STAGE II MELANOMA: IS ADJUVANT TREATMENT APPROPRIATE?

NO

Michael Lowe, MD, MA, FACS, FSSO
Associate Professor of Surgery
Emory University School of Medicine

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EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

NCI Designated Comprehensive Cancer Center

DISCLOSURES

- Research funding: Amgen, BMS, Castle Biosciences, Delcath, Merck, Regeneron, SkylineDx, Vaccinex
- Advisory Board: BMS

OBJECTIVES

- Describe why Melinda is wrong

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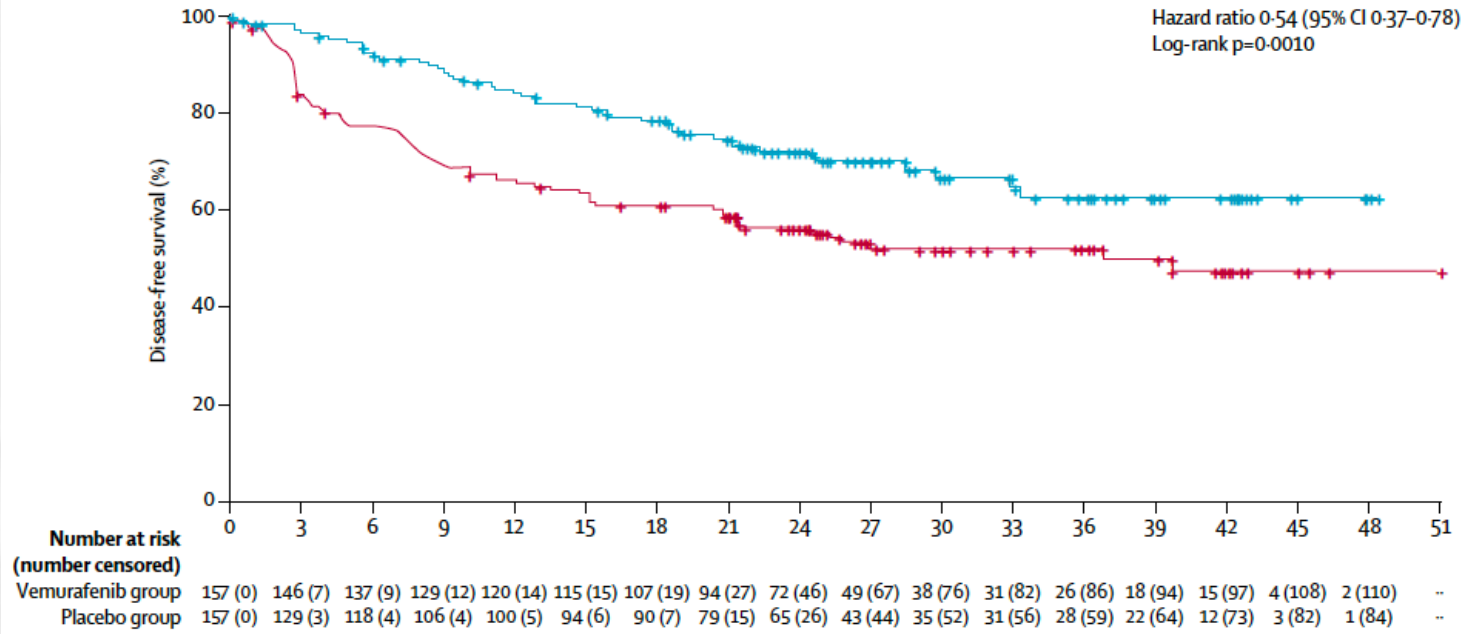
- Describe which therapies are available for patients with fully resected melanoma
- Discuss which patients may benefit from adjuvant therapy
- Determine if the data available justifies treatment of node-negative stage II melanoma

BACKGROUND: BRIM8

Adjuvant vemurafenib in resected, *BRAF*^{V600} mutation-positive melanoma (BRIM8): a randomised, double-blind, placebo-controlled, multicentre, phase 3 trial

