Society for Immunotherapy of Cancer

Advances in Cancer Immunotherapy™

Melanoma 2022

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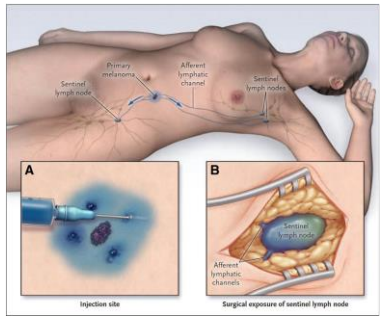
Disclosures

- Consulting Fees: Bristol Myers Squibb, Merck, Novartis, Pfizer
- Contracted Research: Merck
- Royalties: Up-to-Date
- I will be discussing non-FDA approved indications during my presentation.

Treatment of Melanoma

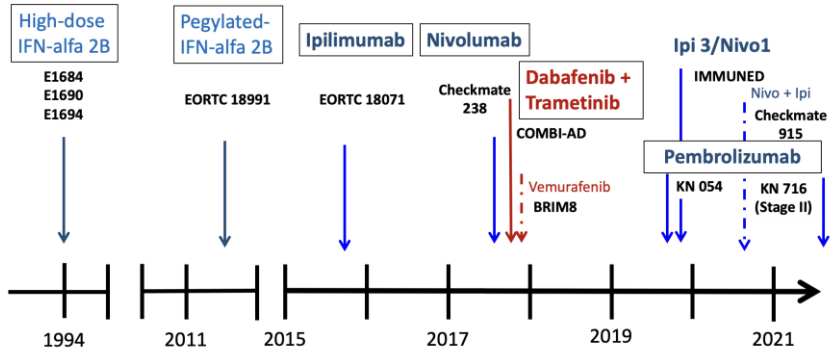
Neo-Adjuvant therapy

Curative intent surgery



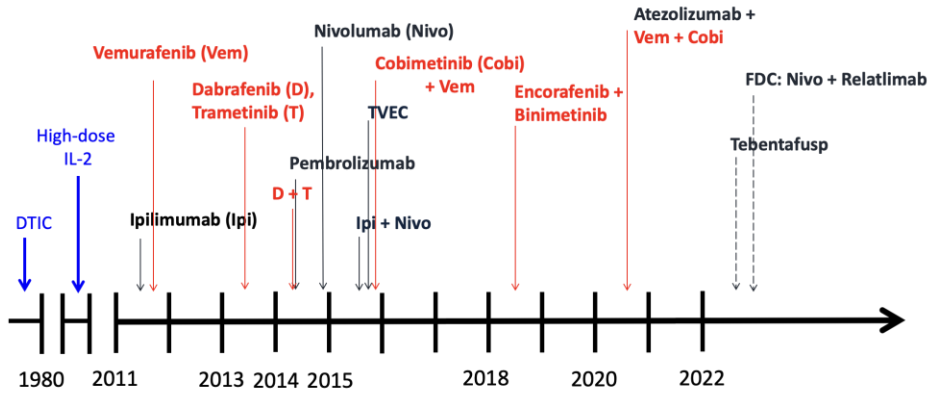
Gershenwald et al. NEJM

Adjuvant therapy



Diagnosis

Systemic therapy for 'advanced' melanoma



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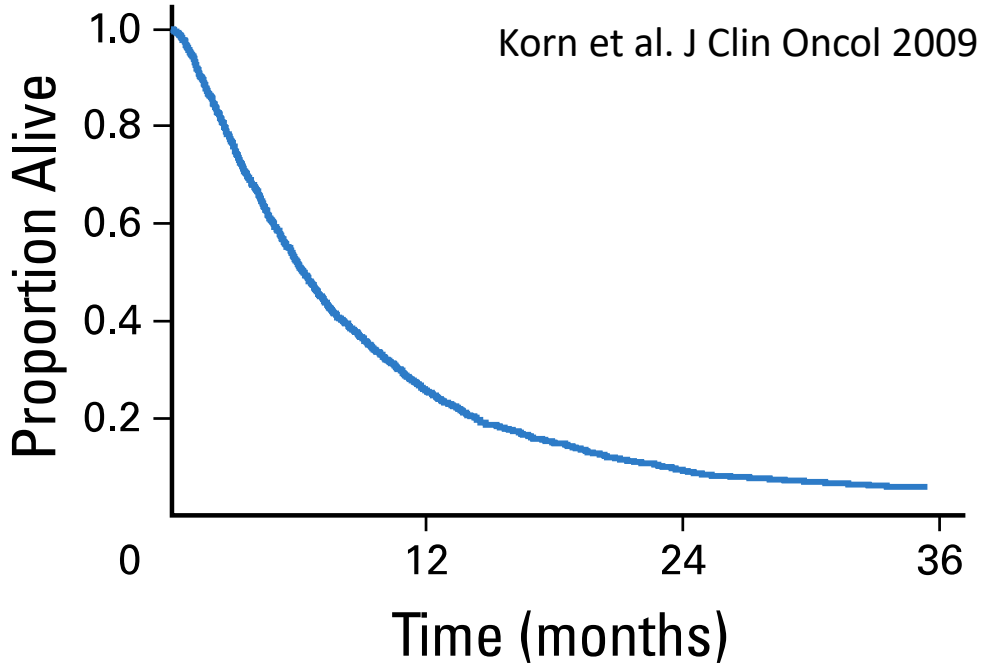
Traditionally there were few effective therapies

An Era of Futility:
1975-2005



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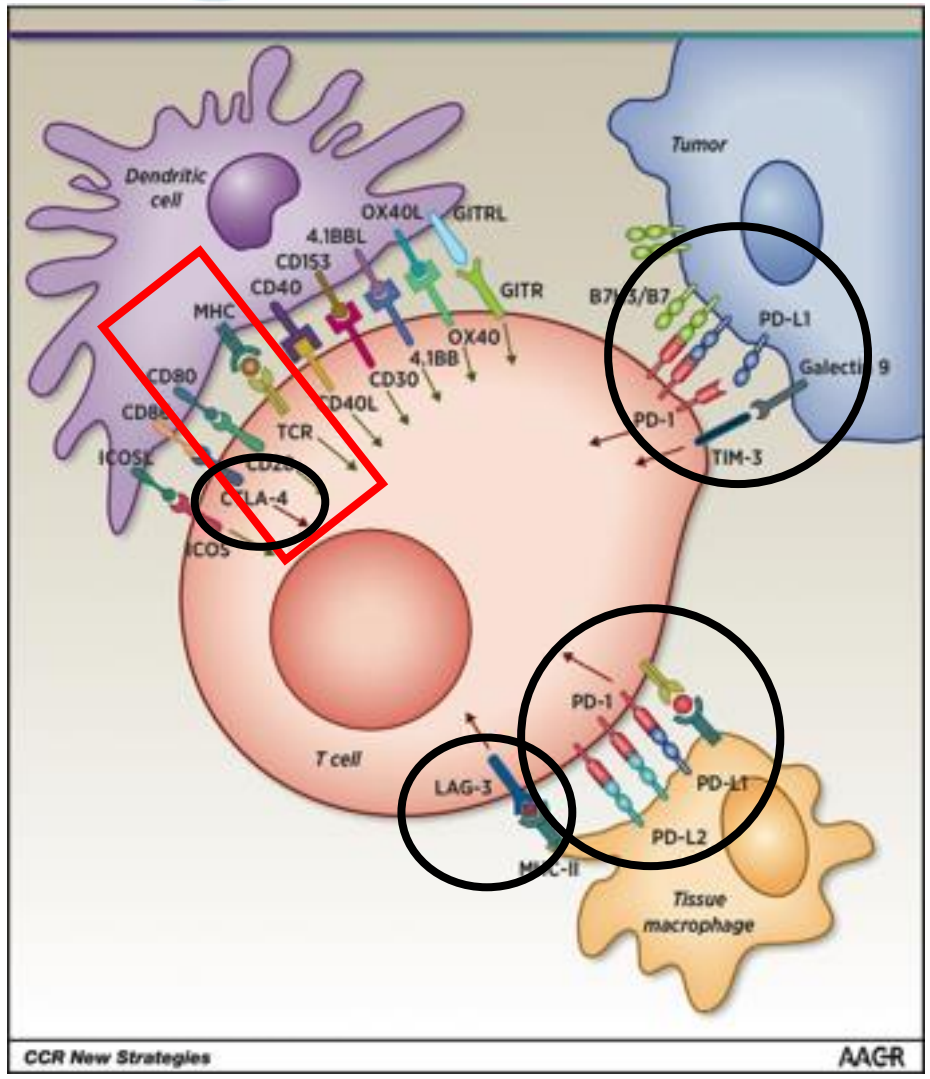
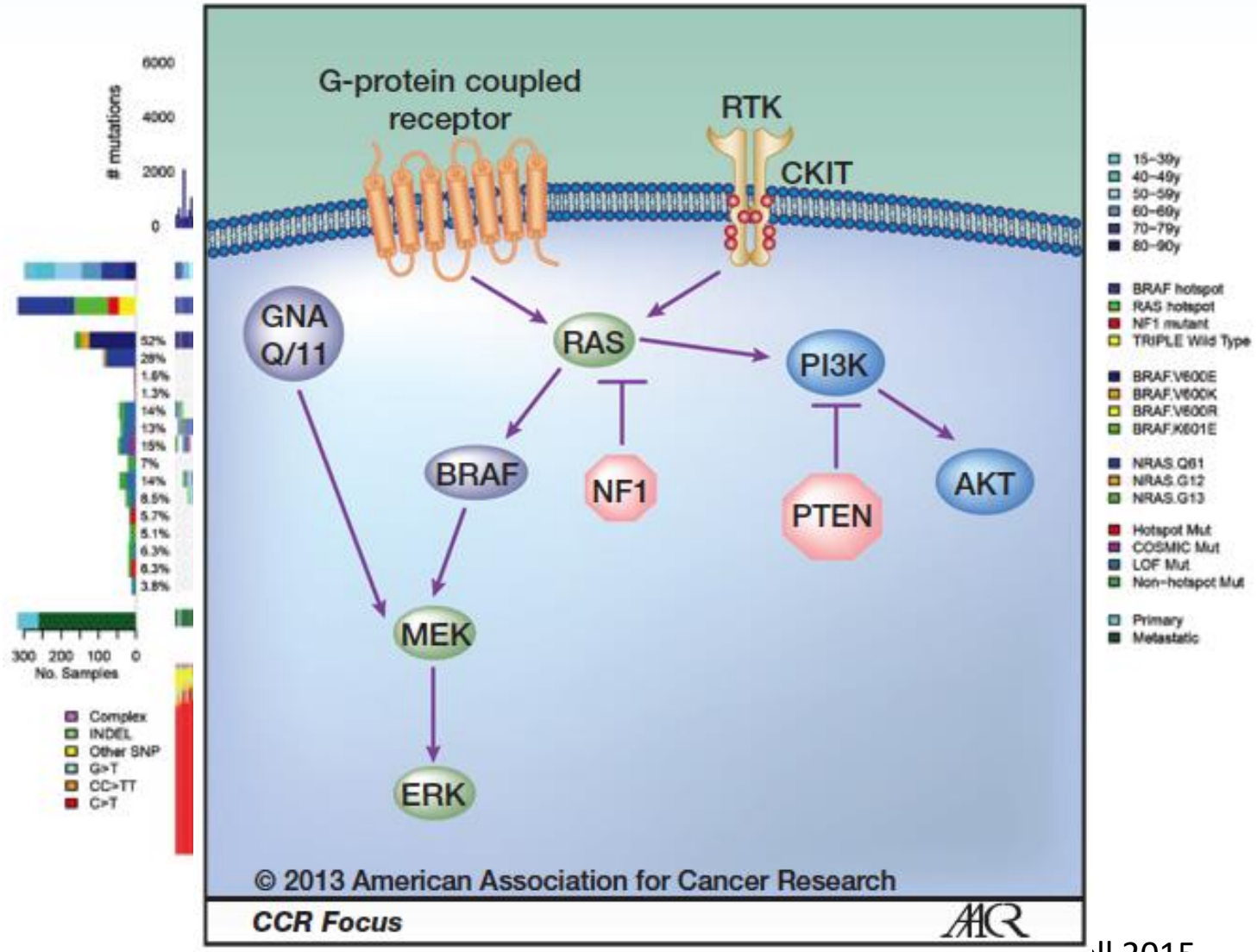
During the "Era of Futility: Two fundamental and translatable discoveries occurred





Sullivan and Flaherty. Clin Cancer Res. 2015

Melanoma TCGA. Cell 2015

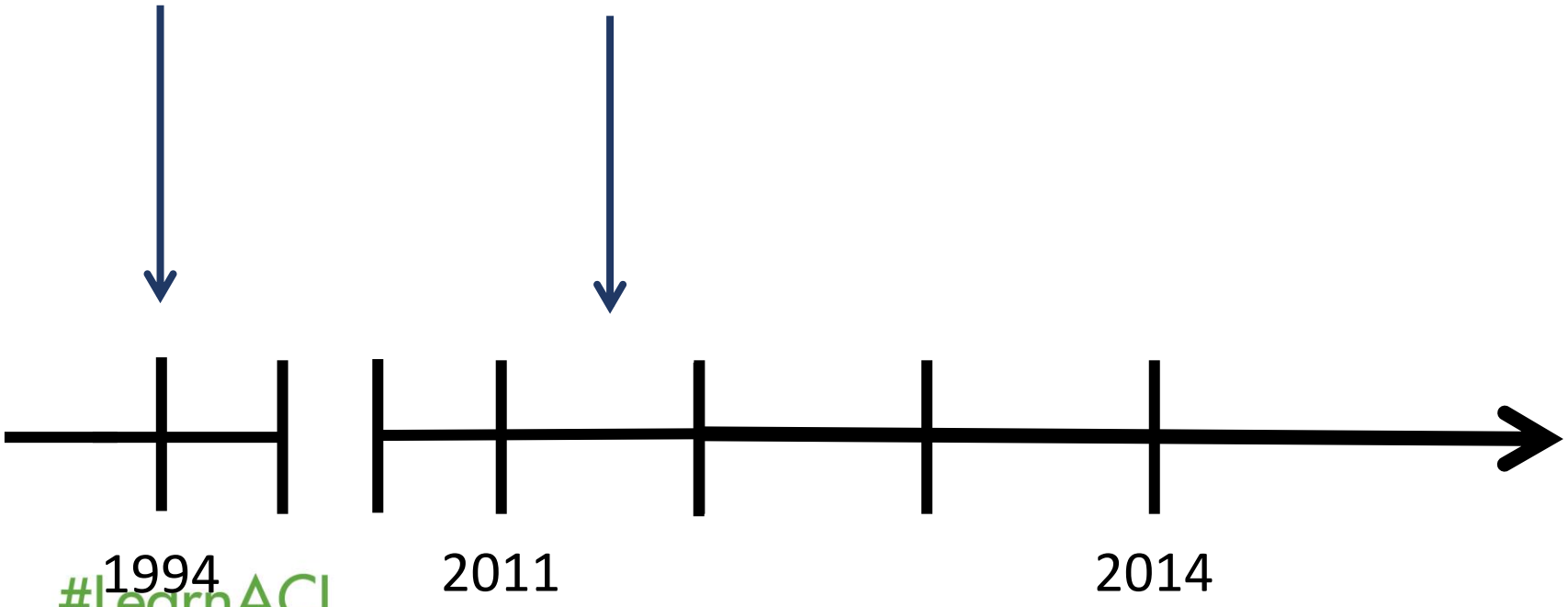
Adjuvant Melanoma Treatment Landscape 2014

