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Adjuvant Therapy for Melanoma and Practical Considerations for Immunotherapy

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Adjuvant Therapy for Melanoma

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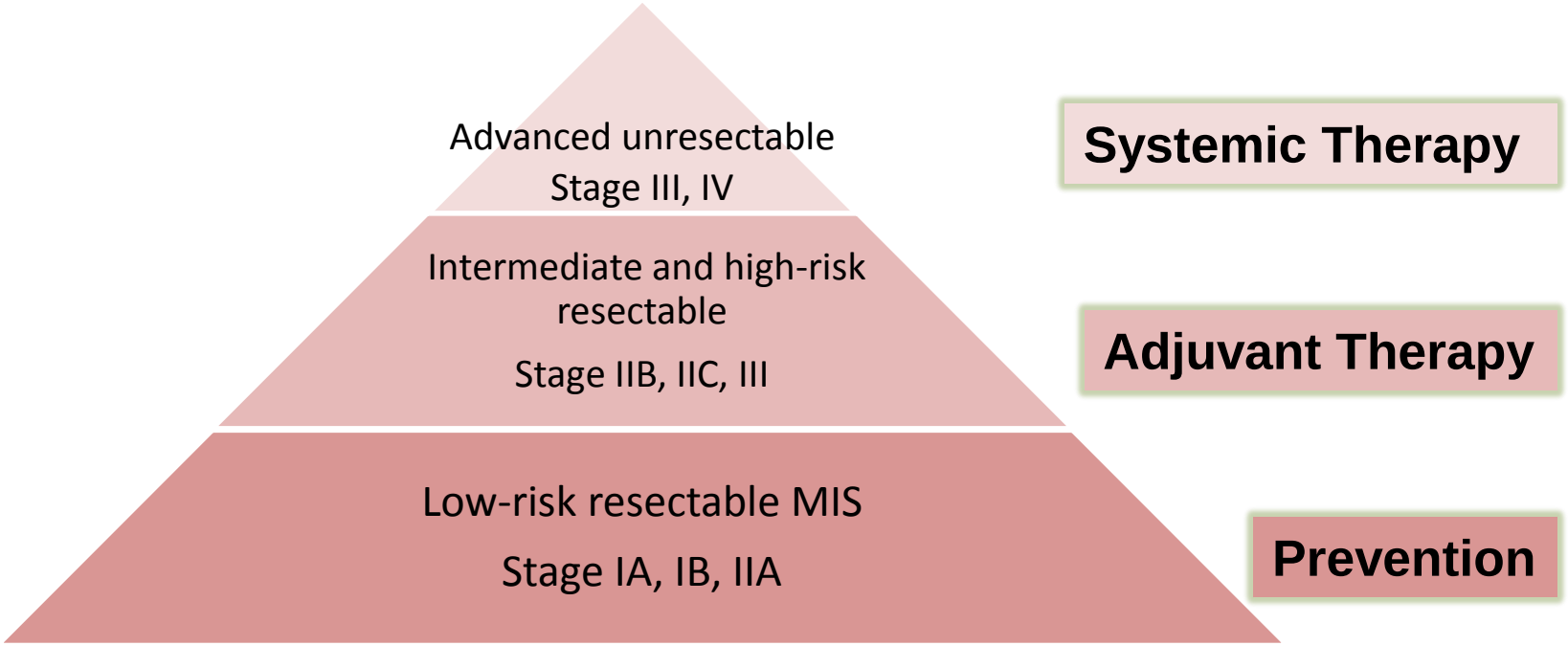
Distribution of Melanoma Burden by Stage



The burden of high-risk disease dwarfs that of advanced melanoma and is an important clinical problem.

Adjuvant Therapy

- The Old
  - Interferon
- The New
  - Ipilimumab
- The Future

Adjuvant IFN-α Regimens

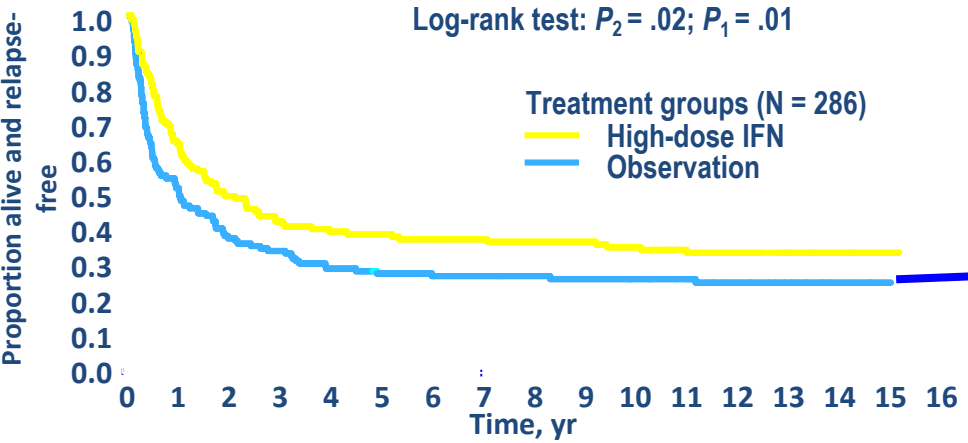
Schedule	Dose	Frequency	Duration
Low Dose			
	3 MIU	3 x weekly	18 – 24 months
Intermediate Dose			
Induction	10 MIU	5 x weekly	4 weeks
Maintenance	10 MIU	3 x weekly	12 -24 months
	5 MIU	3 x weekly	24 months
High Dose			
Induction	20 MIU/m^2	5 x weekly	4 weeks
Maintenance	10 MIU/m^2	3 x weekly	11 months
Short Course			
Induction X 1	20 MIU/m^2	5 x weekly	4 weeks
Intermittent			
Induction X 3	20 MIU/m^2	20 MIU/m^2	5 x weekly for 4 weeks Q 4 months

Interferon Trials Leading To Regulatory Approval

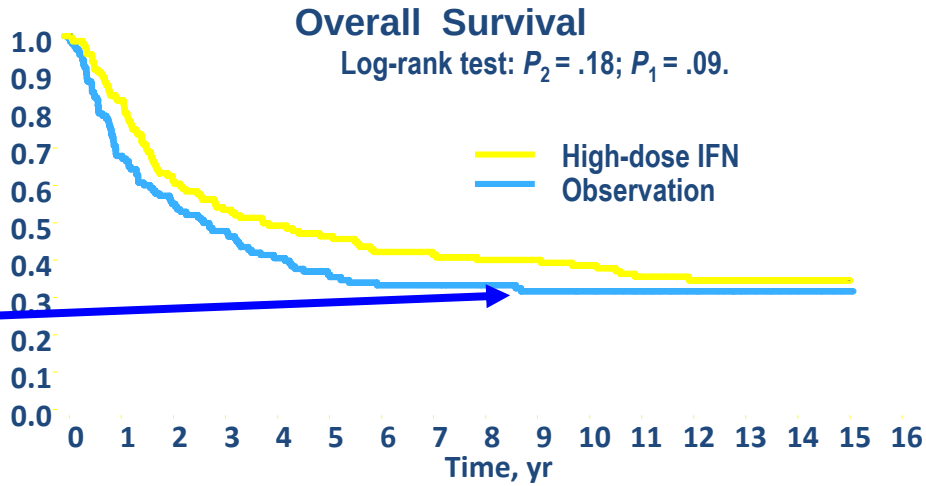
Study/PI	Stage	N	Treatment agent/ dosage/duration	Median Follow up (yr)	Impact on		Comment
					RFS	OS	
E1684	T4, N+	**287**	**IFNα2b 20 MU/m2/D IV for 1 month. Then, 10 MU/m2 SC TIW for 11 months vs. Observation**	**6.9**	**0.61; p=.001**	**0.67; p=.01**	**LMN staging . Recurrent nodes 64%. Greatest benefit microscopic nodal disease. Competing causes of death at 12.6yrs FU.**
				12.6	**0.72; p=.02**	**0.82; p=.18**	
E1690	T4, N+	**642**	**IFNα2b 20 MU/m2/D IV for 1 month. Then, 10 MU/m2 SC TIW for 11 months vs. 3 MU/D given SC TIW for 2 years vs. Observation**	**4.3**	**0.78; p=.05**	**1.0**	**51% nodal recurrent. Cross over of obs pts to HDI at relapse (n=38 pts). 17 pts in obs arm received HDI for nodal relapse.**
				6.6	**0.81; p=0.09**	**1.0**	
E1694	T4, N+	**880**	**IFNα2b 20 MU/m2/D IV for 1 month. Then 10 MU/m2 SC TIW for 11 months vs. GMK vaccine for 96 wks**	**1.3**	**0.67; p=.0004**	**0.72; p=.023**	**Early closure for vaccine futility at 2 yrs. Benefit greatest in node -ve.**
				2.1	**0.75; p=.006**	**0.76; p=.04**	
EORTC 18991	N1-2	**1256**	**PegIFNα2b given SC at 6 µg/kg/week (8 weeks) then 3 µg/kg/week (5 years) vs. Observation**	**3.8**	**0.82; P=.011**	**0.98**	**Impact on RFS, DMFS and OS in ulcerated tumour & 1 microscopic node. No benefit if not ulcerated.**
				7.6	**0.87; P=0.055**	**.96**	