Lancet Oncol 2018; 19: 510–20



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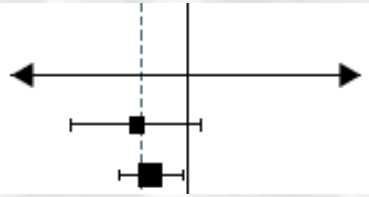
	Placebo group (n=157)		Vemurafenib group (n=157)		
	Events (n)/ patients (N)	Median disease-free survival, months (95% CI)	Events (n)/ patients (N)	Median disease-free survival, months (95% CI)	
Pathological stage					
Stage IIC	6/12	36·9 (15·2–NE)	0/15	NE (NE)	<0·01 (0·00–NE)
Stage IIIA	15/39	NE (24·4–NE)	8/36	NE (29·8–NE)	0·52 (0·22–1·23)
Stage IIIB	51/106	25·8 (14·5–NE)	37/106	NE (32·9–NE)	0·63 (0·41–0·96)



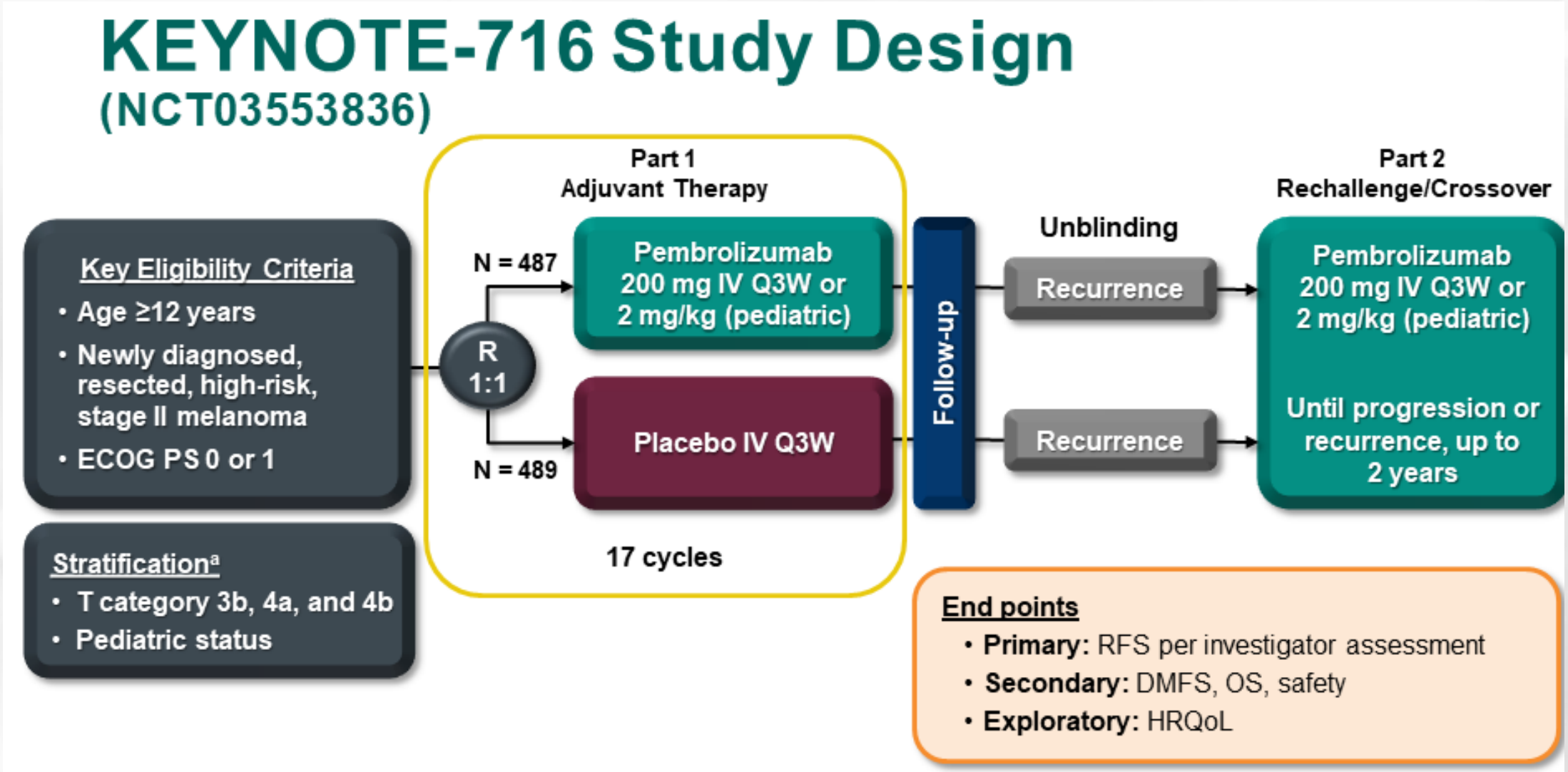
KEYNOTE-716

Pembrolizumab versus placebo as adjuvant therapy in completely resected stage IIB or IIC melanoma (KEYNOTE-716): a randomised, double-blind, phase 3 trial

