

Molecular diagnostics in melanoma

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Relevant Disclosures

- Consulting Fees: AstraZeneca, Bristol Myers Squibb, Eisai, Iovance, Merck, Novartis, Pfizer, Oncosec, Replimune
- Contracted Research: Merck

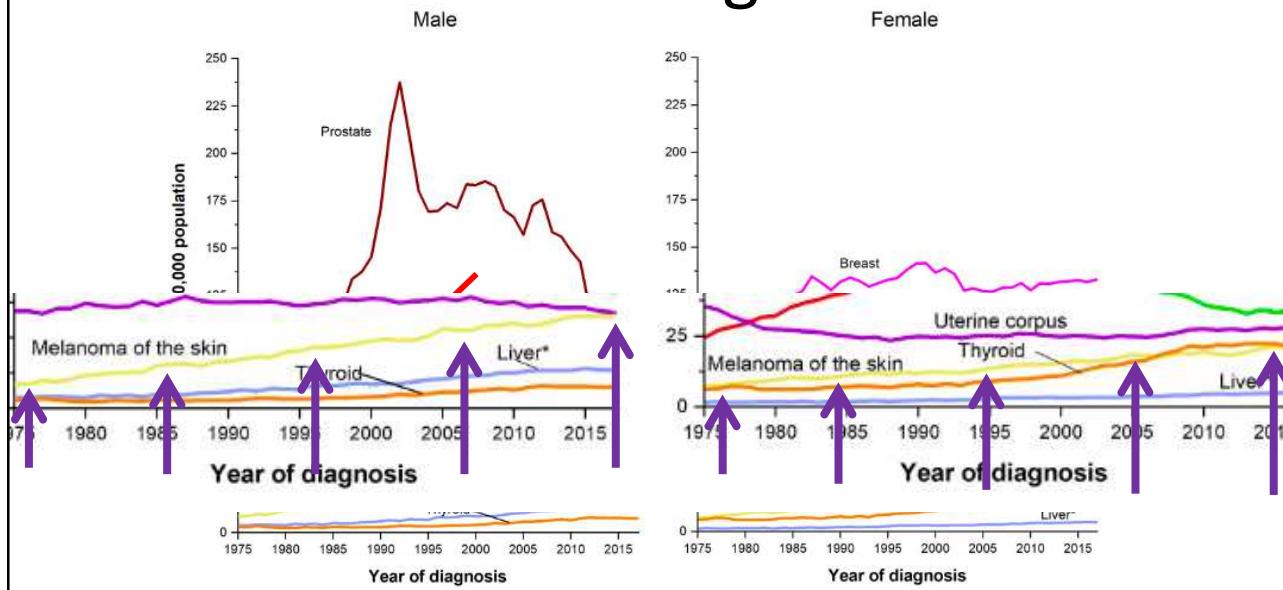
Melanoma is common...

Estimated New Cases

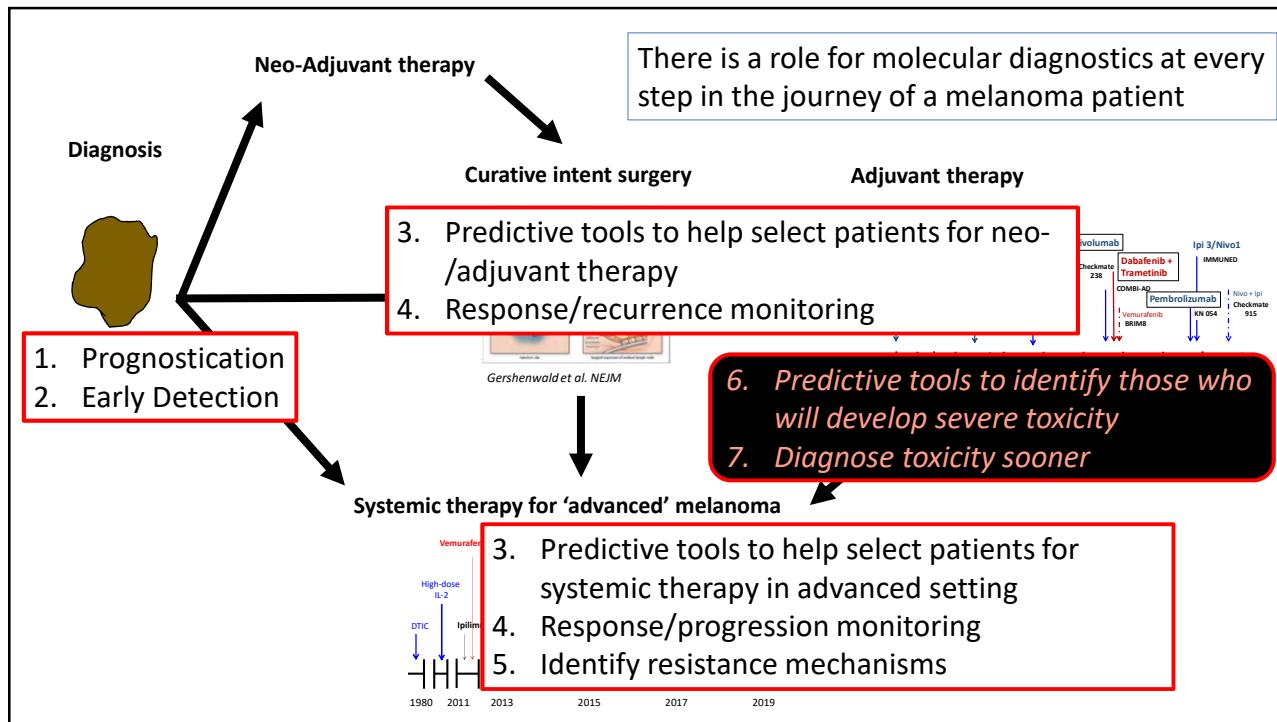
	Males	Females			
Prostate	248,530	26%	Breast	281,550	30%
Lung & bronchus	119,100	12%	Lung & bronchus	116,660	13%
Colon & rectum	79,520	8%	Colon & rectum	69,980	8%
Urinary bladder	64,280	7%	Uterine corpus	66,570	7%
Melanoma of the skin	62,260	6%	Melanoma of the skin	43,850	5%
Kidney & renal pelvis	48,780	5%	Non-Hodgkin lymphoma	35,930	4%
Non-Hodgkin lymphoma	45,630	5%	Thyroid	32,130	3%
Oral cavity & pharynx	38,800	4%	Pancreas	28,480	3%
Leukemia	35,530	4%	Kidney & renal pelvis	27,300	3%
Pancreas	31,950	3%	Leukemia	25,560	3%
All Sites	970,250	100%	All Sites	927,910	100%