High-dose IFN-alfa 2B

E1684
E1690
E1694

Pegylated-IFN-alfa 2B

EORTC 18991



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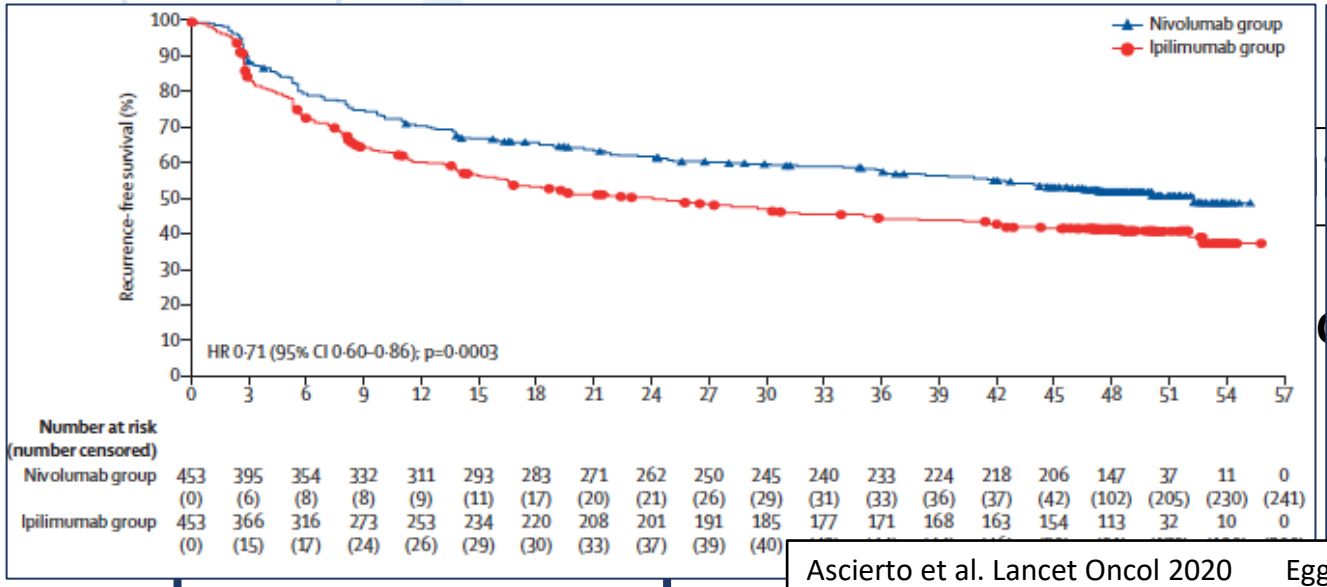
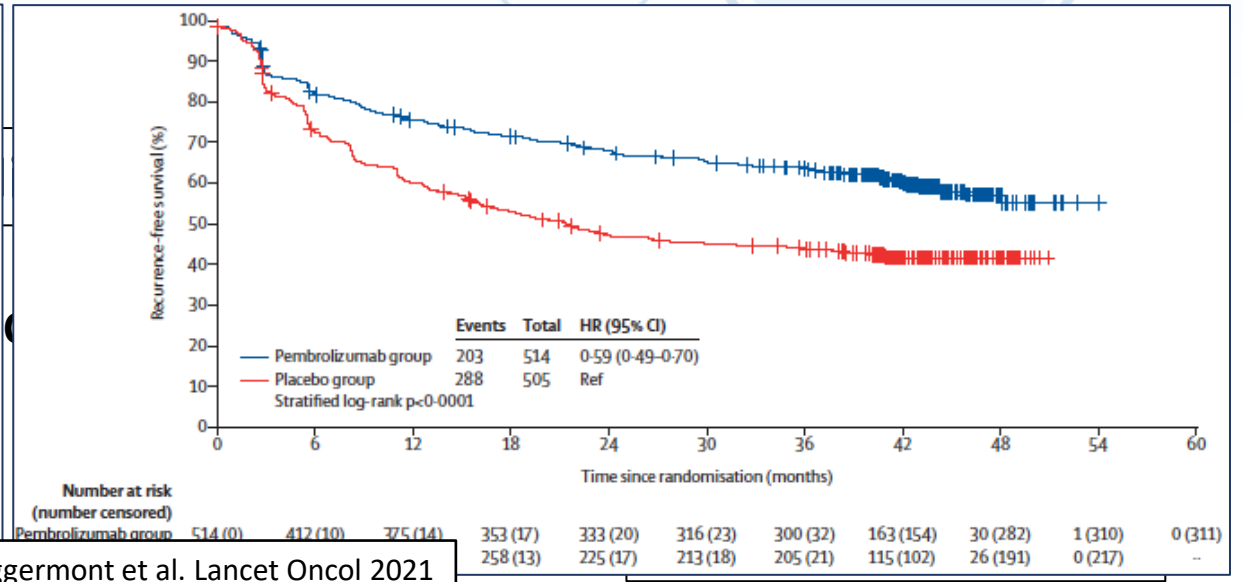
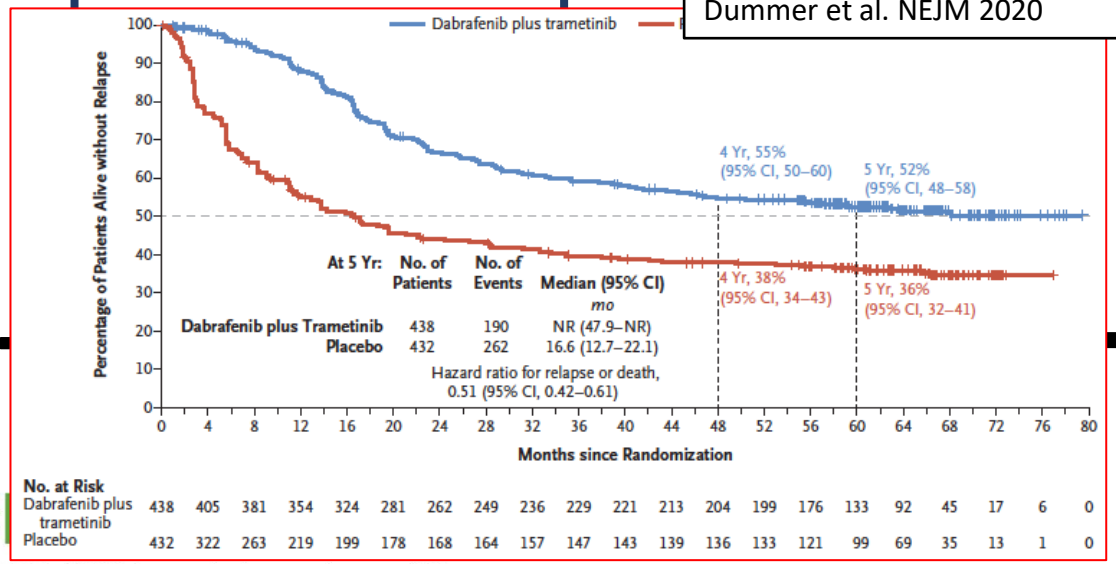
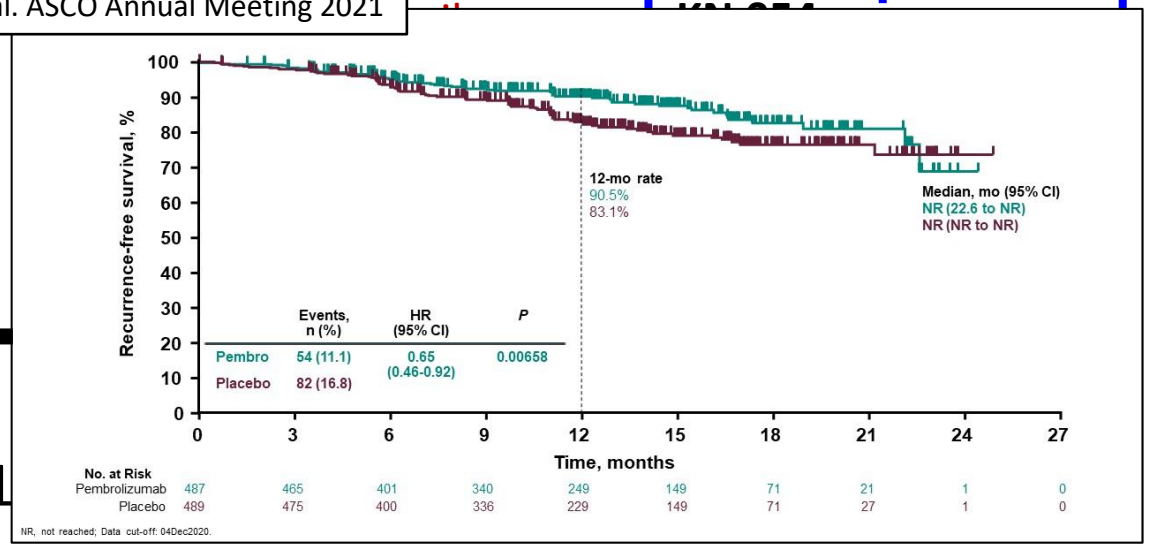
Adjuvant Melanoma Treatment Landscape 2022





Ascierto et al. Lancet Oncol 2020 Eggermont et al. Lancet Oncol 2021
Dummer et al. NEJM 2020 Luke et al. ASCO Annual Meeting 2021

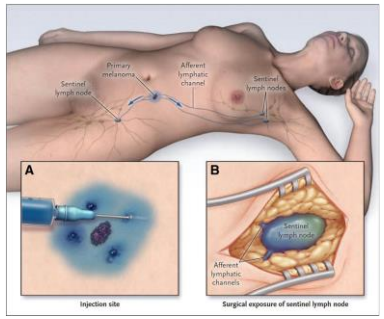




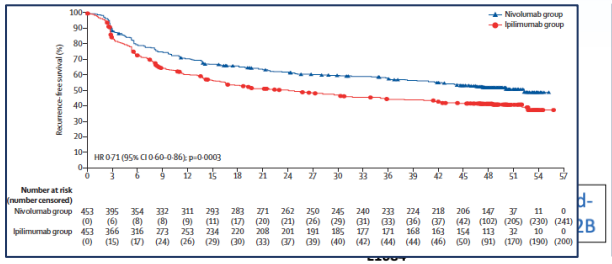
Adjuvant therapy

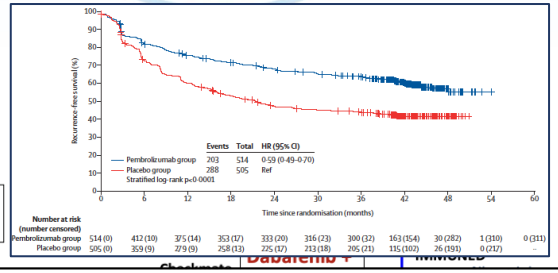
Neo-Adjuvant therapy

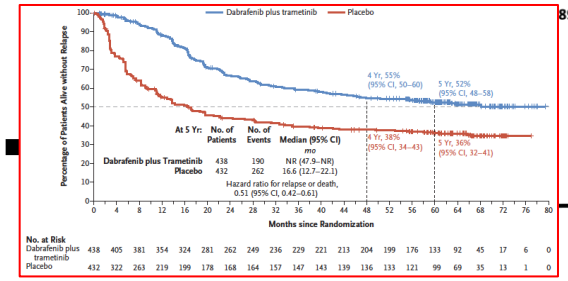
Curative intent surgery

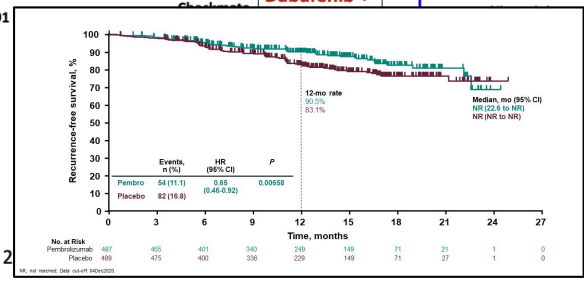


Gershenwald et al. NEJM









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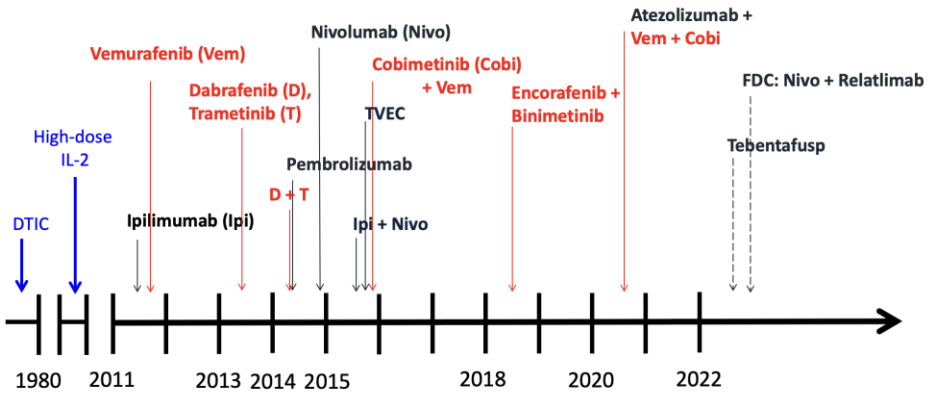
Diagnosis

Systemic therapy for 'advanced' melanoma



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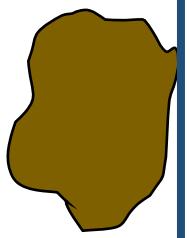
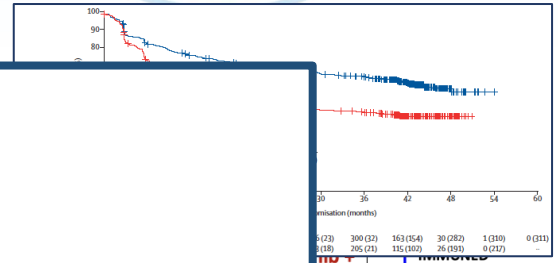
Adjuvant therapy

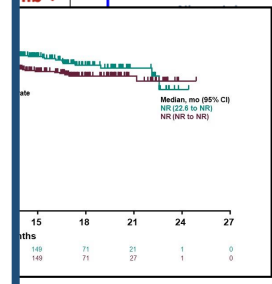
Neo-Adjuvant therapy

- Current data with Stage III Melanoma
  - Anti-PD1 therapy is SOC (BRAF status independent)
  - No benefit of ipi/nivo vs nivo (CM 915) in Stage III
  - Possible benefit of ipi/nivo vs nivo in resected Stage IV (IMMUNED)
  - BRAF/MEK combo is an alternative SOC for BRAF MT
- Current data with Stage II Melanoma
  - Anti-PD1 therapy is expected to become the SOC
- Pending trials:
  - Stage IIB/C nivo vs placebo
  - Stage III pembro + PCV (Moderna) vs pembro
  - Stage III nivo + bempegaldesleukin vs nivo

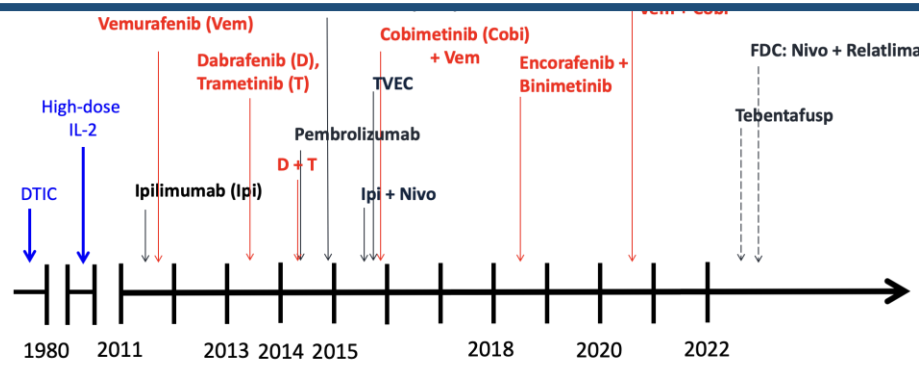


Diagnosis





)ncol 2021
eting 2021



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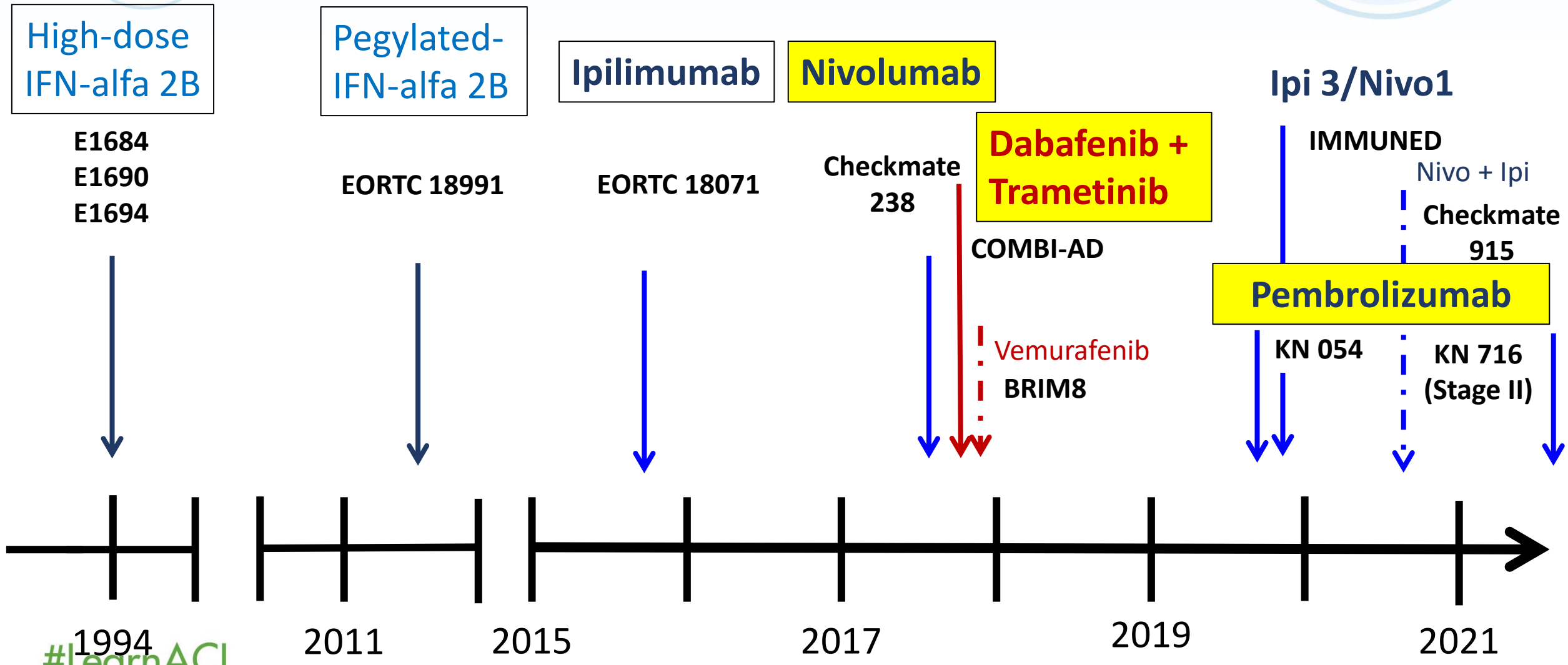
Adjuvant Melanoma Treatment Stage III Options



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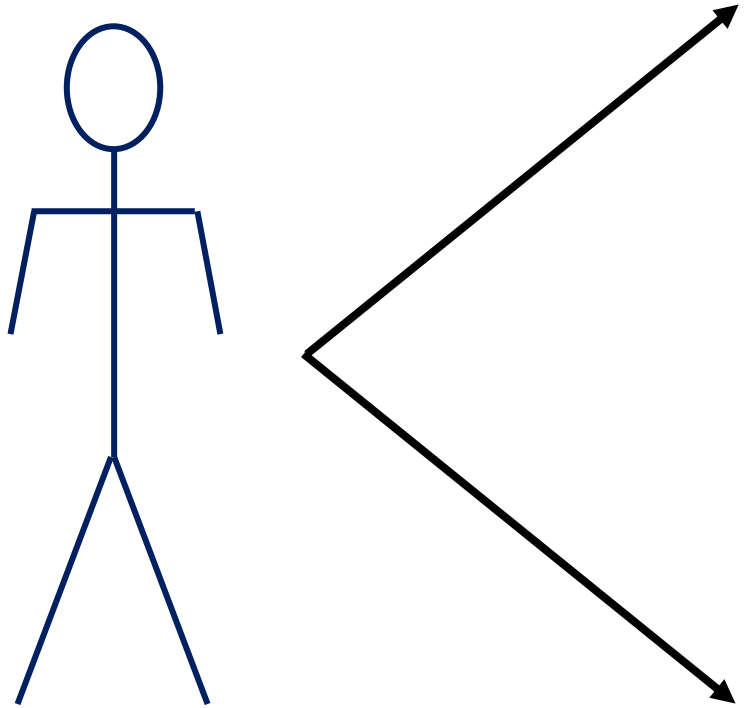
What do we do?

