F, McArthur JG, Ghross JA, Raulet DH Allison JP. Nature 1992;356:607-609
Linsley PS et al. J Exp. Med 1991;173:721-30

T cell Response – CTLA-4 Co-regulation



CTLA-4 Knockout mice have fatal lymphoproliferative disorder
Anti-B7 antibodies cause activation of T cells
Anti-CD28 antibodies inhibited T cell responses
Anti-CTLA-4 antibodies enhanced T cell responses
CTLA-4 has critical negative regulatory role

T cell Response – CTLA-4 Co-regulation

- CTLA-4 is a member of the Ig superfamily
- CTLA-4 binds to B7 and can negatively impact T cell activation
- Binding of CTLA-4 to B7 opposes the effect of CD28 on T cells and regulates the T cell co-stimulatory interactions

Brunet JF et al. Nature 1987;328:267-70
LinsleyPS et al. J Exp. Med. 1991;174:561-569
Walunas TL et al. Immunity 1994;1:405-413
Krummel MF, Allison JP. J Exp. Med. 1995;182:459-465
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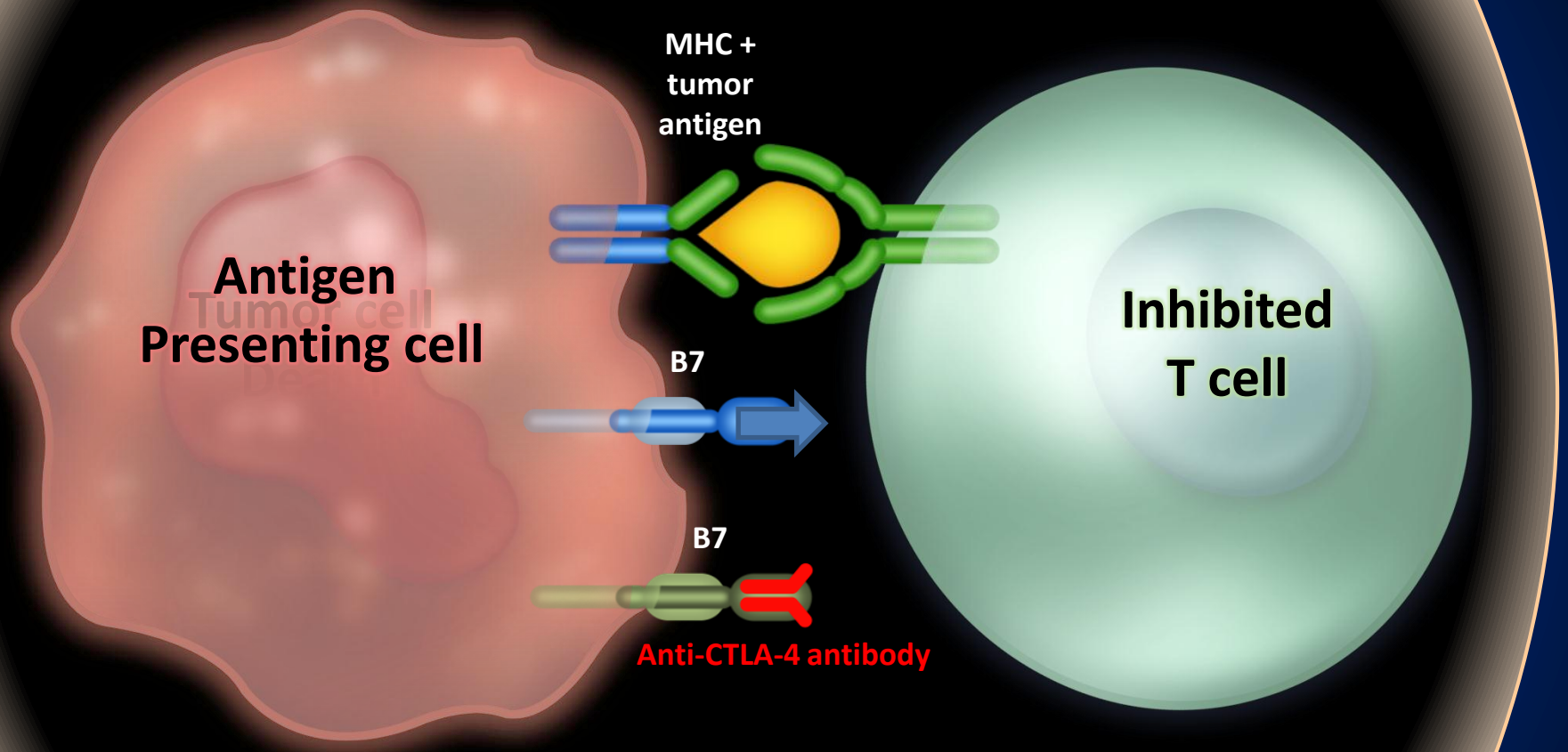
CTLA-4 Blockade



1. Antigen recognition by T cell
2. CD28-B7 interaction leads to T cell activation
3. CTLA-4 expression and interaction with B7 results in negative regulation of T cell
4. CTLA-4 blockade allows for ongoing T cell activation

CTLA-4 Blockade

- CTLA-4 binds to B7 with higher affinity and blocks CD28 mediated activation of T cells and acts as a negative regulator
- Manipulation of CTLA-4 signals can enhance T cell anti-tumor response
- CTLA-4 blockade synergistic with GM-CSF in murine mammary carcinoma and B-16 melanoma, prostate cancer models
- CTLA-4 inhibition – tool for immunotherapy

Linsley PS et al. Immunity. 1994;1:793-801,
Walunas TL et al. J Exp. Med. 1996;183:2541-50
Krummel MF, Allsion JP. J Exp. Med 1995;182:459-65
Allison JP et al. Curr Opin Immunol 1995; 7:682-86.
Leach D et al. Science 1996;271:1734-36

Chamber CA et al. Immunol Rev 1996;153:27-46.
Chamber CA et al. Annu. Rev Immunol. 2001;19:565-94
Hurwitz AA et al. Proc. Natl. Acad. Sci USA 1998;95:10067-71
Van Elsas A et al. J Exp.Med 1999;190:355-66
Hurwitz AA et al. Cancer Res 1999: 60:2444-48

Clinical Settings

- Malignant Melanoma

Ovarian cancer
Renal cell carcinoma
Colon cancer
Prostate cancer

Pancreatic cancer
NSCLC
Lymphoma
Breast cancer

Phan GQ et al. Proc Natl Acad Sci USA. 2003;100:8372-7
Hodi FS et al. N Engl J Med. 2010;363:711
Robert C et al. N Engl J Med. 2011;364;2517
Hodi FS et al. Proc Natl Acad Sci USA. 2003;100:4712-7
Yang JC et al. J Immunother. 2007;30;825-830

