2022 AHNS/AAO Head & Neck Surgery Symposium for Residents & Fellows

MELANOMA

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1

DISCLOSURE SLIDE

Thomas J. Ow, MD, MS
Site P.I. for multicenter clinical trial supported by:

PRESAGE BIOSCIENCES, INC

Takeda (Millennium Pharmaceuticals, Inc.)

Bristol Myers Squibb (discontinued)

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Objectives:

- Key Features of Melanoma
- Principles and pearls of treatment
- Updates in management
- Future Directions

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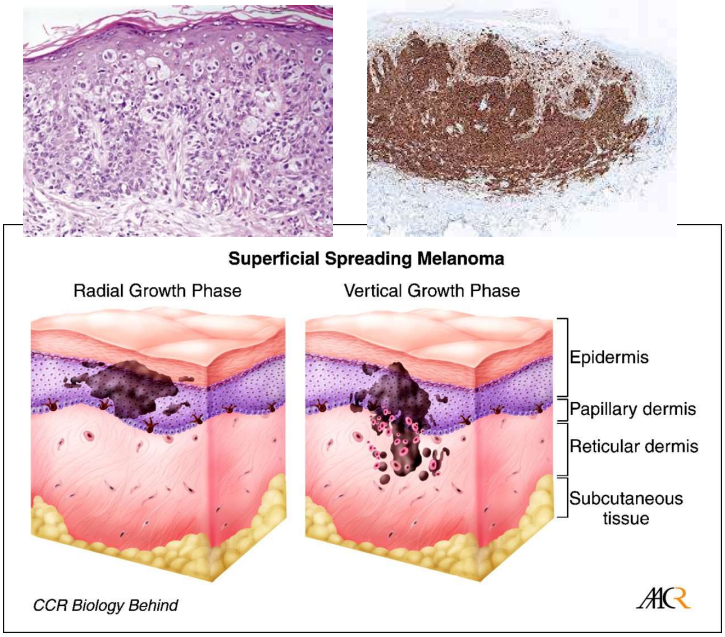
Biology

- Neural crest origin
- Great Masquerader (stain HMB-45, Melan-A, S100)
- DNA damage caused by UV light
- Horizonal vs. vertical growth phase



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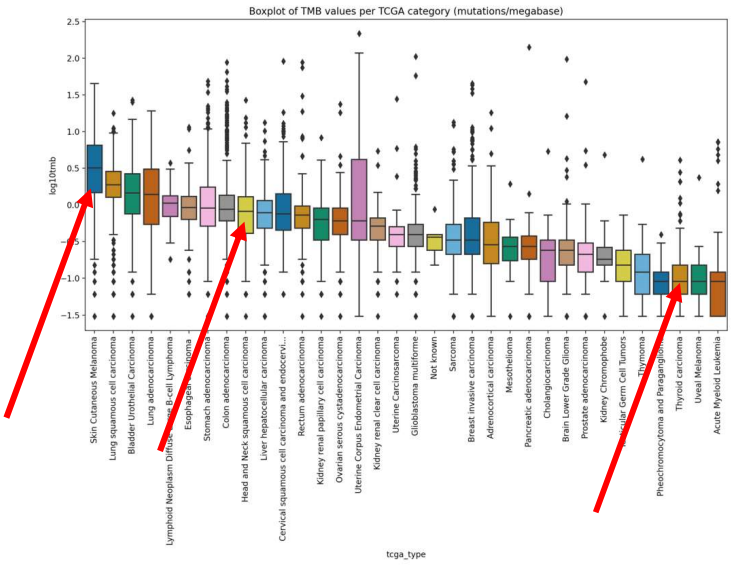
BIOLOGY – GENOMICS….