ASCO 2016

E1684: Updated Efficacy (ITT at 12.6 yr Median Follow-up)



	Total	Dead or relapsed	Alive or relapsed-free	Median
Observation	140	106	34	1.0
High-dose IFN	146	95	51	1.7

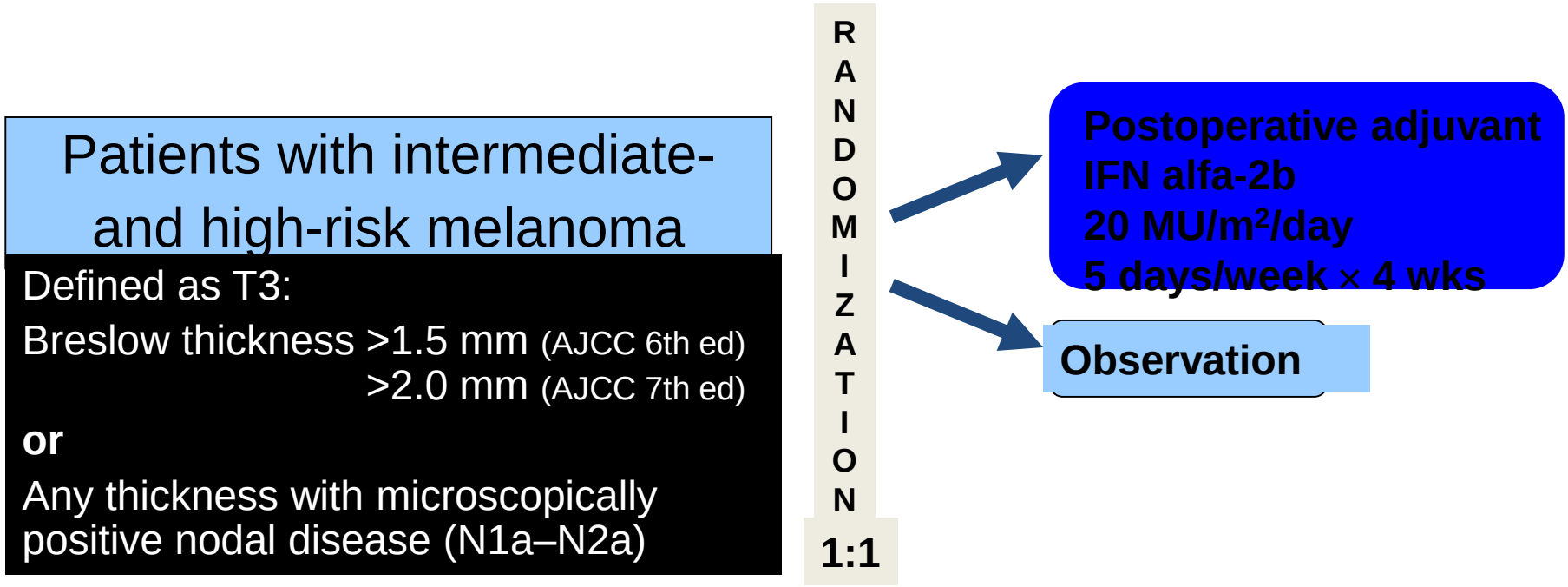


	Total	Dead	Alive	Median
Observation	140	95	45	2.7
High-dose IFN	146	93	53	3.8

Tweaking Interferon

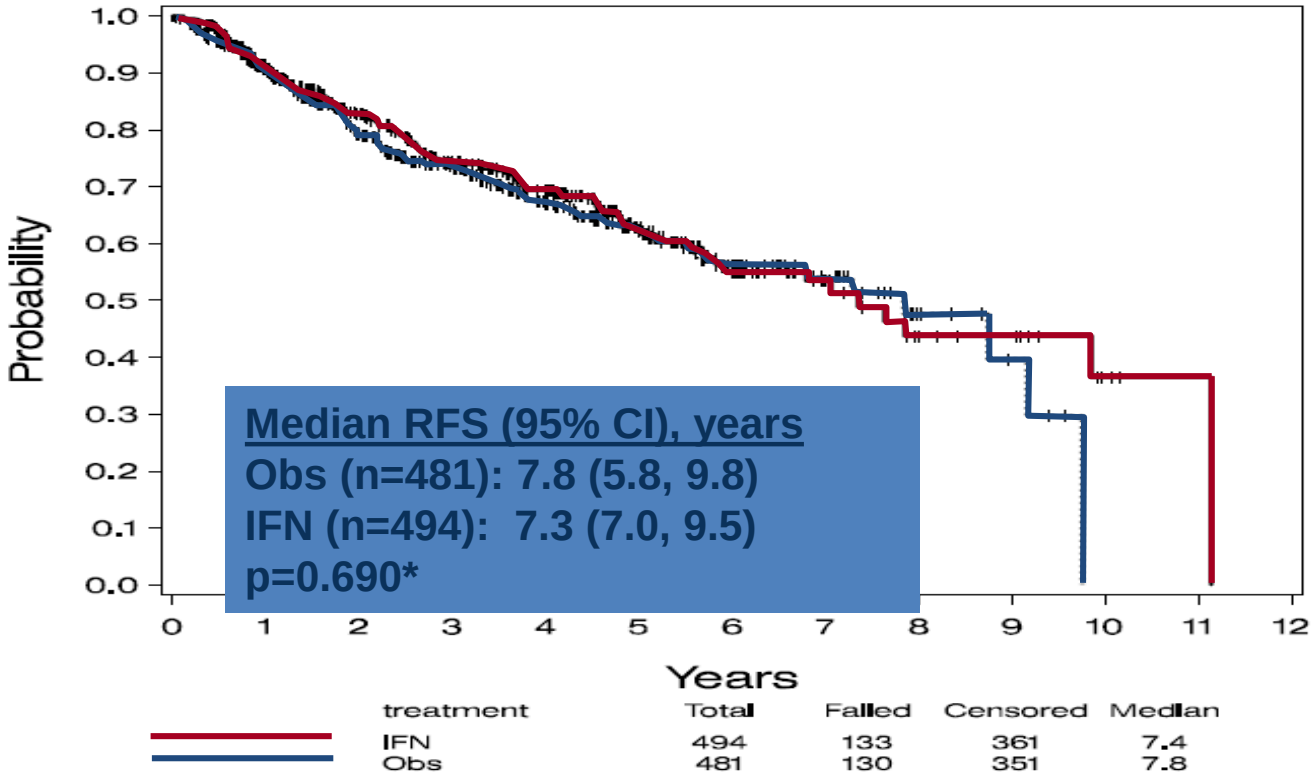
- Lower the dose
- Shorten the duration of HDI – high dose IV only
- Use pegylated IFN – once weekly dosing, lower dose with comparable AUC

Study design: ECOG 1697



Agarwala SS, et al. *JCO*. January 2017

Relapse-free survival (n=975)



*Stratified log-rank test

Agarwala SS, et al. *JCO*. January 2017

Adjuvant Therapy

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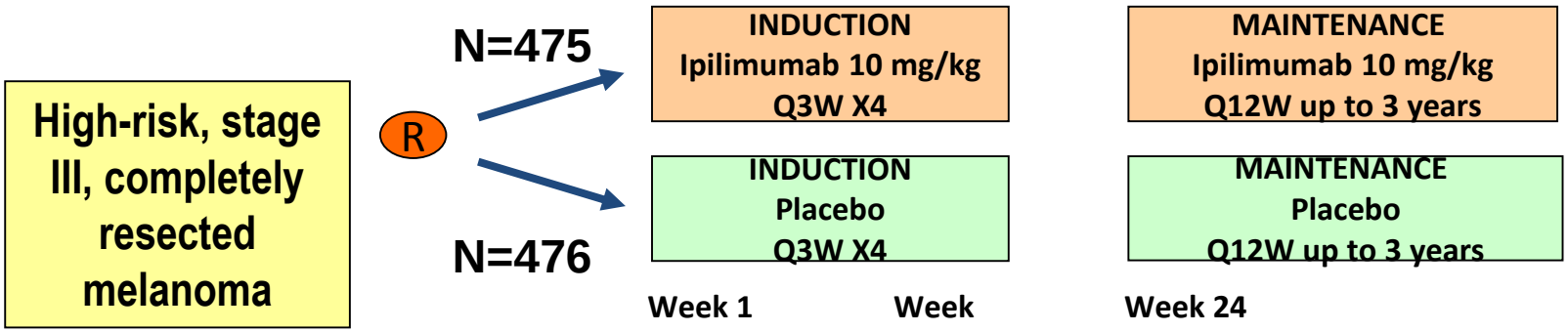
Ipilimumab (HD) vs Placebo
EORTC 18071/CA184-029: Study Design



Treatment up to a maximum 3 years, or until disease progression, intolerable toxicity, or withdrawal

