Por que fazer adjuvância com anti-PD1

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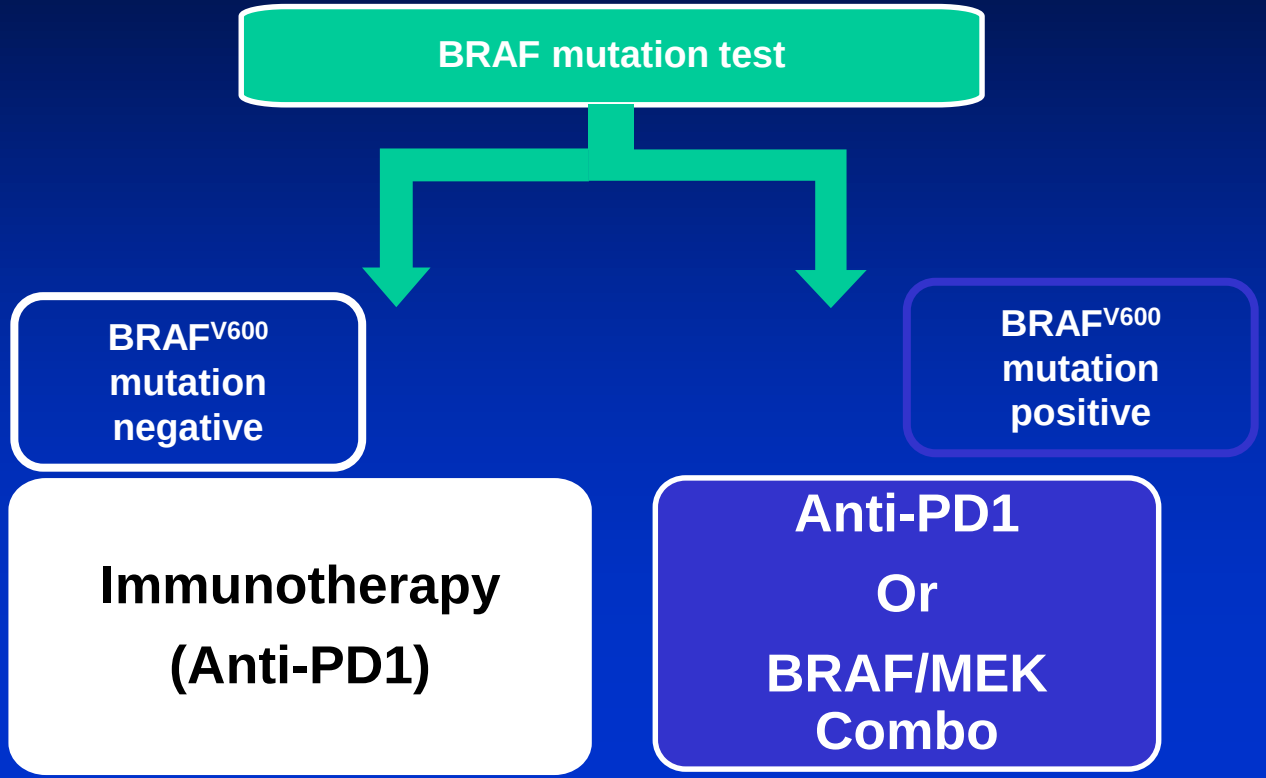
Disclosure

- I was assigned this topic by Drs. Buzaid and Schmerling
- I have not been bribed by any immunotherapy company!

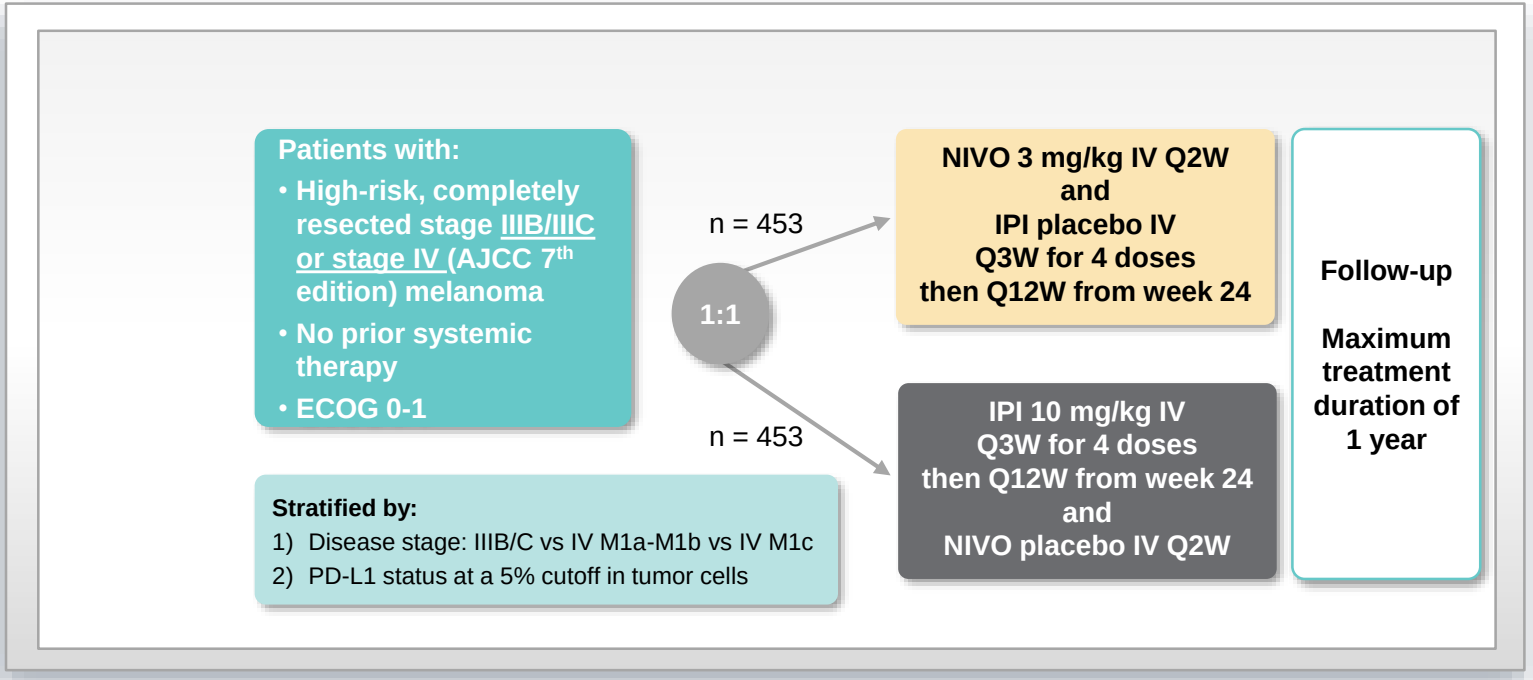
Decision Point….