- Activating BRAF mutations (V600E)
- Activating RAS mutations
- NF1, TP53, CDKN2A (tumor suppressors lost)
- High tumor mutation burden (TMB)



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Subtypes

- Superficial Spreading
- Nodular
- Lentigo Maligna Melanoma
- Acral Lentiginous

- **OTHER subtypes and considerations:**
  - Mucosal melanoma
  - Desmoplastic
  - Amelanotic…
  - Regression…

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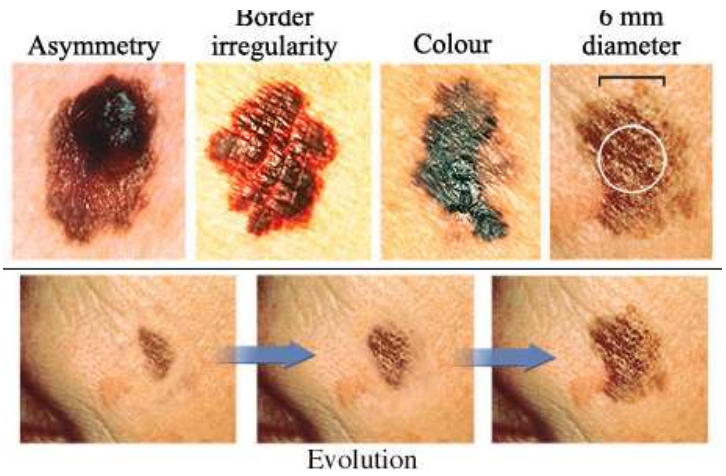
Diagnosis

- ABCDEs
- Punch vs. Shave vs. Excisional
- Other Considerations….
  - DEPTH
  - Don't LOSE IT…..
- Parotid and Comprehensive Neck Exam
- Assess for Satellitosis



Source: NCI Visuals Online. Skin Cancer Foundation. http://visualsonline.cancer.gov/about.cfm

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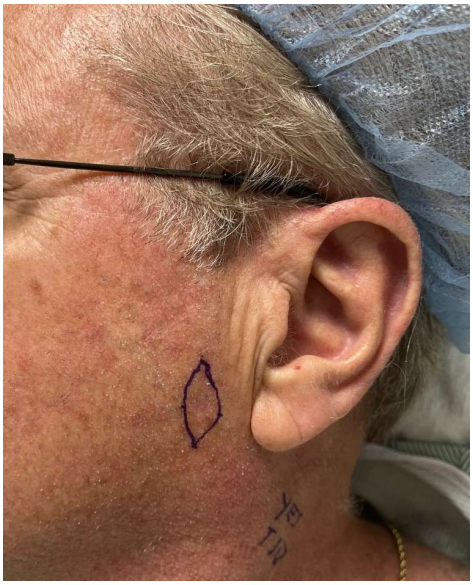
7



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Definition of Primary Tumor (T) - AJCC 8th Edition

T Category	Thickness	Ulceration status
Tis (melanoma *in situ*)	Not applicable	Not applicable
T1	≤1.0 mm	Unknown or unspecified
T1a	<0.8 mm	Without ulceration
T1b	<0.8 mm	With ulceration
	0.8–1.0 mm	With or without ulceration
T2	>1.0–2.0 mm	Unknown or unspecified
T2a	>1.0–2.0 mm	Without ulceration
T2b	>1.0–2.0 mm	With ulceration
T3	>2.0-4.0 mm	Unknown or unspecified
T3a	>2.0–4.0 mm	Without ulceration
T3b	>2.0–4.0 mm	With ulceration
T4	>4.0 mm	Unknown or unspecified
T4a	>4.0 mm	Without ulceration
T4b	>4.0 mm	With ulceration

Gershenwald, Scolyer, et al. Melanoma. In Amin, M.B., Edge, S.B., Greene, F.L., et al. (Eds.) AJCC Cancer Staging Manual. 8th Ed. New York: Springer; 2017

9

TREATMENT - EXCISION

Tumor Thickness	Recommended Margins
In Situ	0.5 cm
≤ 1.0 mm	1.0 cm
1.01 – 2.0 mm	1-2 cm
2.01 – 4.0 mm	2.0 cm
> 4.0 mm	2.0 cm

* If feasible …
* what about depth?
* CoC - Surgical synoptic reporting

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COMMENT ON RECONSTRUCTION – simple or DELAY

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11

TREATMENT – MANAGING THE N0 NECK

MSLT-I

- *Morton et al; MSLT Group. Sentinel-node biopsy or nodal observation in melanoma. N Engl J Med. 2006 Sep 28;355(13):1307-17
- *Morton et al. MSLT Group. Final trial report of sentinel-node biopsy versus nodal observation in melanoma. N Engl J Med. 2014 Feb 13;370(7):599-609.