*Jason J Luke, Piotr Rutkowski, Paola Queirolo, Michele Del Vecchio, Jacek Mackiewicz, Vanna Chiarion-Sileni, Luis de la Cruz Merino, Muhammad A Khattak, Dirk Schadendorf, Georgina V Long, Paolo A Ascierto, Mario Mandala, Federica De Galitiis, Andrew Haydon, Reinhard Dummer, Jean-Jacques Grob, Caroline Robert, Matteo S Carlino, Peter Mohr, Andrew Poklepovic, Vernon K Sondak, Richard A Scolyer, John M Kirkwood, Ke Chen, Scott J Diede, Sama Ahsan, Nageatte Ibrahim, Alexander M M Eggermont, on behalf of the KEYNOTE-716 Investigators**

Lancet 2022; 399: 1718–29

KEYNOTE-716


KEYNOTE-716 Study Design
(NCT03553836)
Part 1
Adjuvant Therapy
Part 2
Rechallenge/Crossover
Key Eligibility Criteria
• Age ≥12 years
• Newly diagnosed, resected, high-risk, stage II melanoma
• ECOG PS 0 or 1
Stratification[a]
• T category 3b, 4a, and 4b
• Pediatric status
R
1:1
N = 487
N = 489
Pembrolizumab 200 mg IV Q3W or 2 mg/kg (pediatric)
Placebo IV Q3W
17 cycles
Follow-up
Unblinding
Recurrence
Recurrence
Pembrolizumab 200 mg IV Q3W or 2 mg/kg (pediatric)
Until progression or recurrence, up to 2 years
End points
• Primary: RFS per investigator assessment
• Secondary: DMFS, OS, safety
• Exploratory: HRQoL

KEYNOTE-716 – STATISTICS

Pembrolizumab versus placebo as adjuvant therapy in completely resected stage IIB or IIC melanoma (KEYNOTE-716): a randomised, double-blind, phase 3 trial

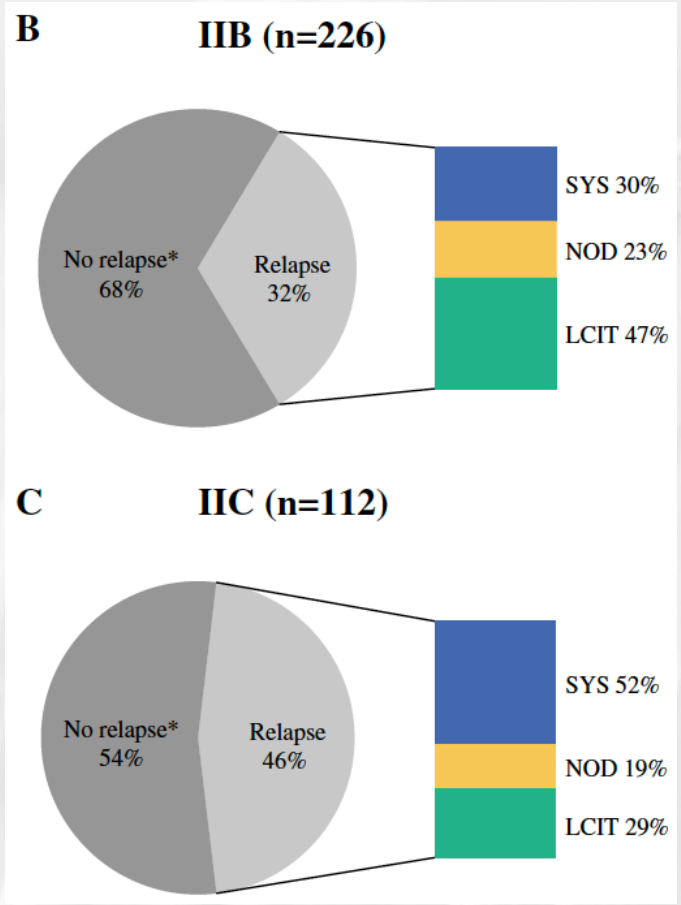
Lancet 2022; 399: 1718–29

We based sample size and power calculations on a cure model with a long-term recurrence-free survival of 50% and estimated 60-month recurrence-free survival of 68% (control group)

The primary endpoint was met if recurrence-free survival was significantly improved for pembrolizumab versus placebo at either of the first two interim analyses under multiplicity control.