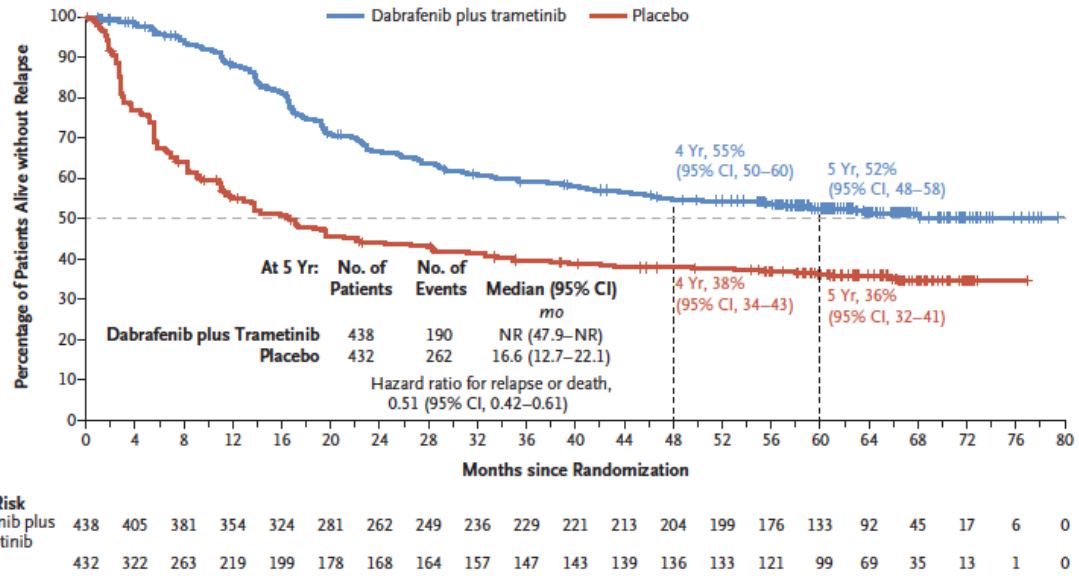
BRAF MT, resected
Stage III melanoma



BRAF targeted therapy

Immune targeted therapy

COMBI-AD Summary (5 yr follow up)



Dummer et al. NEJM 2020

- Randomized Phase III trial of adjuvant dab/tram in patients with Stage III, BRAF mutant melanoma
- Met its primary endpoint (RFS, HR 0.51) and secondary endpoint (DMFS, HR 0.55)
- Improvement maintained in all subgroups
- Predictable, reversible toxicity
- 26% discontinuation rate in dab/tram arm (3% in placebo arm)
- No significant difference in rate of additional malignancies

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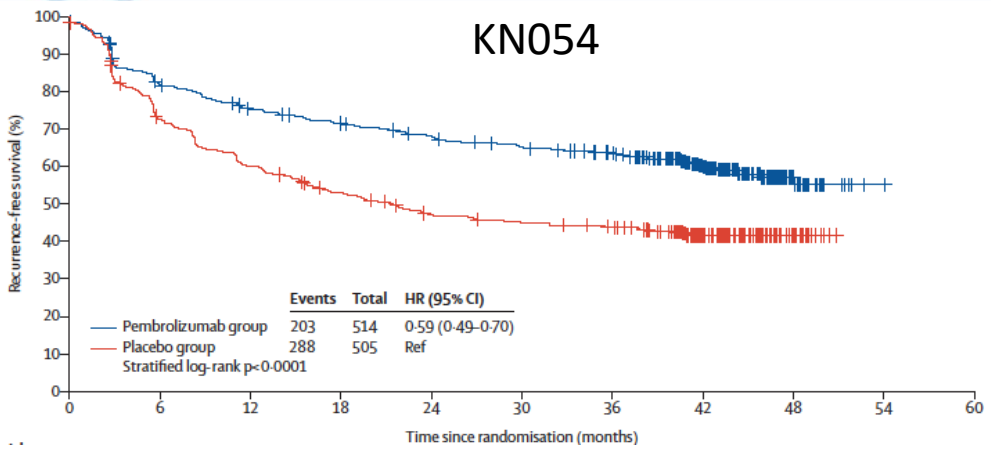
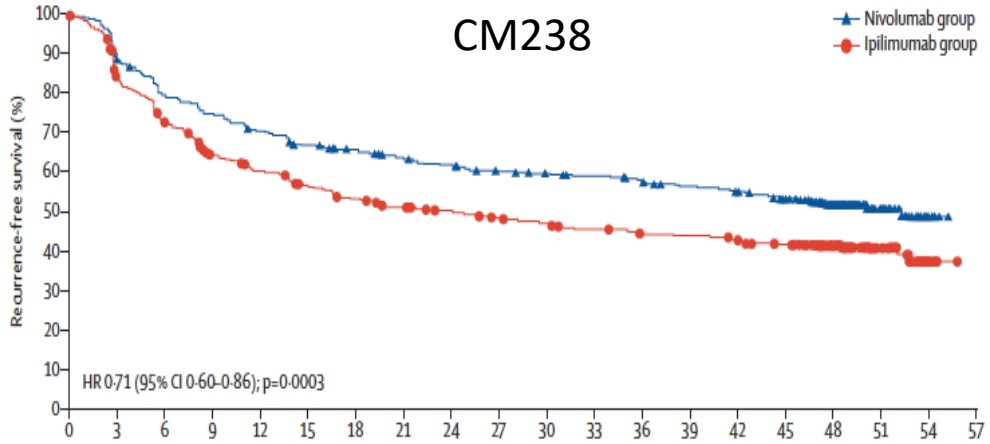
Summary of Adjuvant anti-PD-1 (~4 yr follow up)

Eggermont et al. Lancet Oncol. 2021



Ascierto et al. Lancet Oncol. 2020



PEMBRO (KN054)

- Met its primary endpoint (RFS, HR 0.59) and secondary endpoint (DMFS, HR 0.60)
- Improvement maintained in most subgroups including BRAF MT (initial HR for RFS 0.59; for DMFS 0.55)
- Significant toxicity in a minority of patients
  - irAEs associated with improved RFS
  - Endocrine toxicity (mostly irreversible) in 23% of patients

NIVO (CM238)

- Met its primary endpoint (RFS, HR 0.71) and one secondary endpoint (DMFS, HR 0.79), but was not associated with OS advantage (HR 0.87, p =0.31),
- Improvement maintained in most subgroups including BRAF MT (HR for RFS 0.79)
- Nivo much better tolerated than Ipi
- Significant toxicity in a minority of patients with Nivo
  - Endocrine toxicity (mostly irreversible) in 24%

Summary of Adjuvant Therapy Effectiveness

Endpoint	COMBI-AD (DT v placebo)	KN054 (pembro v placebo)	CM238 (nivo v ipi)
Primary Endpoint			
RFS (HR)	0.51	0.59	0.71
4 YR RFS	55%	60% (3.5 yr RFS)	52%
Secondary Endpoint			
DMFS (HR)	0.55	0.60	0.79
OS (HR)	NA	NA	0.87

Dummer et al. NEJM 2020
Eggermont et al. Lancet Oncol 2021
Ascierto et al. Lancet Oncol 2020

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Summary of Adjuvant Therapy Side Effects

Severity/Frequency			Permanence		
Observation	<<	Interferon	Observation	<	Interferon
Placebo	<<<	Ipilimumab	Placebo	<<<	Ipilimumab
Nivolumab	<<	Ipilimumab	Nivolumab	~	Ipilimumab
Placebo	$<^{+}$	Pembrolizumab	Placebo	<<<	Pembrolizumab
Placebo	<<<	Dab/Tram	Placebo	~	Dab/Tram

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More on chronicity of irAEs…

- 387 patients treated with adjuvant anti-PD-1 at 8 academic centers in US and Australia
- 267 (69%) had irAE
  - 53 (19.5%) – Gr 3-5

Table 2. Incidence of Chronic Immune-Related Adverse Events (irAEs)

Chronic irAEs	Patients, No. (%)	
	With chronic irAEs	Ongoing chronic irAE at last follow-up
Total chronic irAEs	167 (100)	NA
Required steroids	55 (32.9)	NA
Symptomatic	82 (49.1)	NA
Resolved	24 (14.4)	NA
≥Grade 2	90 (53.9)	NA
Grade 3-5	6 (3.6)	NA
irAE Type[a]		
Adrenal insufficiency	12 (3.1)	12 (100)
Arthritis/arthralgias	22 (5.7)	22 (100)
Colitis/diarrhea	6 (1.6)	2 (33.3)
Dermatitis/pruritus	19 (6.6)	17 (89.5)
Xerostomia[b]	9 (2.3)	8 (88.9)
Hypophysitis	8 (2.1)	8 (100)
Neuropathy	3 (1.8)	1 (33.3)
Ocular toxic effect[c]	5 (1.3)	5 (100)
Other neurotoxicity[d]	8 (2.1)	5 (63.0)
Pneumonitis	6 (1.6)	4 (66.7)
Thyroiditis/hypothyroid	54 (14.0)	54 (100)

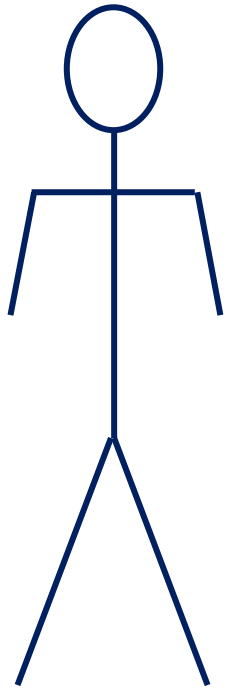
Patrinely et al. JAMA Onc 2021

Key points of consideration

1. Patients with the least amount of disease may be the best group to treat with BRAF targeted therapy.
2. BRAF targeted therapy and anti-PD-1 therapy appear to have similar efficacy (e.g. cure a similar percentage of patients) in adjuvant setting
3. Adjuvant nivo is NOT associated with improved overall survival compared to ipi (Effect of “salvage” anti-PD-1 in metastatic setting?)
4. Adjuvant immunotherapy is associated with severe side effects in 15-20% and chronic side effects in >40% of patients

So, what do I do?

BRAF MT, resected
Stage III melanoma



My bias is to give BRAF/MEK combo…

Why?

1. **Potentially curative**
2. **Reversible AEs**
3. **“Salvage” IO in setting of relapse**

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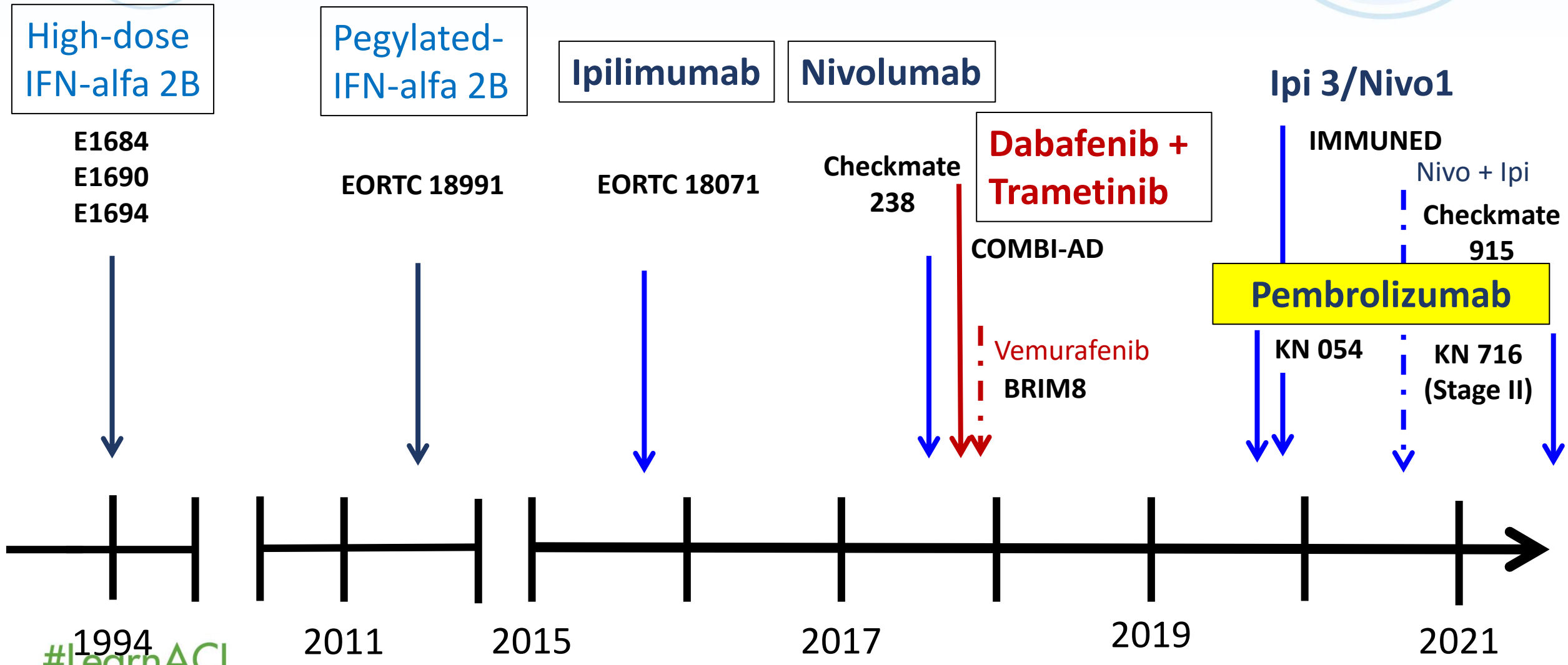
Adjuvant Melanoma Treatment Stage II Options



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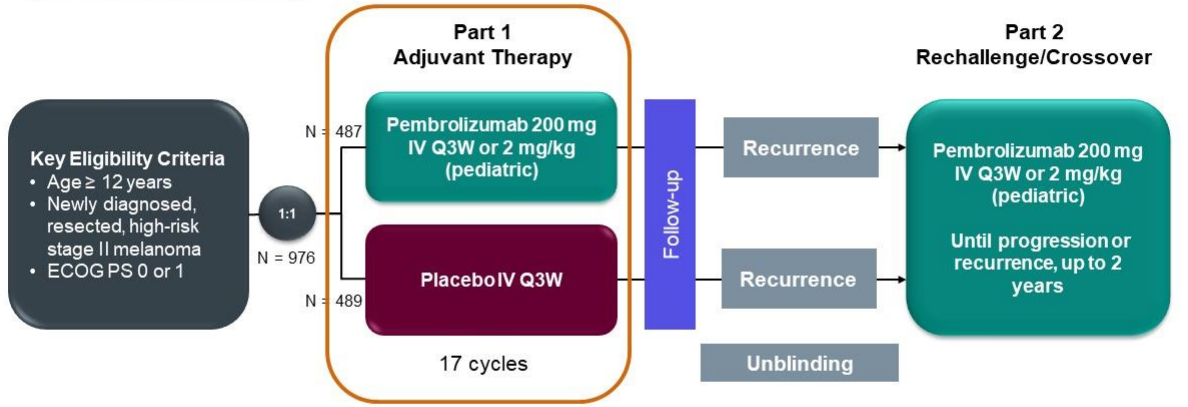
Pembrolizumab Versus Placebo After Complete Resection of High-risk Stage II Melanoma: Efficacy and Safety Results From the KEYNOTE-716 Double-blind Phase 3 Trial

Jason J. Luke[1]; Piotr Rutkowski[2]; Paola Queirolo[3]; Michele Del Vecchio[4]; Jacek Mackiewicz[5, 6]; Vanna Chiarion-Sileni[7]; Luis de la Cruz Merino[8]; Muhammad A Khattak[9,10]; Dirk Schadendorf[11]; Georgina V. Long[12,13], Paolo A Ascierto[14]; Mario Mandala[15]; Federica De Galitiis[16]; Vernon Sondak[17]; Richard A. Scolyer[12,18]; John M. Kirkwood[1]; Ke Chen[19]; Nageatte Ibrahim[19]; Sama Ahsan[19]; Alexander M. M. Eggermont[20]

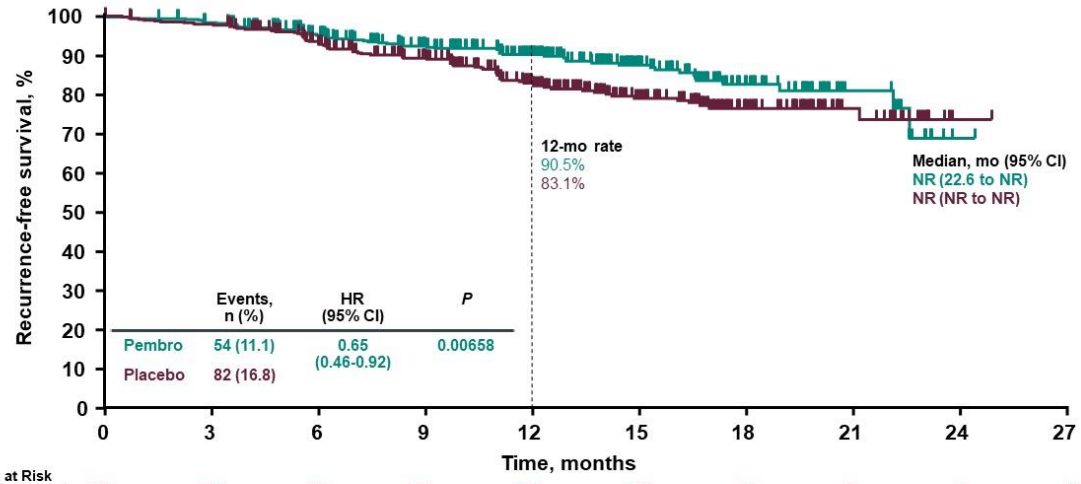
[1]UPMC Hillman Cancer Center, Pittsburgh, PA, USA; [2]Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; [3]Istituto Europeo di Oncologia - IRCCS, Milano, Italy; [4]Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy; [5]Poznan University of Medical Sciences, Poznan, Poland; [6]Greater Poland Cancer Center, Poznan, Poland; [7]Istituto Oncologico Veneto, IOV-IRCCS, Padova, Italy; [8]Hospital Universitario Virgen Macarena, Seville, Spain; [9]Fiona Stanley Hospital, Perth, Australia; [10]Edith Cowan University, Perth, Australia; [11]University Hospital Essen & German Cancer Consortium Partner Site, Essen, Germany; [12]Melanoma Institute Australia, The University of Sydney, Sydney, Australia; [13] Royal North Shore & Mater Hospitals, Sydney, Australia; [14]Istituto Nazionale Tumori IRCCS Fondazione Pascale, Naples, Italy; [15]University of Perugia, Perugia, Italy; [16]Dermopathic Institute of the Immaculate IDI-IRCCS, Rome, IT; [17]H. Lee Moffitt Cancer Center and Research Institute in Tampa, FL, USA; [18]Royal Prince Alfred Hospital and NSW Health Pathology, Sydney, Australia; [19]Merck & Co., Inc., Kenilworth, NJ, USA; [20]University Medical Center Utrecht & Princess Máxima Center, Utrecht, NL

KEYNOTE-716 Study Design (NCT03553836)



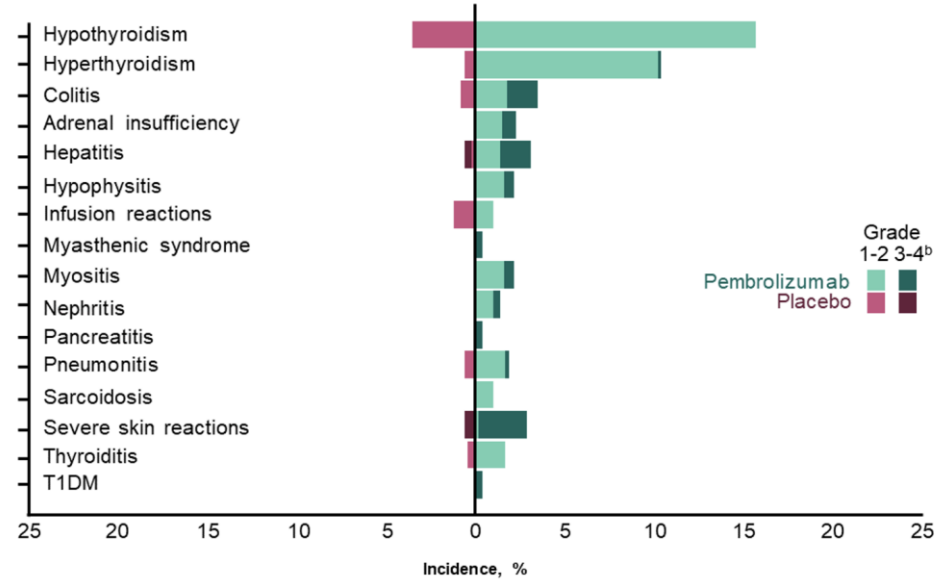
HRQoL, health related quality of life; OS, overall survival; Q3W, every 3 weeks; RFS, time from randomization to recurrence of melanoma at any site (skin, regional lymph nodes or distant) or death from any cause, whichever occurred first.