Siegal et al. CA Cancer J Clin. 2021

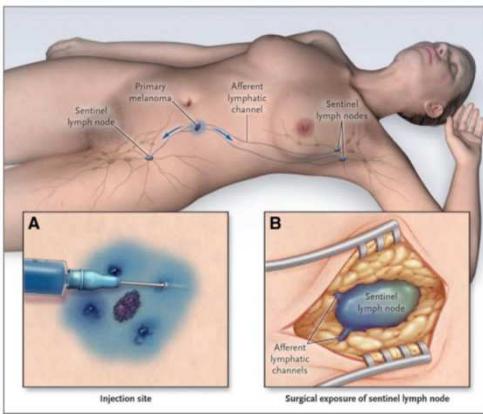
...and becoming more so



Siegal et al. CA Cancer J Clin. 2021

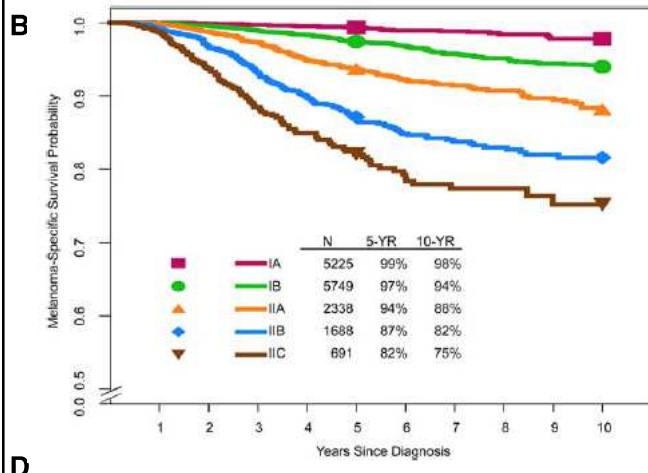


Most melanomas are cured with surgery



Gershenwald and Ross. New Engl J Med. 2011

Melanoma Prognosis: AJCC Stage I-II



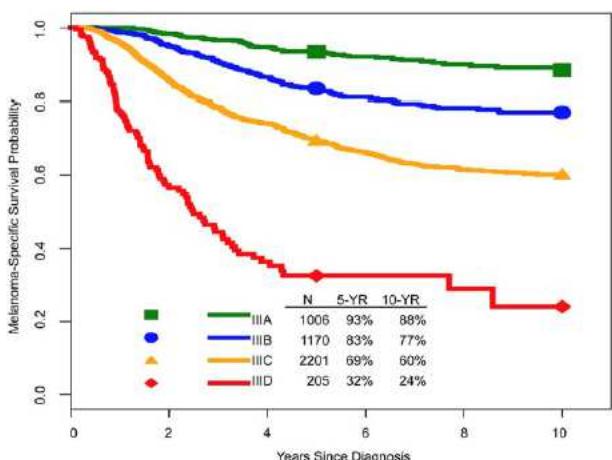
Factors associated with prognosis

- Depth
- Ulceration
- Mitoses
- Gender (Female > Male)
- Age (Younger better)
- Location (Extremities better than trunk, H&N)
- Subtype (Nodular worse)

D

Gershenwald et al. CA Cancer J Clin 2017

Melanoma Prognosis: AJCC Stage III

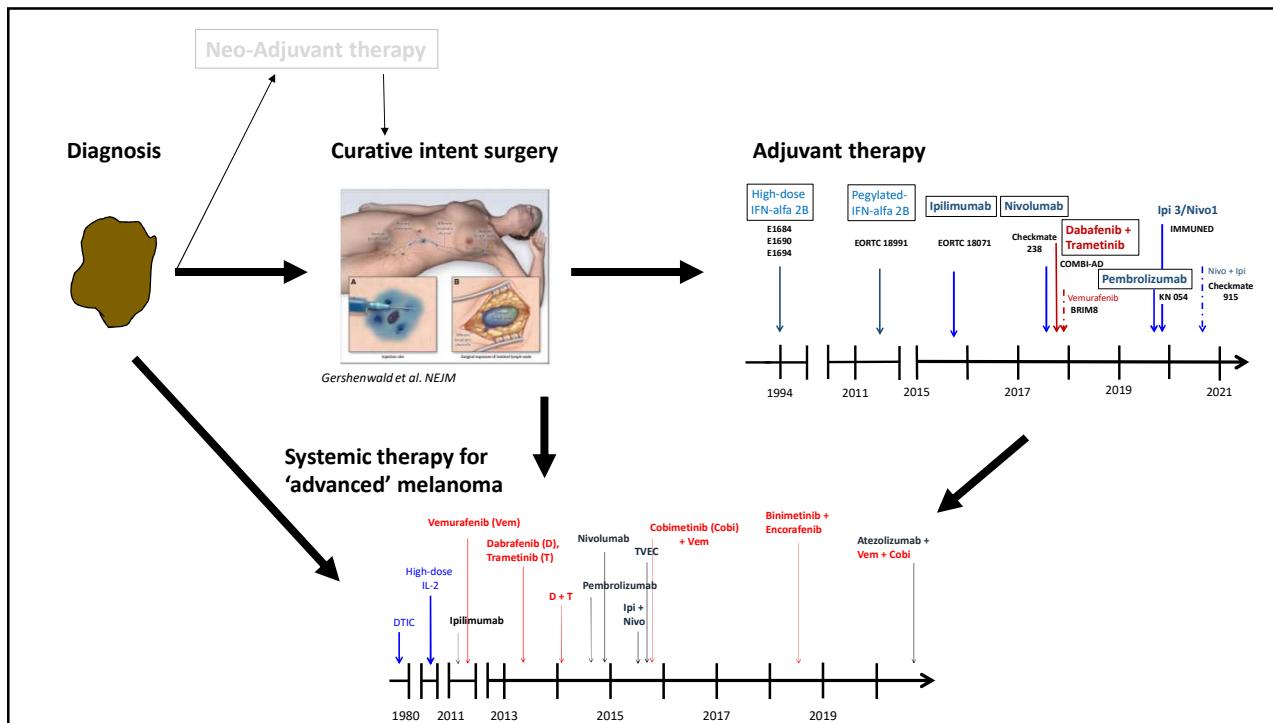
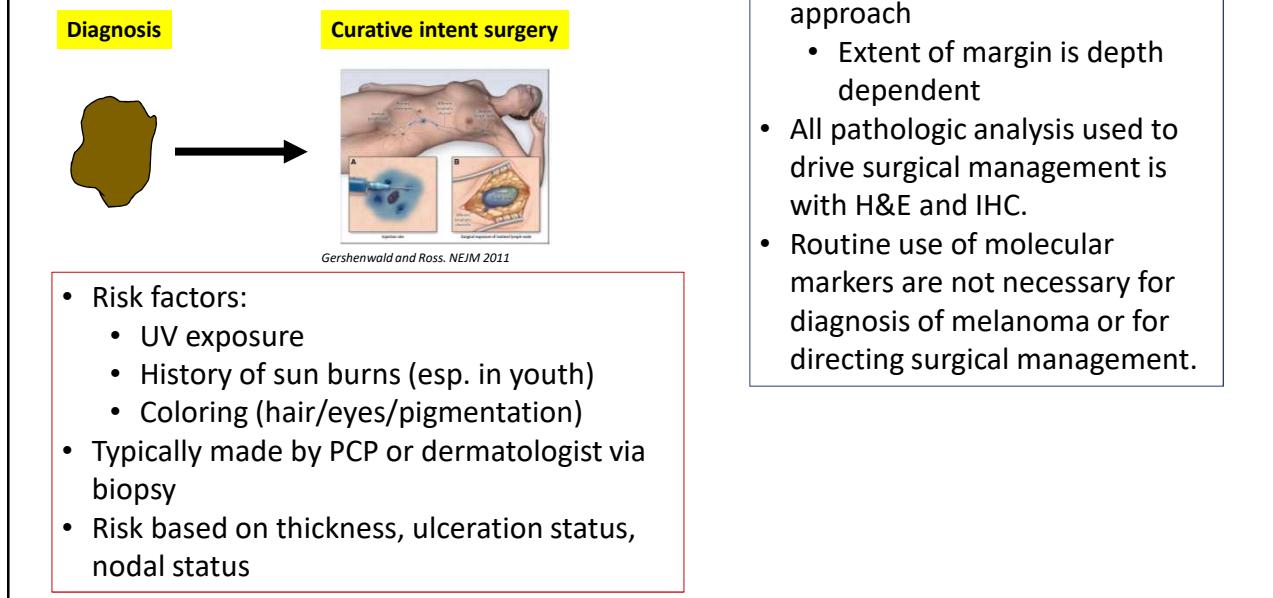