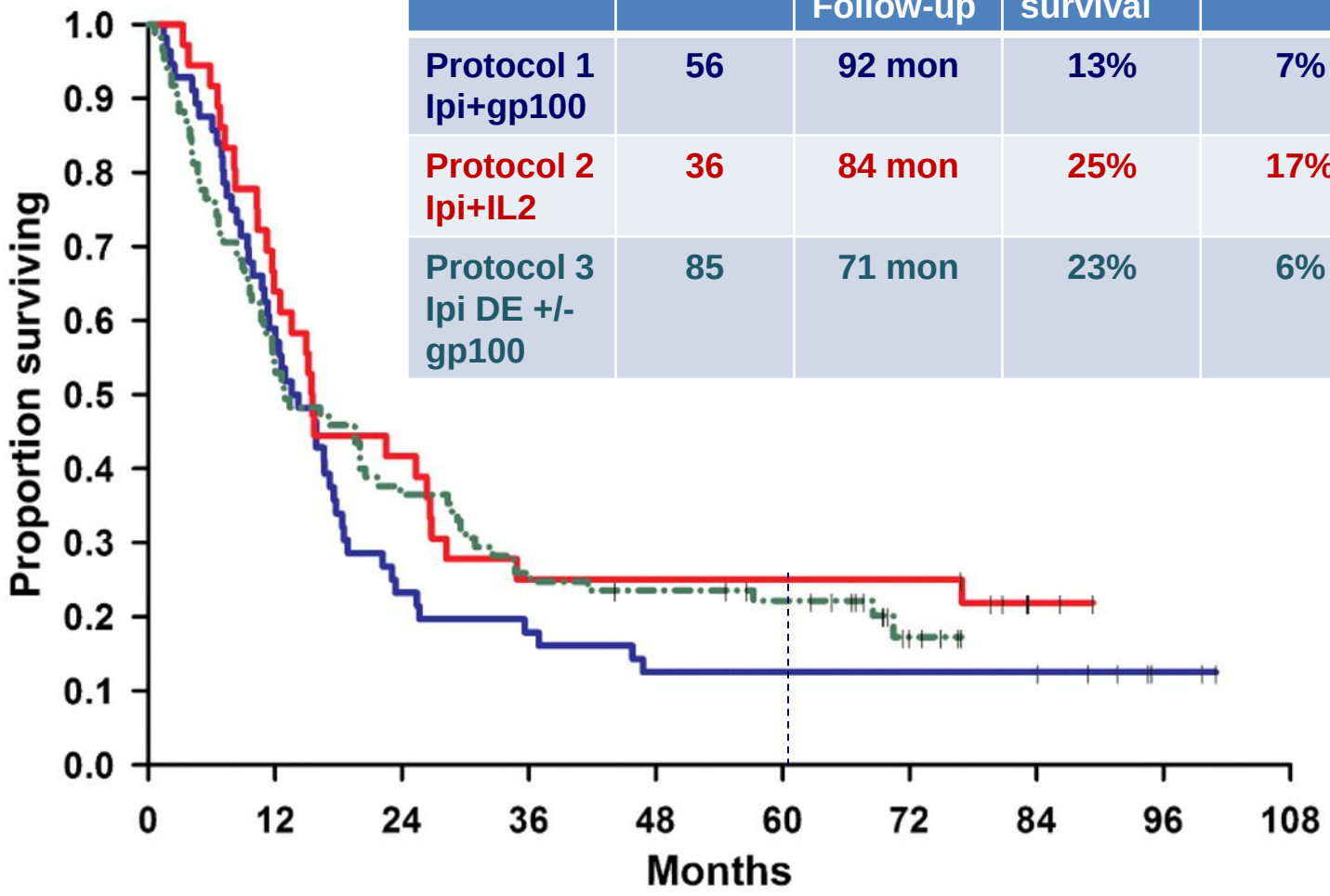
Lynch TL et al. J Clin Oncol. 2012;302046-2054
O'Mahoney D et al. Clin Cancer Res. 2007;13:958-64
Small EJ et al. Clin Cancer Res. 2007;13:1810-5
Fong L et al. J Clin Oncol.2007;25(18S):3001
Vonderheide RH et al. J Clin Oncol. 2009;27 Suppl 15s

CTLA-4 Inhibitors

- Ipilimumab (MDX-010)
  - Fully human IgG1
- Tremelimumab (CP-675,206)
  - Fully human IgG2

CTLA-4 Inhibition – Long term Follow-up

Study	Number	Median Follow-up	5 yr survival	CR rate
Protocol 1 Ipi+gp100	56	92 mon	13%	7%
Protocol 2 Ipi+IL2	36	84 mon	25%	17%
Protocol 3 Ipi DE +/- gp100	85	71 mon	23%	6%



Prieto, PA et al. Clin Cancer Res. 2012;18:2039

Phase III – Tremelimumab

Previously treated unresectable or metastatic melanoma
LDH ≤ 2x ULN
(n=655)

Normal hepatic and renal function
ECOG PS ≤ 1
Patients with brain metastases excluded

Treme 15mg/kg IV q90 days x4
(n=328)

Tumor assessment every 90 days

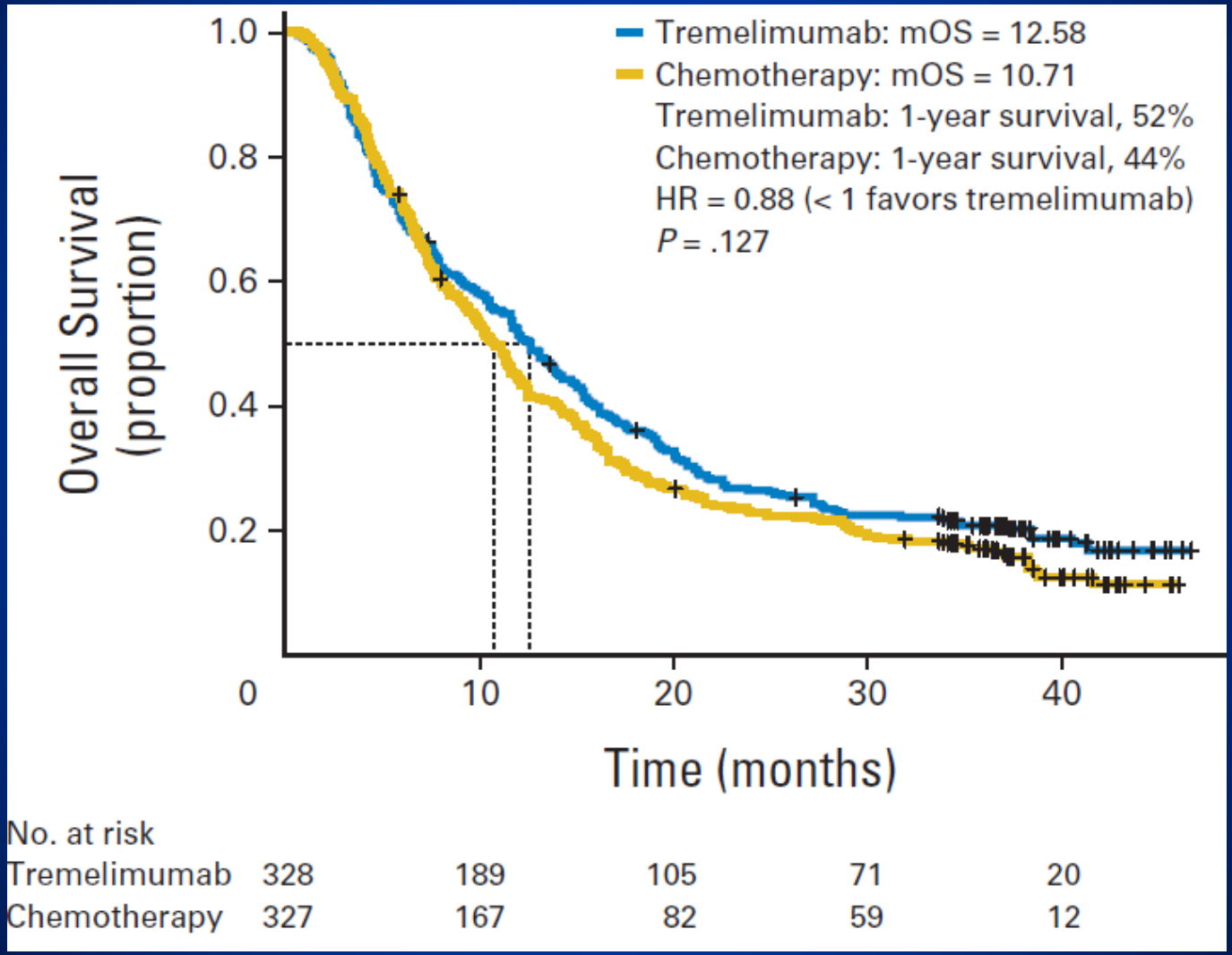
Chemotherapy
(n=327)