Recurrence-Free Survival (Primary Endpoint)



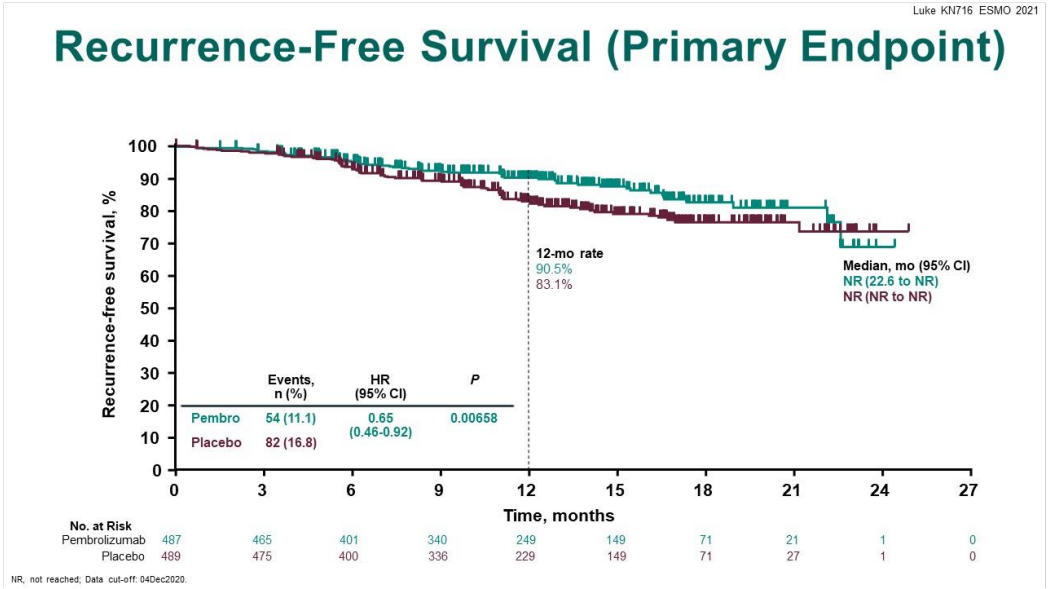
NR, not reached; Data cut-off: 04Dec2020.

Adverse Events of Interest[a]



T1DM, Type 1 Diabetes Mellitus.
[a]Immune-mediated AEs and infusion reactions occurring in at least 2 patients in decreasing incidence; [b]No grade 5 events occurred in the pembrolizumab arm; Data cut-off: 04Dec2020

Summary of Adjuvant PEMBRO for Stage IIB/C

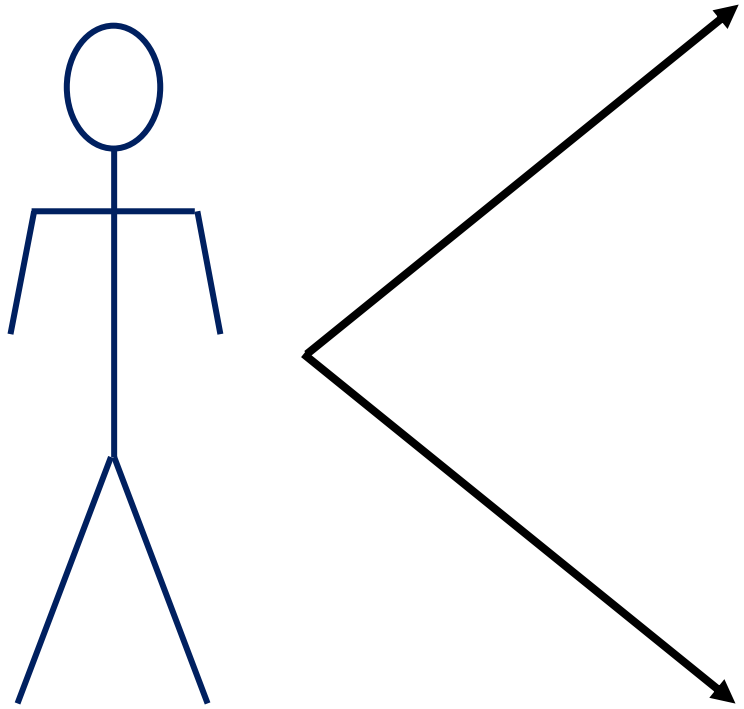


PEMBRO

- KN 716 et its primary endpoint (RFS, HR 0.65). Benefit seemingly maintained in all subgroups analyzed
- Significant toxicity in a minority of patients
  - irAEs (Grade 3 or 4) in 17%
  - 16% of patients discontinued early
  - Endocrine and cutaneous toxicity most common
- No overall survival data available
- No biomarker data available

To treat or not to treat?

New patient with Stage IIB/C, melanoma



Pembrolizumab

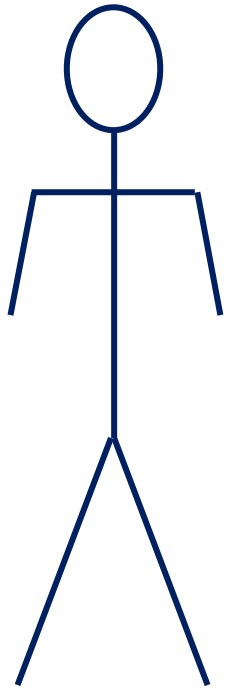
Active Surveillance

Key points of consideration

1. There is NO data with improved overall survival at this point
   - Conceivable that “salvage” anti-PD-1 based therapy will be effective at time of recurrence
2. There IS value to not having recurrent disease
3. Adjuvant immunotherapy (in Stage III patients) is associated with severe side effects in 15-20% and chronic side effects in >40% of patients (no reason to think this is different in Stage II)

So, what do I do?

New patient with Stage IIB/C, melanoma



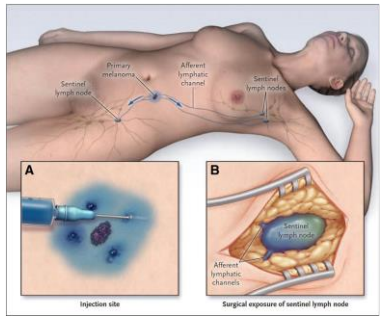
I have LONG conversations with patients about goals, risks, benefits

A brief word about neoadjuvant therapy

Neo-Adjuvant therapy

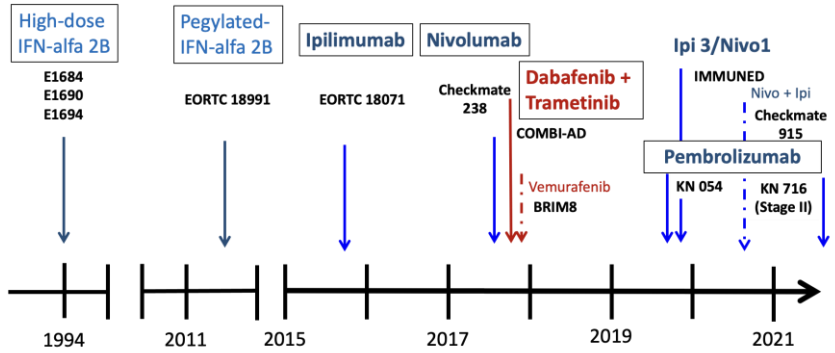
Diagnosis

Curative intent surgery

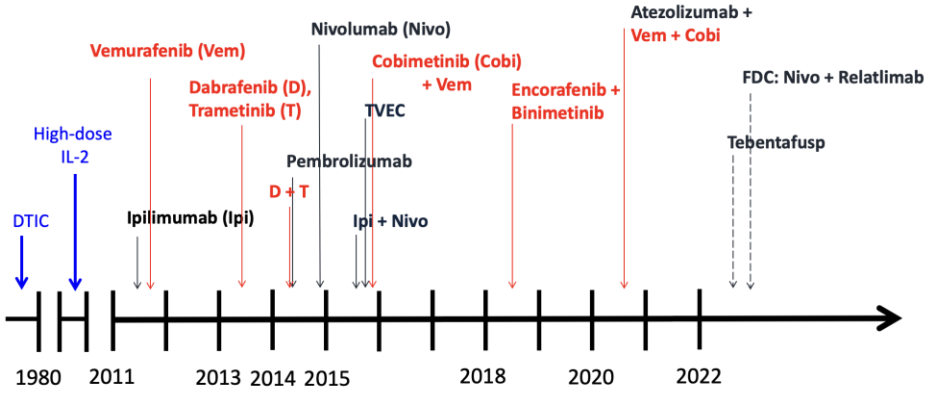


Gershenwald et al. NEJM

Adjuvant therapy



Systemic therapy for 'advanced' melanoma



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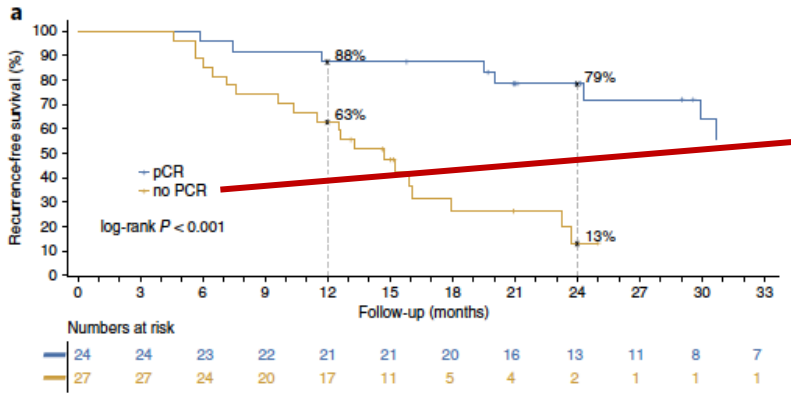
Neoadjuvant Therapy

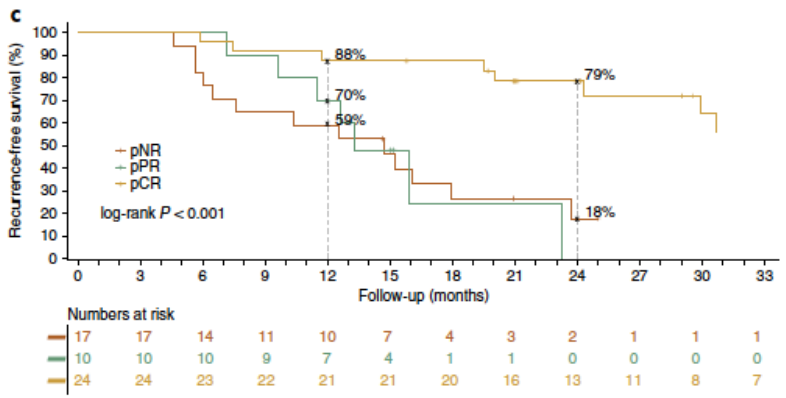
- Potential Benefits:
  - Down-staging, improve surgical resectability (TT > IO)
  - Assess response to treatment – tailor adjuvant tx
  - Immunotherapy: broaden T cell responses
  - Use pResponse as surrogate marker for RFS and/or OS
- Concerns:
  - Disease progression during therapy
  - Tx-related toxicity
  - Early resistance to therapy
  - May not be needed with adjuvant therapy
- Well-established roles/diseases:
  - Breast Cancer
  - GIST
  - Rectal Cancer
  - Esophageal Cancer

Why Neoadjuvant Therapy?

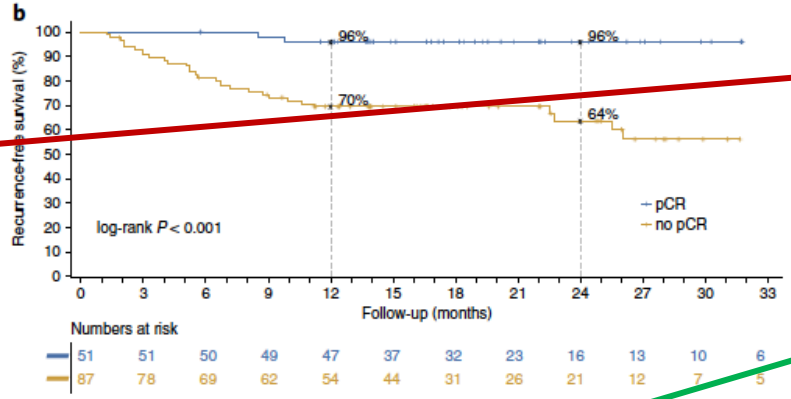
A. Clarifies who benefits

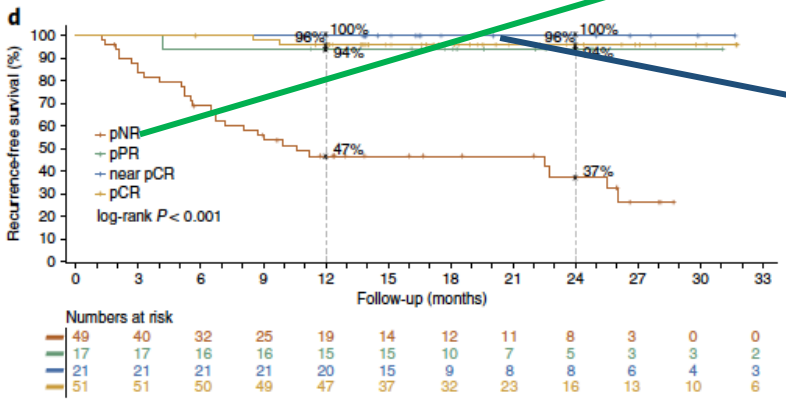
Neoadjuvant BRAFi/MEKi





Neoadjuvant IO





B. May help guide next steps

No pCR with neoadjuvant BRAFi/MEKi?
- Need something else

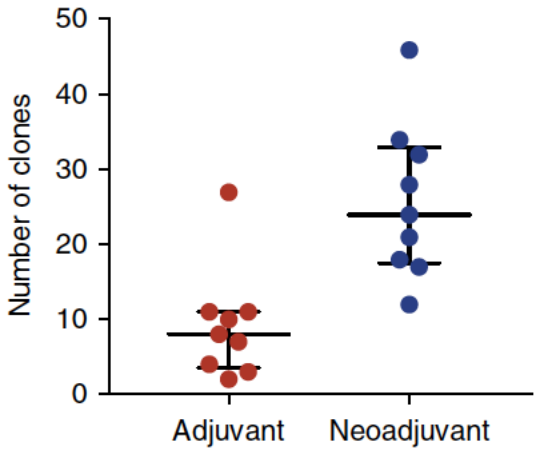
pNR IO?
- Need something else

pCR/near pCR/pPR IO?
- No adjuvant therapy

Menzies et al. Nature Med. 2021

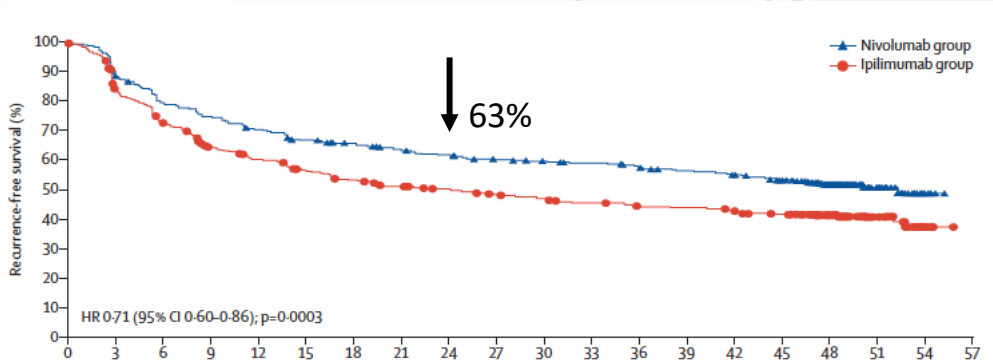
Improves outcomes?