Factors associated with prognosis

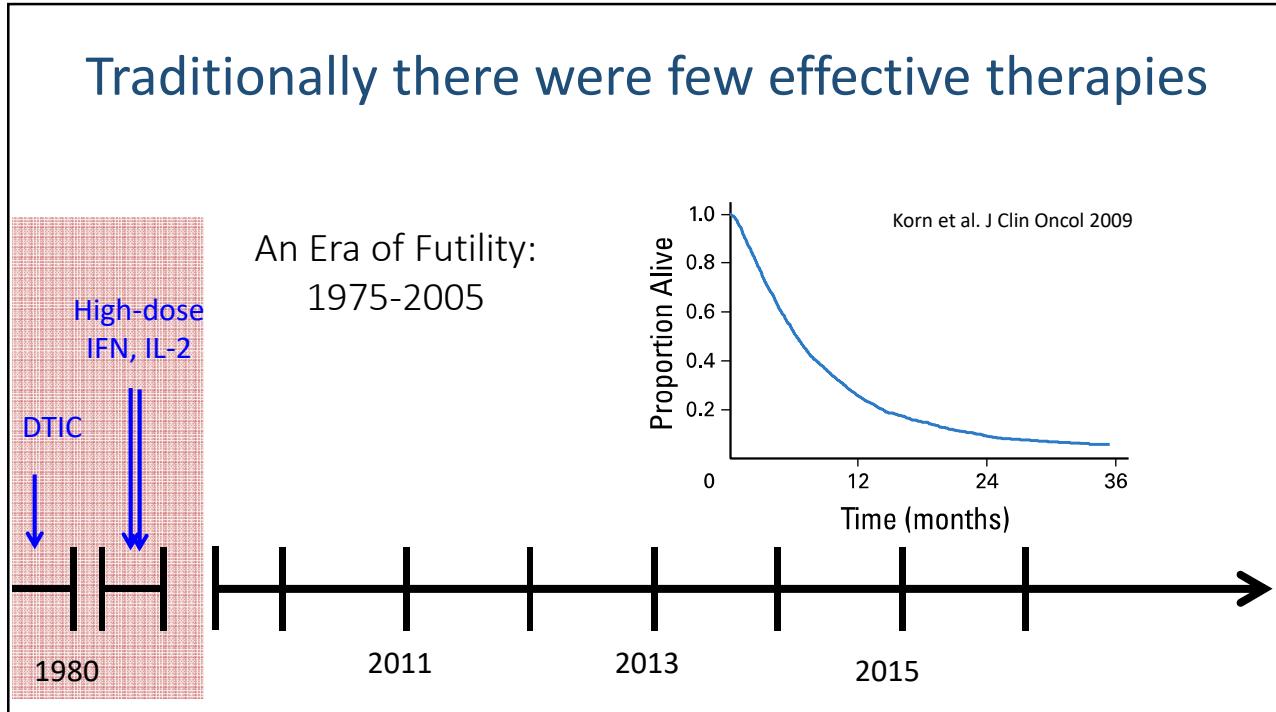
- Number of nodes involved
 - 1 > 2-3 > 4
- Satellites / in transit disease
- Macroscopic involvement
- All the factors mentioned for Stage I-II