KEYNOTE-716 – DESIGN CONCERN #1

Statistical plan based on historical data



Lee, et al. *Ann Surg Onc*. 2017:24;939-946.

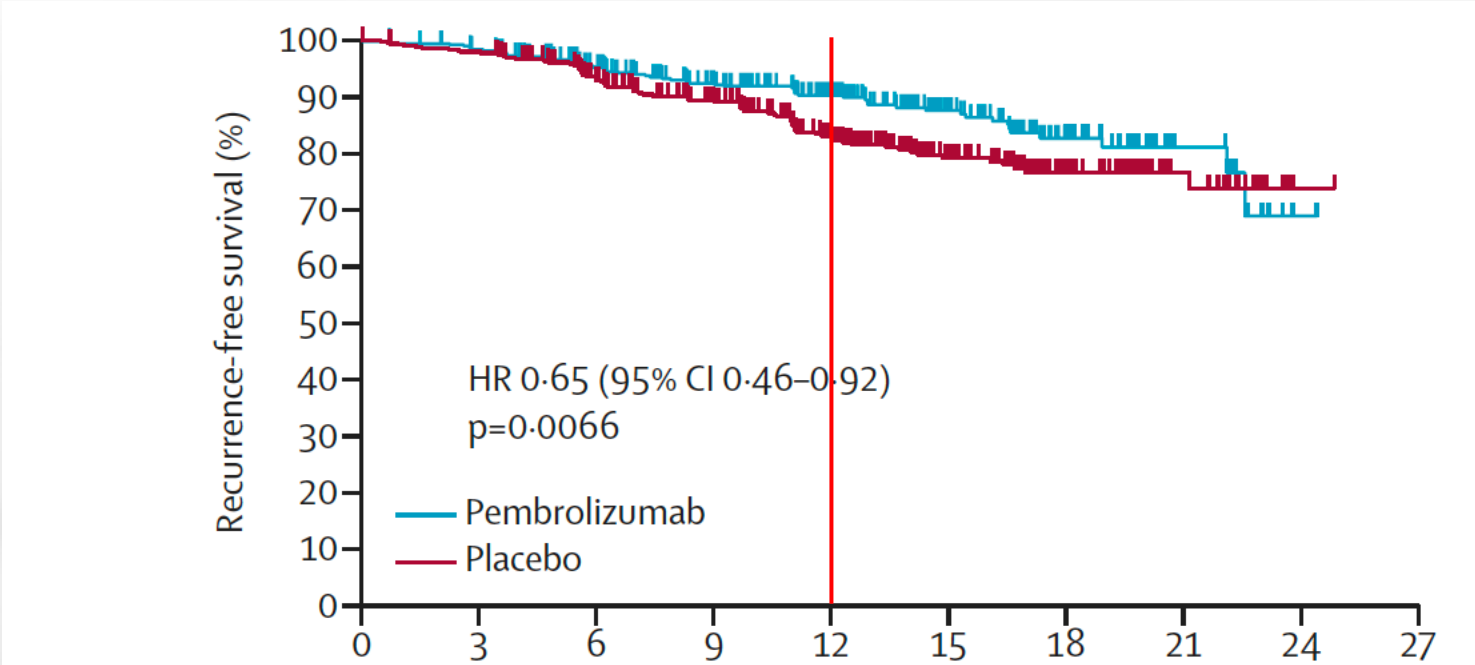
KEYNOTE-716 – DESIGN CONCERN #2

No prospective (or retrospective) data to support a 60-month RFS rate of 68%

> We based sample size and power calculations on a cure model with a long-term recurrence-free survival of 50% and estimated 60-month recurrence-free survival of 68% (control group)