Dacarbazine: assessment every 42 days
Temozolomide: assessment every 56 days

Primary endpoint: Overall survival
Secondary endpoints: PFS
BORR
Duration of response

Ribas A et al. J Clin Oncol. 2013;31:616-622

Tremelimumab – Phase III OS



Ribas A et al. J Clin Oncol. 2013;31:616-622

Phase III – Ipilimumab

Previously treated unresectable or metastatic melanoma
HLA-A2*201 positive
(n=676)

- Ipi 3mg/kg IV q3w x4 (n=137)
- Ipi 3mg/kg IV q3w x4 + gp100 (n=403)
- gp 100 (n=136)

Normal hepatic and renal function
Patients with active auto-immune disease or receiving immunosuppression excluded
Tumor assessment every 12 weeks

Primary endpoint: OS in ipi + gp100 arm vs gp100
Secondary endpoints: OS in ipi + gp100 vs ipi and ipi vs gp100
BORR at week 24
Duration of reponse

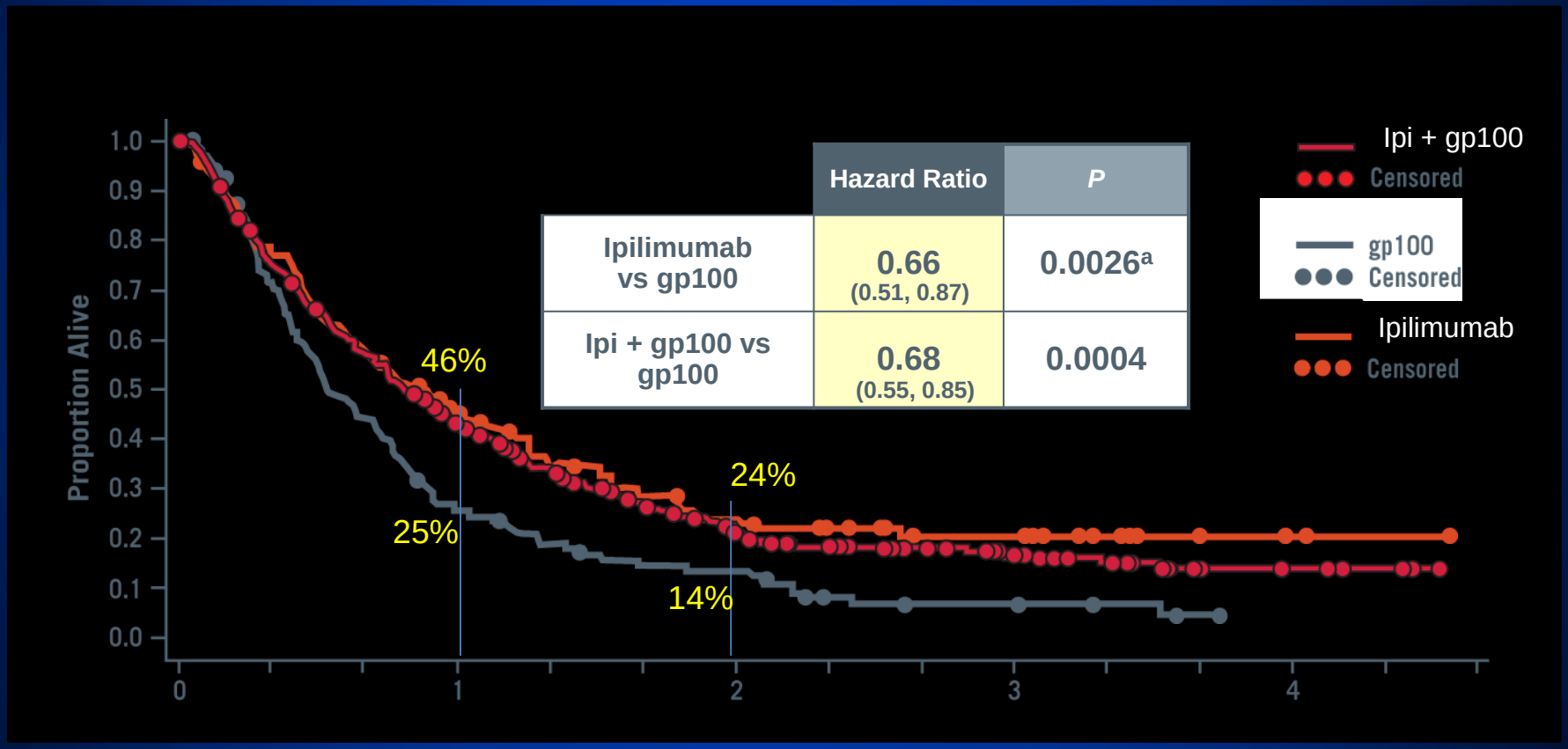
Hodi S et al. N Engl J Med. 2010;363:711-723

Baseline Patient Characteristics

Variable	Patient Population N=676
Age, yrs median	57
Sex, n(%) Male Female	 58% 42%
ECOG PS, (%) 0-1	 98%
Previously treated brain metastasis	12%
Prior Interleukin-2	23%
M1c disease	71%
Elevated LDH, n(%)	38%