Gershenwald et al. CA Cancer J Clin 2017

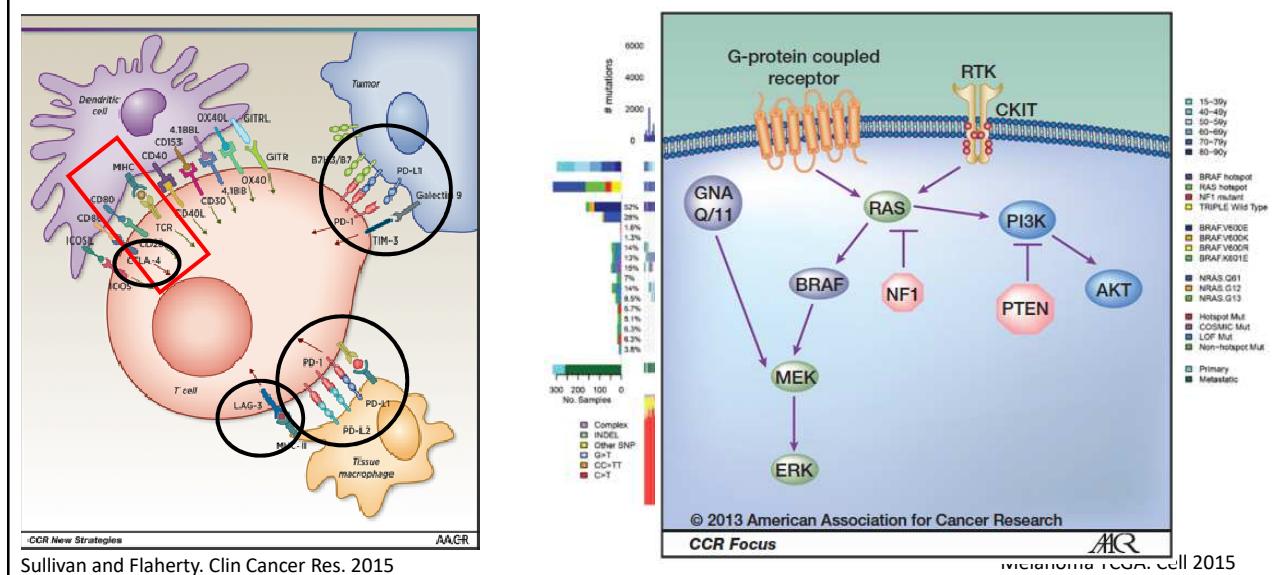
Summary



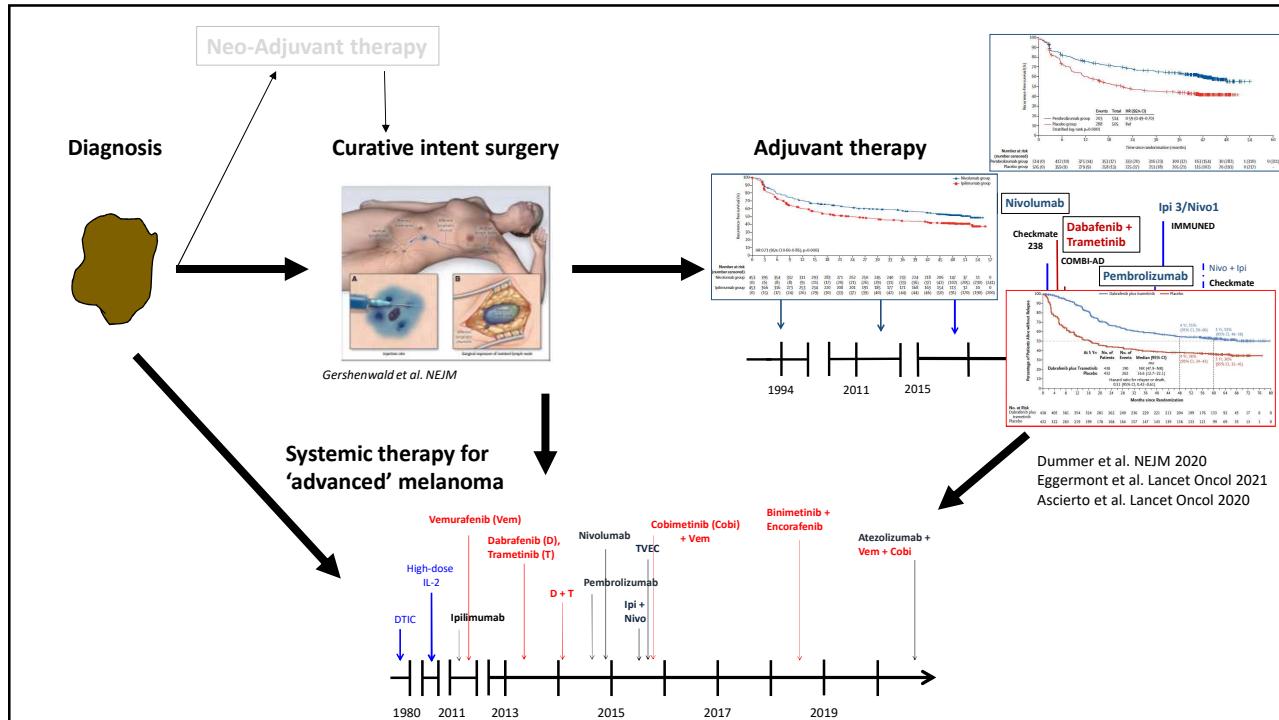
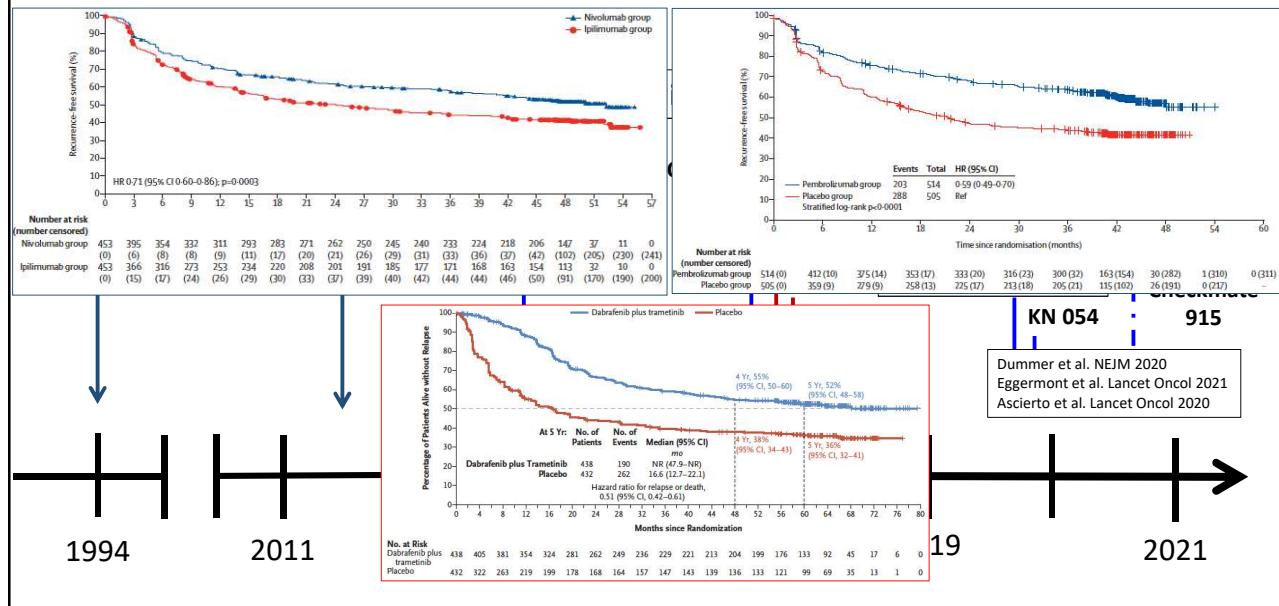
Traditionally there were few effective therapies