Factors to Consider

- The data
- The mechanism
- Always plan ahead

CheckMate 238 Study Design[1]



Enrollment period: March 30, 2015 to November 30, 2015

1. Weber J, Mandala M, Del Vecchio M, et al. Adjuvant therapy with nivolumab (NIVO) versus ipilimumab (IPI) after complete resection of stage III/IV melanoma: Updated results from a phase III trial (CheckMate 238). Presented at: American Society of Clinical Oncology 2018 Annual Meeting; June 4, 2018; Chicago, IL.

CheckMate 238 Baseline Patient Characteristics and Treatment Summary[1]

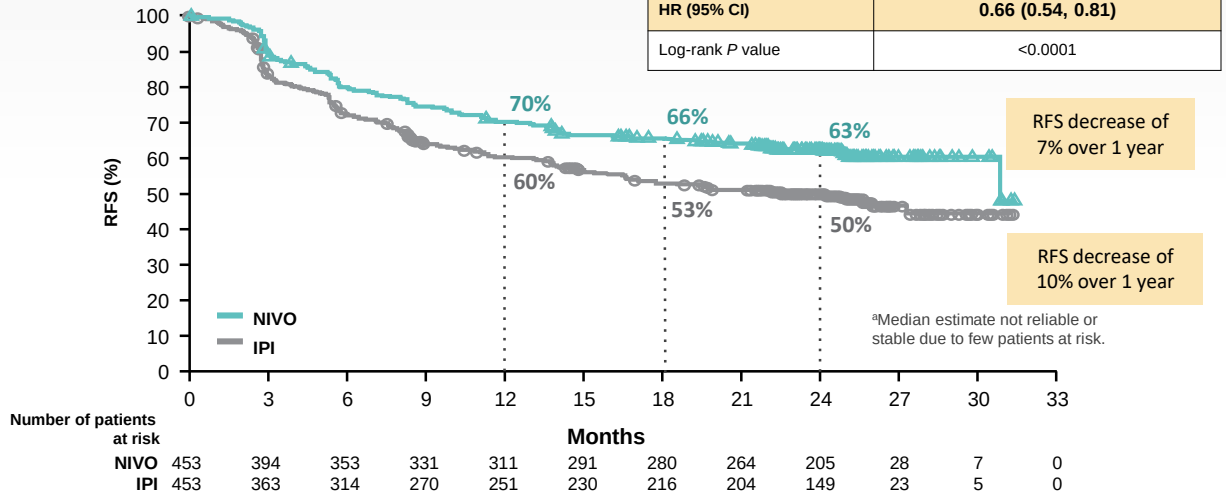
	NIVO (n = 453)	IPI (n = 453)
Median age, years	56	54
Male, %	57	59
Stage IIIB+IIIC, %	81	81
Macroscopic lymph node involvement (% of stage IIIB+IIIC)	60	58
Ulceration (% of stage IIIB+IIIC)	42	37
Stage IV, %	18	19
M1c without brain metastases (% stage IV)	17	17
PD-L1 expression ≥5%, %	34	34
***BRAF* mutation, %**	41	43
LDH ≤ ULN, %	91	91
Melanoma subtype, %		
Cutaneous	86	83
Mucosal	4	3
Acral	4	4

- **Median doses were 24 (1-26) in the NIVO group and 4 (1-7) in the IPI group**
- **61% of patients in the NIVO group and 27% in the IPI group completed 1 year of treatment**

1. Weber J, Mandala M, Del Vecchio M, et al. Adjuvant therapy with nivolumab (NIVO) versus ipilimumab (IPI) after complete resection of stage III/IV melanoma: Updated results from a phase III trial (CheckMate 238). Presented at: American Society of Clinical Oncology 2018 Annual Meeting; June 4, 2018; Chicago, IL.

CheckMate 238
Primary Endpoint RFS in All Patients[1]

	NIVO	IPI
Events/patients	171/453	221/453
Median (95% CI)	30.8 (30.8, NR)[a]	24.1 (16.6, NR)
HR (95% CI)	**0.66 (0.54, 0.81)**	
Log-rank *P* value	<0.0001	



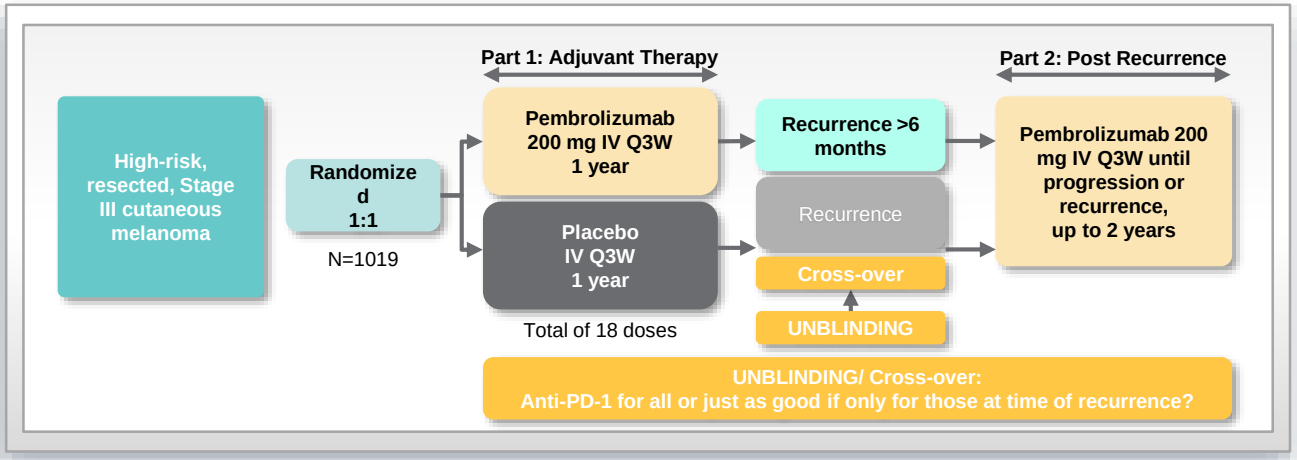
RFS decrease of 7% over 1 year

RFS decrease of 10% over 1 year

[a]Median estimate not reliable or stable due to few patients at risk.