Indications for SLNBx

- T1b or greater
- Other adverse prognostic variables to consider:
  - Tumor extension to deep margin
  - Ulceration
  - Lymphovascular invasion
  - Extensive regression to 1.0 mm
  - Young age
  - High mitotic rate (≥ 1mm)

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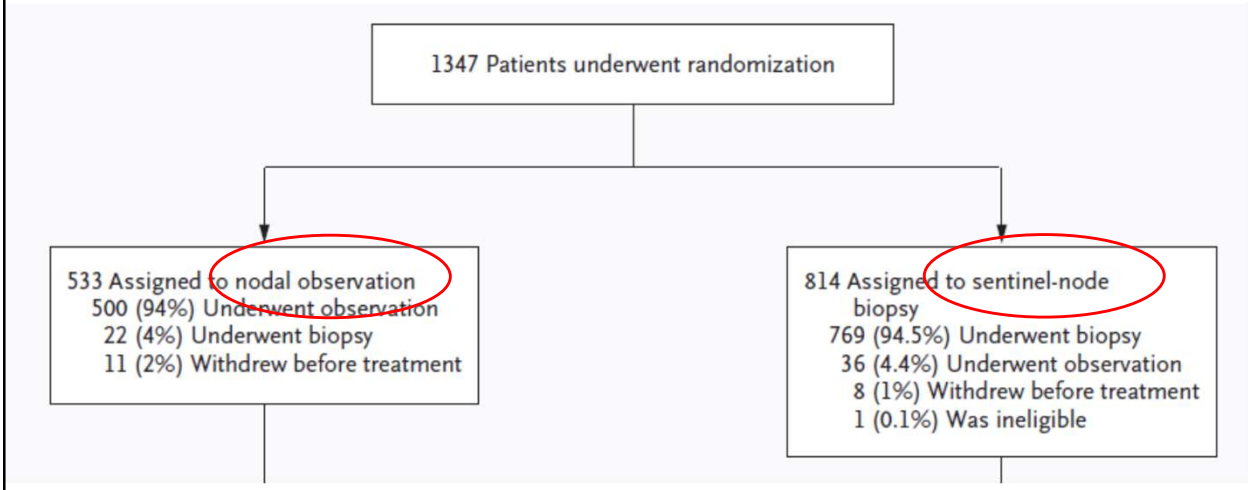
12

MSLT-I - key data and conclusions…



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13

MSLT-I - key data and conclusions…

Table 1. Baseline Characteristics of the Patients.*

Characteristic	All Patients†		Patients with Nodal Metastases‡		
	Observation (N=500)	Biopsy (N=769)	Observation (N=78)§	Biopsy, Positive Node (N=122)¶	Biopsy, False Negative Node (N=26)‖
Positive nodes‡‡					
1 — %			39.2	70.5	61.9
2 or 3 — %			35.1	27.9	9.5
4 or more — %			25.7	1.6	28.6
No. of positive nodes — mean ±SE			3.3±0.5	1.4±0.1	4.3±1.6
Site of first recurrence — no. (%)					
Nodal	65 (13.0)	32 (4.2)			
Distant	39 (7.8)	85 (11.0)			
Local or in-transit	30 (6.0)	42 (5.5)			
No recurrence — no. (%)	366 (73.2)	610 (79.3)			

- SLNBx (+) = 122/769 = **~16%**
- Note ~26 false negative (26/647 negative SLNB = **4%**)

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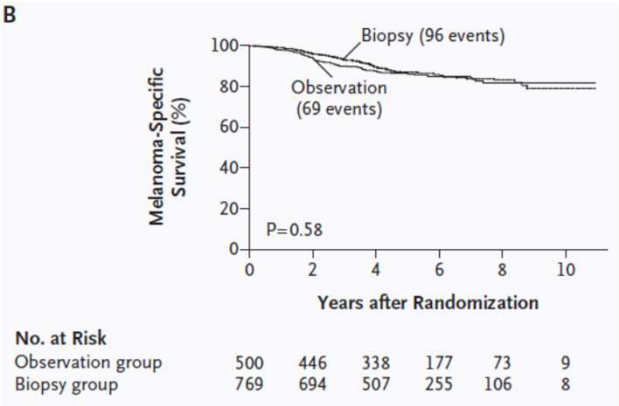
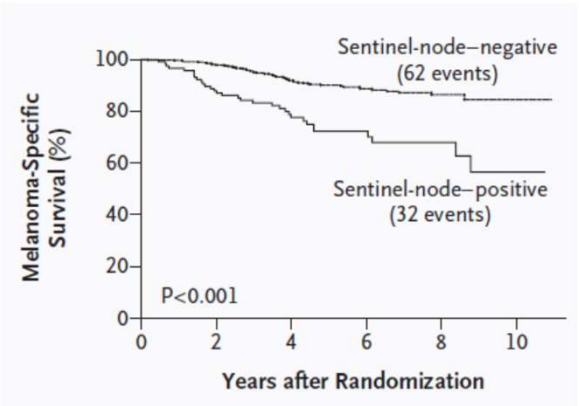
14