Neoadjuvant (vs adjuvant) IO leads to increased numbers of peripheral blood clones of tumor-resident TCRs



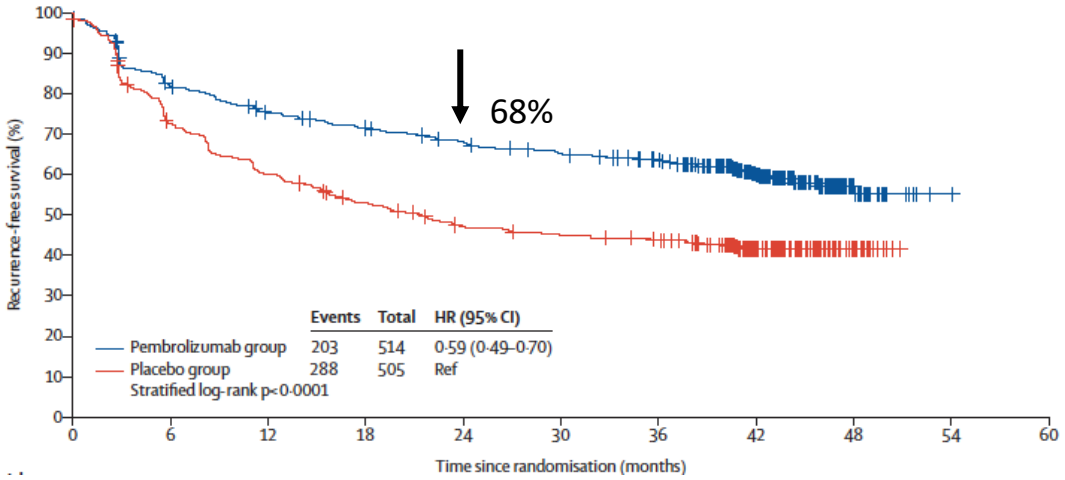
Blank et al. Nature Med. 2018

Ascierto et al.
Lancet Oncol. 2020



CM238

Eggermont et al.
Lancet Oncol. 2021



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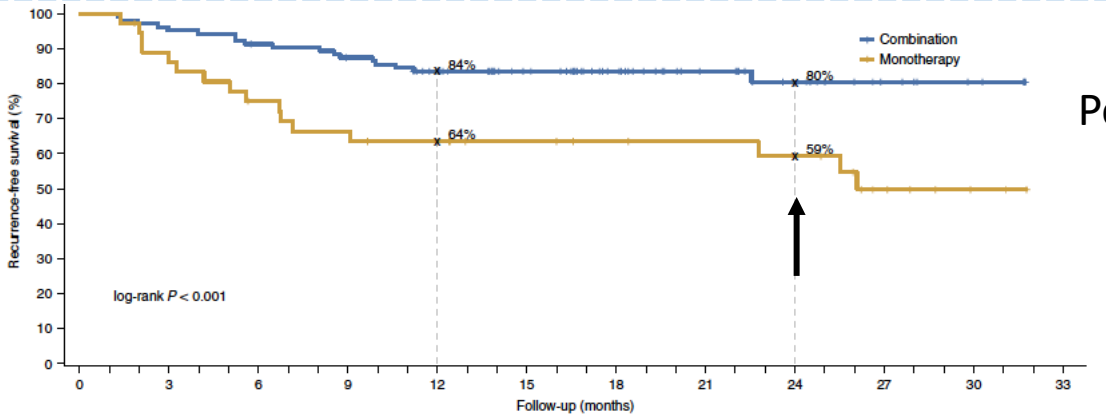
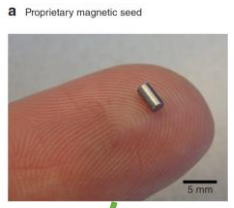
Menzies et al.
Nature Med. 2021



Pooled

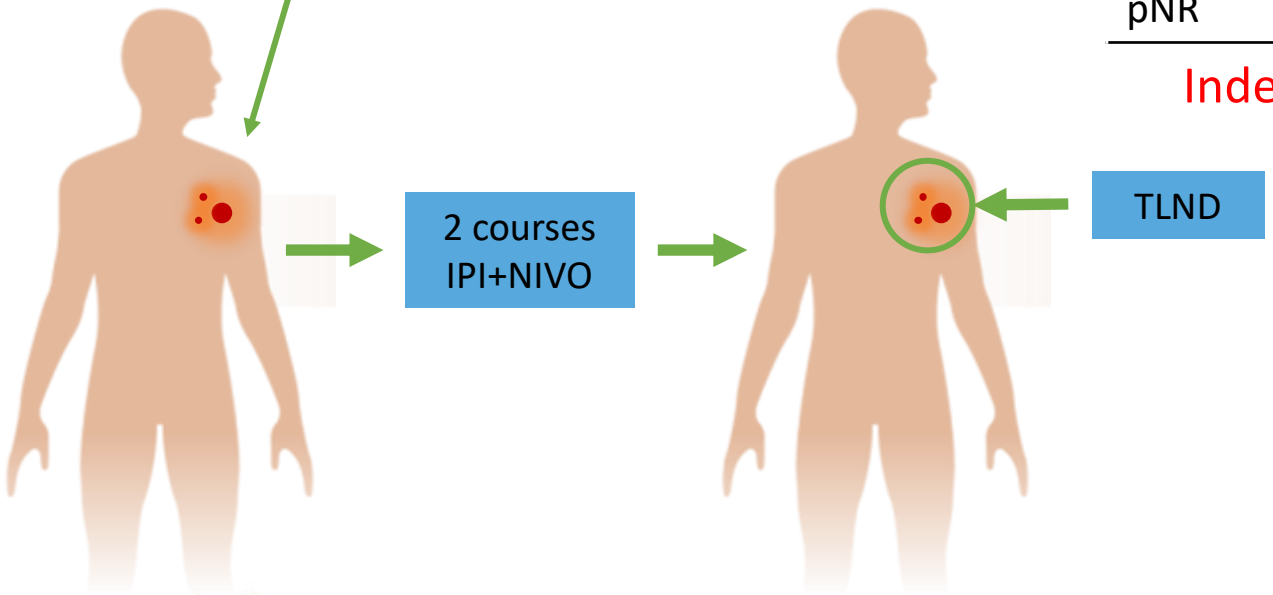
Changes surgical management?

The pathologic response in the largest lymph node (**index node**) represents the entire lymph node bed



Pathologic response	Index node	Total basin
pCR	7	7
Near-pCR	3	3
pPR	1	1
pNR	1	1

Index node congruent with total basin = 12/12 cases



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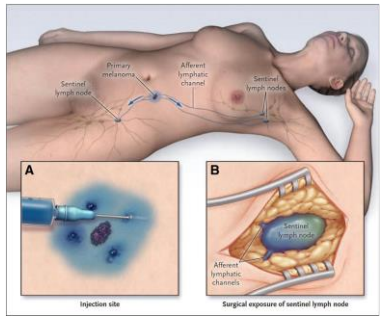
Prof. dr. C.U. Blank, presented ASCO 2020 Schermers et al., BJS 2019

Summary: Neoadjuvant Therapy 2022

- No approved neoadjuvant regimens
- A number of neoadjuvant therapies have been tested in high-risk stage III/IV patients
  - Neoadjuvant immunotherapy in Stage III melanoma:
    1. Leads to pathologic responses is a significant % of patients
    2. Those with pathologic response (pPR, near pCR, pCR) have remarkable RFS (>90% at 2 years), albeit with limited follow up
    3. The regimen of 2 doses of nivo (3 mg/kg) and ipi (1 mg/kg) followed by no adjuvant therapy is well tolerated and has been adopted as the standard neoadjuvant approach

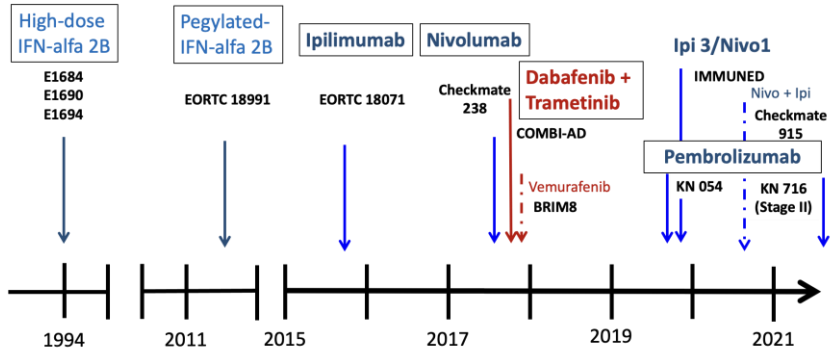
Neo-Adjuvant therapy

Curative intent surgery



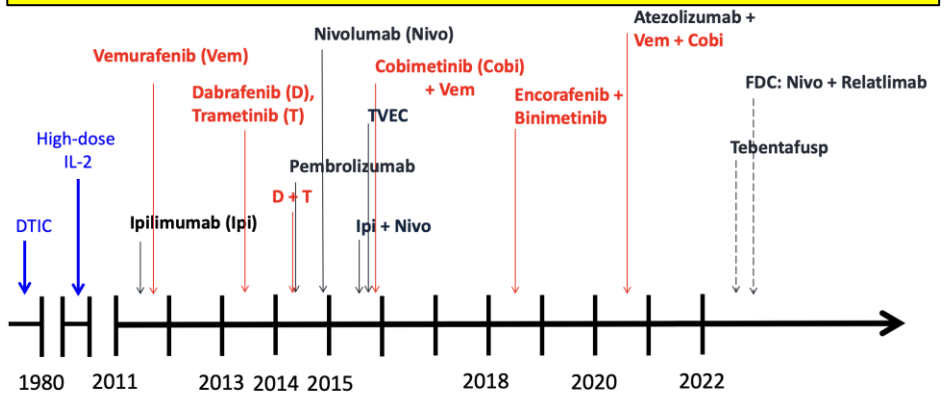
Gershenwald et al. NEJM

Adjuvant therapy



Diagnosis

Systemic therapy for 'advanced' melanoma



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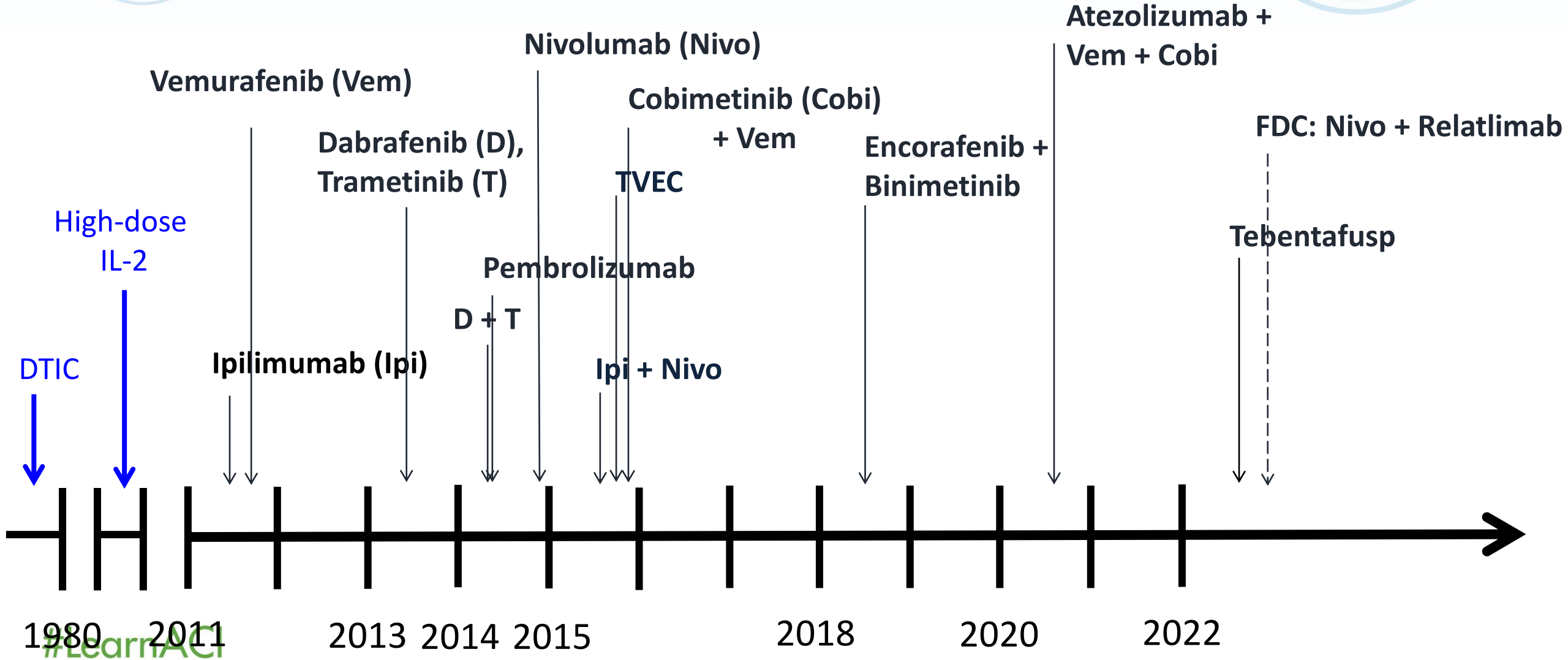
Advances in Cancer Immunotherapy™

Advanced Melanoma Treatment Landscape 2022



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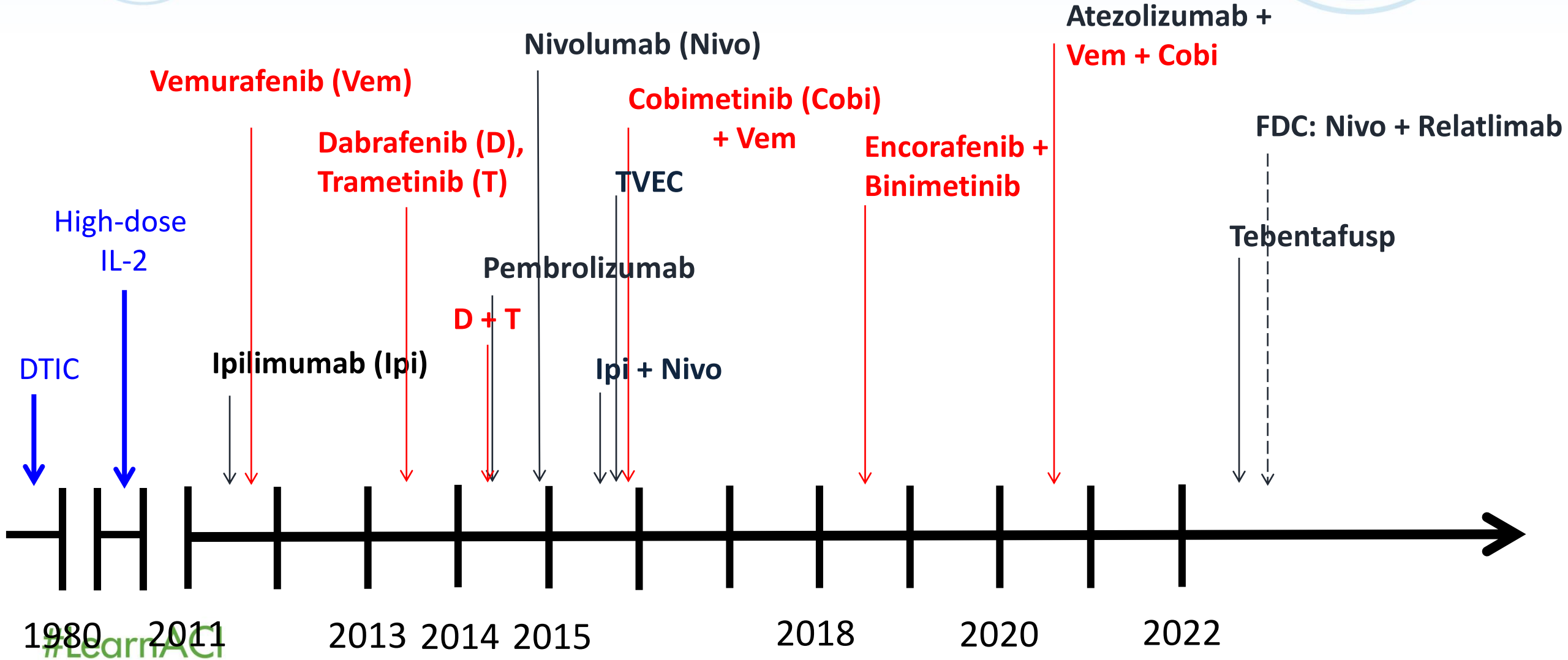
sitc
Society for Immunotherapy of Cancer

Advances in Cancer Immunotherapy™

Advanced Melanoma Treatment Landscape 2022



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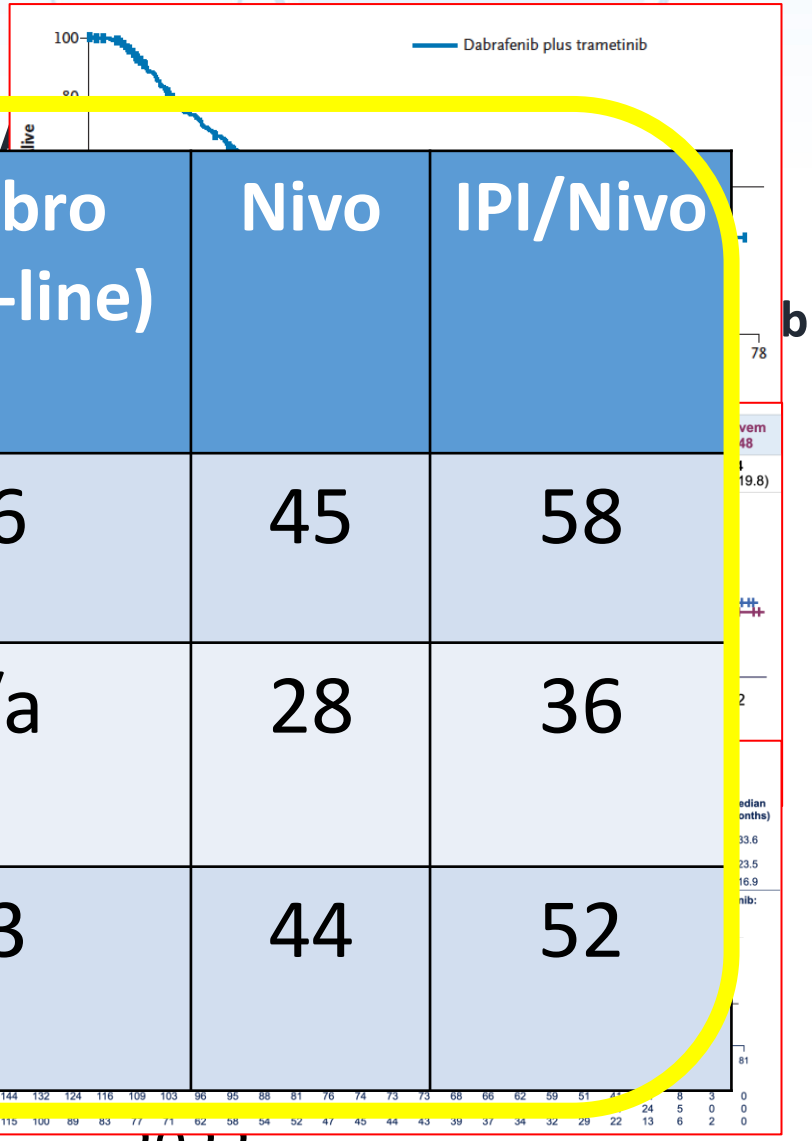
Overall Survival: First Line Patients

	Events, n (%)	Median OS (95% CI)	HR[a] (95% CI)

Agent(s)	Dab/Tram	Vem/cobi	Enco/Bini	Pembro (front-line)	Nivo	IPI/Nivo
ORR (%)	64	70	64	46	45	58
5-yr PFS (%)	19	14	23	n/a	28	36
5-yr OS (%)	34	30	35	43	44	52