Hodi S et al. N Engl J Med. 2010;363:711-723

Ipilimumab – OS



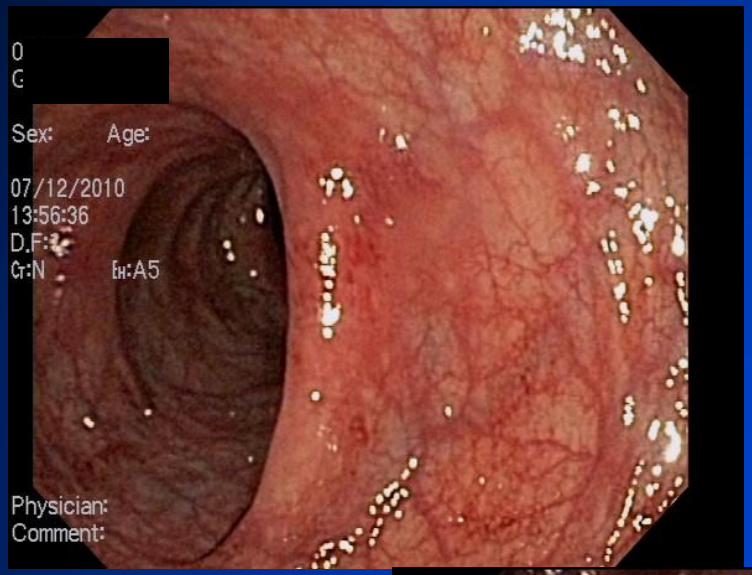
Hodi S et al. N Engl J Med. 2010;363:711-723

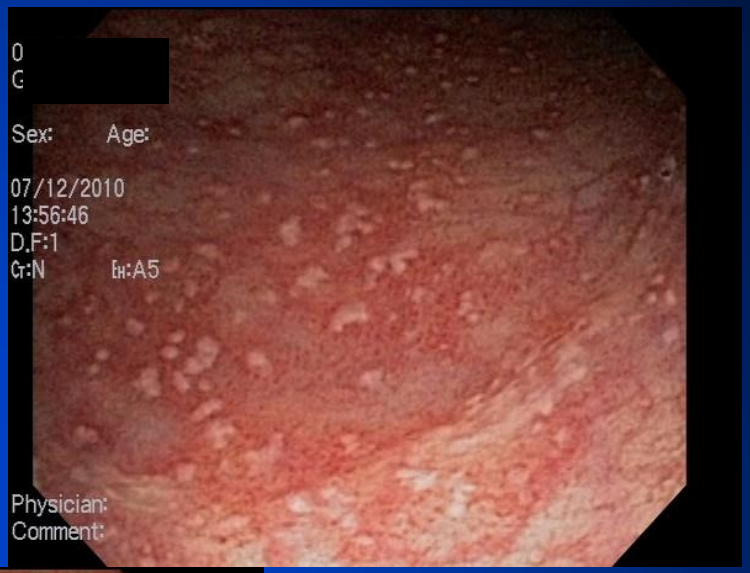
Safety – Grade 3-4 AEs

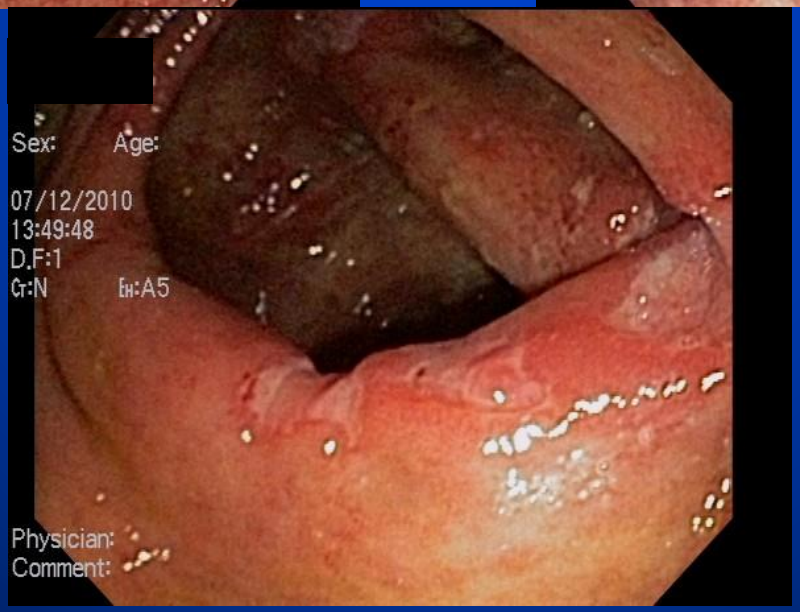
Severe to Fatal Immune-Mediated Adverse Reactions in the Phase 3 Study		
	Patients, %	
Event	**Ipilimumab 3 mg/kg (n = 131)**	**Ipilimumab 3 mg/kg + gp100 (n = 380)**
Any Immune-Mediated Adverse Reaction	**15**	**12**
Enterocolitis[a]	**7**	**7**
Hepatotoxicity[a]	**1**	**2**
Dermatitis	**2**	**3**
Neuropathy	**1**	**<1**
Endocrinopathy	**4**	**1**
Hypopituitarism	**4**	**1**
Adrenal insufficiency	**0**	**1**
Other		
Pneumonitis	**0**	**<1**
Meningitis	**0**	**<1**
Nephritis	**1**	**0**
Eosinophilia	**1**	**0**
Pericarditis	**0**	**<1**

Hodi S et al. N Engl J Med. 2010;363:711-723

Autoimmune Colitis







Auto-immune Colitis

Median time of onset: 6-7 weeks from dose 1

Clinical signs and symptoms
Diarrhea, blood with stools, abdominal cramping

	Grade 1	Grade 2	Grade 3	Grade 4
No of Stools	< 4/day	4-6/day	≥ 7/day	Life threatening
IV fluid need	NA	< 24 hrs	≥ 24 hrs	Hemodynamic Instability
ADLs	NA	Not Effected	Interference with ADLS	

NO REFLEX: Anti-diarrheal agents

Auto-immune Colitis – Management

Grade 3/4:

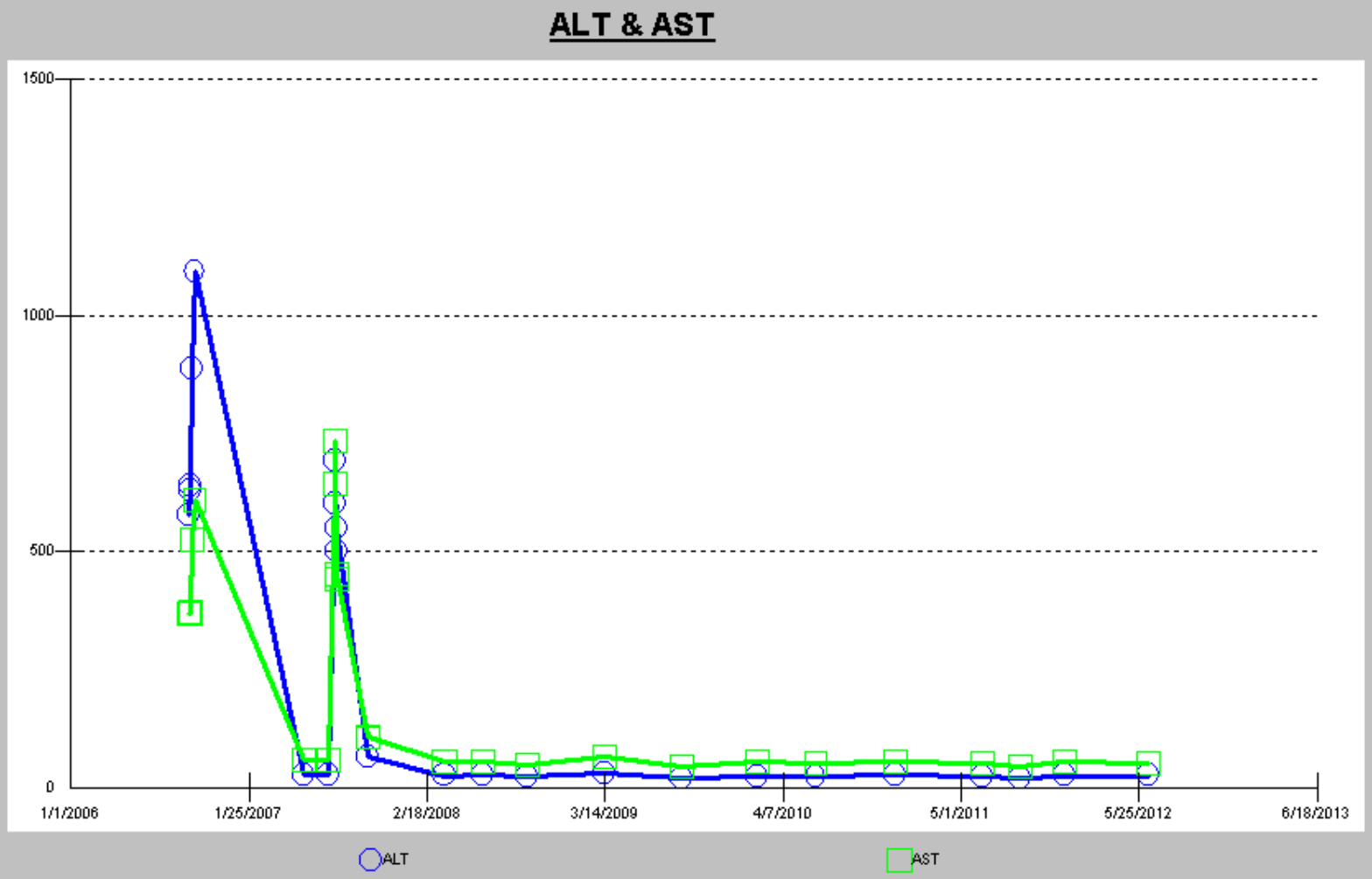
Admit to hospital

IV fluids: 125cc/hr
Strict I &Os including stool
Diet: NPO, clears, progress to BRAT
Labs: CBCD, CMP, Mg, Phos
Stool studies: C Diff, O & P, Lactoferrin
Radiology: CT scan of abd/pelvis

Consult GI: for consideration of endoscopy
Clinically stable: NO REFLEX SEROIDS if GI evaluation within 24 hrs
Clinically unstable: Methylprednisolone 125 mg IV at time of admission
If fever/leukocytosis: consider adding antibiotics

If no response to high dose steroids – consideration for infliximab

Auto-immune Hepatitis



Auto-immune Hepatitis – Management

AST/ALT > 5 x ULN and/or tbili > 3 x ULN & patient stable Initiate work up:

Rule out progressive hepatic disease

ANA, SMA, hepatitis panel

Labs: CBCD, CMP, direct and indirect bilirubin, GGT

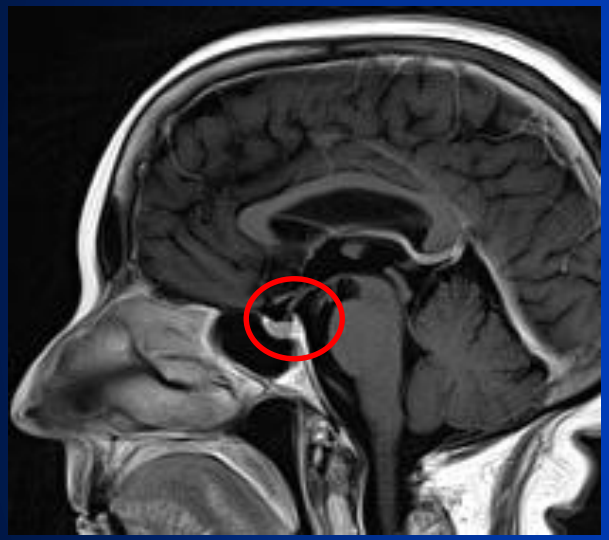
Monitor LFTs q 24 hrs.

If increasing trend in LFTs – consider admission

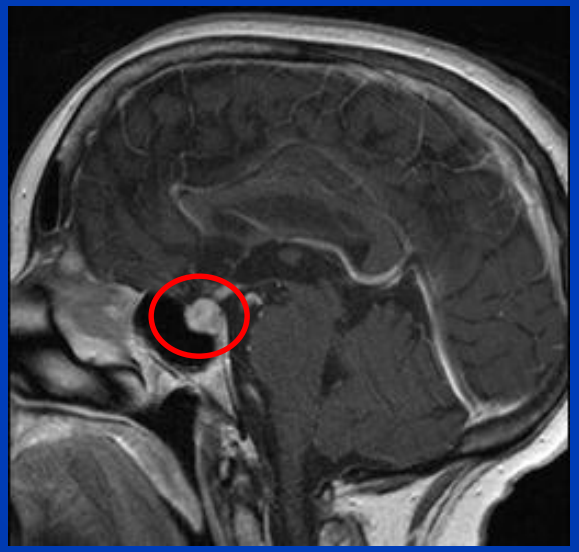
AST/ALT > 8 x ULN then admit and start steroids – Methylprednisolone 125 mg IV

If no response may need mycophenolate mofetil

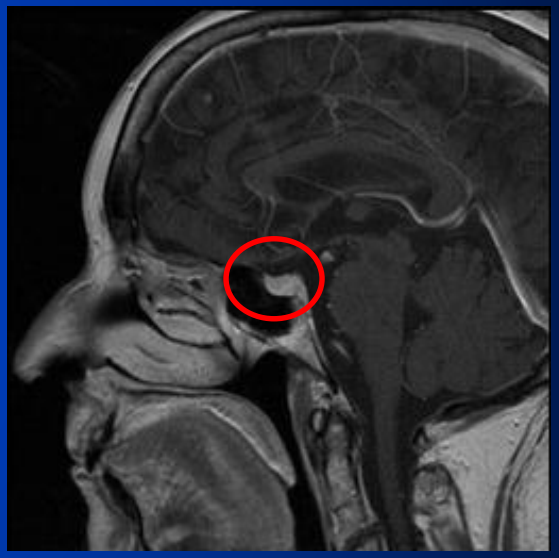
Autoimmune Hypophysitis



Pre- treatment



Post- treatment with anti-CTLA4 antibody



Post- treatment with steroids

Auto-immune Endocrinopathy

Median time of onset: 11 weeks from dose 1

Rule out Sepsis, Progression of CNS disease

Pituitary gland – Hypophysitis
New headache, visual field defects, diplopia, fever