MSLT-I - key data and conclusions…
*SLNBx is PROGNOSTIC





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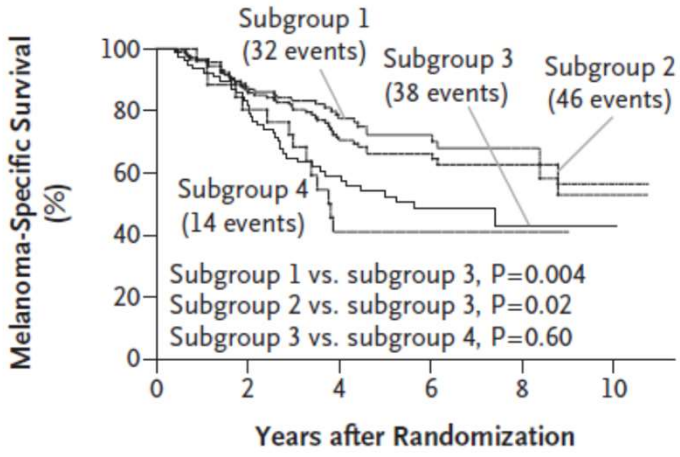
15

MSLT-I - key data and conclusions…
*Identifying + nodes earlier improves MSS



- SG1 = + SLNBx
- SG2 = +SLNBx + FN
- SG3 = + after Obs
- SG4 = FN

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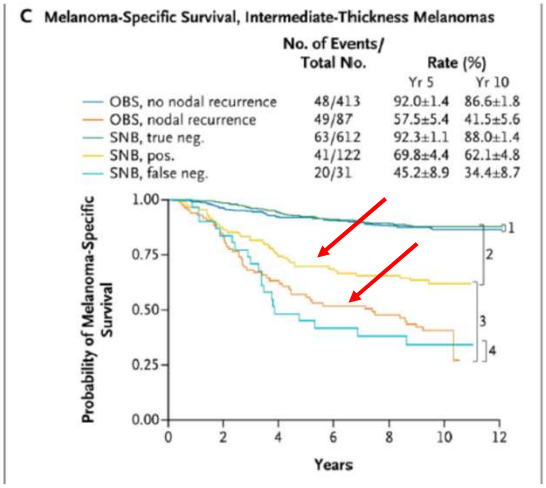
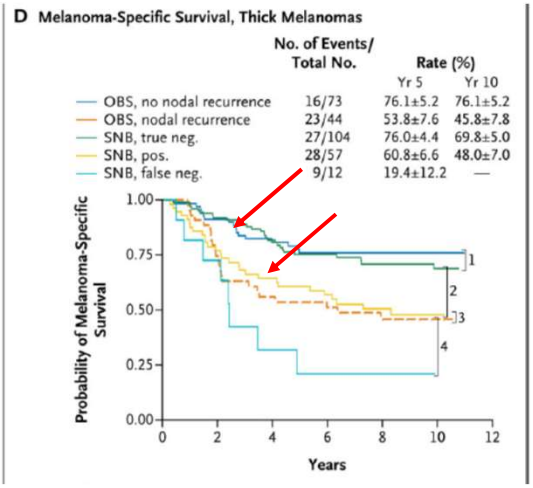
16

MSLT-I final report - key data and conclusions…



Effective? (Survival advantage with SLNBx)



Prognostic

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17

MSLT-1…. Some Conclusions

- SLNBx is PROGNOSTIC
- SLNBx arm not improved MSS compared to observation arm
- SLNBx positives seem to have better MSS than observation patients who develop regional disease
- FNR = 4% (even in best of scenarios)
- So, is completion neck dissection helpful….????