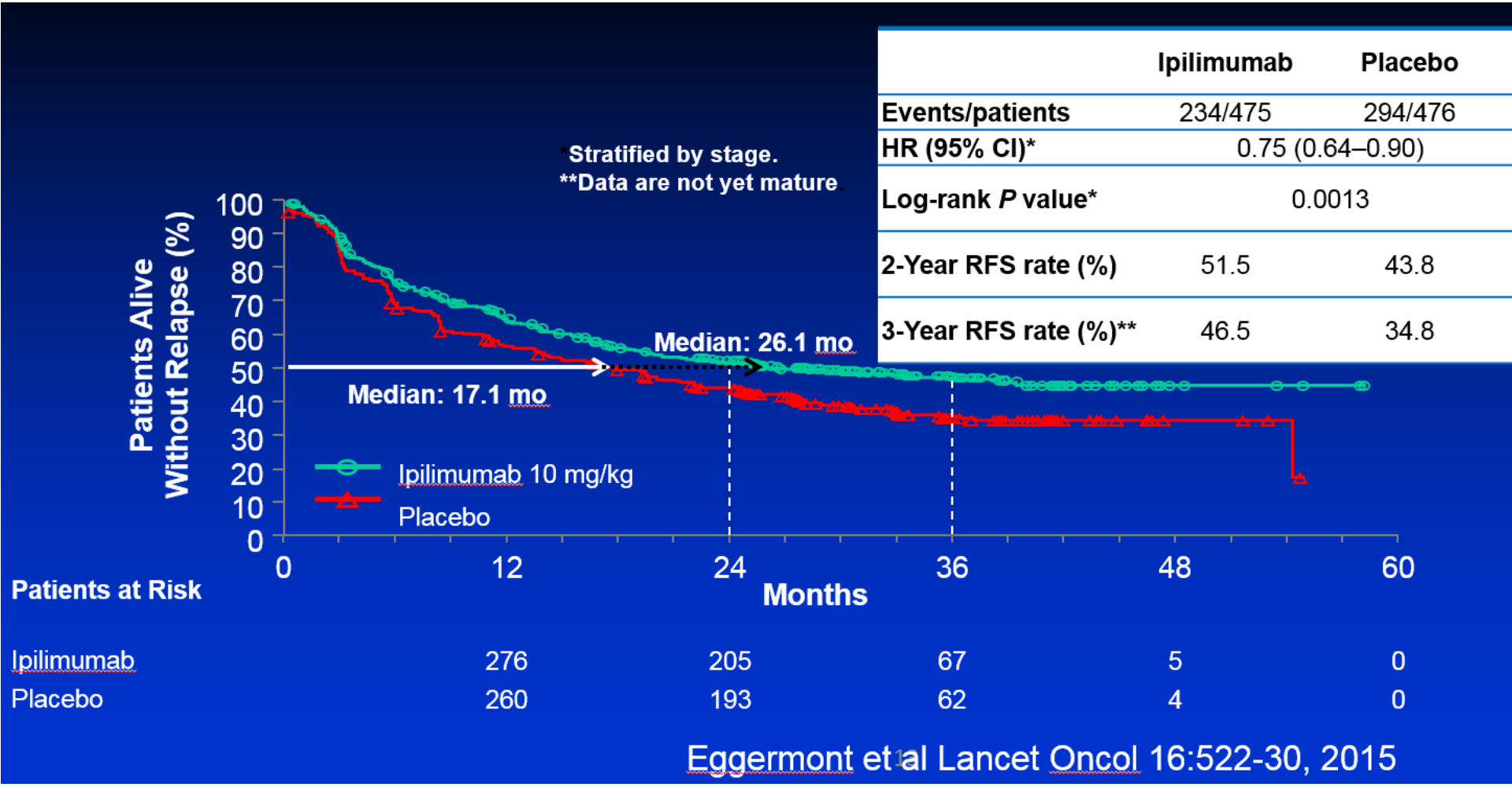
Stratification factors:

- Stage (IIIA vs IIIB vs IIIC 1-3 positive lymph nodes vs IIIC ≥4 positive lymph nodes)
- Regions (North America, European countries and Australia)

Eggermont, et al. *Lancet Oncol.* 2015;16:522-30.

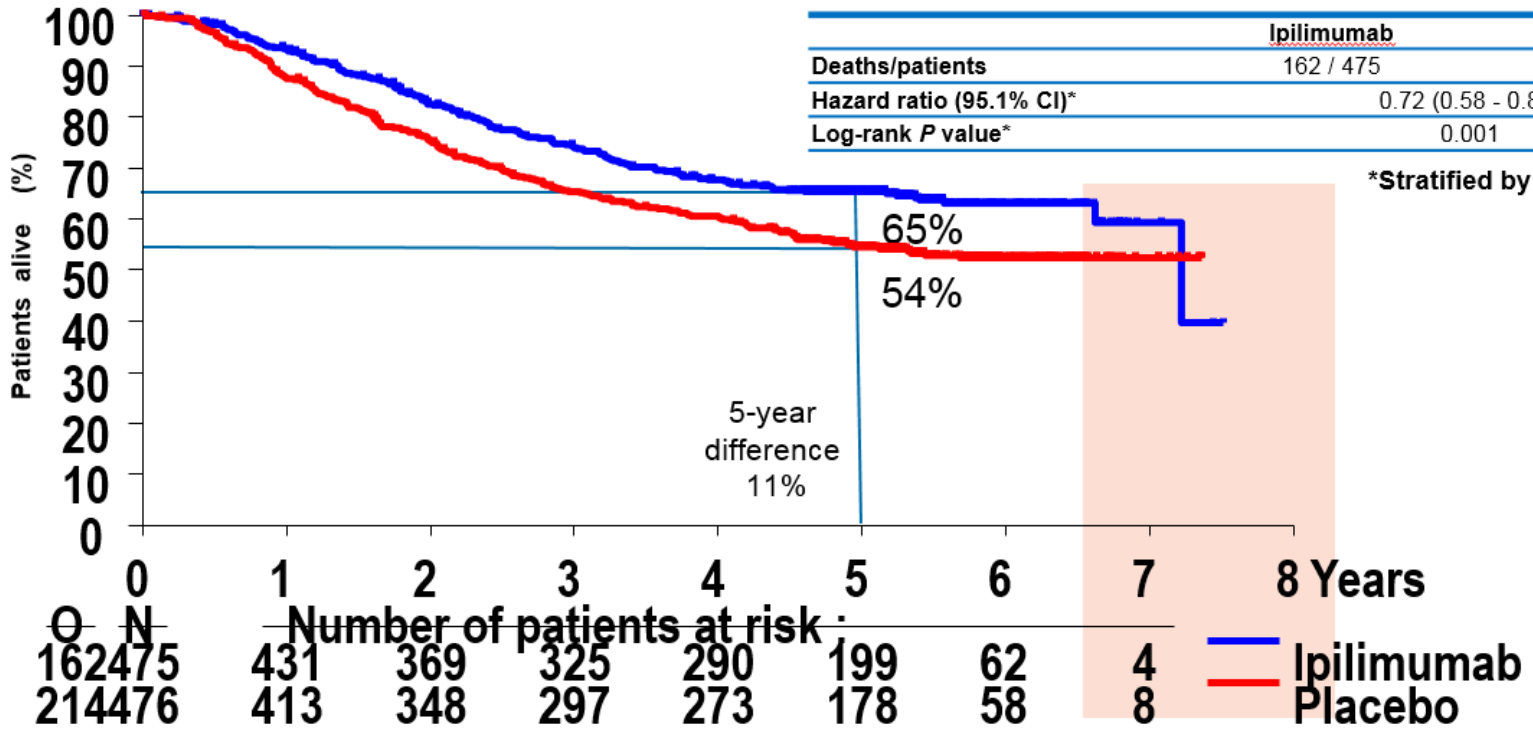
Primary Endpoint: Recurrence-free Survival (IRC)

	Ipilimumab	Placebo
Events/patients	234/475	294/476
HR (95% CI)*	0.75 (0.64–0.90)	
Log-rank *P* value*	0.0013	
2-Year RFS rate (%)	51.5	43.8
3-Year RFS rate (%)**	46.5	34.8



Eggermont et al Lancet Oncol 16:522-30, 2015

EORTC 18071: Overall Survival



	Ipilimumab	Placebo
Deaths/patients	162 / 475	214 / 476
Hazard ratio (95.1% CI)*	0.72 (0.58 - 0.88)	
Log-rank *P* value*	0.001	

*Stratified by stage at randomization

CI = confidence interval; NR = not reached.