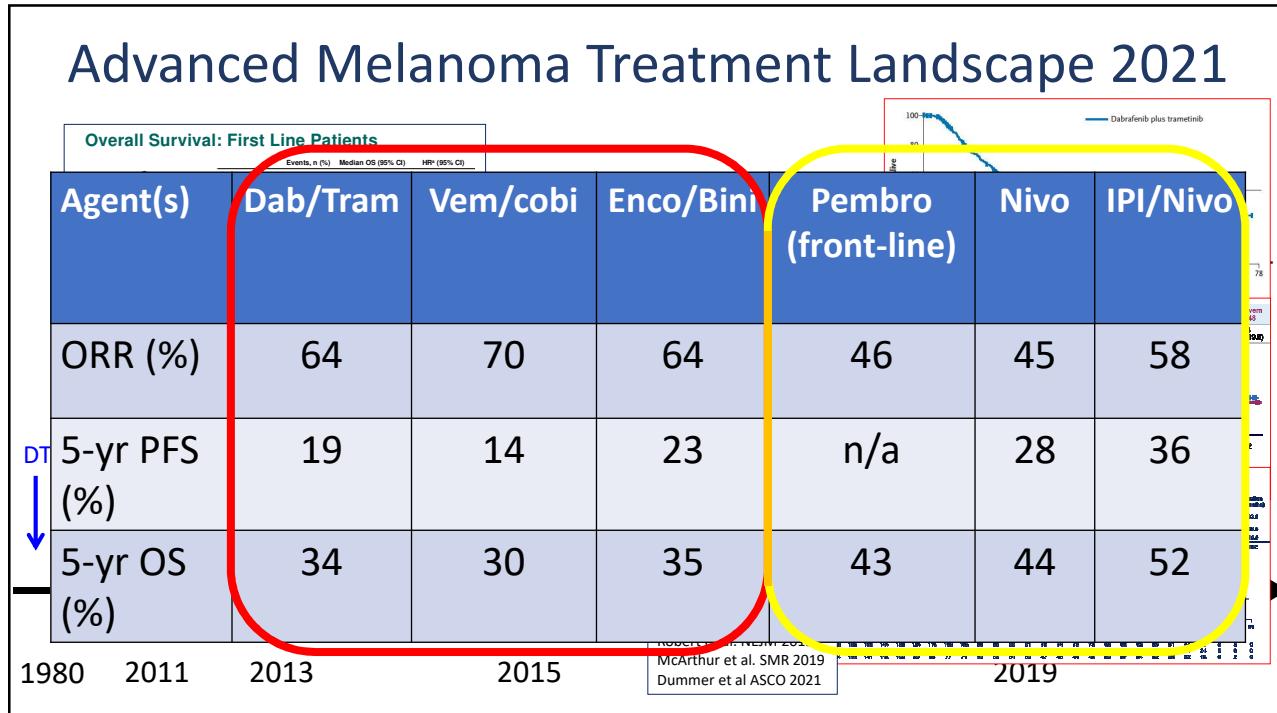
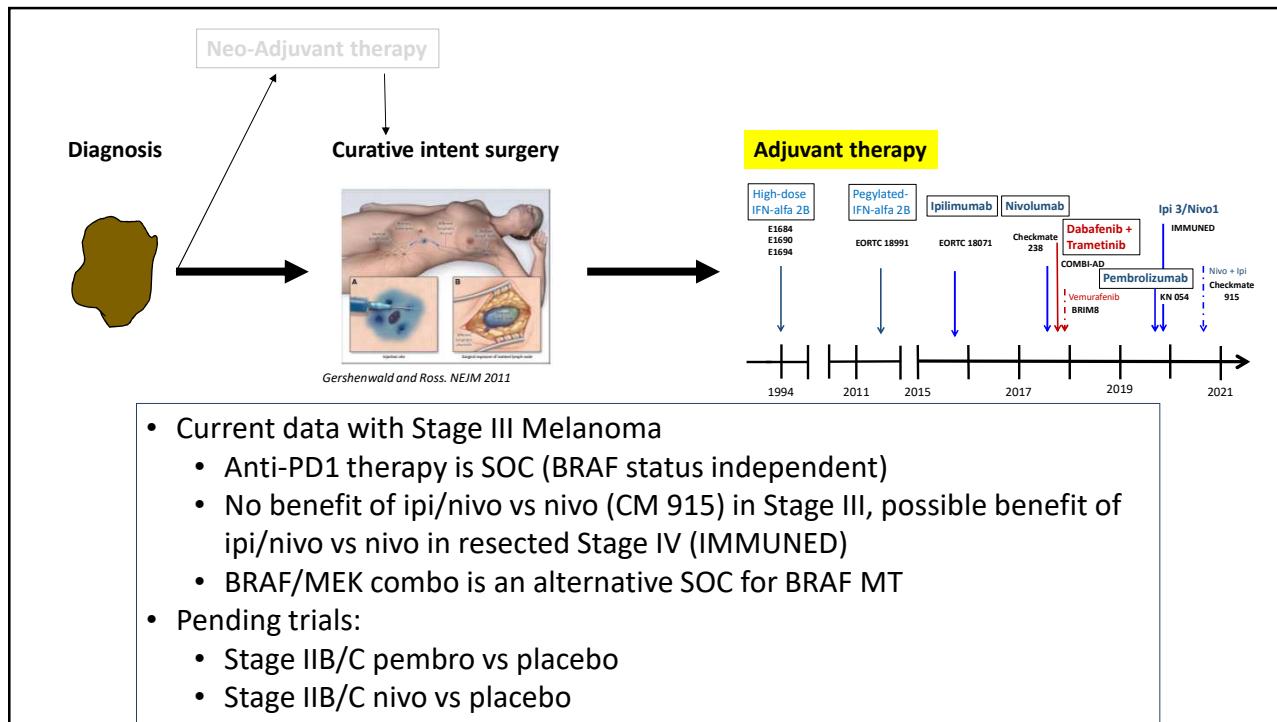


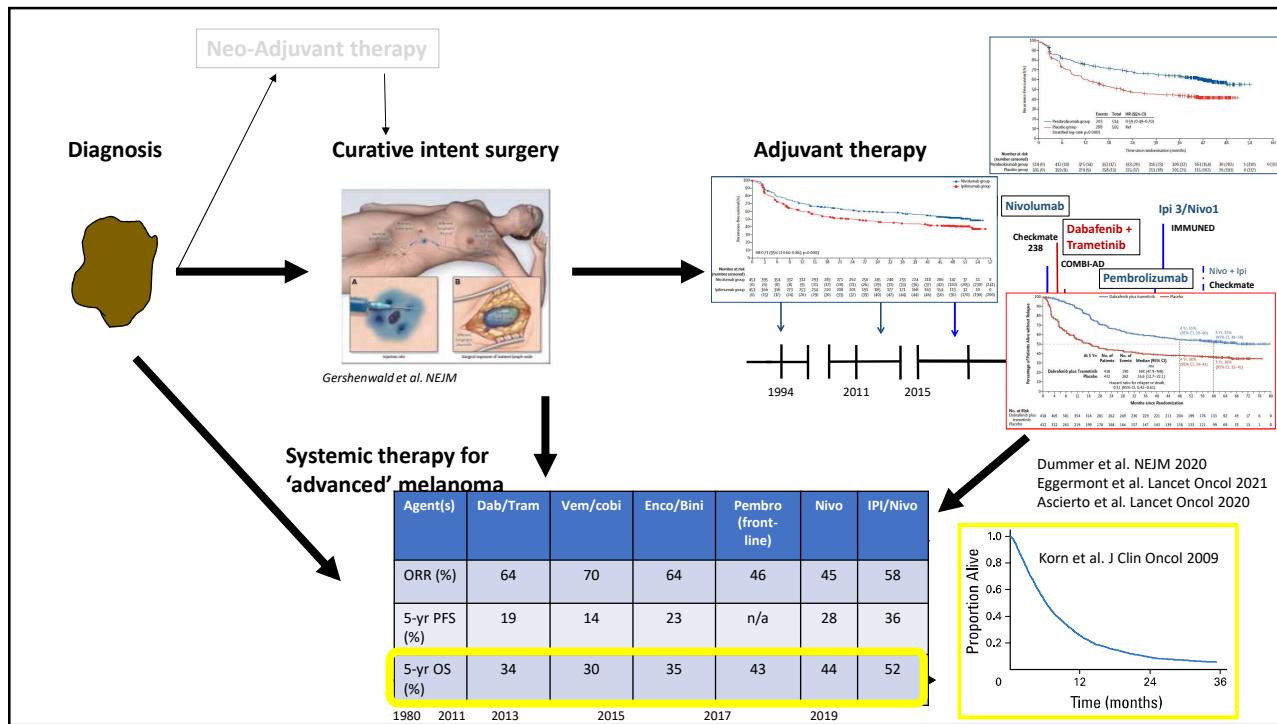
During the “Era of Futility: Two fundamental and translatable discoveries occurred