Thyroid gland – Hypo/Hyperthroidism
Fatigue, weakness, asthenia

Adrenal gland – Hypoadrenalism
Fatigue, weakness, asthenia, nausea, hypotension

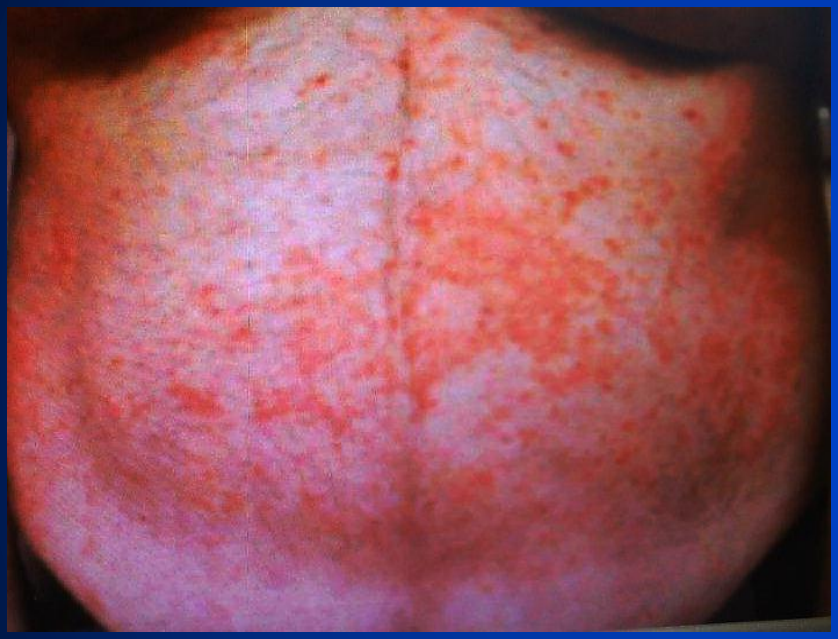
Auto-immune Endocrinopathy

Endocrine Labs:
TSH, free T4, T3
ACTH, AM cortisol
LH, FSH, testosterone, prolactin

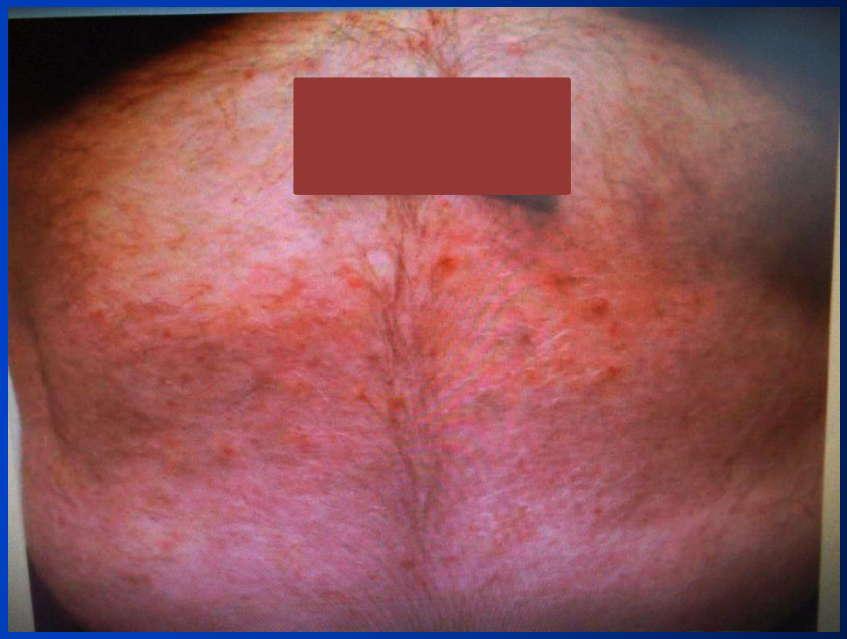
Radiology:
MRI of brain with pituitary cuts (with and without contrast)

Management:
Steroids – Initial methylprednisolone or dexamethasone
Replacement as needed

Auto-immune Dermatitis



Post anti-CTLA 4 antibody treatment



Post steroid treatment

Auto-immune Dermatitis

Median time of onset: As early as week 1
Clinical signs and symptoms: Rash, Pruritis

Management:

If < 10% of body – H1 blocker and OTC steroid preparation as needed

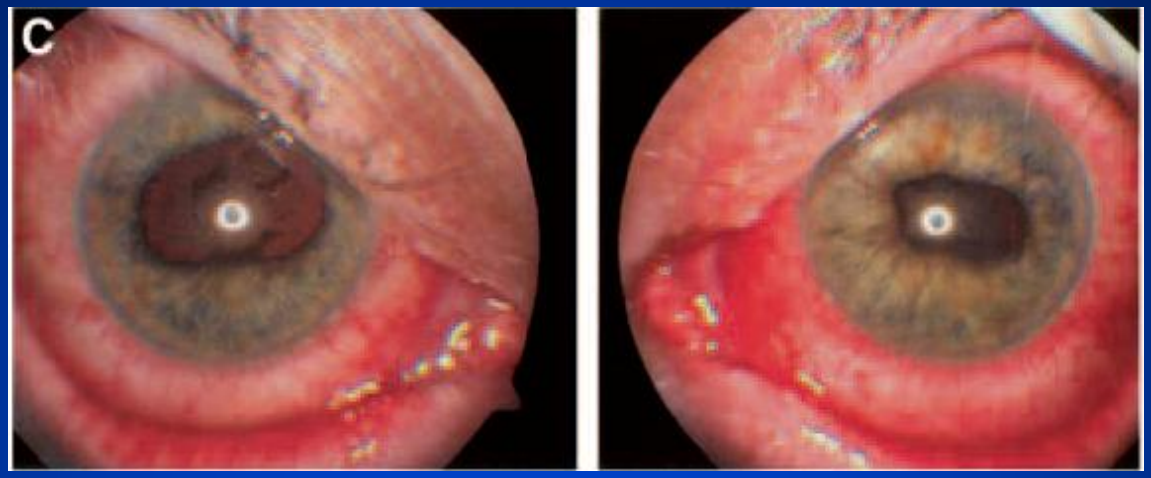
If 10-30% of body effecting ADLs – start H1 & H2 blockers, topical OTC steroid preparation, consider low dose steroids

If > 30% of body – high dose steroids

Immune AEs <1%

Other Immune-Mediated Adverse Reactions, Including Ocular Manifestations	
• Nephritis	• Uveitis
• Pneumonitis	• Iritis
• Meningitis	• Conjunctivitis
• Pericarditis	• Blepharitis
• Arthritis	• Episcleritis
• Autoimmune thyroiditis	• Scleritis
• Myocarditis	• Leukocytoclastic vasculitis
• Angiopathy	• Erythema multiforme
• Temporal arteritis	• Psoriasis
• Vasculitis	• Pancreatitis
• Polymyalgia rheumatica	• Hemolytic anemia