Eggermont AMM et al NEJM 2016

Safety Summary

	Ipilimumab (n = 471)		Placebo (n = 474)	
	Any Grade	Grade 3/4	Any grade	Grade 3/4
Any AE, %	**98.7**	**54.1**	**91.1**	**26.2**
Treatment-related AE, %	**94.1**	**45.4**	**59.9**	**4.0**
Treatment-related AE discontinuation, %	**48.0**	**32.9**	**1.5**	**0.6**
Any immune-related AE, %	**90.4**	**41.6**	**39.7**	**2.7**

- No new deaths due to drug-related AEs compared with the primary analysis
  - 5 patients (1.1%) in the ipilimumab group
    - 3 patients with colitis (2 with gastrointestinal perforations)
    - 1 patient with myocarditis
    - 1 patient had multiorgan failure with Guillain-Barré syndrome
  - No deaths related to study drug in the placebo group

E1609 Phase III Ipilimumab vs IFN

Patients with resectable stage IIIB or IIIC or IV (M1a or M1b)

N=1500 +

A N D O M I Z

- **Ipilimumab 10mg/kg**
- **Ipilimumab 3mg/kg**
- **High dose interferon**

Primary Endpoint: RFS, OS
Secondary Endpoints: Safety, Quality of life, immunologic correlates of RFS, OS
Completed accrual: 8/2014- Results anticipated: 2018

Clinicaltrials.gov

Adjuvant Therapy

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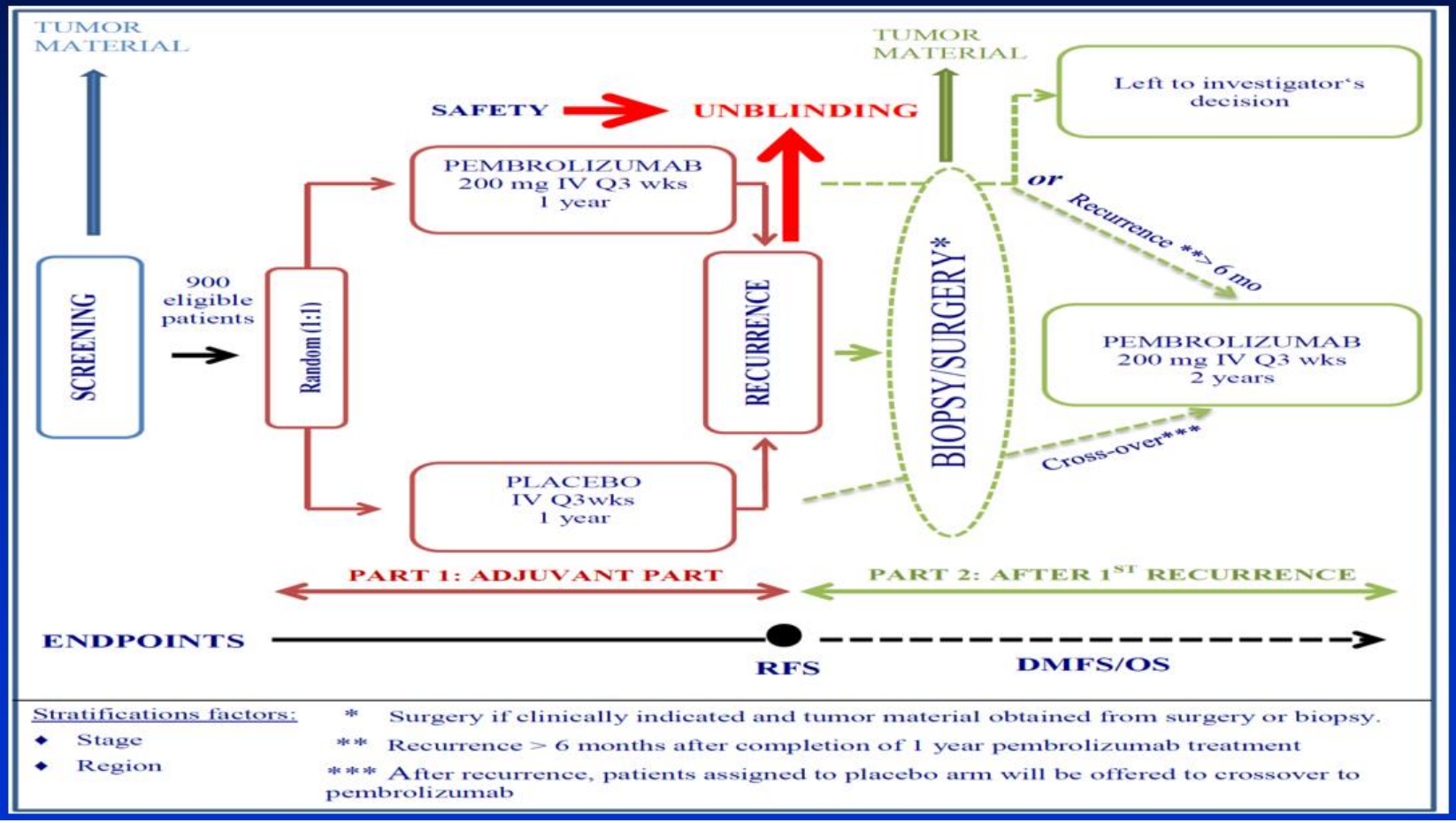
PD1 Pathway Inhibitor Trials

Study	N	TNM Stage	Therapy	Dose and Schedule – Treatment Arm	Primary Endpoint
CheckMate 238*	800	IIIB, IIIC, IV	Nivolumab Vs. Ipilimumab	Nivo 3 mg/kg IV v Ipilimumab 10 mg/kg	**RFS**
KEYNOTE-054	900	IIIA [> 1 mm met], IIIB, IIIC	Pembrolizumab Vs. Placebo	Pembrolizumab 200 mg IV on q 3 w33kw for up to 1 year	**RFS, RFS in PDL1+**
S1404	1378	IIIA(N2) IIIB, C, IV	Pembrolizumab Vs. HD IFN or HD Ipi	Pembro 200 mg IV Q3 wks x 1 yr vs HD IFN regimen or ipi 10 mg/kg	**RFS, OS in all and PDL1+**

* Completed accrual 10/15

EORTC 1325/ KEYNOTE 054

Is adjuvant therapy more effective than treatment in the metastatic setting?



Ongoing Adjuvant Trials Using MAP-K targeted Therapy

Study	No of Pts	TNM Stage	Therapy	Dose and Schedule – Treatment Arm	Primary Endpoint
COMBI-AD	852	III (BRAF V600E/K)	Dabrafenib + Trametinib Vs. Placebo	Dabrafenib (150 mg twice daily) and trametinib (2 mg once daily) orally for 12 months	**RFS**
BRIM 8	725	IIC, III (BRAF V600; Cobas)	Vemurafenib Vs. Placebo	Vemurafenib 960 mg orally twice daily for 52 weeks	**RFS**

Adjuvant Therapy Summary

- IFN is still a standard option for many patients.
- Ipilimumab (high dose) is also an option
  - but no data comparing it to IFN
  - High toxicity (is it justifiable in the adjuvant setting?
- Should we await data for adjuvant anti PD-1?
- BRAF targeted adjuvant therapy for BRAF+ patients?

Practical Considerations for Immunotherapy

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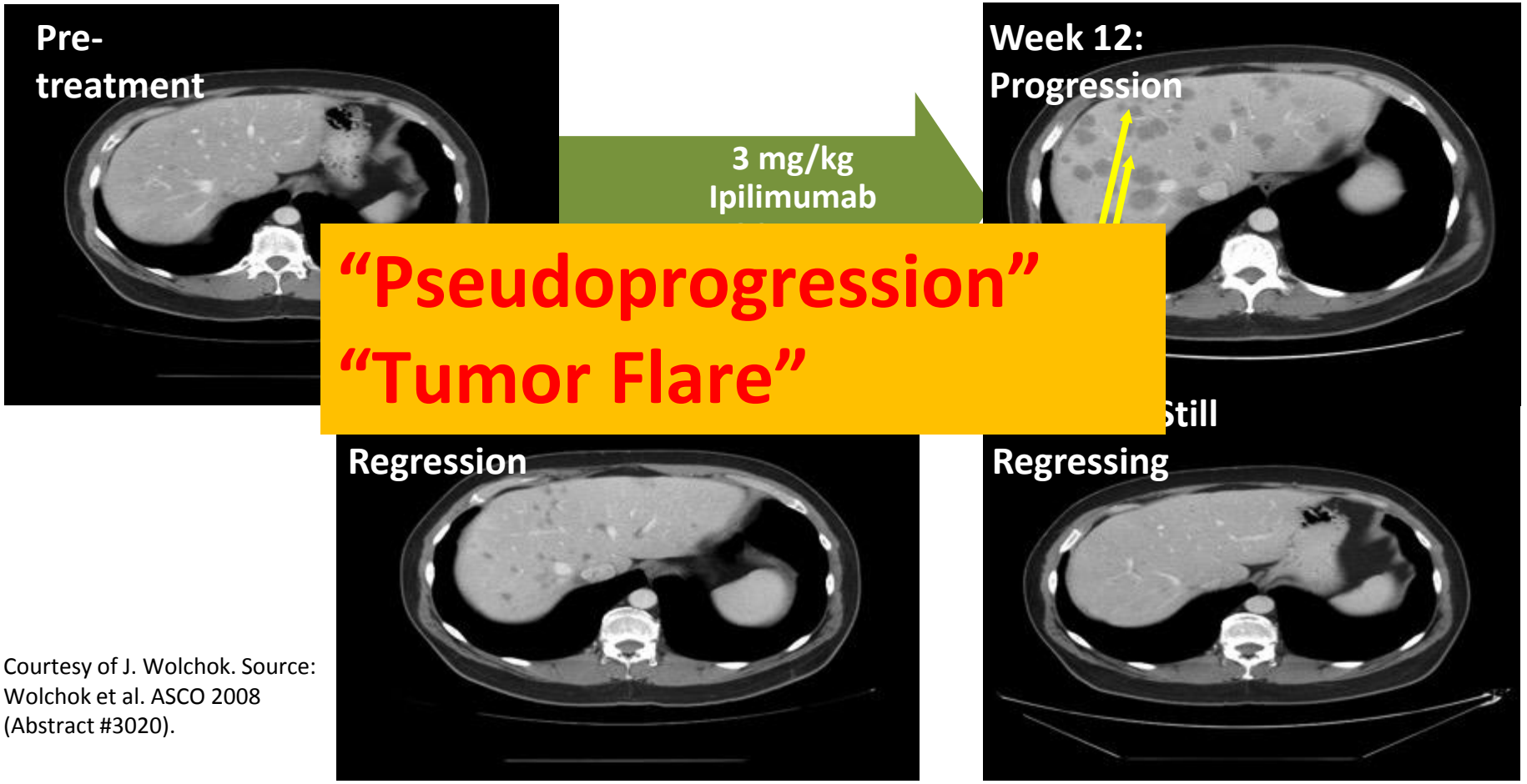
Unique Practical Aspects of Immunotherapy