Adjuvant Melanoma Treatment Landscape 2021

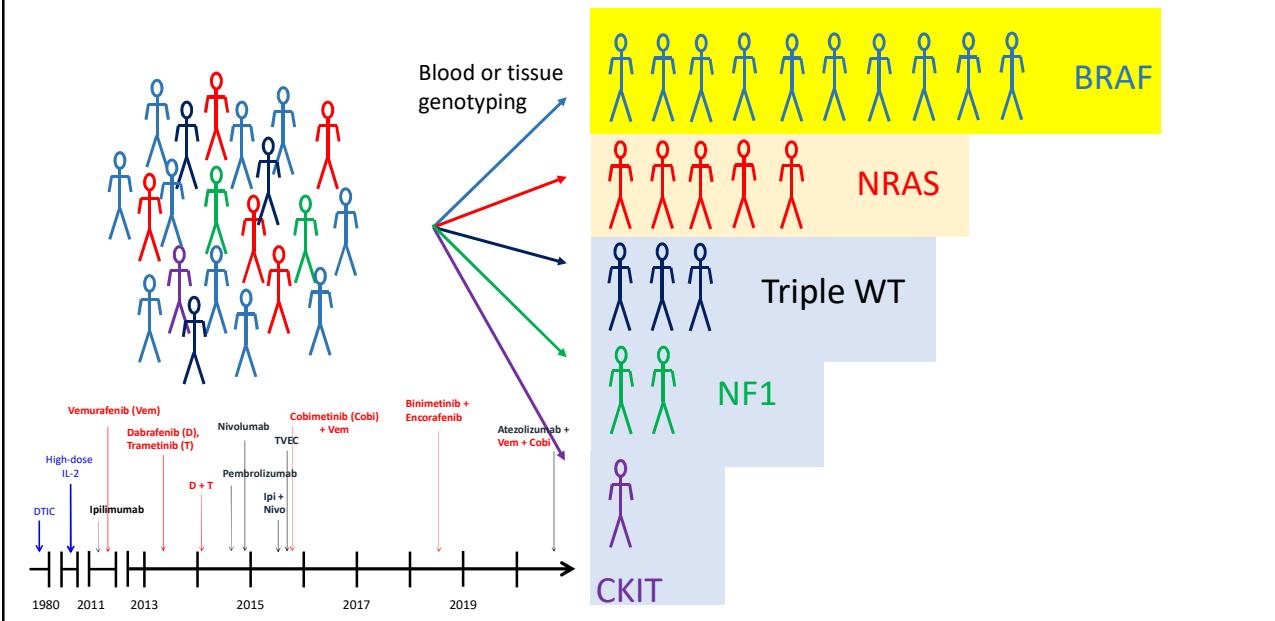






How do we use molecular analyses to aid in treatment selection?

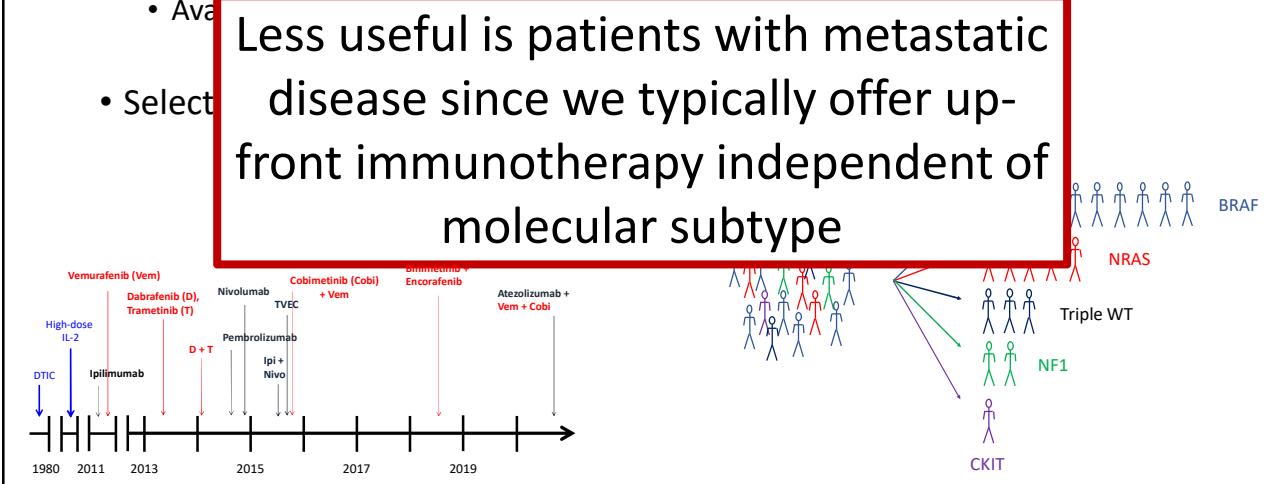
Optimizing Selection Strategy: Melanoma Model #1



Optimizing Selection Strategy: Melanoma Model #1

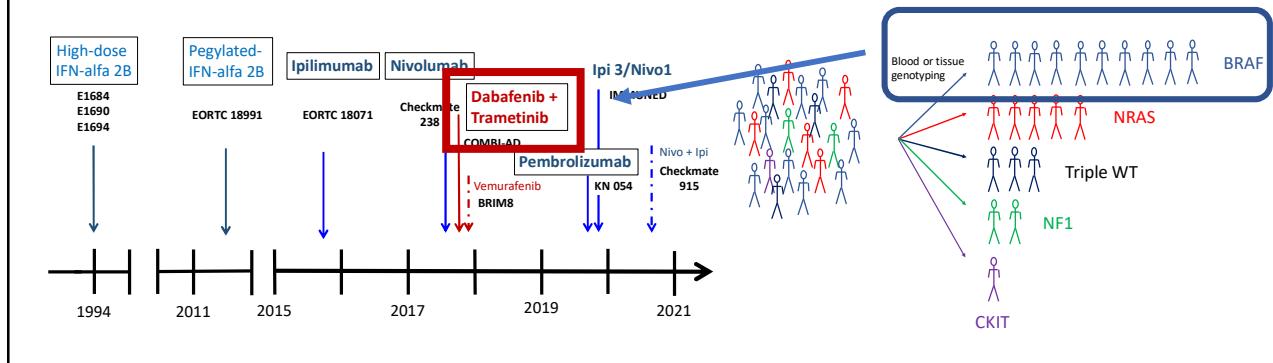
- Entirely dependent on:
 - Genotyping (blood or tissue)
 - Availability of targeted therapies

Less useful is patients with metastatic disease since we typically offer up-front immunotherapy independent of molecular subtype

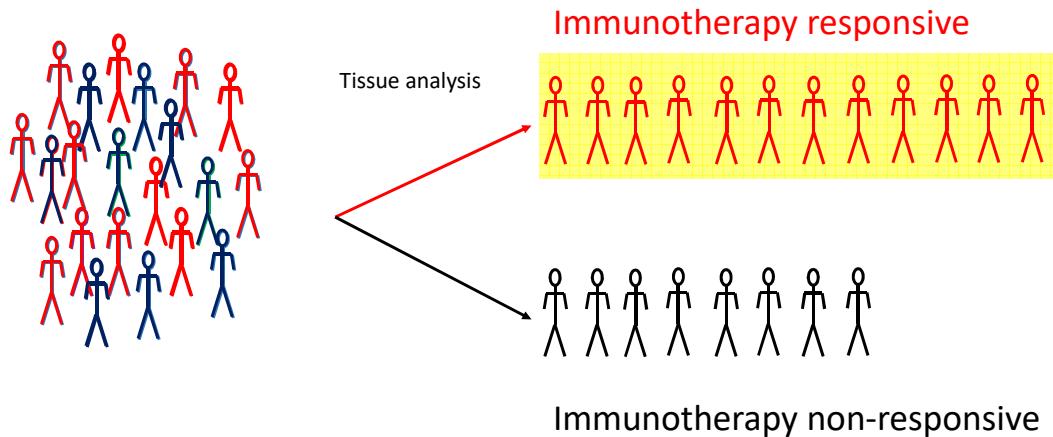


Optimizing Selection Strategy: Melanoma Model #1

- In the adjuvant setting, there is significant reason to consider BRAF/MEK therapy in BRAF mutant patients.
- Selection of immunotherapy by default (BRAF wild-type) or gestalt (bulkier disease...maybe)