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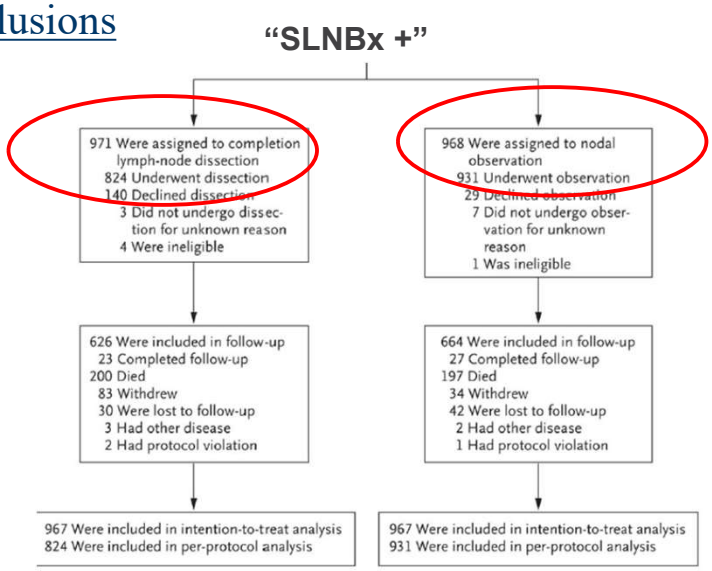
18

MSLT-2 Key data and conclusions

- *Faries MB et al. Completion Dissection or Observation for Sentinel-Node Metastasis in Melanoma. N Engl J Med. 2017 Jun 8;376(23):2211-2222.



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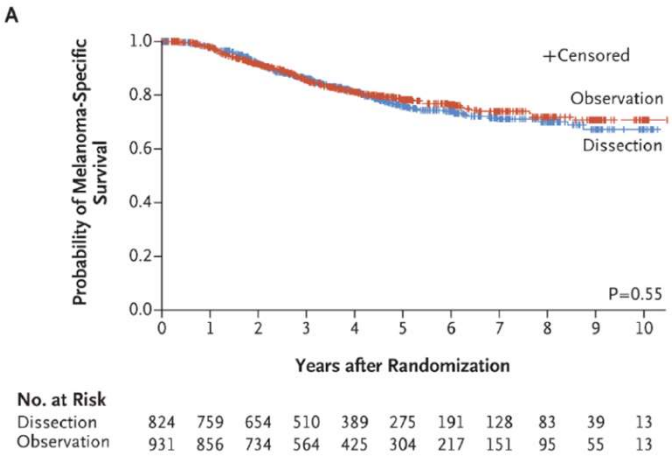
19



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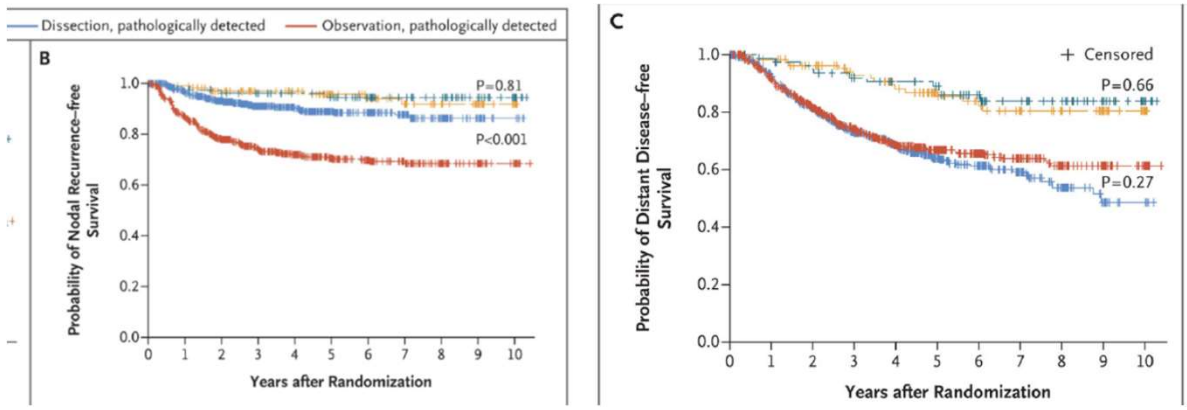
20



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21

MSLT-2 – Summary, Conclusions, and Thoughts…

- Completion nodal dissection was NOT associated with significantly improved MSS
- Does improve regional control….