- Response Assessment
  - Unique response patterns
  - Timing of imaging
- Toxicity Recognition and Management

Immune-Related Patterns of Response with anti-CTLA4:

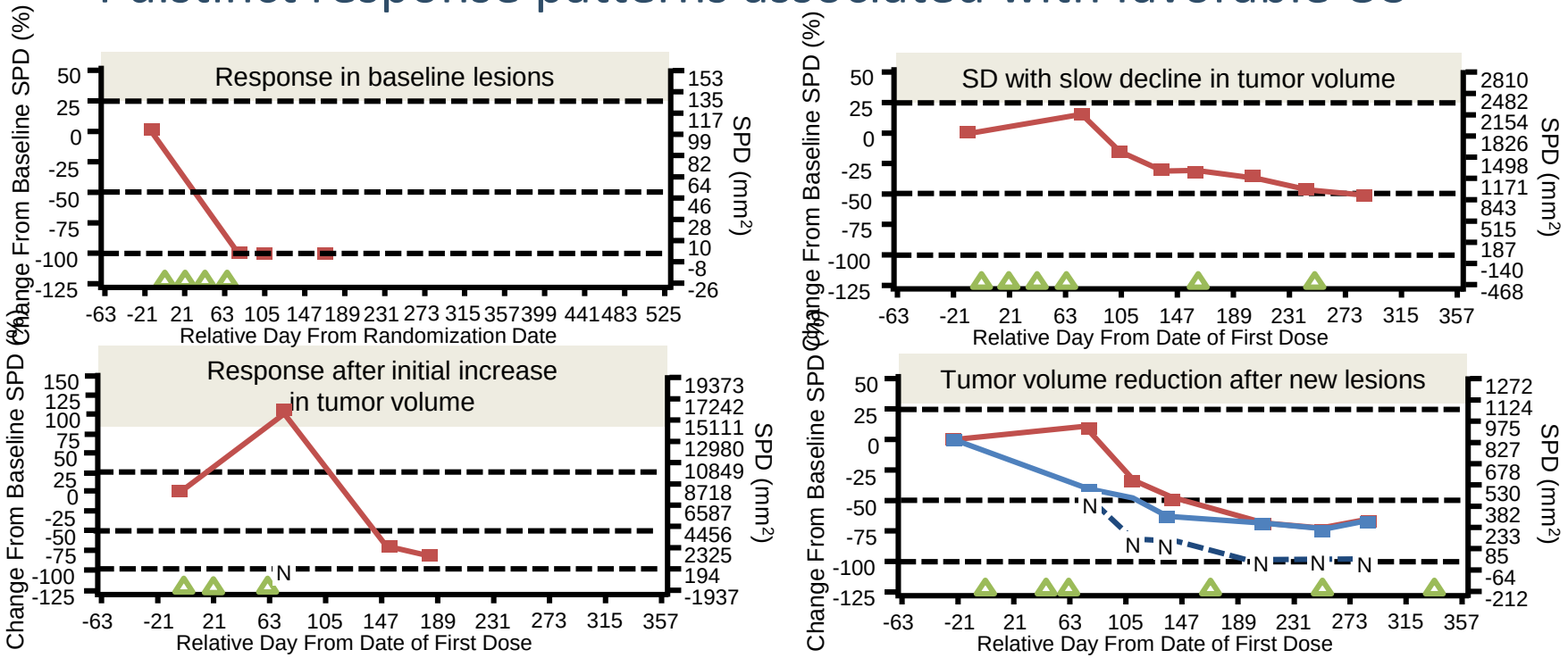
Melanoma Response After the Appearance and Subsequent Disappearance of New Lesions



Courtesy of J. Wolchok. Source: Wolchok et al. ASCO 2008 (Abstract #3020).

Ipilimumab Heterogeneous Response Patterns

- 4 distinct response patterns associated with favorable OS



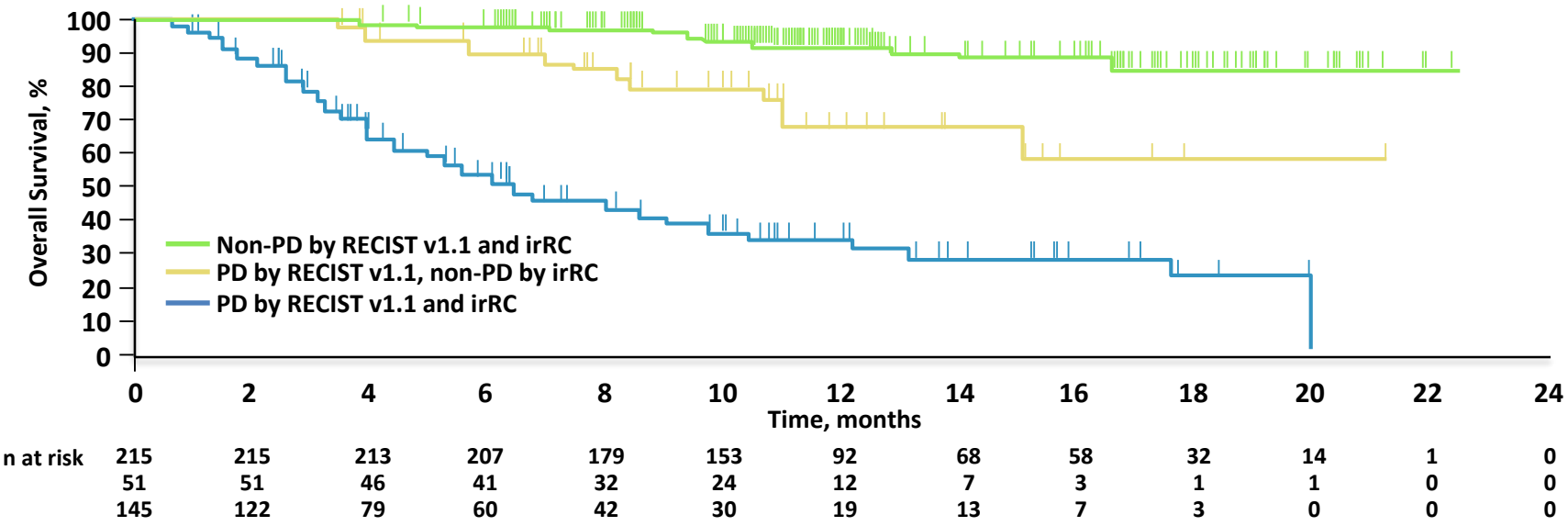
Wolchok JD, et al. *Clin Cancer Res*. 2009;15:7412-7420.

Response Assessment: RECIST vs. irRC

Category	RECIST v1.1[1]	mWHO[2]	irRC[3]
Measurement: tumor burden	• **Unidimensional:** Sum Longest Diameter	• **Bidimensional:** Sum Product Diameter (SPD)	• **Bidimensional:** SPD
Complete Response (CR)	• Disappearance of all target and non-target lesions • Confirmation required: two consecutive observations no less than 4 weeks apart		
Partial Response (PR)	• **≥ 30% ↓** in tumor burden compared to baseline • Confirmation required	• **≥ 50% ↓** in tumor burden compared to baseline • Confirmation required	• **≥ 50% ↓** in tumor burden compared to baseline† • Confirmation required
Progressive Disease (PD)	• **≥ 20% + 5 mm absolute ↑** in tumor burden compared to nadir • **New lesion** • **No confirmation required**	• **≥ 25% ↑** in tumor burden compared to nadir • **New lesion** • **No confirmation required**	• **≥ 25% ↑** in tumor burden compared to baseline, nadir, or reset baseline† • **New lesions added to tumor burden** • **Confirmation required**
Stable Disease	• Neither PR nor PD		

1. Eisenhauer EA, et al. *Eur J Cancer.* 2009;45(2):228-247.
2. Miller AB, et al. *Cancer.* 1981;47:207-14.
3. Wolchok JD, et al. *Clin Cancer Res.* 2009;15(23):7412-20.