1. Weber J, Mandala M, Del Vecchio M, et al. Adjuvant therapy with nivolumab (NIVO) versus ipilimumab (IPI) after complete resection of stage III/IV melanoma: Updated results from a phase III trial (CheckMate 238). Presented at: American Society of Clinical Oncology 2018 Annual Meeting; June 4, 2018; Chicago, IL.

EORTC 1325/KEYNOTE-54 Study Design[1]



Stratification factors:

- ✓ **Stage:** IIIA (>1 mm metastasis) vs. IIIB vs. IIIC 1-3 positive lymph nodes vs. IIIC ≥4 positive lymph nodes
- ✓ **Region:** North America, European countries, Australia/New Zealand, other countries

Primary Endpoints:

- **RFS (per investigator) in overall population,** and **RFS in patients with PD-L1-positive tumors**

Secondary Endpoints:

- **DMFS and OS** in all patients, and in patients with PD-L1-positive tumors; **Safety, Health-related quality of life**

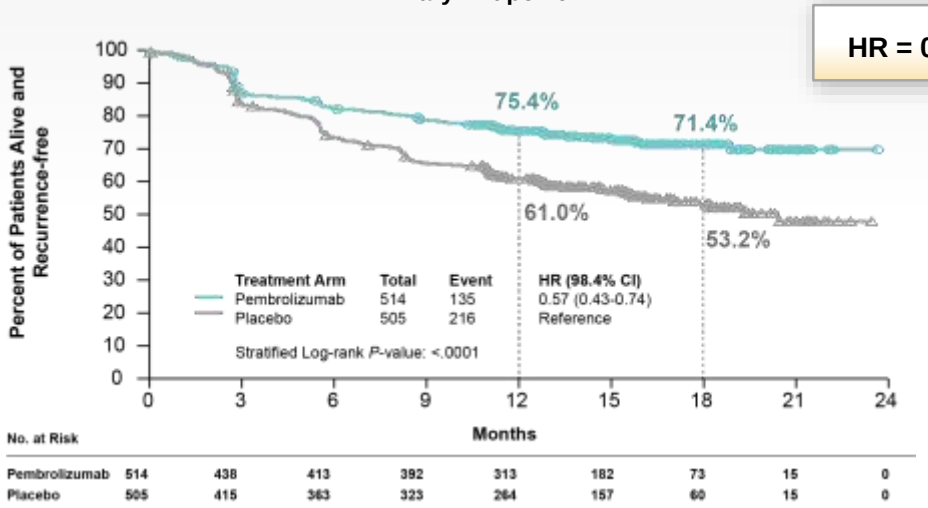
1. Eggermont AMM, Blank CU, Mandala M, et al. Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma [published online ahead of print April 15, 2018]. *N Engl J Med.* doi: 10.1056/NEJMoa1802357.

EORTC 1325/KEYNOTE-54 Baseline Patient Characteristics[1]

	Pembrolizumab (N=514)	Placebo (N=505)
Median age (years)	**54**	**54**
Male (%)	**63**	**60**
Stage (%)		
IIIA	**15**	**15**
IIIB	**47**	**46**
IIIC with 1-3 positive LN	**17**	**19**
IIIC with ≥4 positive LN	**21**	**20**
Ulceration of primary (%)	**41**	**39**
1 vs. 2-3 vs. ≥4 positive LN (%)	**44 vs. 34 vs. 21**	**47 vs. 33 vs. 20**
Lymph node involvement (%)		
Microscopic	**36**	**32**
Macroscopic	**64**	**68**

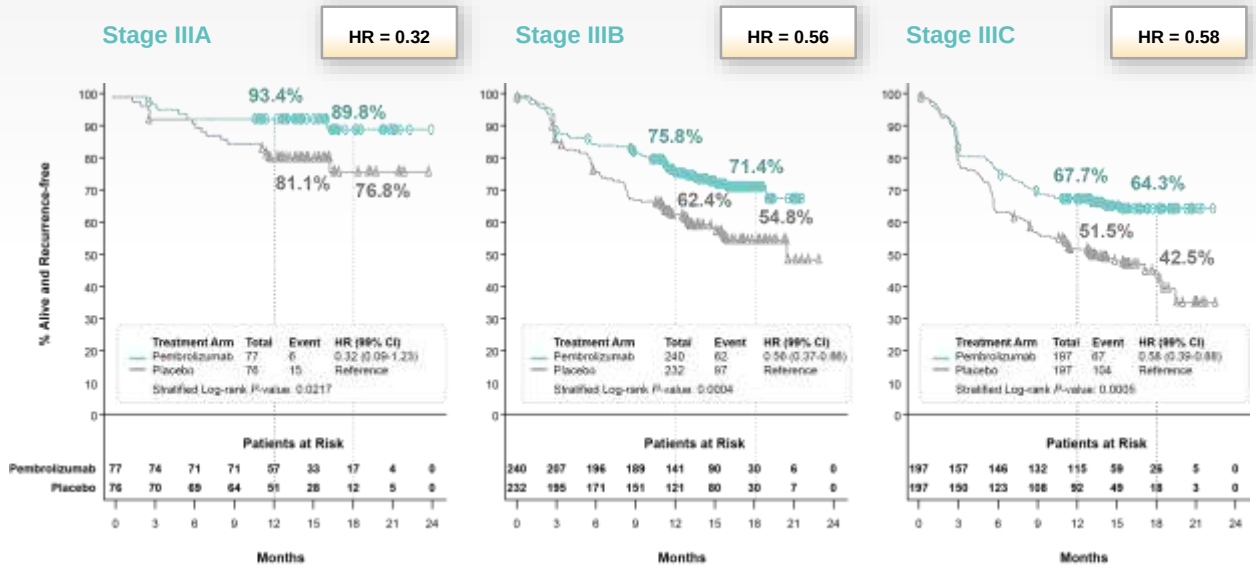
1. Eggermont AMM, Blank CU, Mandala M, et al. Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma [published online ahead of print April 15, 2018]. *N Engl J Med.* doi: 10.1056/NEJMoa1802357.