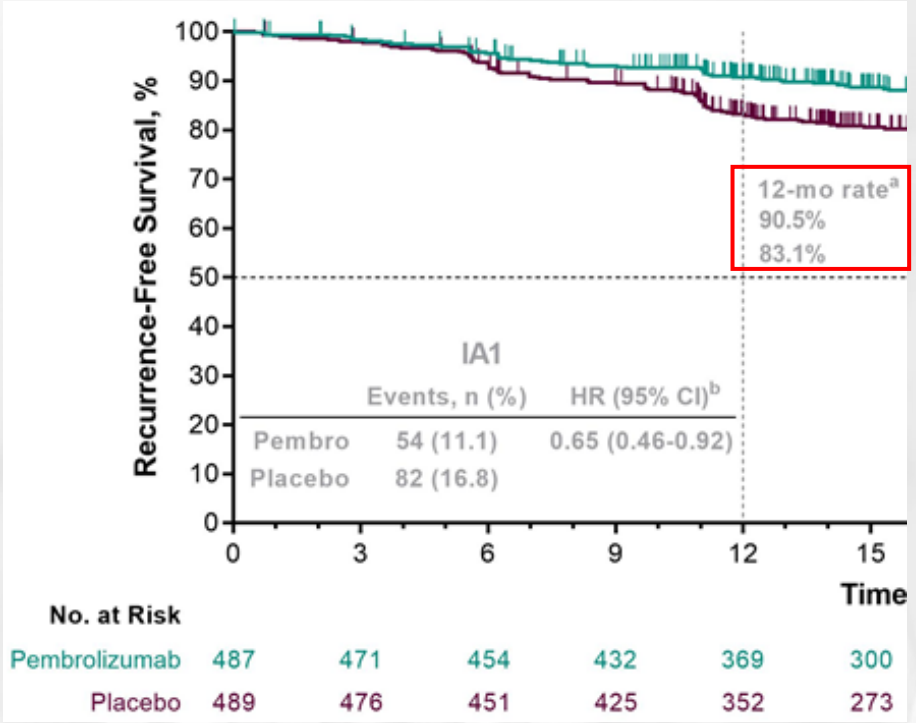
Yushak M, Mehnert J, Luke J, Poklepovic A. Approaches to high-risk resected stage II and III melanoma. *Am Soc Clin Oncol Educ Book* 2019; 39: e207–11.

KEYNOTE-716 – RESULTS



Number at risk (number censored)										
Pembrolizumab	487	465	401	340	249	149	71	21	1	0
	(0)	(14)	(65)	(115)	(199)	(294)	(365)	(414)	(432)	(433)
Placebo	489	475	400	336	229	149	77	27	1	0
	(0)	(4)	(59)	(106)	(192)	(263)	(331)	(381)	(406)	(407)

KEYNOTE-716 – RESULTS



12-month RFS
Pembro: 90.5%
Placebo: 83.1%
Difference: **7.4%**

FDA approves pembrolizumab for adjuvant treatment of Stage IIB or IIC melanoma

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pembrolizumab-adjuvant-treatment-stage-iib-or-iic-melanoma

Courtesy of Jason Luke

KEYNOTE-716 – RESULTS

	Events/patients		Hazard ratio (95% CI)
	Pembrolizumab	Placebo	
T category			
T3b	18/200	44/200	0·40 (0·23–0·69)
T4a	11/109	24/116	0·49 (0·24–1·00)
T4b	39/171	45/169	0·82 (0·54–1·26)

KEYNOTE-716 – ADVERSE EVENTS

	Pembrolizumab group (n=483)		Placebo group (n=486)	
	Any	Grade ≥3	Any	Grade ≥3
Any cause adverse event	449 (93%)	125 (26%)	433 (89%)	83 (17%)*
Any treatment-related adverse event	386 (80%)	78 (16%)	296 (61%)	21 (4%)

NCCN RECOMMENDATIONS

Clinical trial for Stage II
or
Observation
or
Pembrolizumab for pathologically Staged IIB or IIC[z,aa]

[a] Adjuvant pembrolizumab is active in reducing relapse events for resected Stage IIB and IIC melanoma. However, longer followup is needed to evaluate the impact of adjuvant pembrolizumab on overall survival. Clinicians considering adjuvant pembrolizumab therapy for Stages IIB or IIC disease should have a detailed discussion with the patient, to weigh the pros and cons of treatment benefit vs toxicity. Factors to be considered, in addition to stage, include patient's age, performance status, personal/family history of autoimmune disease, and tolerance for risk.

Pathologic staging (with SLNB) for stage IIB and IIC melanoma is strongly preferred prior to the recommendation of adjuvant pembrolizumab - to enhance risk/benefit patient discussions and optimize local/regional disease control.

CONCLUSIONS

- Pembrolizumab is approved for use in stage II melanoma patients that have undergone wide excision and SLNB
- We need more data to recommend its widespread use in this population
- We need to better predict which stage II patients might benefit from adjuvant therapy instead of just giving it to all of them
- Think before acting (in this case…infusing)