Association of Overall Survival With Tumor Response



- Of the 196 patients with PD by RECIST v1.1, the 51 patients (26%) with non-PD by irRC had favorable OS compared with the 145 patients with PD by both criteria.
- A landmark analysis showed similar results.

Immune Checkpoint Blockade

Key Points About Evaluating Activity

- Antitumor activity may appear to be delayed compared to response times associated with cytotoxic therapies; **imaging every 12 weeks.**
- Patients may experience response after the appearance of progressive disease.
- Development of progressive disease should be confirmed prior to discontinuation of therapy.
- Development of small lesions in the presence of other responsive lesions may be clinically insignificant.
- Durable stable disease may be indicative of response.

Agarwala SS. *Semin Oncol*. 2015.

Unique Practical Aspects of Immunotherapy

- Response Assessment
  - Unique response patterns
  - Timing of imaging

- Toxicity Recognition and Management

Select Immune-related Adverse Reactions

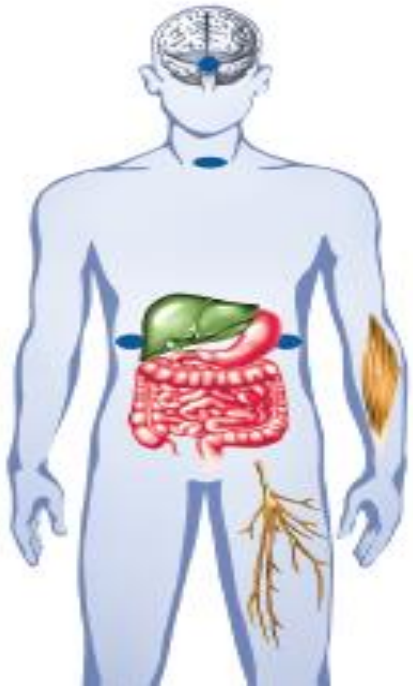
hypophysitis

thyroiditis

adrenal insufficiency

enterocolitis

dermatitis



pneumonitis

hepatitis

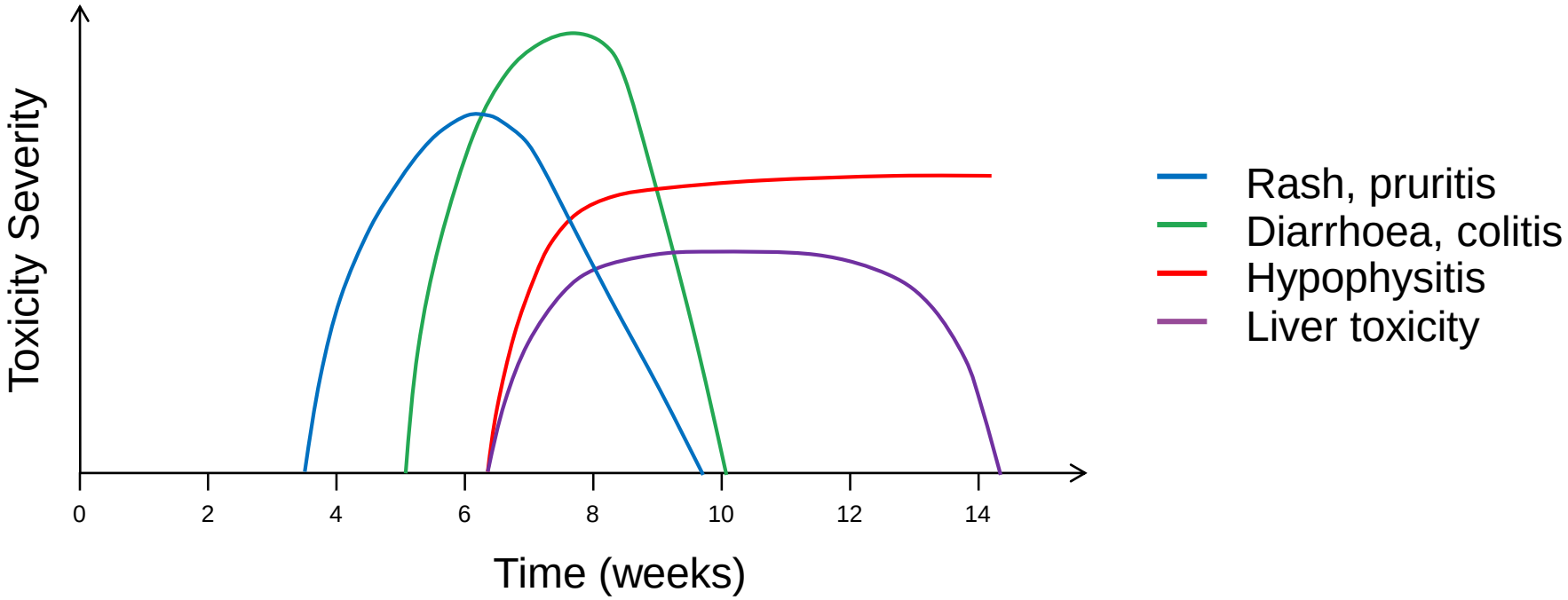
pancreatitis

motor & sensory neuropathies

arthritis

Ipilimumab adverse reaction management guide.

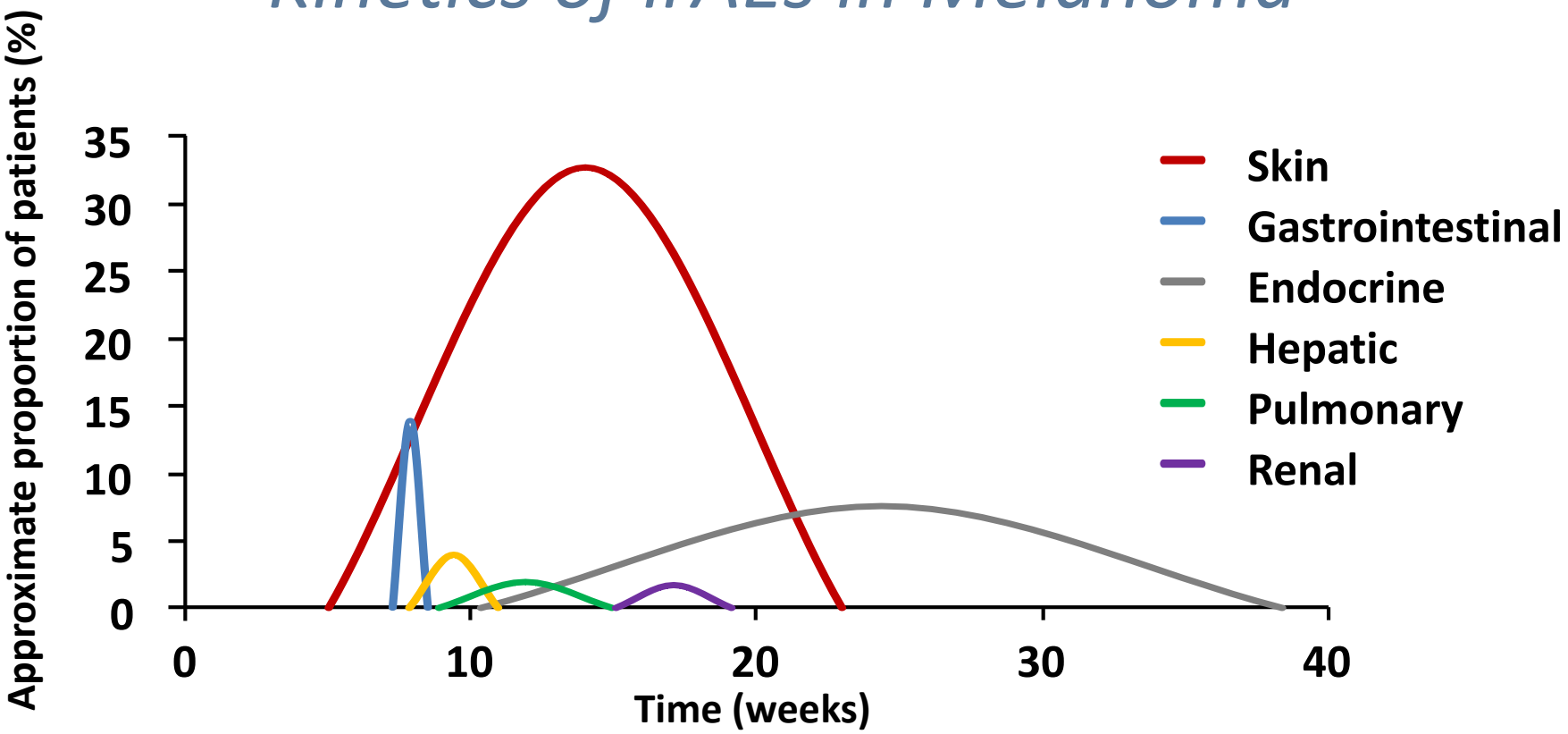
Timing of Immune-related AEs



Adapted from: Weber, et al. *J Clin Oncol.* 2012; 30:2691-2697; Weber, et al. *J Clin Oncol.* 2015.