Autoimmune Uveitis



Steroids 1 week

Attia P et al. J Clin Oncol 2005;23:6044

Auto-immune Opthalmologic Toxicity

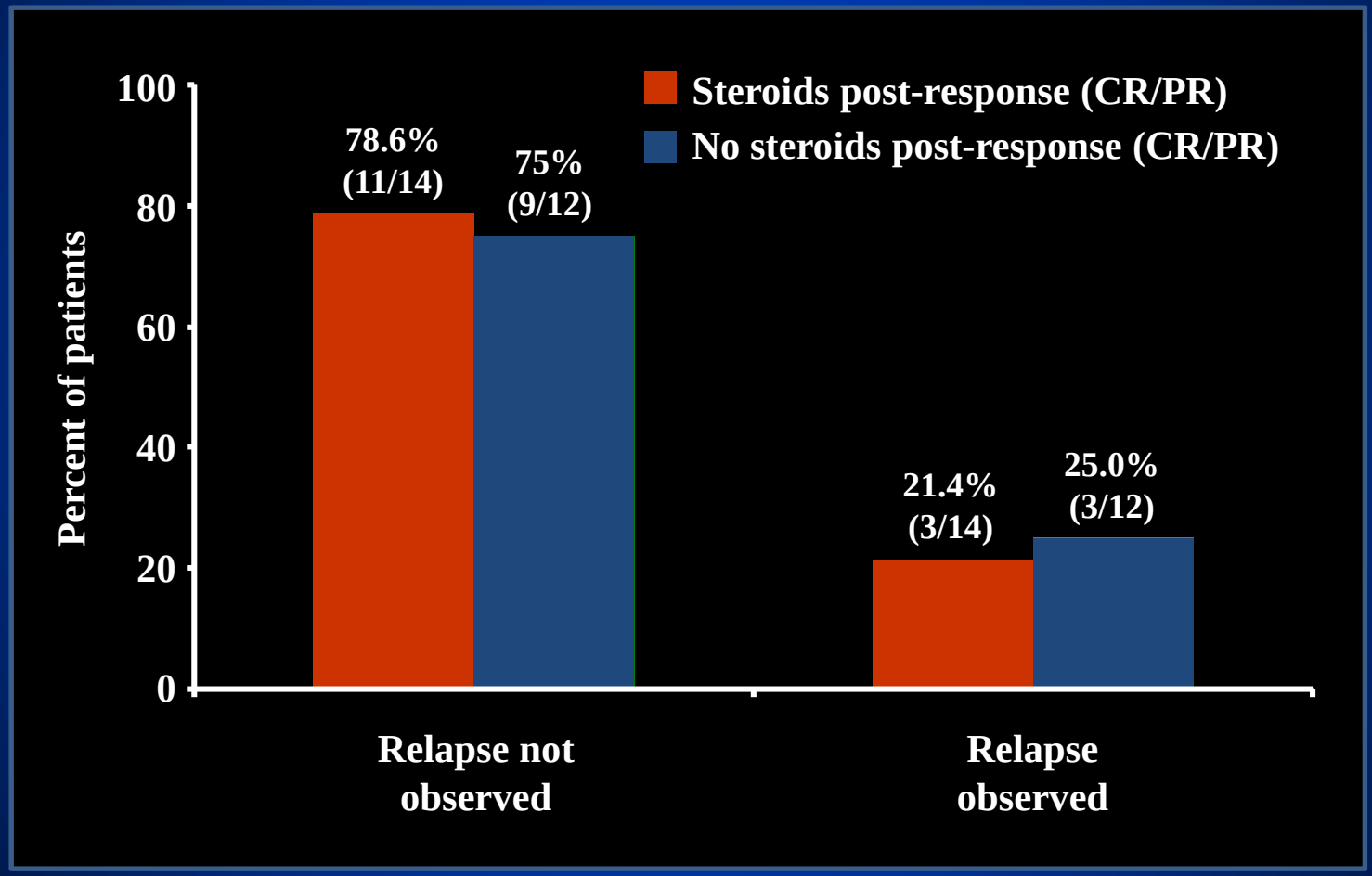
Manifestations: Blepharitis, Iritis, Conjunctivitis, Uveitis

Clinical signs and symptoms: Blurred vision, Diplopia, Loss of vision

Management:

Suspected Uveitis
Urgent Opthalmology consultation
If severe may need initiation of iv steroids in addition to high strength topical preparation.

Does steroid use decrease anti-tumor efficacy?



Amin A et al. ASCO 2009. Abstr 9037

Pooled Analysis of Long-term Survival Data From Phase II and Phase III Trials of Ipilimumab in Metastatic or Locally Advanced, Unresectable Melanoma

Schadendorf D, Hodi FS, Robert C, Weber JS, Margolin K, Hamid O, Chen TT, Berman DM, Wolchok JD