DT

1980 2011 2013 2014 2015 2022

McArthur et al. SMR 2019
Dummer et al ASCO 2021

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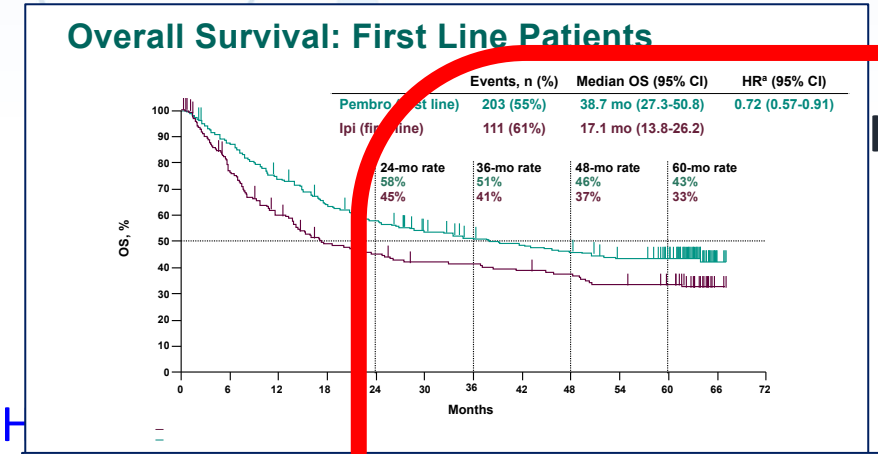
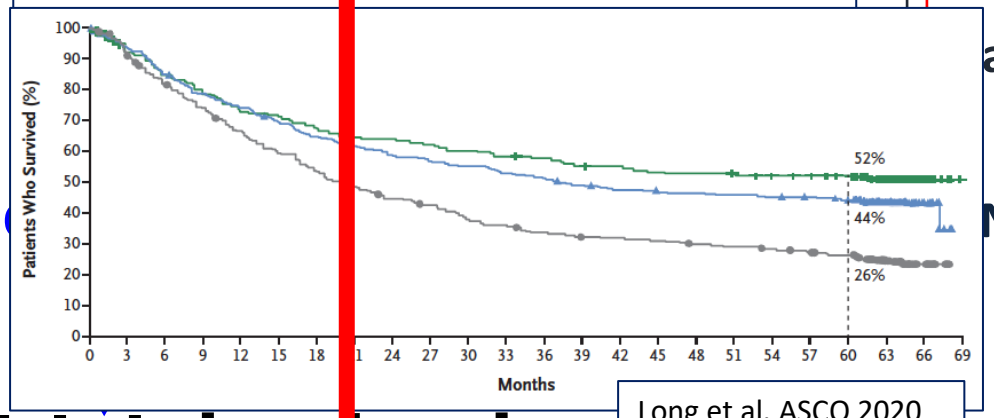
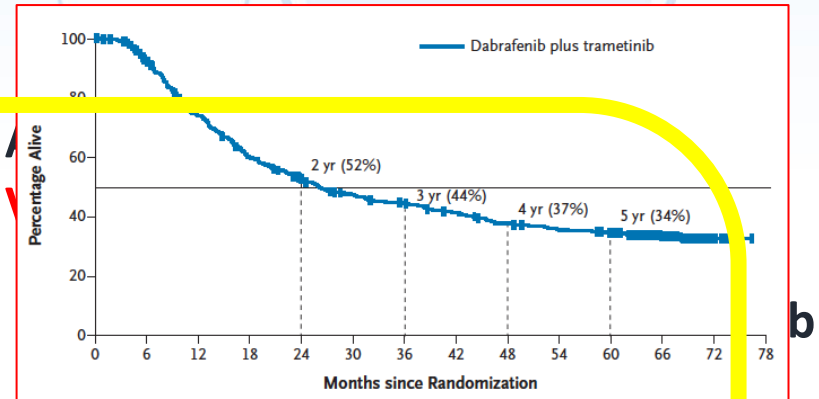
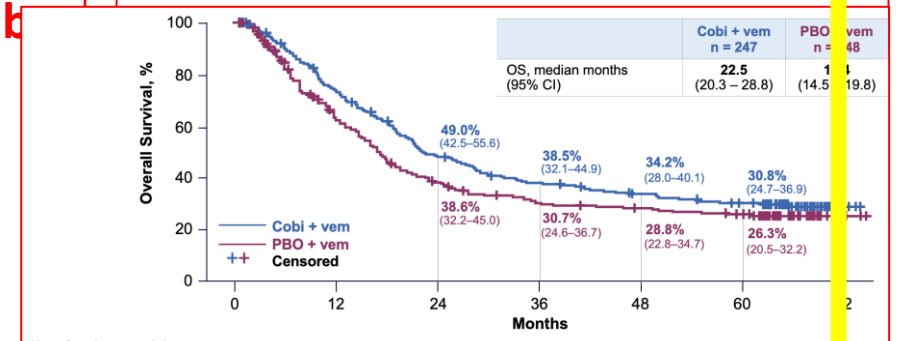
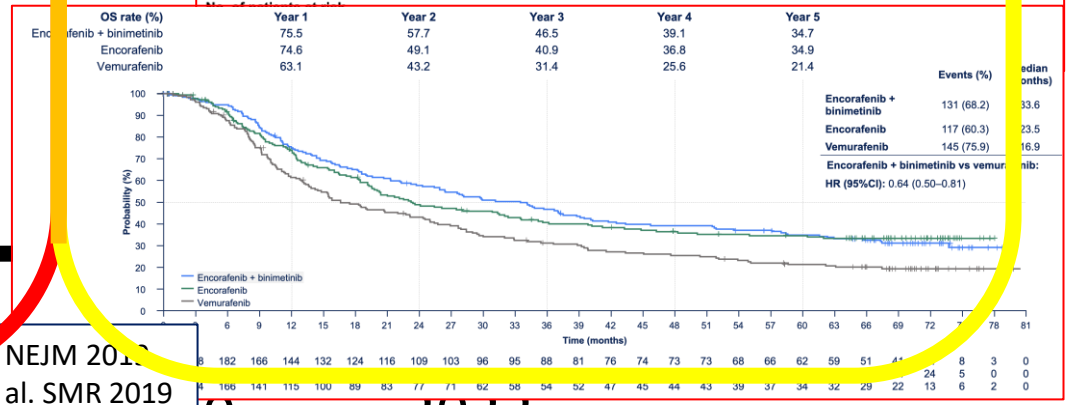




Long et al. ASCO 2020
Larkin et al. NEJM 2019





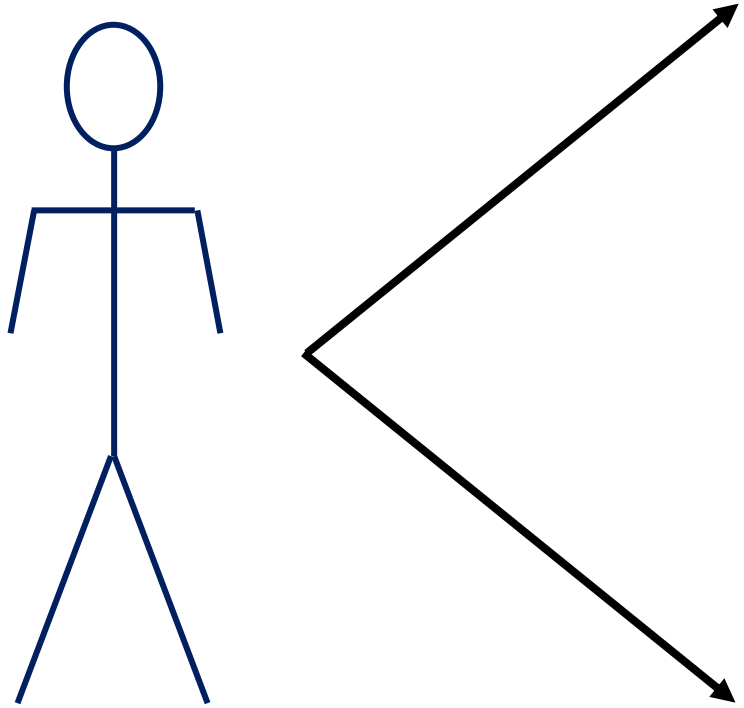


Robert et al. NEJM 201
McArthur et al. SMR 2019
Dummer et al ASCO 2021

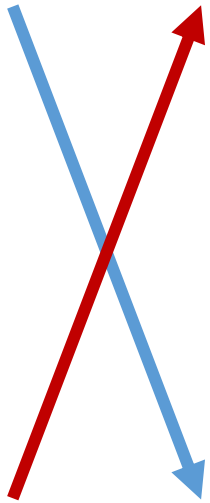
lumab (Nivo)
Cobimetinib (Cobi)
+ Vem
Enco rafenib +
Binimetinib
TVEC
ab
Nivo
DTI
1980 2011 2013 2014 2015 0 2022

What do we do?

New patients with advanced,
BRAF MT melanoma



BRAF targeted therapy

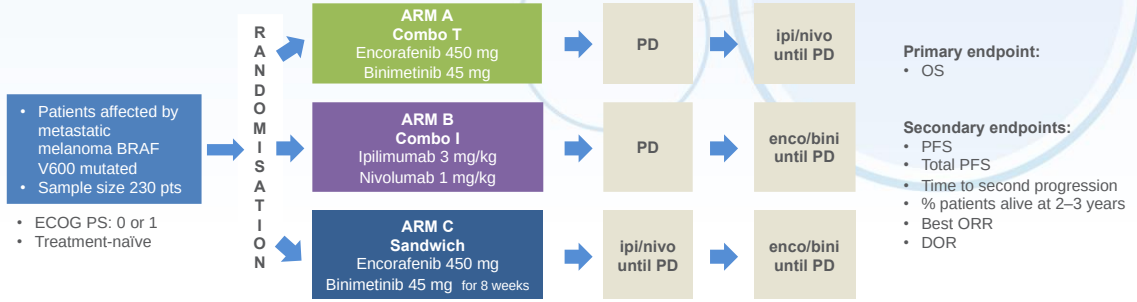


Immune targeted therapy

This is not an either or choice…

What to do? Look to randomized clinical trial data

SEQUENTIAL COMBO IMMUNO AND TARGET THERAPY (SECOMBIT)



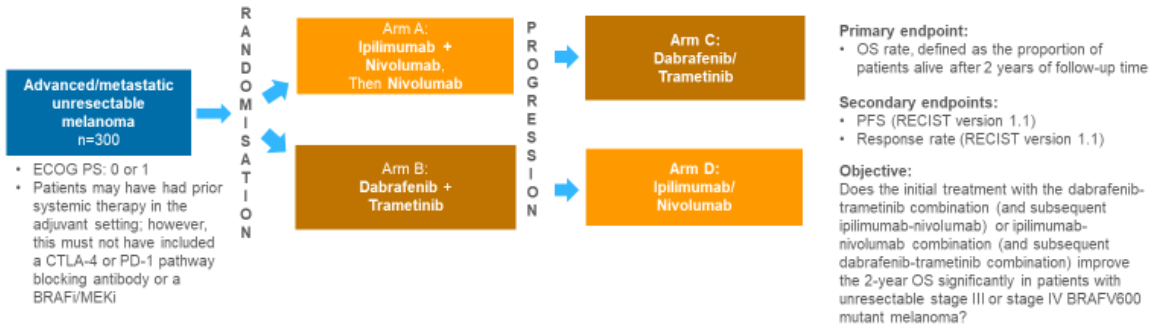
Stratification Factors:
- IIIb/c – M1a – M1b
- M1c with normal LDH (≤ 2ULN)
- M1c with elevated LDH (> 2 ULN)

DOR, duration of response; ECOG-PS, Eastern Cooperative Oncology Group performance status; LGX = encorafenib (BRAFi); MEK162 = binimetinib (MEKi); ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PD, progressive disease.

Clinicaltrials.gov: NCT02631447.

NCT02224781: Phase 3 Study of Dabrafenib + Trametinib Followed by Ipilimumab + Nivolumab vs Ipilimumab + Nivolumab Followed by Dabrafenib + Trametinib

Randomised Phase 3 trial of dabrafenib + trametinib followed by ipilimumab + nivolumab at progression vs ipilimumab + nivolumab followed by dabrafenib + trametinib at progression in patients with advanced BRAF V600 mutant melanoma



ECOG-PS, Eastern Cooperative Oncology Group performance status; OS, overall survival; PFS, progression-free survival; Q2W, every 2 weeks; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.

Clinicaltrials.gov: NCT02224781.

2021 ESMO congress

SECOMBIT: the best sequential approach with combo immunotherapy [ipilimumab (I) /nivolumab (N)] and combo target therapy [encorafenib (E)/binimetinib (B)] in patients with BRAF mutated metastatic melanoma. A phase II randomized study

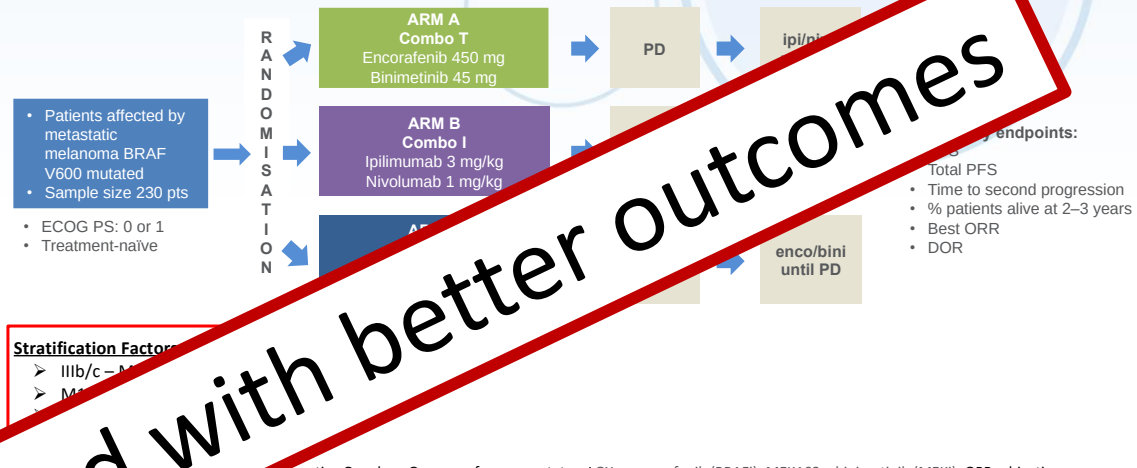
Ascierto PA,[1] Mandalà M,[2] Ferrucci PF,[3] Rutkowski P,[4] Guidoboni M,[5] Arance AM,[6] Ferraresi V[7], Maiello E,[8] Guida M,[9] Del Vecchio M,[10] Fierro MT,[11] Queirolo P,[3-12] Lebbè C,[13] Helgadottir H,[14] Melero I,[15] Palmieri G,[16] Giannarelli D,[17] Grimaldi AM,[1] Dummer R,[18*] Chiarion Sileni V,[19*].

1-Department of Melanoma, Cancer Immunotherapy and Development Therapeutics. I.N.T. IRCCS Fondazione "G. Pascale" Napoli; 2-Department of Oncology and Haematology, Papa Giovanni XXIII Cancer Center Hospital, Bergamo, Italy; 3-Biotherapy of Tumors Unit, Department of Experimental Oncology, European Institute of Oncology, IRCCS, - Milan, Italy; 4-Department of Soft Tissue/Bone Sarcoma, Maria Sklodowska Curie National Research Institute of Oncology, 02-781 - Warsaw/PL; 5-Immunotherapy and Cell Therapy Unit, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy; 6-Department of Medical Oncology, Hospital Clínic Barcelona, 08036 - Barcelona/ES; 7-Department of Medical Oncology 1; 7-IRCCS Regina Elena National Cancer Institute, Rome, Italy; 8-Department of Oncology, Fondazione IRCCS Casa Sollievo della Sofferenza, Foggia, Italy; 9-Medical Oncology Department, National Cancer Research Centre "Giovanni Paolo II", Bari, Italy; 10-Unit of Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; 11-Department of Medical Sciences, Dermatologic Clinic, University of Turin, Turin, Italy; 12-IRCCS Ospedale Policlinico San Martino, Skin Cancer Unit, Genova, Italy; 13-Institut de Recherche Saint Louis (IRSL), Université de Paris, F-75010 Paris, France; 14-Department of Oncology-Pathology, Karolinska Institutet and Karolinska University Hospital Solna, Stockholm, Sweden; 15-Department of Immunology and Immunotherapy, Clínica Universidad de Navarra, Pamplona, Spain; 16-Unit of Cancer Genetics, CNR, Sassari, Italy; 17-Regina Elena National Cancer Institute, IRCCS - Biostatistical Unit, Rome, Italy; 18-Department of Dermatology, University and University Hospital Zurich, Zurich, Switzerland; 19-Melanoma Oncology Unit, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy.

*contributed equally to this study

Abstract Number LBA#1997

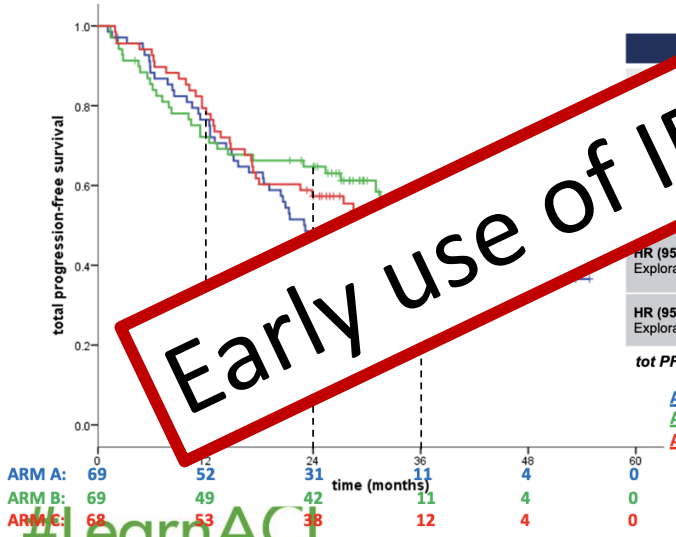
SEQUENTIAL COMBO IMMUNO AND TARGET THERAPY (SECOMBIT)



operative Oncology Group performance status; LGX = encorafenib (BRAFi); MEK162 = binimetinib (MEKi); ORR, objective response rate; survival; PD, progressive disease.

Clinicaltrials.gov: NCT02631447.