PD-1 Blockade With Nivolumab

Kinetics of irAEs in Melanoma



Weber JS, et al. *ASCO*. 2015.

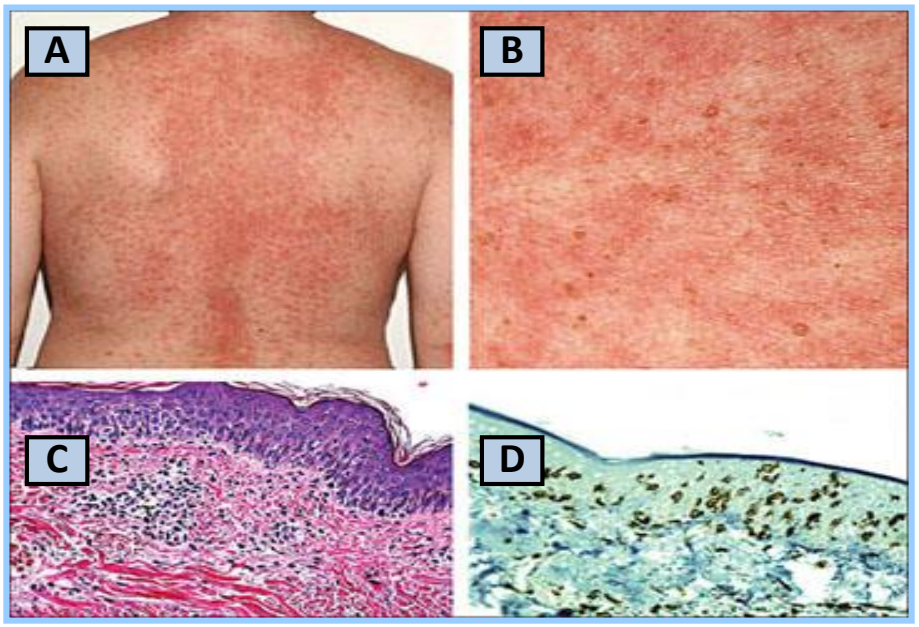
Management of irAEs Overview

- Responsibility of all healthcare providers
- Early reporting by patients with close monitoring, and early intervention by health care providers
- Provide thorough and continuous patient education about the signs and symptoms of irAEs
- Assess for signs and symptoms of irAEs before each cycle of immunotherapy
- Know management algorithm specific to each irAE
  - Safety profiles of immunosuppressants
- Monitor and manage toxicities of immunosuppressants
  - Hyperglycemia and diabetes
  - Opportunistic infection

Immunotherapy-Associated Dermatitis

Back:

Confluent red rash



Back:

Papular lesions (Close up)

Right upper arm:

Vacuolar changes (magnification x20)

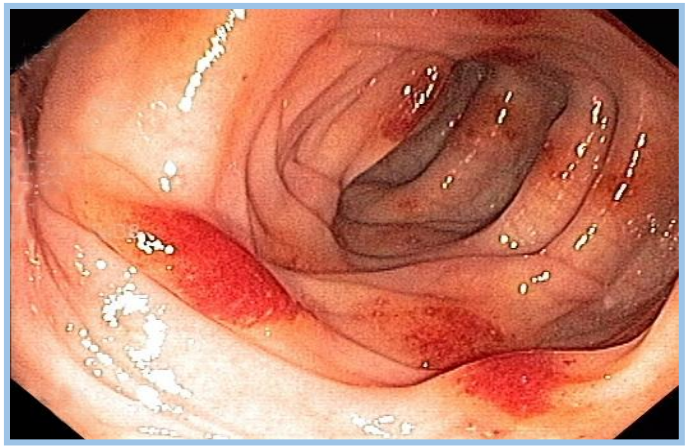
Anti-CD8 staining:

Extensive epidermal exocytosis (magnification x20)

Jaber SH, et al. *Arch Dermatol*. 2006.

Colitis and Enteritis

- Colonoscopy
  - Multifocal circumscribed erythematous lesions
- Histopathology
  - Predominantly chronic inflammation
  - Eosinophils and focal active cryptitis



Management of Gastrointestinal AEs

Grade	No Colostomy	Colostomy
1	Increase of <4 stools per day (over baseline)	Mild increase in ostomy output (over baseline)
2	Increase of 4 – 6 stools per day	Moderate increase in output
3	Increase of >7 stools per day Incontinence Admission indicated	Severe increase in output Limiting self care ADL
4	Life-threatening Urgent intervention indicated	Life-threatening Urgent intervention indicated

CTCAE v4.0

- Increase oral fluids
- Hold immunotherapy

- As G2 plus:
- Admit, IV hydration
- Steroids 1–2mg/kg per day prednisolone (or equiv)
- If no improvement in 2–3d: add infliximab 5mg/kg
  (NB. Infliximab contraindicated with sepsis or perforation)
- Sigmoidoscopy and biopsy
- When G1, taper steroids over minimum 1m
  (Up to 3ms for severe cases)
- Infliximab may be re-administered at 2 and 6weeks

- As G3 pus:
- Permanently discontinue immunotherapy
- Involve gastroenterologist
- Involve surgical team

Spain, et al. *Cancer Treat Rev.* (2016):44,51-60.

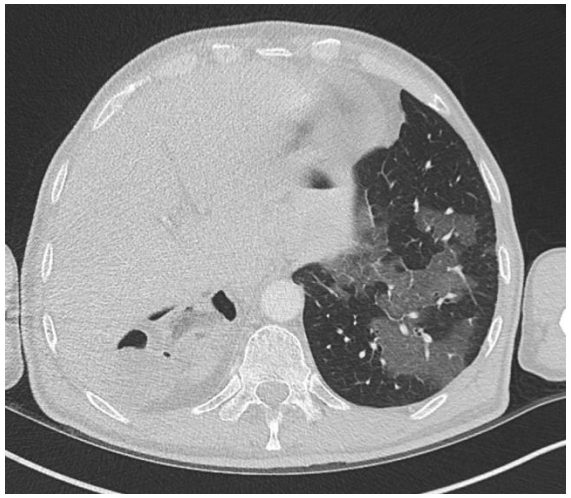
Pulmonary Toxicities

- **Pneumonitis** NSCLC (5-8%) > melanoma (2%)

  Median time to onset 2.1 months

  Median time to resolution 1.4 months

- Cough, dyspnoea, 'LRTI'



Management of Pneumonitis

Grade	
1: Asymptomatic	• Hold immunotherapy • Steroids (e.g. prednisone 1mg/kg/day or equivalent) • Re-assess 3 weeks: continue treatment if completely resolved
2: Symptomatic, limiting ADLs	As G1 plus: • Consider admission • Prednisone 1–2mg/kg/day PO or equivalent • Empiric antibiotics if suspicious for concurrent infection • Re-assess every 1–3 days • If improving taper steroids, continue treatment if symptoms resolve

CTCAE v4.0

Spain, et al. *Cancer Treat Rev.* (2016): 44, 51-60
Adapted from London Cancer Alliance Acute Oncology clinical guidelines, April 2016

Management of Pneumonitis

Grade	
3: Symptomatic, limiting self-care ADLs	• Discontinue immunotherapy permanently • Hospitalize • High dose steroids (methylprednisolone 1g/day IV) • Prophylactic antibiotics • Consider bronchoscopy with biopsy • Re-assess daily • If not improving after 48h or worsening, consider infliximab, mycophenylate, or immunoglobulins • If improving, taper steroids
4: Life threatening	As G3 plus: • Intensive care input

CTCAE v4.0

Spain, et al. *Cancer Treat Rev.* (2016): 44, 51-60
Adapted from London Cancer Alliance Acute Oncology clinical guidelines, April 2016

Hepatotoxicity

- Mainly asymptomatic AST and/or ALT rise
- Occasionally: pyrexia, bilirubin elevation

Initial approach

- Exclude new / progressive liver metastases
- Review medications and alcohol intake

Adapted from London Cancer Alliance Acute Oncology clinical guidelines, April 2016

Management Hepatotoxicity

Grade	Definition
1	AST/ALT ≤3 x ULN BR ≤1.5 x ULN
2	AST/ALT = 3-5 x ULN BR = x1.5-3 ULN
3	AST/ALT = 5-20 x ULN BR = 3-10 x ULN
4	AST/ALT >20 ULN BR > 10 x ULN

- Continue immunotherapy
- Investigations as listed

- Hold immunotherapy
- Prednisolone 1–2mg/kg/day or IV equivalent **Or**
- If patient is well, re-check liver function every 2 days and initiate steroids if no improvement or worsening.
- Taper steroids over 4 weeks once G1 or baseline

- As G2 plus:
- Prednisolone 1–2mg/kg/day or IV equivalent
- Consider permanent discontinuation of immunotherapy

- As G3 pus:
- Hepatology review
- Permanently discontinue immunotherapy
- Consider mycophenylate