FOR completion dissection

- Head and neck under-represented in MSLT study
- Regional control may be more important for HN
- Parotid/Neck dissection less morbid than other nodal basins?

AGAINST completion dissection

- The neck dissection can be quite extensive in setting of no survival advantage
- Real morbidity of dissection
- Difficult to convince patients of benefit…
- AND…..

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22

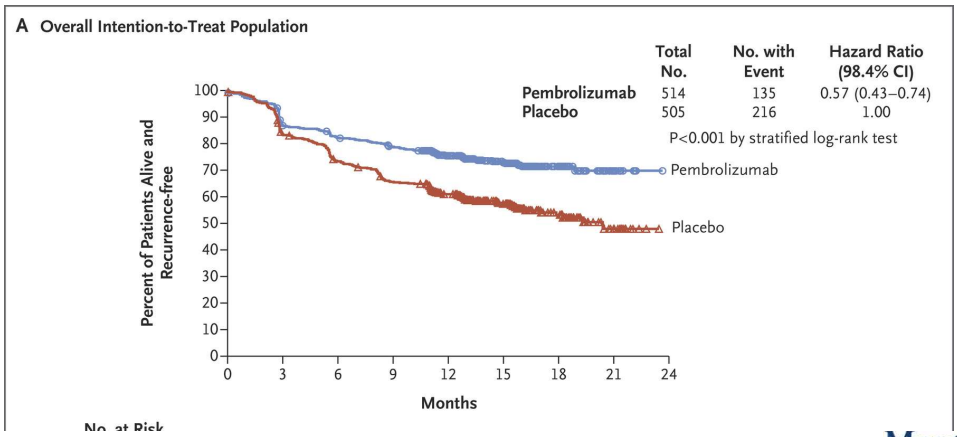
MANAGEMENT - CHEMOTHERAPY

Drugs Approved for Melanoma	
Kimmtrak (Tebentafusp-tebn)	affinity-enhanced T-cell receptor fused to an anti-CD3 effector - redirect T cells to target glycoprotein 100-positive cells
Braftovi (Encorafenib)	BRAF
Dabrafenib Mesylate	BRAF
Tafinlar (Dabrafenib Mesylate)	BRAF
Vemurafenib	BRAF
Ipilimumab	CTLA4
Dacarbazine	cytotoxic
Aldesleukin	IL-2
Intron A (Recombinant Interferon Alfa-2b)	INF-Alpha2b
Peginterferon Alfa-2b	INF-Alpha2b
Binimetinib	MEK1/2
Cobimetinib Fumarate	MEK1/2
Mekinist (Trametinib)	MEK1/2
Imlygic (Talimogene Laherparepvec)	oncolytic virus + GM-CSF
Keytruda (Pembrolizumab)	PD1
Nivolumab	PD1
Pembrolizumab	PD1
Opdualag (Nivolumab and Relatlimab-rmbw)	PD1 and LAG3

23

Adjuvant PD-1 inhibition for stage III melanoma

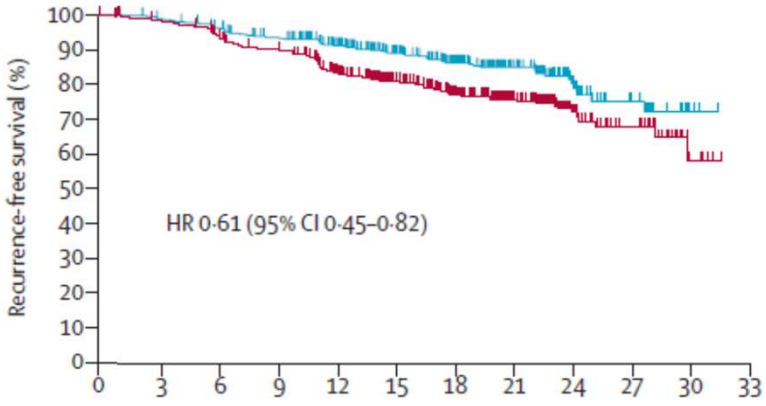
Eggermont AMM, et al. Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma. N Engl J Med. 2018 May 10;378(19):1789-1801.