EORTC 1325/KEYNOTE-54
Recurrence-Free Survival in the ITT Population[1]
Primary Endpoint



1. Eggermont AMM, Blank CU, Mandala M, et al. Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma [published online ahead of print April 15, 2018]. *N Engl J Med.* doi: 10.1056/NEJMoa1802357.

EORTC 1325/KEYNOTE-54 Recurrence-Free Survival[1]



1. Eggermont AMM, Blank CU, Mandala M, et al. Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma [published online ahead of print April 15, 2018]. *N Engl J Med*. doi: 10.1056/NEJMoa1802357.

EORTC 1325/KEYNOTE-54 Immune-Related Adverse Events (irAE)[1]

	Pembrolizumab (N=509)		Placebo (N=502)	
	Any Grade, %	Grade 3-5, %	Any Grade, %	Grade 3-5, %
Any irAE	37.3	7.1	9.0	0.6
Endocrine	23.4	1.8	5.0	0
Gastrointestinal	3.9	2.0	0.8	0.4
Colitis	3.7	2.0	0.6	0.2
Pancreatitis	0.4	0.2	0.2	0.2
Hepatitis	1.8	1.4	0.2	0.2
Other irAE	2.9	1.0	1.0	0
Nephritis	0.4	0.4	0.2	0
Uveitis	0.4	0	0	0
Myositis*	0.2	0.2	0.2	0
Myocarditis	0.2	0.2	0	0

* One treatment-related death due to myositis

1. Eggermont AMM, Blank CU, Mandala M, et al. Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma [published online ahead of print April 15, 2018]. *N Engl J Med*. doi: 10.1056/NEJMoa1802357.

Data Comparison in Adjuvant Melanoma Trials

Patient Population	CM238[1]		COMBI-AD[2]		KN054[3]	
	Completely resected stage IIIB / C or IV melanoma		Completely resected, *BRAF* V600E/K -positive stage IIIA / B / C melanoma		Completely resected stage IIIA / B / C melanoma	
Treatment	Nivo	Ipi	Dab/Tram	Placebo	Pembro	Placebo
N	453	453	438	432	514	505
RFS HR	0.65 (97.56% CI:0.51-0.83), P<0.0001		0.47 (95% CI: 0.39–0.58), P<0.001		0.57 (98.4% CI: 0.43–0.74), P<0.001	
1-y RFS Rate, %	71	61	88	56	75	61
18-m RFS Rate, %	66	53	N/A	N/A	71	53
3-y OS Rate, %	N/A	N/A	86	77	N/A	N/A
Grade 3 - 5 TRAEs,%	14	46	31	5	15	3
DC Rate due to AEs, %	10	43	26	3	14	2

These are not head-to-head studies and outcomes should not be directly compared. The information should be used to look for general trends only.

1. Weber J, Mandala M, Del Vecchio M, et al. Adjuvant therapy with nivolumab (NIVO) versus ipilimumab (IPI) after complete resection of stage III/IV melanoma: Updated results from a phase III trial (CheckMate 238). Presented at: American Society of Clinical Oncology 2018 Annual Meeting; June 4, 2018; Chicago, IL.
2. Hauschild A, Santinami M, Long G, et al. Adjuvant dabrafenib (D) plus trametinib (T) for resected stage III BRAF V600E/K–mutant melanoma. Presented at: European Society for Medical Oncology 2017 Congress; September 11, 2017; Madrid, Spain.
3. Eggermont AMM, Blank CU, Mandala M, et al. Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma [published online ahead of print April 15, 2018]. *N Engl J Med*. doi: 10.1056/NEJMoa1802357.

Most Frequent AEs with Adjuvant Therapy

Preferred Term, %	CheckMate 238[1] (n = 452)		Keynote 54[2] (n = 514)		COMBI-AD[3] (n = 438)	
	Any Grade	**Grade 3/4**	Any Grade	**Grade 3/5**	Any Grade	**Grade 3/4**
Total	97	25	93,3	**31,6**	97	
Total (treatment related)	**85**	**14**	77,8	**14,7**	**91**	**41**
Gastro-intestinal	25	2	?	?	33	1
Nausea	-	-	11,4	0	40	1
Vomiting					28	1
Fatigue	?	?	37,1	0,8	47	4
Pulmonary	1		4.7	0.8		
Renal	1		0.4	0.4		
Endocrine			**23,4**	**1.8**		
Adrenal disorder	2		1	0.2		
Pituitary disorder	2		2.2	0.6		
Thyroid disorder	20		27.6	0.2		
Arthralgia			12	**0.6**	**28**	**1**
Headache					39	1
Pyrexia					**63**	**5**
Hepatic	9	2	1.8	1.4		
Skin	**45**	**1**	28.3	**0,2**	**28**	**1**
Hypertension	2	0	0		6	3
Treatment Discontinuation	**10**	**5**	**13.8**		**26**	

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1. Weber J, Mandala M, Del Vecchio M, et al. Adjuvant therapy with nivolumab (NIVO) versus ipilimumab (IPI) after complete resection of stage III/IV melanoma: Updated results from a phase III trial (CheckMate 238). Presented at: American Society of Clinical Oncology 2018 Annual Meeting; June 4, 2018; Chicago, IL.
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Patient Populations in Adjuvant Immunotherapy Trials

Study	Design	Patient population (completely resected disease)				
		IIIA	IIIB	IIIC	IIID (only in AJCC Staging 8th Edition)	IV
CA184-029	IPI 10 mg/kg vs PBO	✔	✔	✔		
US Intergroup E1609	IPI 10 mg/kg and IPI 3 mg/kg vs HD IFN		✔	✔		✔ (M1a/M1b)
CheckMate 238	NIVO vs IPI 10 mg/kg		✔	✔		✔
CheckMate 915	NIVO+IPI vs NIVO[2]		✔	✔	✔	✔
KEYNOTE 054 (EORTC 1325)	PEMBRO vs PBO	✔	✔	✔		
SWOG S1404	PEMBRO or IPI vs HD IFN-α	✔ (N2A)	✔	✔		✔