Optimizing Selection Strategy: Melanoma Model #2

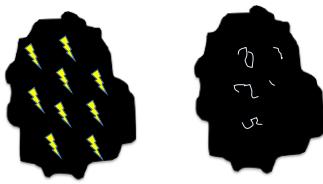


Predictive Model of PD1 responsiveness

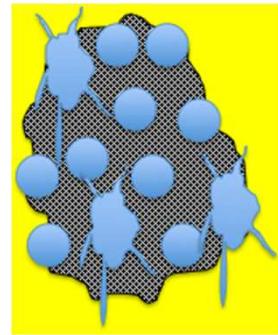
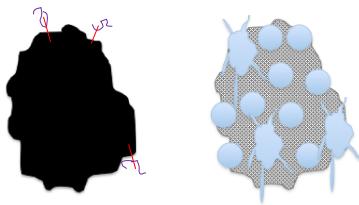
Van Allen et al. Science 2015
Snyder et al. NEJM 2015

Tumeh et al. Nature 2014
Garcia-Diaz et al. Cell Reports 2017
Ayers et al. J Clin Invest 2017

Neoantigen load



T-cell infiltration



Mutational Load

- Van Allen et al. Science 2015
- Snyder et al. NEJM 2015
- Johnson et al. Cancer Immunol Res 2016
- Forschner et al. JTCR 2019
- Rozeman et al. Nat Med 2021

Antigen expression machinery

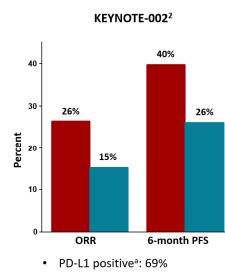
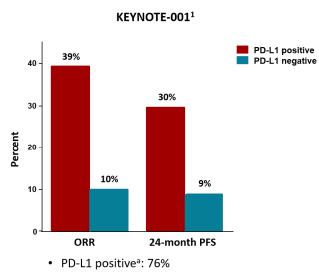
Zaretsky et al. NEJM 2016
Johnson et al. Nat Commun 2016
Sade-Feldman et al. Nat Commun 2017
Rodig et al. Sci Trans Med 2018

PD-L1 expression

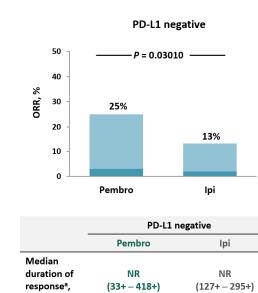
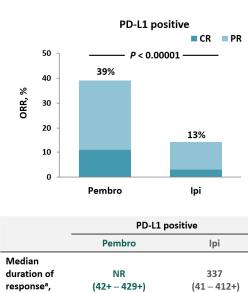
The tumor response
is PD-L1 expression

PD-L1 expression is associated with better responses

PD-L1 Expression Correlates with Improved Response



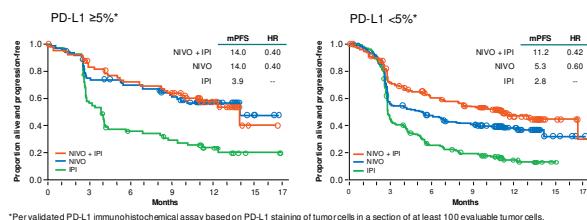
Best Overall Response by PD-L1 Expression



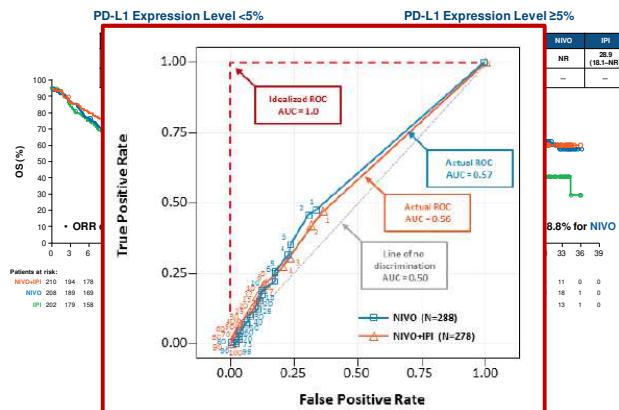
Carlino et al. AACR 2016

PD-L1 status seems to identify patients likely to benefit from IPI/NIVO

PFS by PD-L1 Expression Level (5%)



OS by Tumor PD-L1 Expression, 5% Cutoff



Wolchok et al. ASCO 2015; Larkin et al. NEJM 2015

Wolchok et al. NEJM 2017

PD-L1 status does not seem to identify patients as likely to respond to NIVO vs IPI/NIVO