CTCAE v4.0

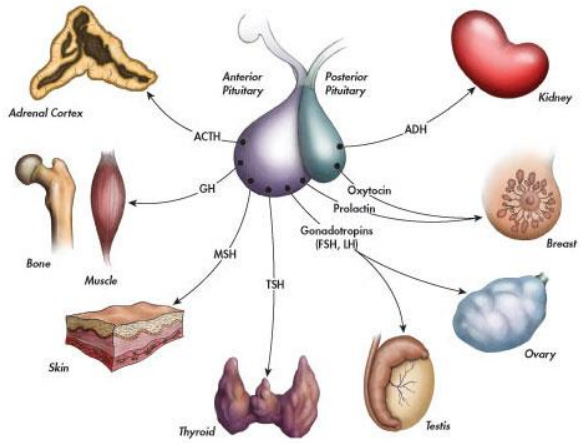
Spain, et al. *Cancer Treat Rev.* (2016): 44, 51-60
Adapted from London Cancer Alliance Acute Oncology clinical guidelines, April 2016

Endocrine Disorders: Pituitary and Thyroid

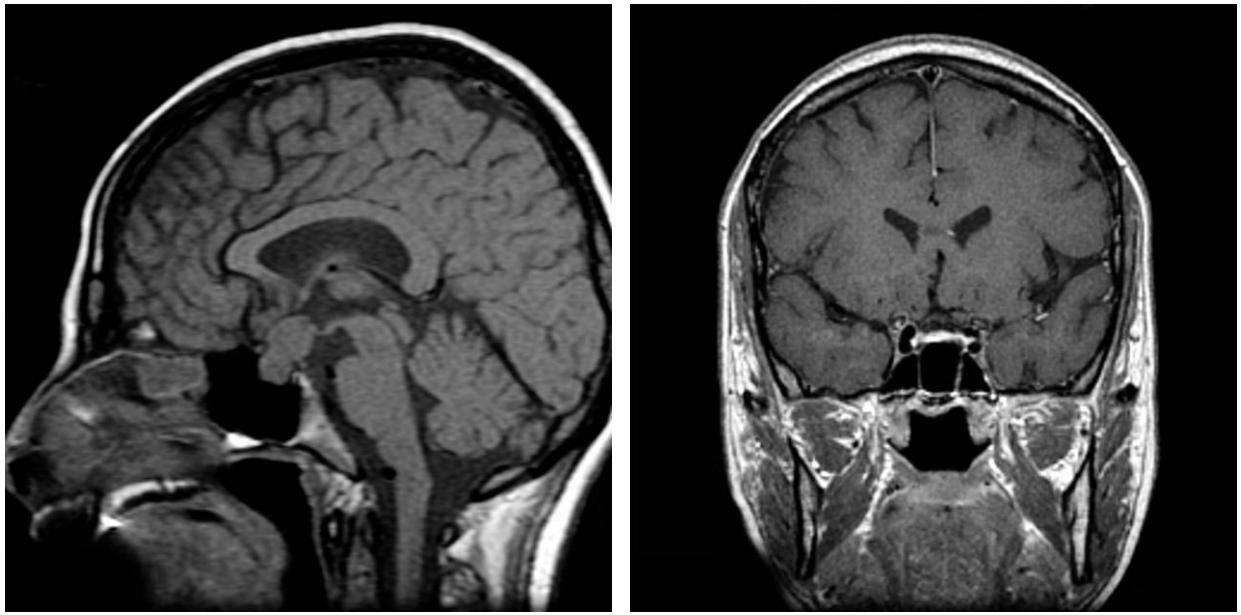
- **Incidence:** Commoner with anti-CTLA-4 (4%) than anti-PD1 (<1%)
- **Symptoms:** Fatigue, headache, visual, arthralgia, behaviour
  Often vague and non-specific
- **Investigations**

↓ ACTH	↓ TSH	↓ GH
↓ FSH	↓ LH	↓ PRL

- **Grading:** None!



Hypophysitis - Imaging



Management of Hypophysitis

① Hold immunotherapy

② Endocrinology input

③ Acute phase: corticosteroids (≈MP 1-2mg/kg/day) may limit hypophysitis

④ Hormone replacement (thyroxine, hydrocortisone) as needed

⑤ Immunotherapy may be re-started after corticosteroid taper

Spain, et al. *Cancer Treat Rev.* (2016): 44, 51-60
Adapted from London Cancer Alliance Acute Oncology clinical guidelines, April 2016

Less Common Toxicities of Immunotherapy

Ocular (<1%)

- Uveitis, episcleritis, conjunctivitis (anti-CTLA4)

Neurological

- Guillaine-Barre syndrome, myaesthenia gravis, PRES

Cardiac

- Myocarditis, heart failure

Management of irAEs

- Describe signs and symptoms, including complications if not treated promptly
- Emphasize early recognition and prompt reporting
- Discuss preventative measures, if applicable
- Instruct patient to present agent-specific wallet card to all healthcare providers
- Stress adherence with corticosteroid therapy
- Provide supportive care instructions
- Enforce early reporting of worsening condition

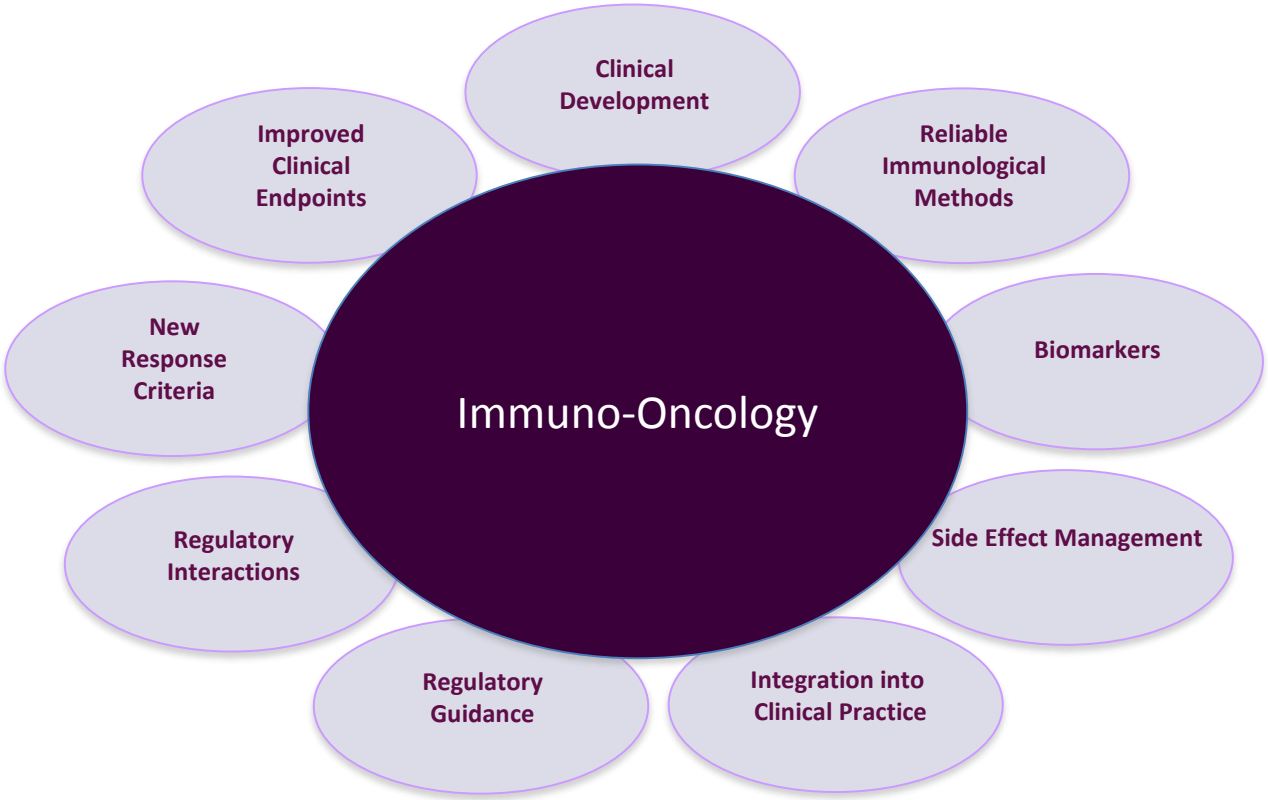
Fecher LA, Agarwala SS, et al. *Oncologist*. 2013.

Patient and Caregiver Education

- Whom to call
- Why to call
- When to call
- Where to call (MUST HAVE 24/7 clinician availability)

Fecher LA, Agarwala SS, et al. *Oncologist*. 2013.

The Immuno-Oncology Framework



Oncoimmunology 1:3, 334–339; May/June 2012;

Practical Considerations: Summary

- Immunotherapy requires a team approach
  - Physician, nurse, patient, family
- Unique response patterns may occur
  - Allow time for treatment to work
  - Pseudoprogression
- Toxicity recognition and management is unique
  - Patient education
  - Steroids as needed
  - Follow guidelines

Questions?

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Thank you for participating in the ICLIO Webinar. Presentation slides and archived recording will be available at accc-iclio.org.

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