SEQUENTIAL COMBO IMMUNO AND TARGET THERAPY (SECOMBIT) STUDY: TOTAL PROGRESSION FREE SURVIVAL

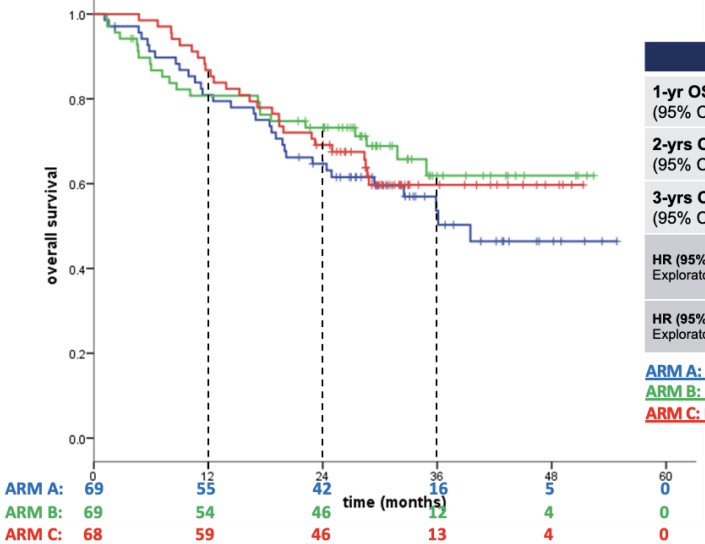


	Arm C
	78% (68-88)
(34-58)	65% (54-76)	57% (45-69)
	41% (29-53)	53% (43-63)	54% (42-66)
HR (95% CI) Arm B vs A Exploratory analysis	0.71 (0.44-1.14)	-	-
HR (95% CI) Arm C vs A Exploratory analysis	0.74 (0.46-1.18)	-	-

tot PFS: time from randomization until the date of the second progression

ARM A: Enco/Bini PD → Ipi/Nivo
ARM B: Ipi/Nivo PD → Enco/Bini
ARM C: Enco/Bini (8 weeks) → Ipi/Nivo PD → Enco/Bini

SEQUENTIAL COMBO IMMUNO AND TARGET THERAPY (SECOMBIT) STUDY: OVERALL SURVIVAL



	Arm A	Arm B	Arm C
1-yr OS% (95% CI)	81% (72-90)	81% (72-90)	87% (69-95)
2-yrs OS% (95% CI)	65% (54-76)	73% (62-84)	69% (58-80)
3-yrs OS% (95% CI)	54% (41-67)	62% (48-76)	60% (58-72)
HR (95% CI) Arm B vs A Exploratory analysis	0.73 (0.42-1.26)	-	-
HR (95% CI) Arm C vs A Exploratory analysis	0.81 (0.48-1.37)	-	-

ARM A: Enco/Bini PD → Ipi/Nivo
ARM B: Ipi/Nivo PD → Enco/Bini
ARM C: Enco/Bini (8 weeks) → Ipi/Nivo PD → Enco/Bini

Early use of IPI/NIVO associated with better outcomes

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ASCO Plenary Series

DREAMseq (Doublet, Randomized Evaluation in Advanced Melanoma Sequencing) a Phase III Trial: ECOG-ACRIN EA6134

Michael B. Atkins[1], Sandra Lee[2], Bartosz Chmielowski[3], Antoni Ribas[3], Ahmad A. Tarhini[4], Thach-Giao Truong[5], Diwakar Davar[6], Mark O'Rourke[7], Brendan D. Curti[8], Joanna M. Brell[9], Kari L. Kendra[10], Alexandra P. Ikeguchi[11], Jedd D. Wolchok[12], John M. Kirkwood[6]

[1]Georgetown Lombardi Comprehensive Cancer Center, Washington DC; [2]Dana-Farber Cancer Institute, Boston MA; [3]Jonsson Comprehensive Cancer Center University of California Los Angeles, Los Angeles CA; [4]H. Lee Moffitt Cancer Center and Research Institute, Tampa FL; [5]Kaiser Permanente Northern California, Vallejo CA; [6]Pittsburgh Cancer Institute, Pittsburgh PA; [7]Greenville Health System Cancer Institute, Greenville SC; [8]Providence Cancer Institute, Portland OR; [9]MetroHealth Medical Center, Cleveland OH; [10]Ohio State University Comprehensive Cancer Center, Columbus OH; [11]University of Oklahoma Medical Center, Oklahoma City OK; [12]Memorial Sloan Kettering Cancer Center, New York NY

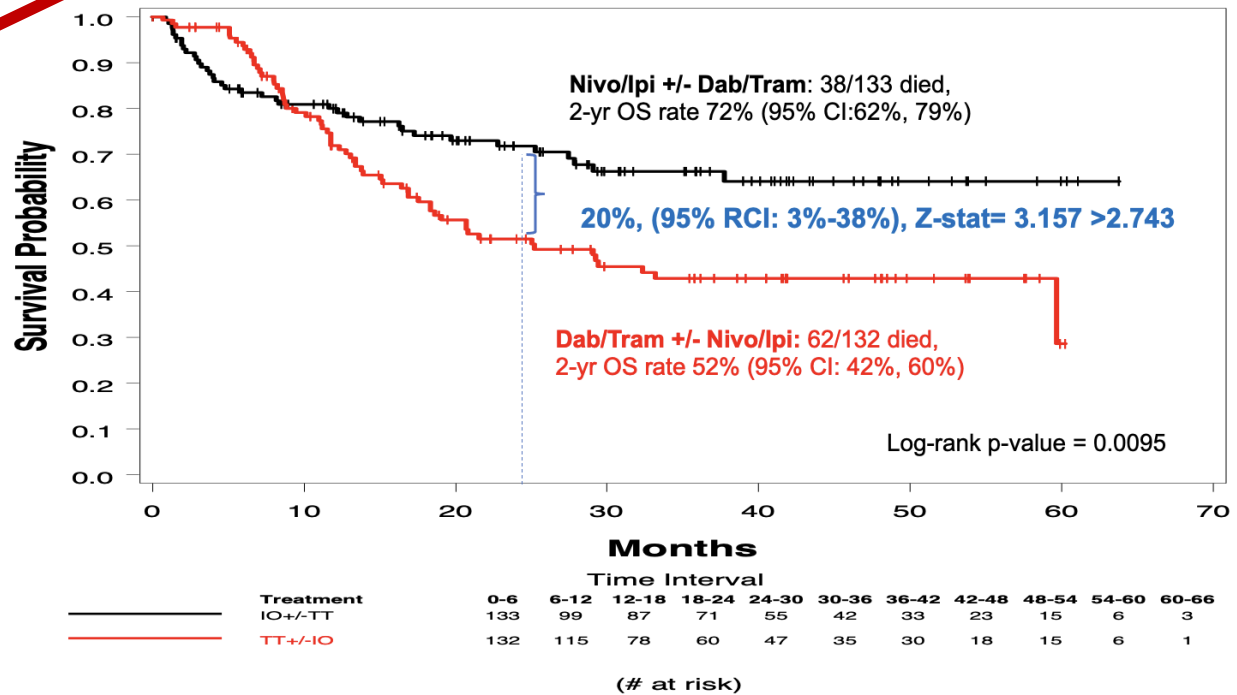
NCT02224781: Phase 3 Study of Dabrafenib + Trametinib Followed by Ipilimumab + Nivolumab vs Ipilimumab + Nivolumab Followed by Dabrafenib + Trametinib

Randomised Phase 3 trial of dabrafenib + trametinib followed by ipilimumab + nivol… progression vs ipilimumab + nivolumab followed by dabrafenib + trametinib at… patients with advanced BRAF V600 mutant melanoma

…cology Group performance status; OS, overall survival; PFS, progression-free …Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.

Clinicaltrials.gov: NCT02224781.

Characteristic	Arm A-IO (n=133)	…)
Age (years)	61 (range: 25-85	…30-84)
Sex % Male	61%	…%
ECOG PS 0 (%)		67%
Stage		(n=130)
III unresectabl…	…)	17 (13%)
M1A	16 (12%)	14 (11%)
M1B	24 (18%)	23 (18%)
M1C	81 (62%)	76 (58%)
LDH > ULN (%)	53 (40%)	53 (40%)
Prior Treatment (adjuvant)*	16 (12%)	21 (17%)



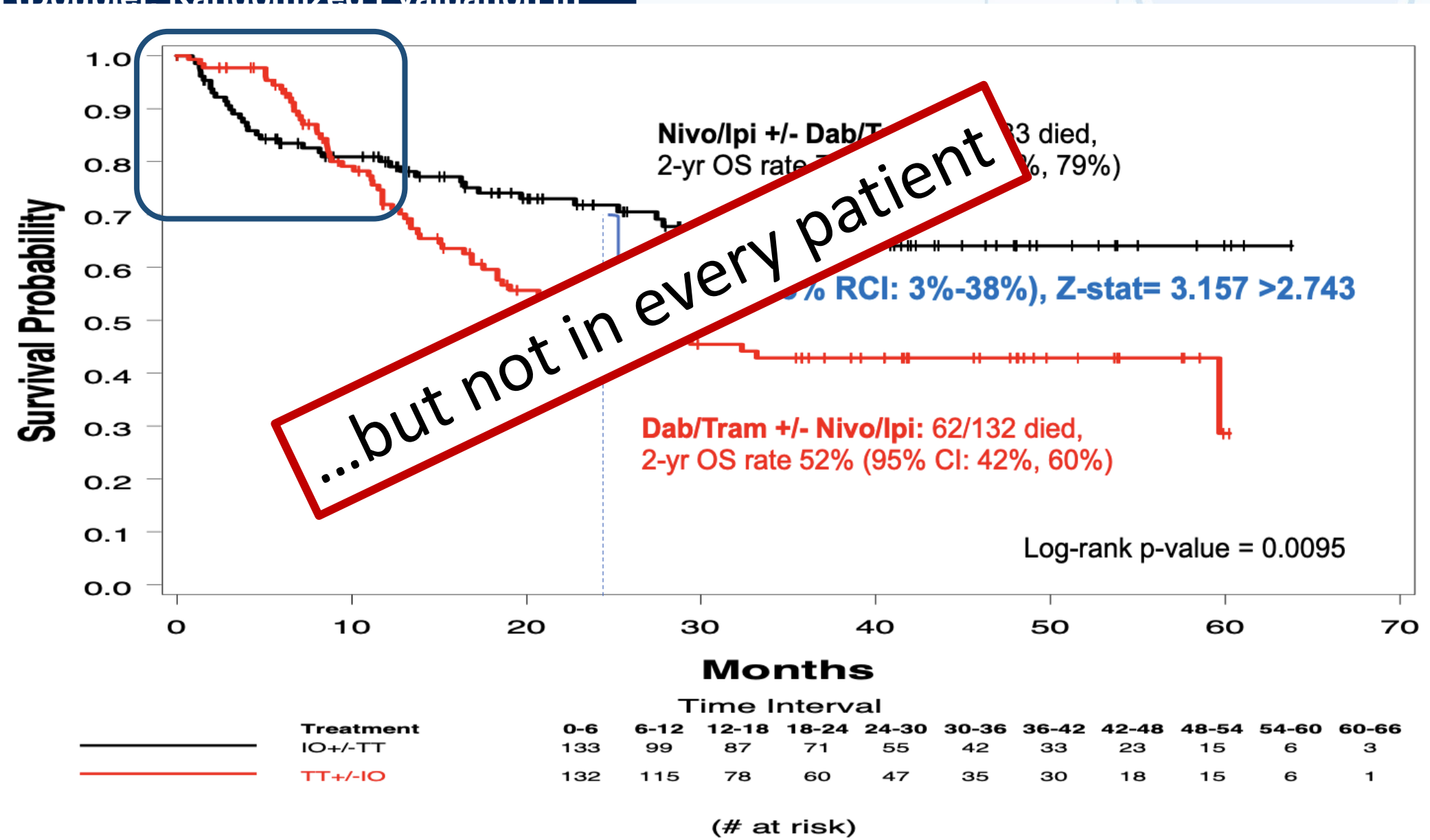
Front line IPI/NIVO is associated with better outcomes

DREAMseq (Doublet, Randomized Evaluation in Advance

Michael B. Atkins[1],
Thach-Giao Truong[5]
Kari L. Kendra

[1]Georgetown Lombardi Comprehensive Cancer C Institute, Tampa FL; [5]Kaiser System Cancer Institute, [10]Ohio State University Cor

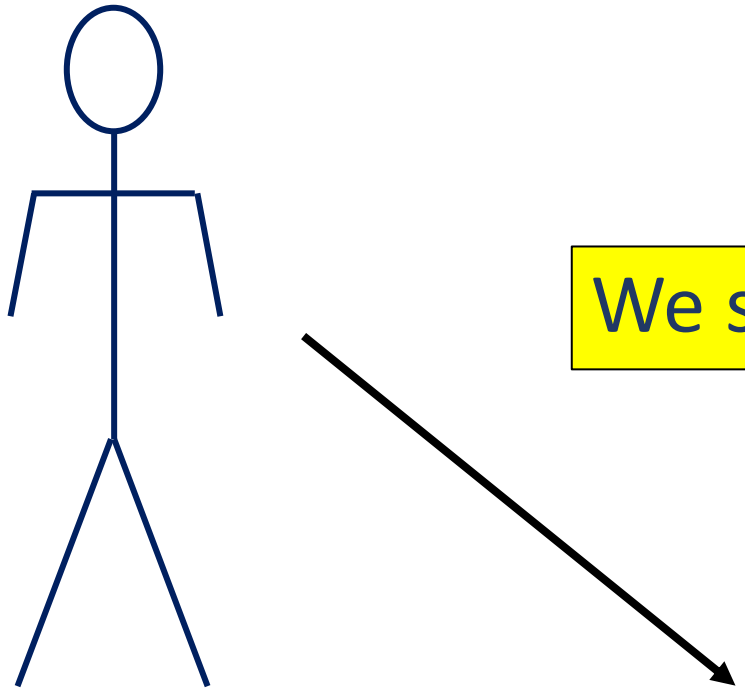
ASCO Plenary Series #ASCOPle



#LearnAC

So, what do we do?

New patients with advanced,
BRAF MT melanoma



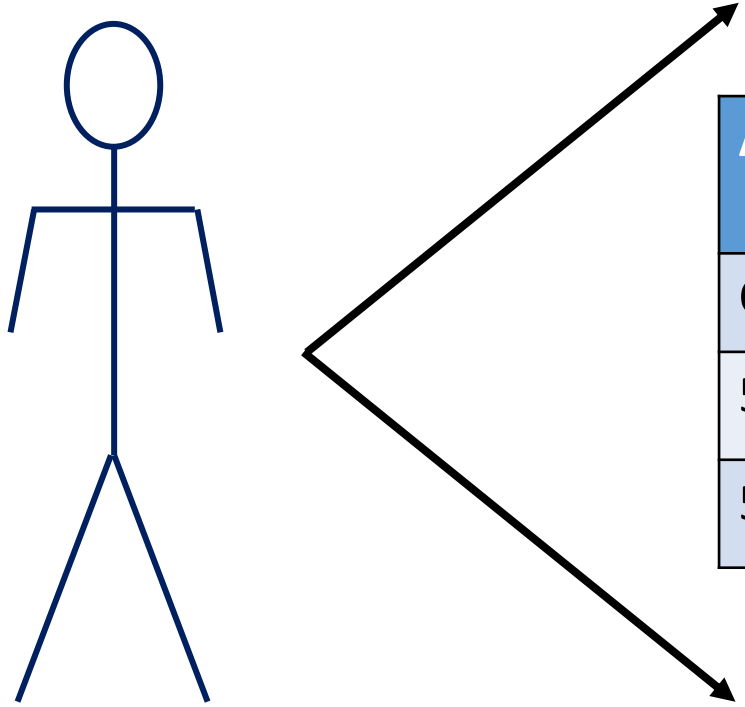
BRAF targeted therapy

We start with anti-PD-1 based therapy

Immune targeted therapy

What do we do?

New patients with advanced,
BRAF MT or BRAF WT melanoma



Single-agent anti-PD-1

Agent(s)	Pembro (front-line)	Nivo	IPI/Nivo
ORR (%)	46	45	58
5-yr PFS (%)	n/a	28	36
5-yr OS (%)	43	44	52

Long et al. ASCO 2020
Larkin et al. NEJM 2019

Combined anti-PD-1/anti-CTLA4

Why not always combined anti-PD-1/anti-CTLA-4 in the first-line?

TOXICITY

Combined IPI/NIVO is associated with more frequent, more severe, and multiple toxicities than NIVO or IPI

Patients Reporting Event, %	NIVO + IPI (N=313)		NIVO (N=313)		IPI (N=311)	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Treatment-related adverse event (AE)	95.5	55.0	82.1	16.3	86.2	27.3
Treatment-related AE leading to discontinuation	36.4	29.4	7.7	5.1	14.8	13.2
Treatment-related death	0		0.3		0.3	

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

Are there scenarios where we always consider combined anti-PD-1/anti-CTLA-4 in the first-line?

CNS disease

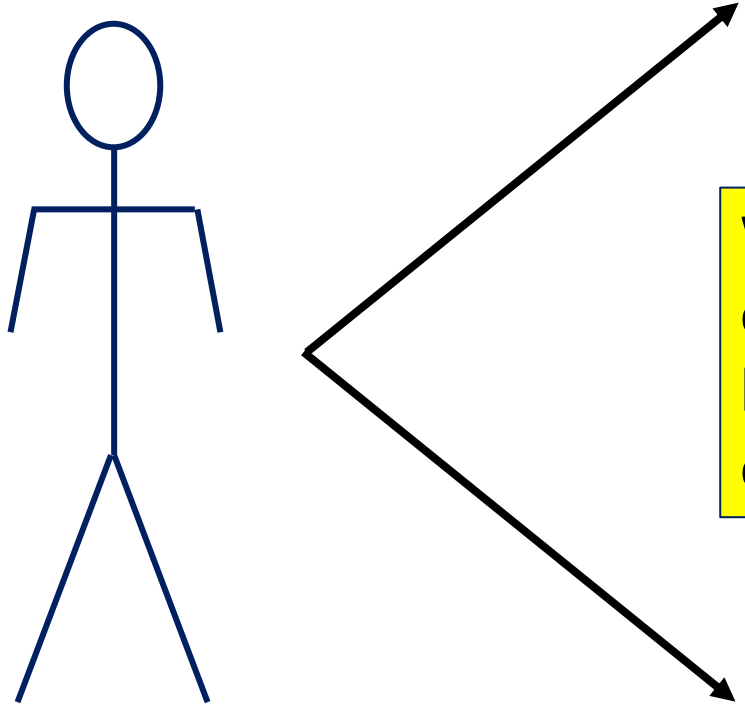
Summary of Contemporary Regimens in CNS disease

Study	New or Recurrent	Treatment	# of patients	Median PFS (mo)	6 mo PFS (%)	Cerebral RR
Goldberg Lancet Oncol 2016	Both	Pembrolizumab	18	NA	22	22
COMBI-MB Davies Lancet Oncol 2017	New	Dabrafenib and trametinib	Cohort A, 76	5.6	<20	58
CM-204 Tawbi Lancet Oncol 2021	New	Ipilimumab and nivolumab	A: 101 B: 18	NR 1.2	61** 33	54 11
ABC Long Lancet Oncol 2018	New	Nivolumab Ipilimumab and nivolumab	25 26	2.5 NR	20 53	20 46

NA – not available
NR – not reached
** 18 mo OS 75%

So, what do we do?