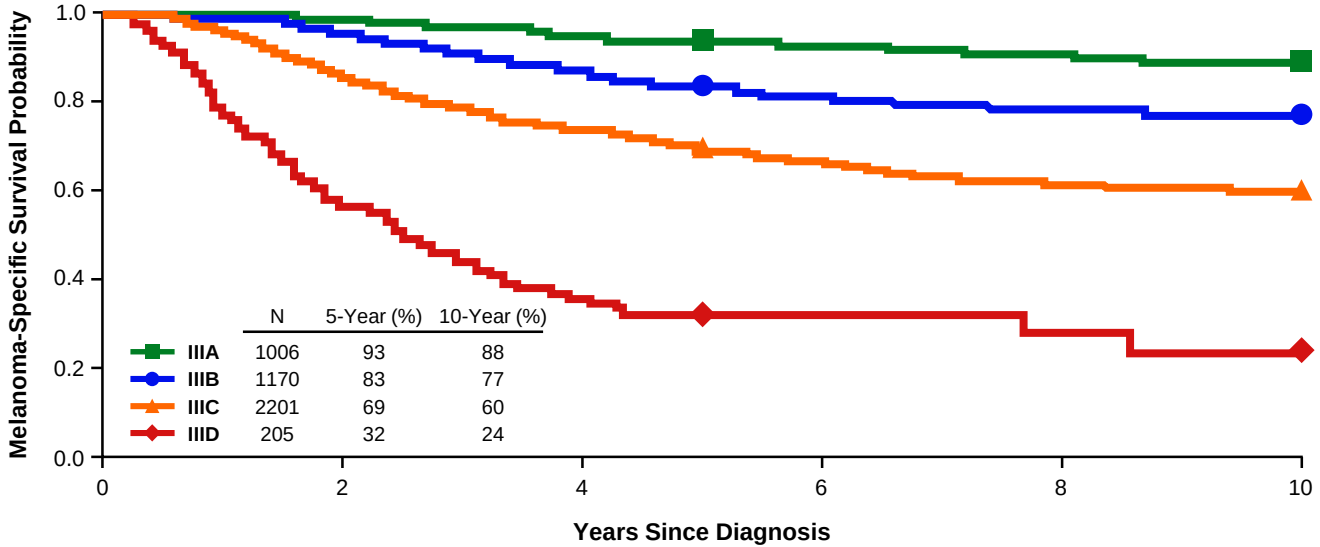
1. www.clinicaltrials.gov. Accessed April 2017. 2. Data on file NIVO 297.

Survival Data AJCC 7 vs. 8

		7th Edition Criteria	8th Edition Criteria	
Publication		**Balch et al., 2009**	**Haydu et al., 2017**	**Gershenwald et al., 2017**
5-Year Survival by Stage	**IIC**	53%	–	82%
	IIIA	78%	81.4%	93%
	IIIB	59%	64.0%	83%
	IIIC	40%	44.5%	69%
	IIID	–	9.8%	32%
% Population by Stage (n/N)*	**IIIA**	36% (1196/3307)	4.8% (220/4540)	22% (1006/4582)
	IIIB	42% (1391/3307)	44.2% (2007/4540)	26% (1170/4582)
	IIIC	22% (720/3307)	37.6% (1709/4540)	48% (2201/4582)
	IIID	–	2.3% (104/4540)	4% (204/4582)

Balch CM, Gershenwald JE, Soong SJ, et al. Final version of the 2009 AJCC melanoma staging and classification. *J Clin Oncol*. 2009;27(36):6199-6206; Haydu LE, Scolyer RA, Lo S, et al. Conditional survival: an assessment of the prognosis of patients at time points after initial diagnosis and treatment of locoregional melanoma metastasis. *J Clin Oncol*. 2017;35(15):1721-1729; Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma staging: evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin*. 2017; doi:10.3322/caac.21409; Amin MB, Edge S, Greene F, et al, eds. *AJCC Cancer Staging Manual*. 8th ed. Berlin, Germany:Springer International Publishing; 2017; Edge S, Byrd DR, Compton CC, Fritz AG, Green FL, Trotti A, et al, eds. *AJCC Cancer Staging Manual*. 7th ed. Berlin, Germany:Springer International Publishing; 2009.

Melanoma-Specific Survival According to Stage III Subgroups: AJCC 8th Edition



AJCC 7th edition 5-year survival

- IIIA: 78%
- IIIB: 59%
- IIIC: 40%

Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma staging: evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin*. 2017; doi:10.3322/caac.21409; Balch CM, Gershenwald JE, Soong SJ, et al. Final version of the 2009 AJCC melanoma staging and classification. *J Clin Oncol*. 2009;27(36):6199-6206