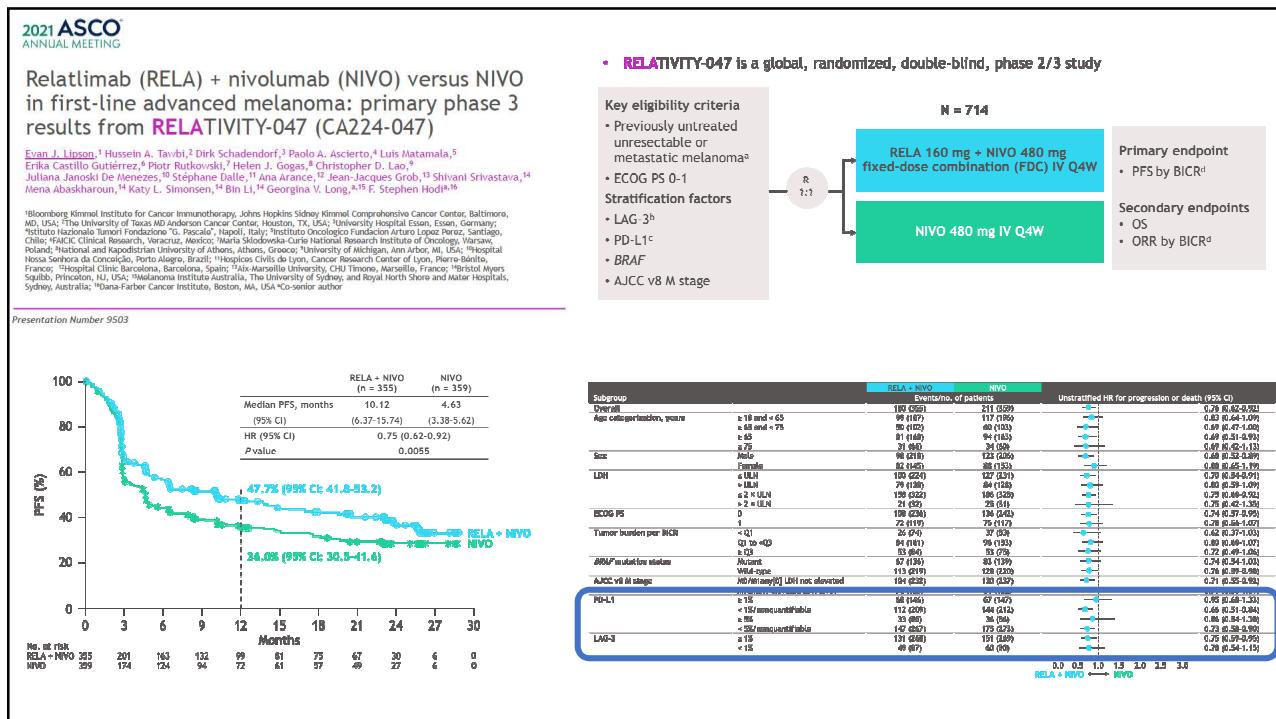
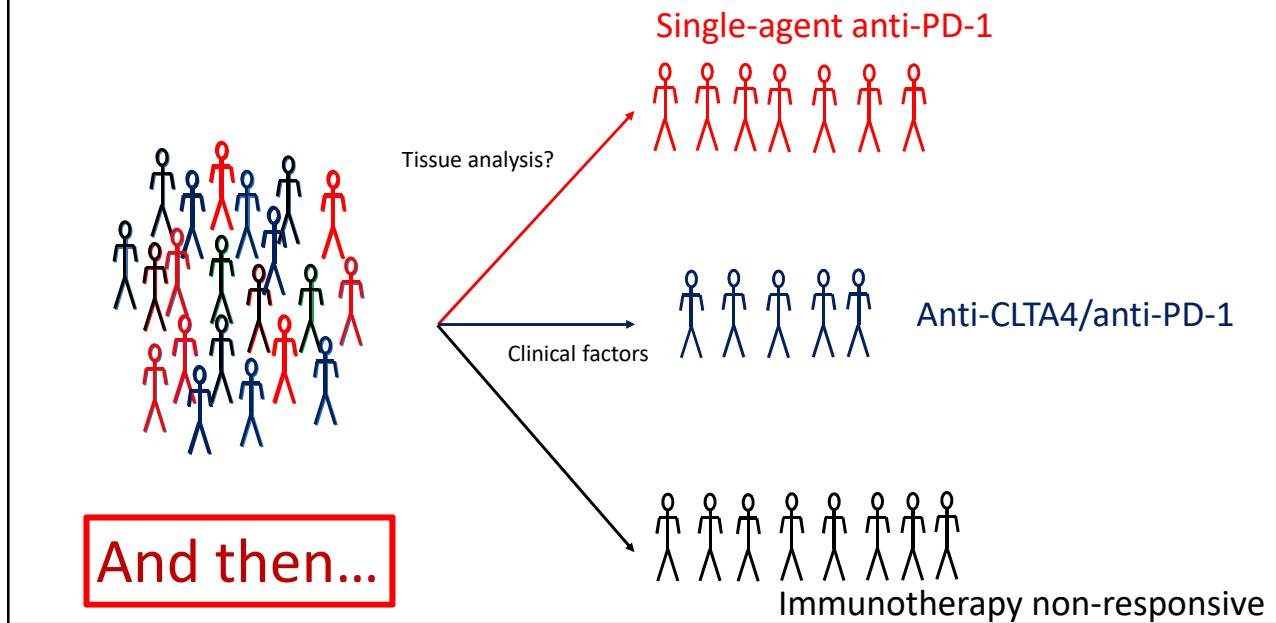
PDL-1 (%)	≥ 1	< 1	≥ 5	< 5	> 10	< 10
Ipilimumab	19%	18%	21%	17%	20%	18%

Based on the available data, I do not recommend tissue PD-L1 analysis to select patients for combination therapy

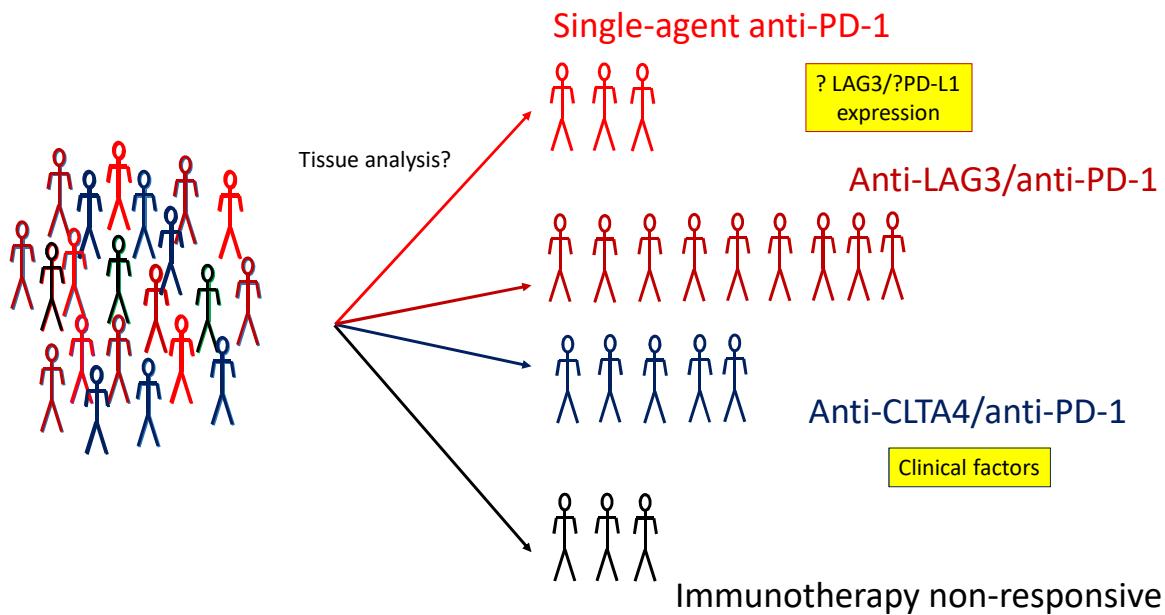
*Reasons to offer IPI/NIVO over single-agent anti-PD-1

1. Brain metastases
2. Patient is not likely to be a candidate for subsequent therapy in 12 weeks

Optimizing Selection Strategy: Melanoma Model #2.1



Optimizing Selection Strategy: Melanoma Model #2.2



Summary of melanoma molecular diagnostics

- Standard H&E and IHC drive decision making in managing primary melanoma
- BRAF targeted therapy is FDA approved for Stage III (adjuvant) and Stage IV disease
 - PCR-based BRAF or NGS is recommended to detect BRAF^{V600} mutations in these patients
 - **Perhaps more critical to have result back in adjuvant setting before choosing treatment (BRAF MT, favor BRAF/MEK therapy)**
- A number of similar, overlapping (and non-overlapping) biomarkers have been implicated in response (TMB, neo-antigens, MHC class I/II, T-cell infiltration) to immunotherapy
- PD-L1 expression is a useful predictive tool in some diseases, but does not appear to have a clear role in decision-making, yet...
- Emergence of anti-LAG3/anti-PD-1 combo may lead to more interest in revisiting tumor PD-L1 expression and LAG3 expression in IHC