24

Adjuvant PD-1 inhibition for stage IIB/IIC melanoma

Luke JJ, et Al. KEYNOTE-716 Investigators. 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 Apr 30;399(10336):1718-1729.



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25

Summary – adjuvant therapy for completely resected patients

- Means the "observation" arms of MSLT1/2 are all improved
- Even less justification for completion neck dissection
- Theoretical justification to maintain microscopic disease when immune checkpoint therapy administered (??)
- Prognostic value of SLNBx important

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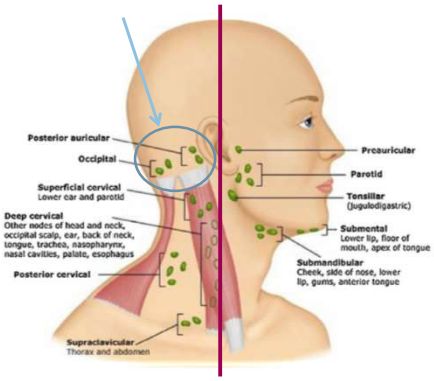
Therapeutic Neck Dissection for SLNBx+ or Grossly Positive Regional Disease

- Primary disease anterior to the line:
  - ANTERIOLATERAL dissection
  - Parotid, perifacial, Level I, II, II, IV, (V)
- Primary disease posterior to the line
  - POSTEROLATERAL
  - Retroauricular, occipital, Level II, III, IV, V



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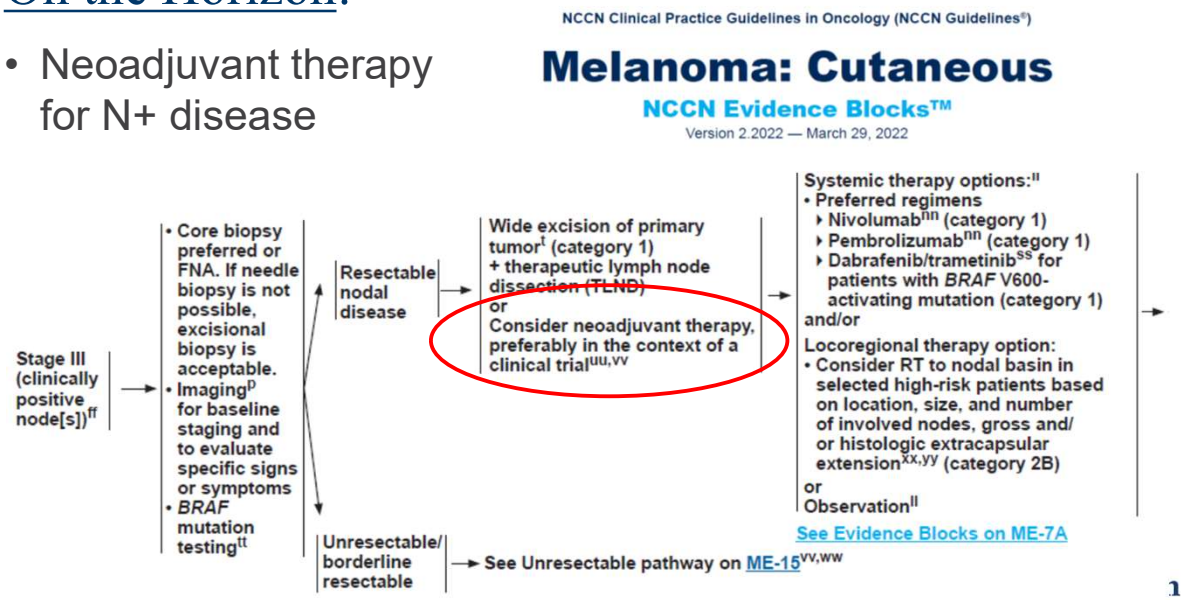
27

On the Horizon:

- Neoadjuvant therapy for N+ disease



28

Concluding remarks

- **Several Principles of management remain:**
  - Depth based risk-stratification
  - Role of SLNBx
- **Advances in system therapy are significantly impacting survival outcomes and treatment decision trees**
- **Future directions:**
  - Neoadjuvant treatment for locoregionally advanced disease
  - More molecular/Immune Biomarkers for response to new agents
- **Not discussed, but important:**
  - Technical nuances, in-transit metastasis, desmoplastic melanoma, mucosal melanoma….

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29

THANK YOU
Questions?

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30