Anti-PD1 Adjuvant Therapy

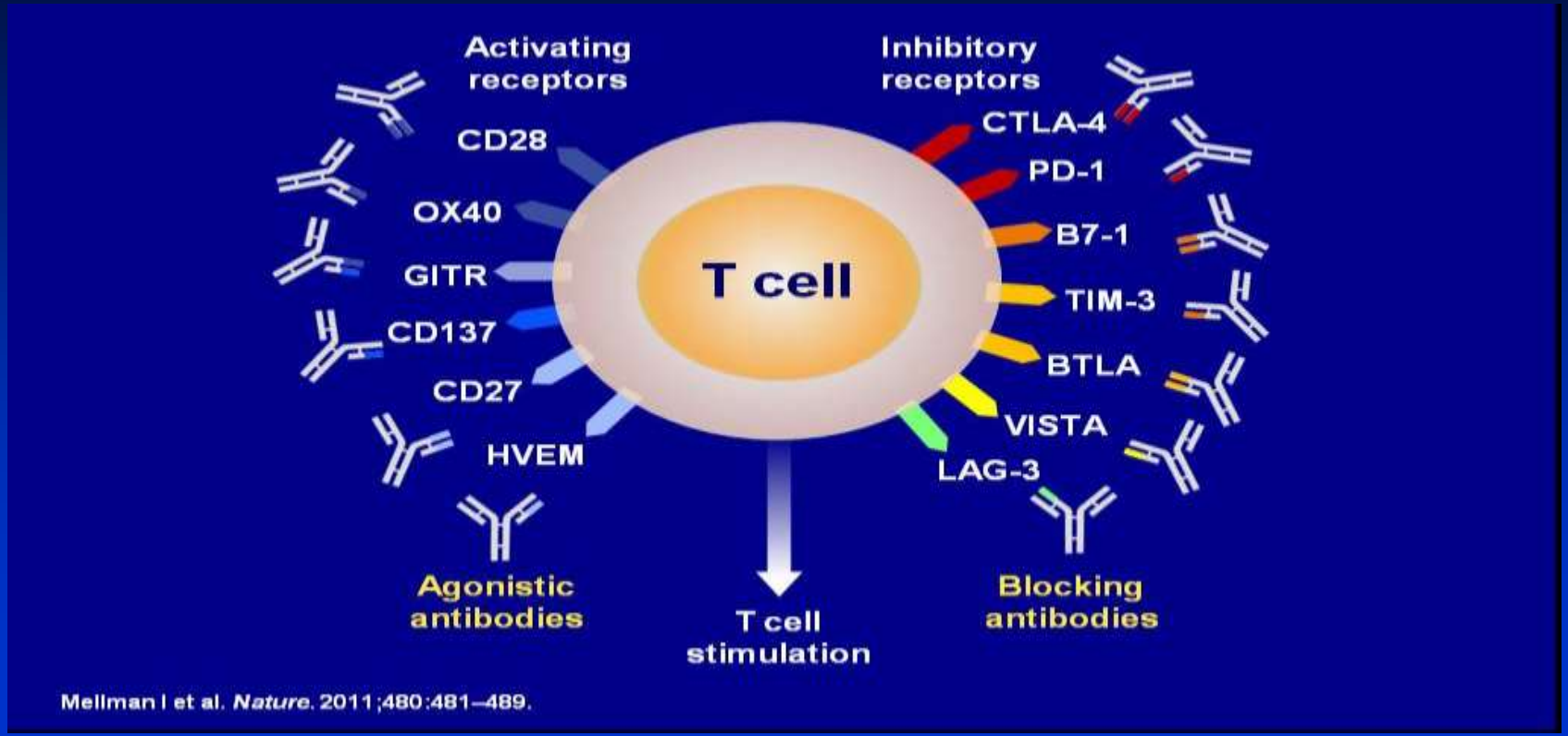
- Two positive trials
- Very manageable toxicity
- Convenient schedule of administration
- Most centers would not treat N1a patients

- Anti-PD1 works well as adjuvant therapy!

Factors to Consider

- The data
- The mechanism
- Always plan ahead

T-Cell Immune Checkpoints



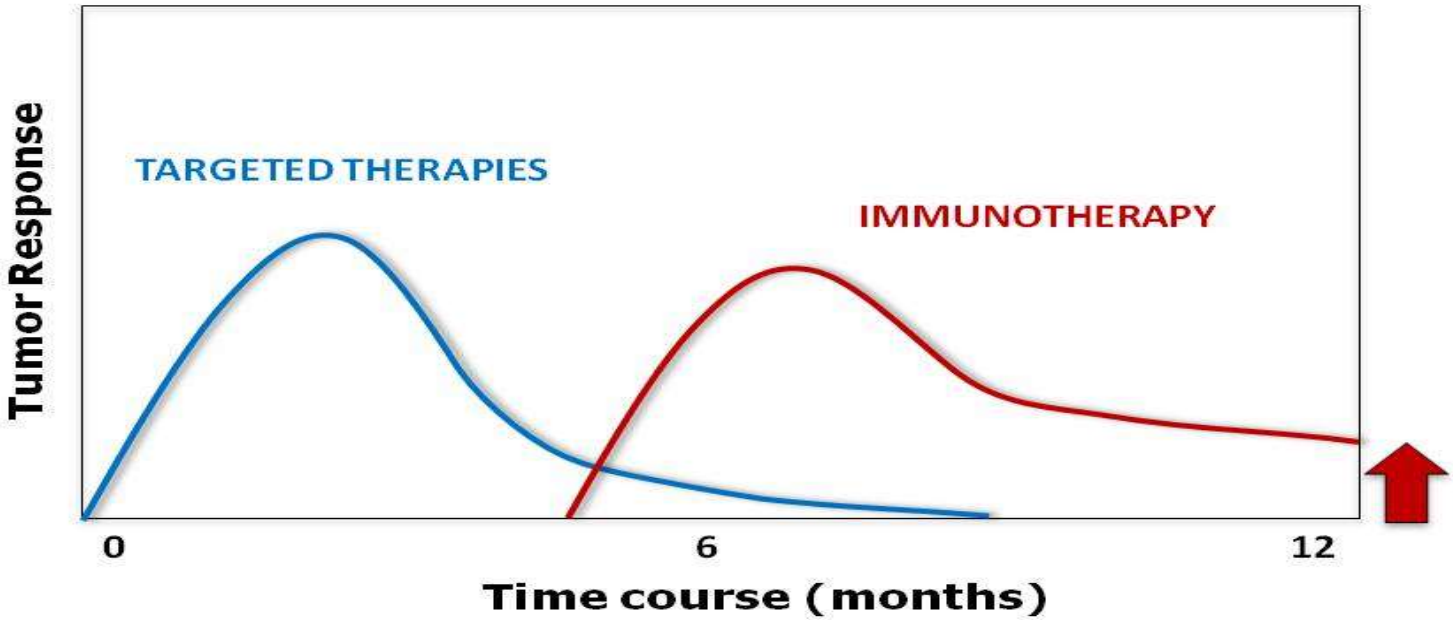
General properties of targeted therapies vs checkpoint immunotherapy

	Targeted Therapy	Immunotherapy
PK	Short (hours)	Long (weeks)
PD	Short (hours)	Long (years)
What kills the cancer	The small molecule stopping an oncogenic signal	A body system designed to kill its targets anywhere in the body
Body distribution	Passive (blood distribution)	Active (T cells searching for antigen)
Memory	No	Yes