New patients with advanced,
BRAF MT or BRAF WT melanoma



Single-agent anti-PD-1

We use clinical factors (CNS disease, rapidity of growth, liver mets, symptomatic disease, high LDH, etc.) to determine which patients to offer combined checkpoint inhibitor therapy

Combined anti-PD-1/anti-CTLA4

And then…

2021 ASCO ANNUAL MEETING

Relatlimab (RELA) + nivolumab (NIVO) versus NIVO in first-line advanced melanoma: primary phase 3 results from RELATIVITY-047 (CA224-047)

Evan J. Lipson,[1] Hussein A. Tawbi,[2] Dirk Schadendorf,[3] Paolo A. Ascierto,[4] Luis Matamala,[5] Erika Castillo Gutiérrez,[6] Piotr Rutkowski,[7] Helen J. Gogas,[8] Christopher D. Lao,[9] Juliana Janoski De Menezes,[10] Stéphane Dalle,[11] Ana Arance,[12] Jean-Jacques Grob,[13] Shivani Srivastava,[14] Mena Abaskharoun,[14] Katy L. Simonsen,[14] Bin Li,[14] Georgina V. Long,[a,15] F. Stephen Hodi[a,16]

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Presentation Number 9503

- **RELATIVITY-047** is a global, randomized, double-blind, phase 2/3 study

Key eligibility criteria
- Previously untreated unresectable or metastatic melanoma[a]
- ECOG PS 0-1

Stratification factors
- LAG-3[b]
- PD-L1[c]
- *BRAF*
- AJCC v8 M stage

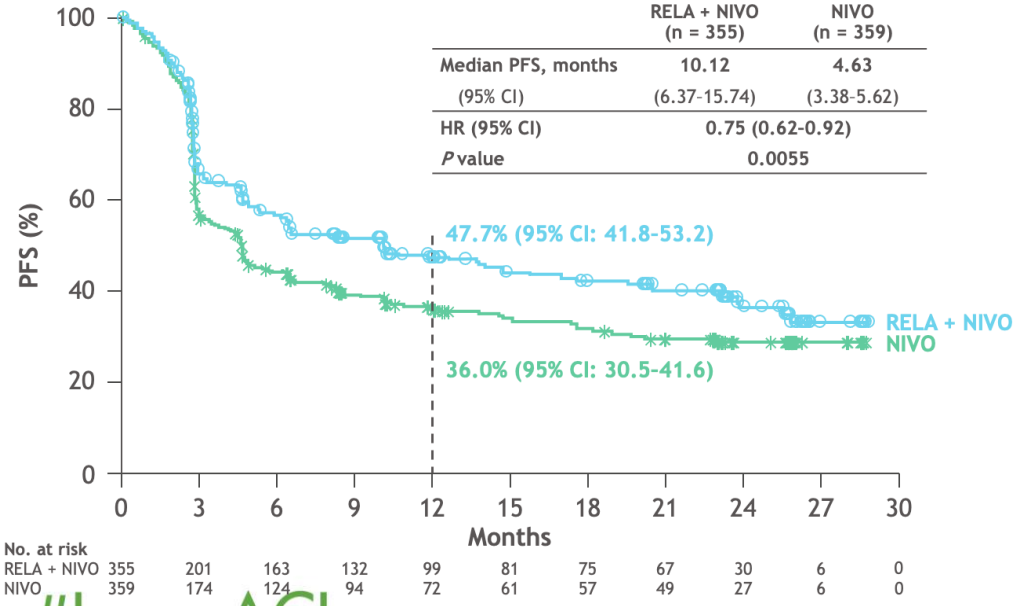
N = 714

R 1:1

- RELA 160 mg + NIVO 480 mg fixed-dose combination (FDC) IV Q4W
- NIVO 480 mg IV Q4W

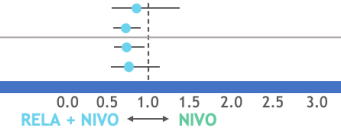
Primary endpoint
- PFS by BICR[d]

Secondary endpoints
- OS
- ORR by BICR[d]



	RELA + NIVO (n = 355)	NIVO (n = 359)
Median PFS, months	10.12	4.63
(95% CI)	(6.37-15.74)	(3.38-5.62)
HR (95% CI)	0.75 (0.62-0.92)	
P value	0.0055	

Subgroup		RELA + NIVO Events/no. of patients	NIVO Events/no. of patients	Unstratified HR for progression or death (95% CI)
Overall		180 (355)	211 (359)	0.76 (0.62-0.92)
Age categorization, years	≥ 18 and < 65	99 (187)	117 (196)	0.83 (0.64-1.09)
	≥ 65 and < 75	50 (102)	60 (103)	0.69 (0.47-1.00)
	≥ 65	81 (168)	94 (163)	0.69 (0.51-0.93)
	≥ 75	31 (66)	34 (60)	0.69 (0.42-1.13)
Sex	Male	98 (210)	123 (206)	0.68 (0.52-0.89)
	Female	82 (145)	88 (153)	0.88 (0.65-1.19)
LDH	≤ ULN	100 (224)	127 (231)	0.70 (0.54-0.91)
	> ULN	79 (130)	84 (128)	0.80 (0.59-1.09)
	≤ 2 × ULN	158 (322)	186 (328)	0.75 (0.60-0.92)
	> 2 × ULN	21 (32)	25 (31)	0.75 (0.42-1.35)
ECOG PS	0	108 (236)	136 (242)	0.74 (0.57-0.95)
	1	72 (119)	75 (117)	0.78 (0.56-1.07)
Tumor burden per BICR	< Q1	26 (74)	37 (83)	0.62 (0.37-1.03)
	Q1 to <Q3	84 (161)	96 (153)	0.80 (0.60-1.07)
	≥ Q3	53 (84)	53 (75)	0.72 (0.49-1.06)
BRAF mutation status	Mutant	67 (136)	83 (139)	0.74 (0.54-1.03)
	Wild-type	113 (219)	128 (220)	0.76 (0.59-0.98)
AJCC v8 M stage	M0/M1any[0] LDH not elevated	104 (232)	130 (237)	0.71 (0.55-0.92)
PD-L1	≥ 1%	68 (146)	67 (147)	0.95 (0.68-1.33)
	< 1%/nonquantifiable	112 (209)	144 (212)	0.66 (0.51-0.84)
	≥ 5%	33 (88)	36 (86)	0.86 (0.54-1.38)
	< 5%/nonquantifiable	147 (267)	175 (273)	0.73 (0.58-0.90)
LAG-3	≥ 1%	131 (268)	151 (269)	0.75 (0.59-0.95)
	< 1%	49 (87)	60 (90)	0.78 (0.54-1.15)



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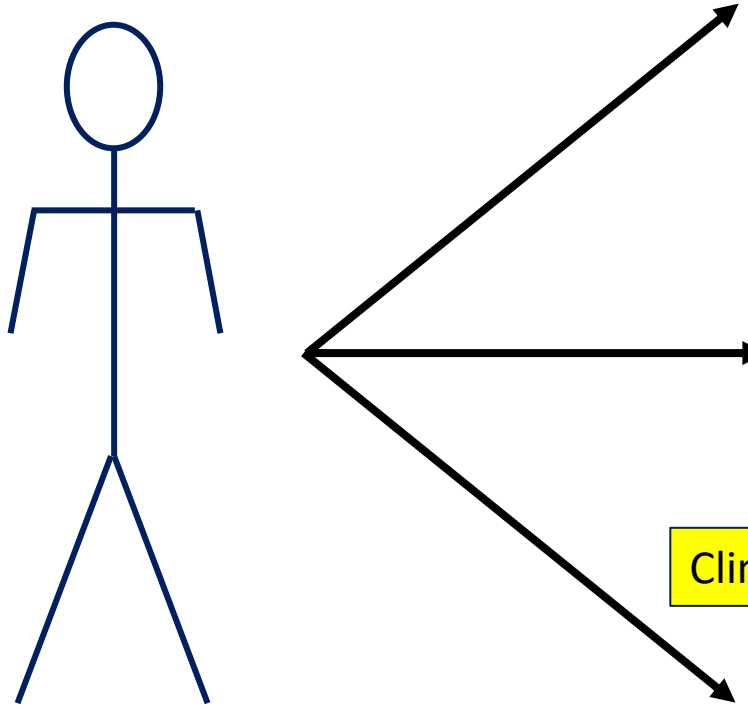
Now what?

New patients with advanced,
BRAF MT or BRAF WT melanoma



Single-agent anti-PD-1

Anti-PD-1/anti-LAG3

? LAG3/?PD-L1 expression

Clinical factors

Combined anti-PD-1/anti-CTLA4

Individualized therapy for advanced melanoma

- BRAF MT status offers multiple options, but anti-PD-1 based therapy is preferred
- Combined immune checkpoint inhibition with IPI/NIVO has numerically higher ORR, PFS, and OS but also higher toxicity
  - No great biomarker to predict who should receive this
  - Consider this for patients with rapidly progressing disease
  - SOC for patients with brain metastases
- Emerging data with combined anti-PD-1 and anti-LAG3 may change treatment landscape in near future
- Better biomarkers are needed to help select front-line immunotherapy when there are three choices: anti-PD-1, combined anti-PD-1/anti-CTLA-4 (IPI/NIVO), combined anti-PD-1/anti-LAG3

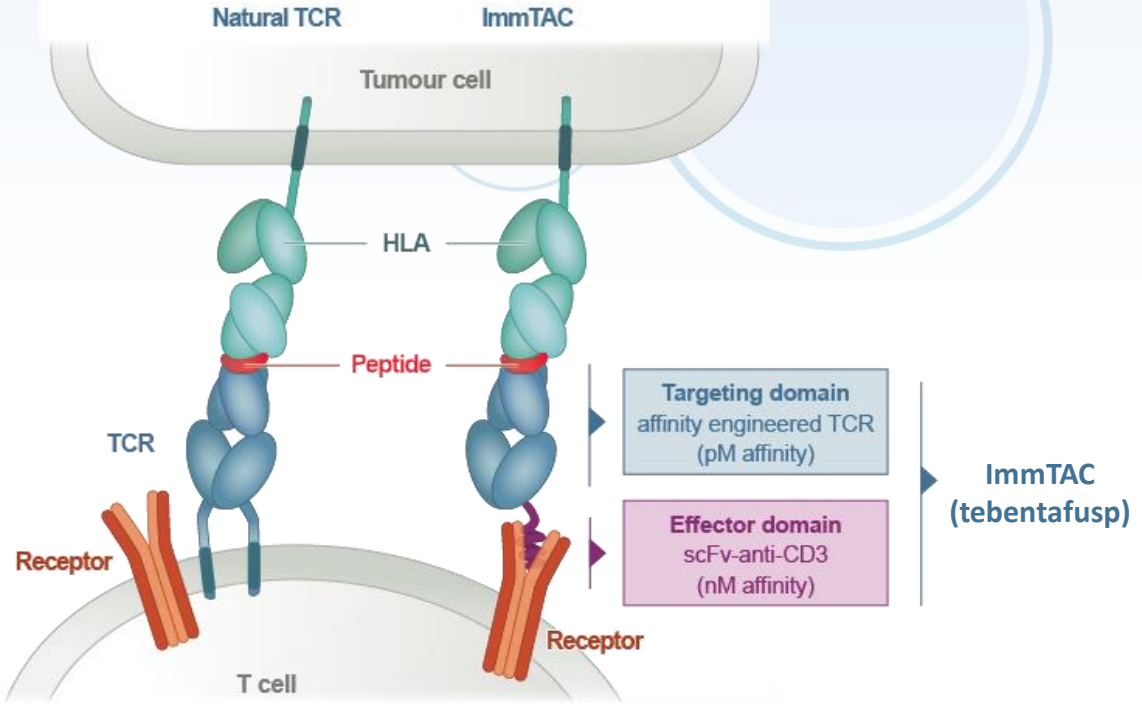
One last thing…

The NEW ENGLAND JOURNAL of MEDICINE

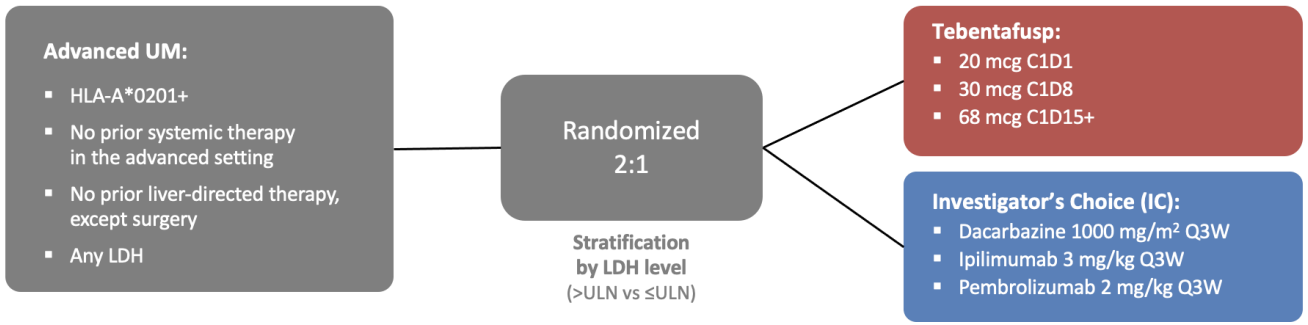
ORIGINAL ARTICLE

Overall Survival Benefit with Tebentafusp in Metastatic Uveal Melanoma

Paul Nathan, M.D., Ph.D., Jessica C. Hassel, M.D., Piotr Rutkowski, M.D., Ph.D., Jean-Francois Baurain, M.D., Ph.D., Marcus O. Butler, M.D., Max Schlaak, M.D., Ryan J. Sullivan, M.D., Sebastian Ochsenreither, M.D., Reinhard Dummer, M.D., John M. Kirkwood, M.D., Anthony M. Joshua, M.D., Ph.D., Joseph J. Sacco, M.D., Ph.D., Alexander N. Shoushtari, M.D., Marlana Orloff, M.D., Josep M. Piulats, M.D., Ph.D., Mohammed Milhem, M.D., April K.S. Salama, M.D., Brendan Curti, M.D., Lev Demidov, M.D., Lauris Gastaud, M.D., Cornelia Mauch, M.D., Ph.D., Melinda Yushak, M.D., M.P.H., Richard D. Carvajal, M.D., Omid Hamid, M.D., Shaad E. Abdullah, M.D., Chris Holland, M.S., Howard Goodall, M.D., and Sophie Piperno-Neumann, M.D., for the IMCgp100-202 Investigators*



IMCgp100-202 – study design



Hassel et al. AACR Annual Meeting 2021
Sullivan et al. Melanoma Bridge Meeting 2021

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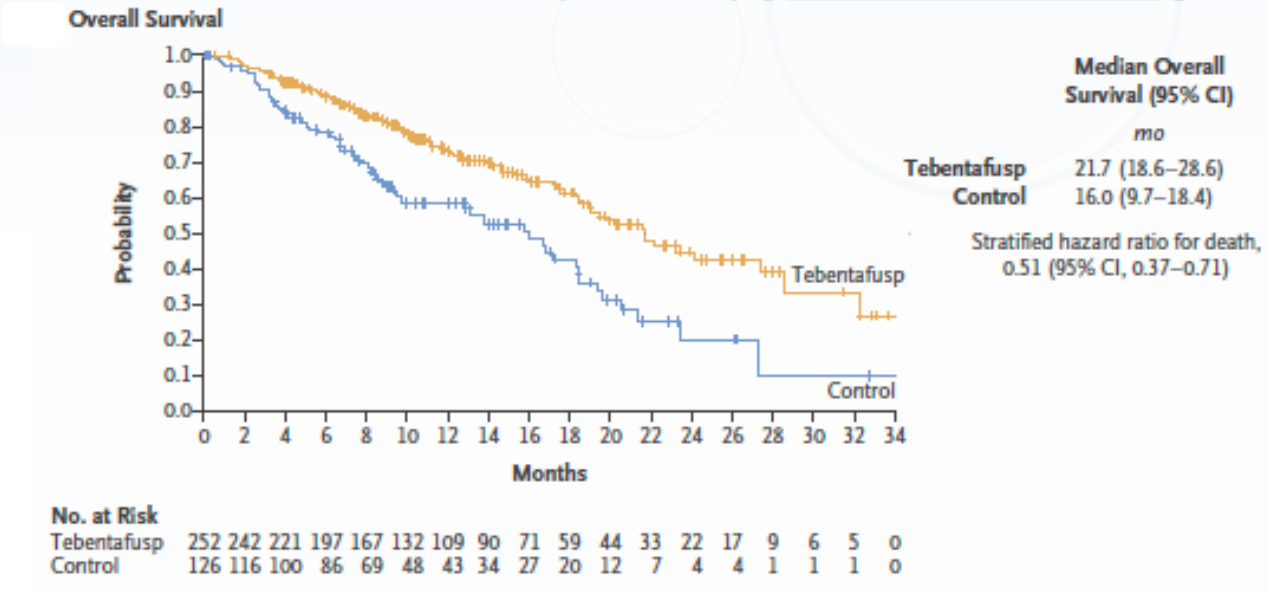
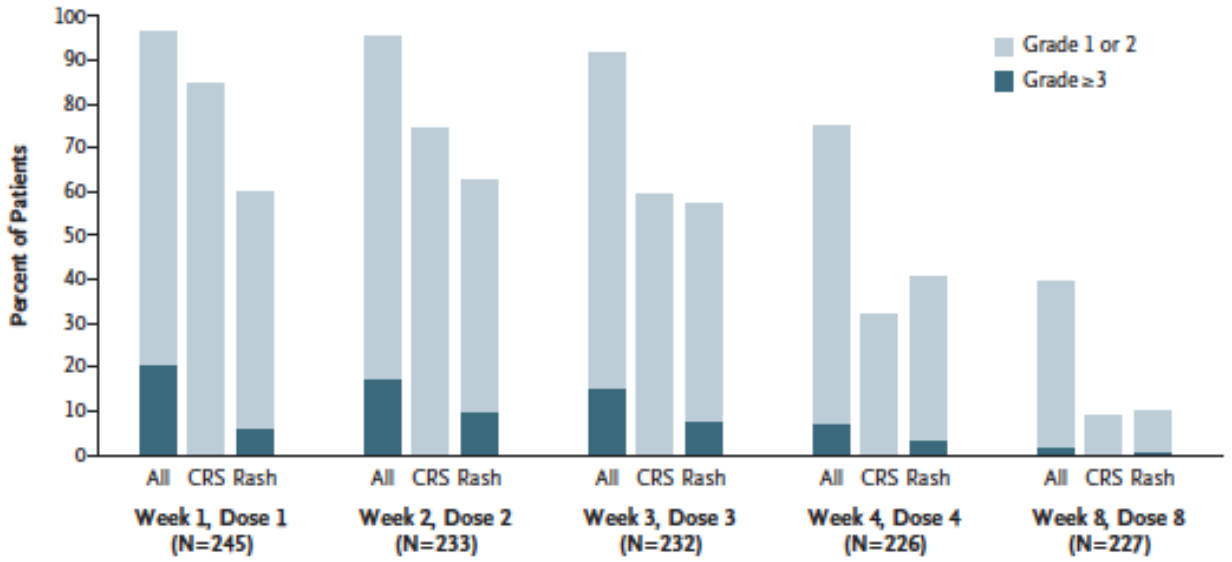
Tebentafusp FDA-approved for HLA-A*0201+, uveal melanoma in January 2022





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Thank you!