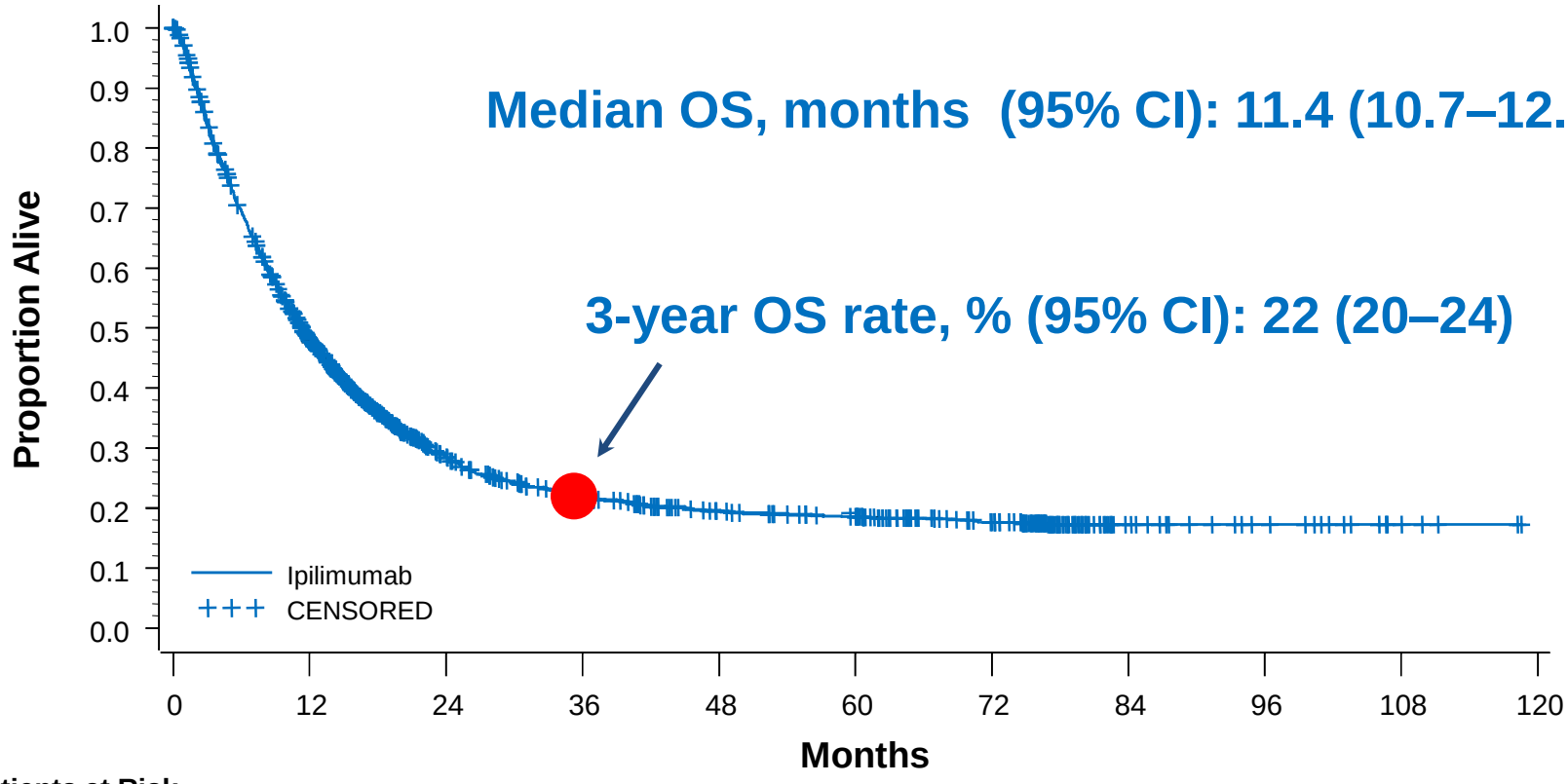
ECCO 2013.Abstract Number 24LBA

Studies Included in OS Analyses*

Study ID	Phase	N	Population	Dose	Retreatment or Maintenance
MDX010-20	3	540	Previously treated	3 mg/kg ± gp100	Retreatment
CA184-024	3	250	Treatment-naive	10 mg/kg + DTIC	Maintenance
CA184-022	2	217	Previously treated	0.3, 3, 10 mg/kg	Maintenance
CA184-008	2	155	Previously treated	10 mg/kg	Maintenance
CA184-007	2	115	Treatment-naive or previously treated	10 mg/kg ± budesonide	Maintenance
CA184-004	2	82	Treatment-naive or previously treated	3, 10 mg/kg	Maintenance
CA184-042	2	72	Melanoma with brain metastases	10 mg/kg	Maintenance
NCI04C0083	1/2	88	Previously treated	3, 5, 9 mg/kg ± gp100	Not included
NCI02C0106	1/2	56	Previously treated	3 mg/kg + gp100 3 → 1 mg/kg + gp100	Not included
NCI03C0109	1/2	36	Previously treated	0.1, 0.3, 1, 2, 3 mg/kg + IL-2	Not included
CA184-338	Observational	160	Treatment-naive	3 mg/kg	No (induction only)
CA184-332	Observational	90	Treatment-naive	3 mg/kg	No (induction only)
CA184-045**	Expanded Access Program (EAP)	2985	Previously treated	3, 10 mg/kg	Maintenance for 10 mg/kg

*Total of 1861 patients for primary analysis; N=4846 patients including EAP. **US EAP treatment protocol.

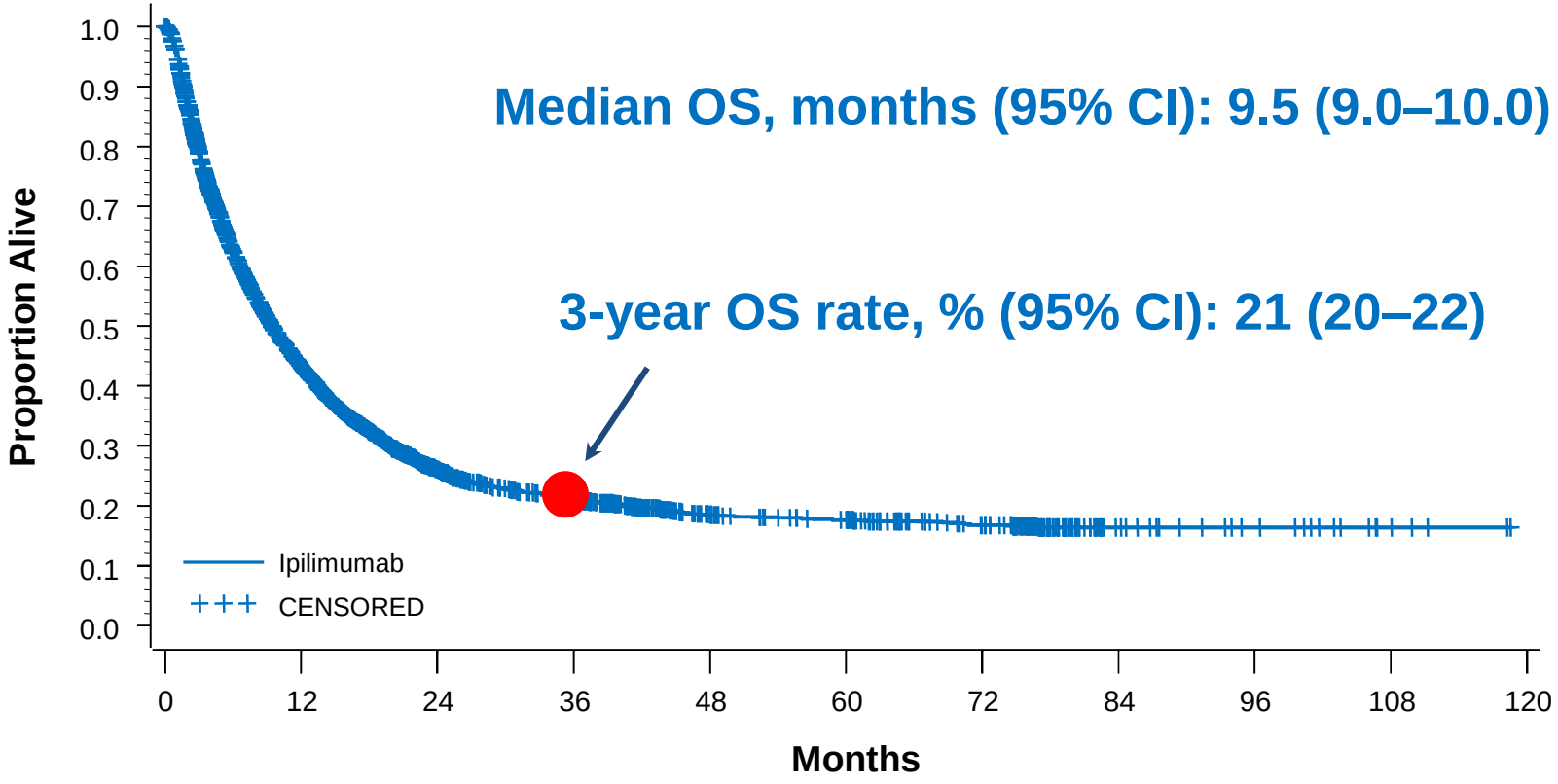
Primary Analysis of Pooled OS Data: 1861 Patients



Patients at Risk

Ipilimumab	1861	839	370	254	192	170	120	26	15	5	0

Pooled OS Analysis Including EAP Data: 4846 Patients



Patients at Risk

Ipilimumab	4846	1786	612	392	200	170	120	26	15	5	0

Conclusions

- Ipilimumab monotherapy improves overall survival in advanced melanoma
- Immune mediated toxicities require close vigilance and are reversible with early appropriate intervention
- Questions ?
  - Best dose and schedule – 3mg vs 10mg
  - Sequential vs combination with PD-1 inhibition
  - Optimal sequence
  - Maintenance vs no maintenance
  - Combination with other agents