Factors to Consider

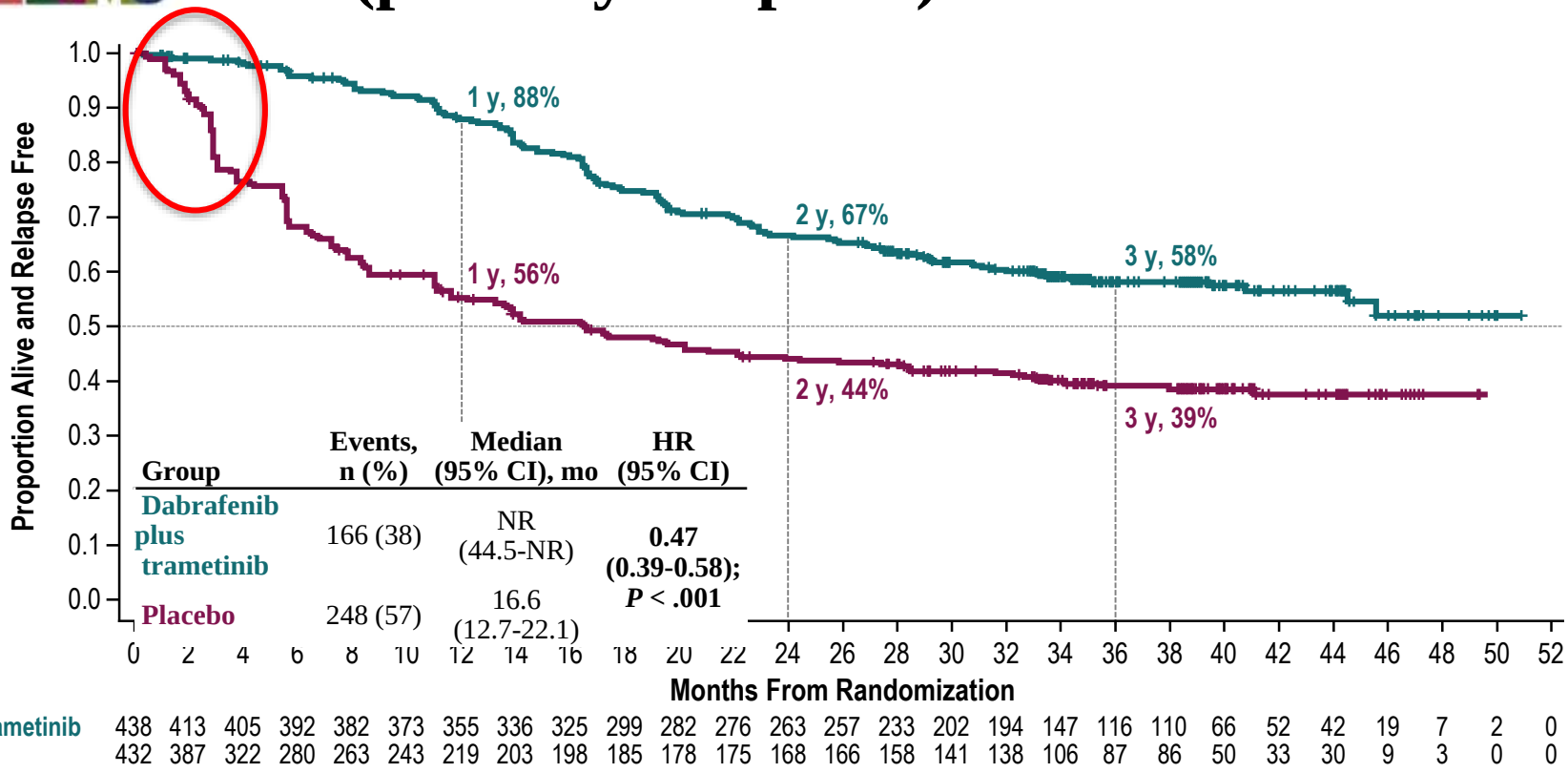
- The data
- The mechanism
- Always plan ahead

Antitumoral response: Targeted therapies vs. Immunotherapies (CTLA-4 antibodies)



Presented By Axel Hauschild at 2014 ASCO Annual Meeting

Relapse-free survival (primary endpoint)



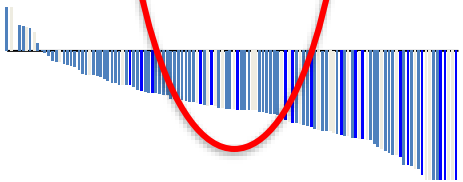
NR, not reached.

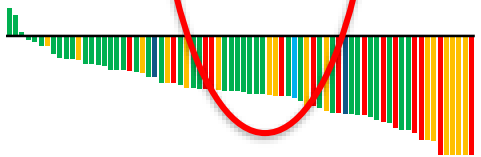
Hauschild A, et al. Oral presented at: ESMO 2017 [abstract LBA6PR].

BRAFi in Metastatic Melanoma

Second line

	Vemurafenib[1]			Dabrafenib[2]		
Phase	1	2	3	1	2	3
RR	56%	57%	57%	56%	59%	59%
PFS		6.7	6.9	5.5	6.3	6.9
OS	13.8	15.9	13.6		13.1	18.2



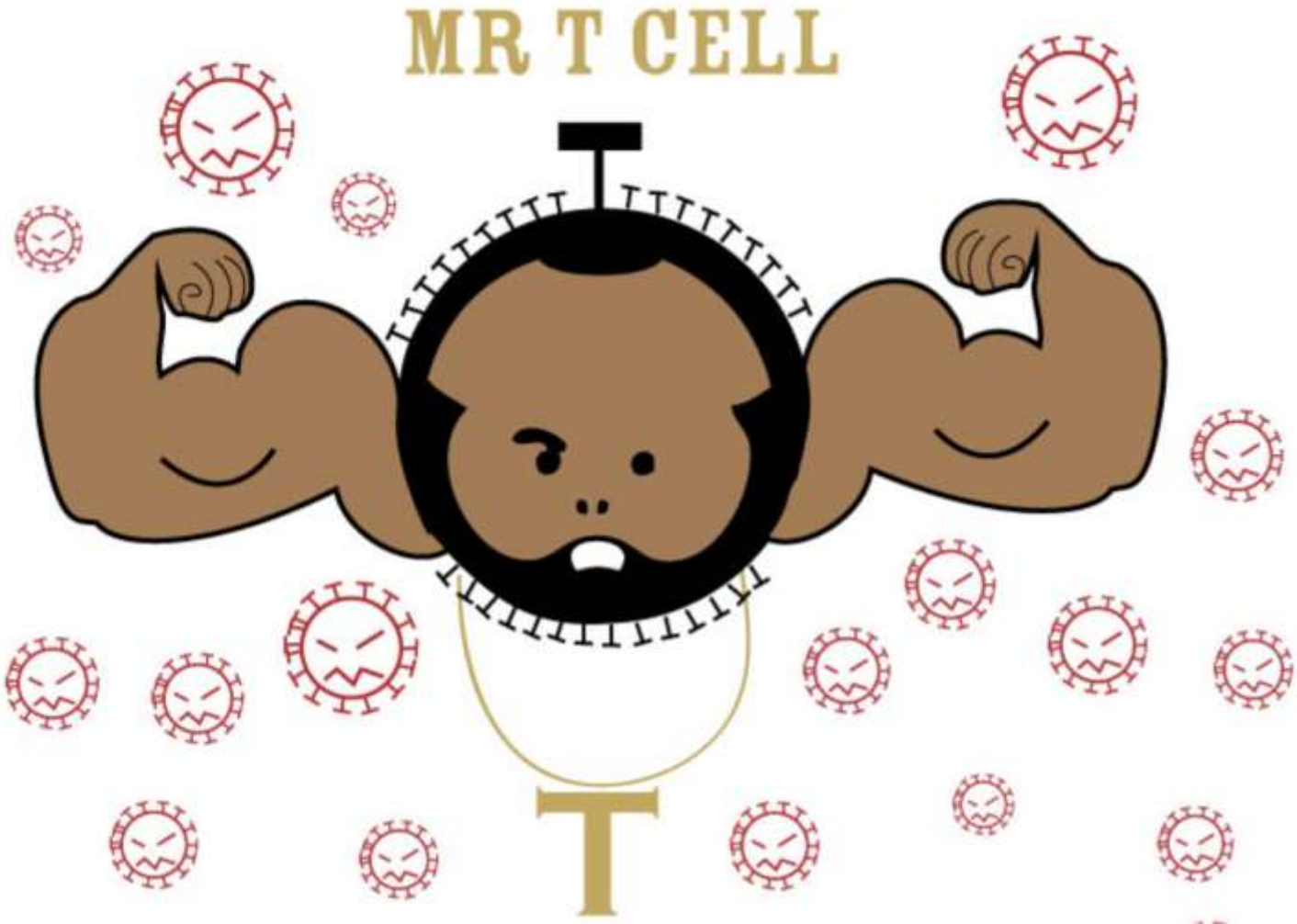


1. Chapman PB, *et al. N Engl J Med* 2011;364:2507–2516 (updated Chapman *et al.* ASCO 2012); Sosman JA, *et al. N Engl J Med* 2012;366:707–714;
2. Hauschild A, *et al. Lancet* 2012;380:358–365 (updated Hauschild *et al.* ASCO 2013); Ascierto PA, *et al. J Clin Oncol* 2013; 31:3205–3211.

So why choose PD-1?

- There is a potential to overtreat patients
  - Risk benefit ratio for stage IIIA?
- Immunotherapy is potentially longer lasting
- Relapse options are more well-defined
  - Switch to BRAF therapy logical
  - Benefit of retreatment with immunotherapy unclear
- Less frequent toxicity

- If you are going to treat someone with something they may not need….
- Wouldn’t you rather use immunotherapy??


MR T CELL
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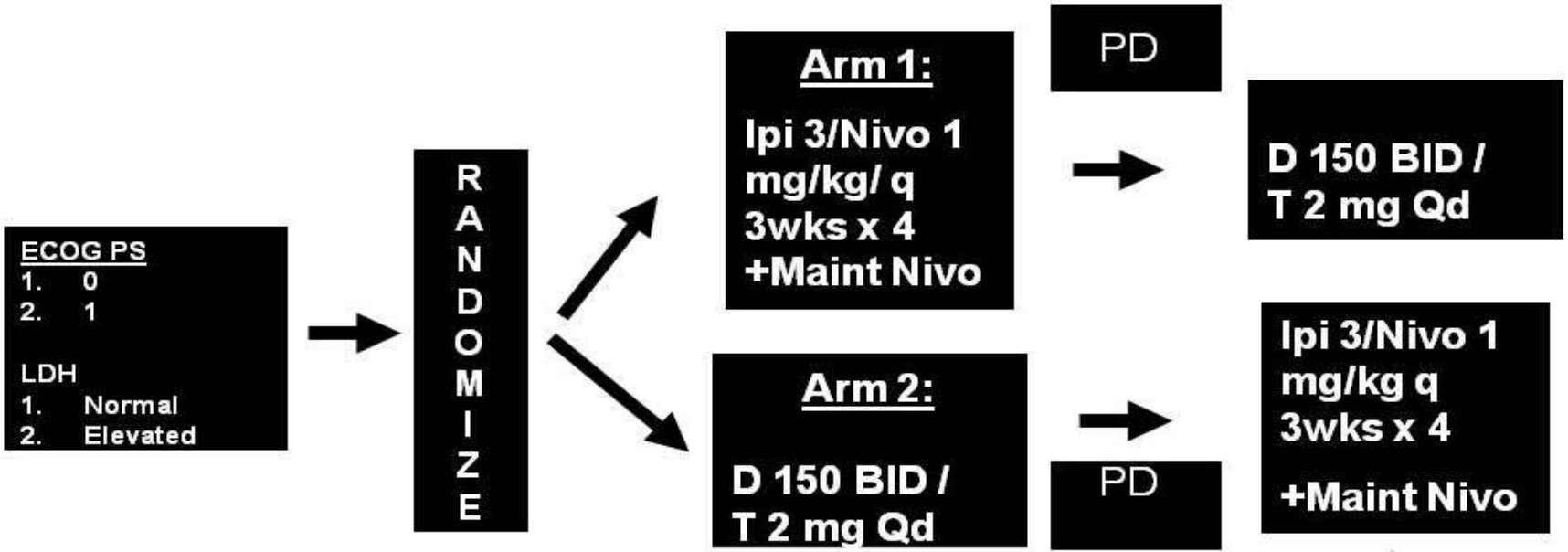
Clinical Trials!

EA6134: Ipi/Nivo to D/T vs D/T to Ipi/Nivo



CRICKET IRELAND

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