BARCELONA 2019 ESMO congress

LOCALISED MELANOMA RESECTED: ADJUVANT THERAPY FOLLOWED BY SYSTEMIC RELAPSE

CLINICAL CASE DISCUSSION

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DISCLOSURE

HONORARIA AS SPEAKER, CONSULTANCY OR ADVISORY ROLE:
Bristol-Myers Squibb, Roche, Amgen, Merck Sharp & Dohme, Novartis, GlaxoSmithKline, Pierre-Fabre

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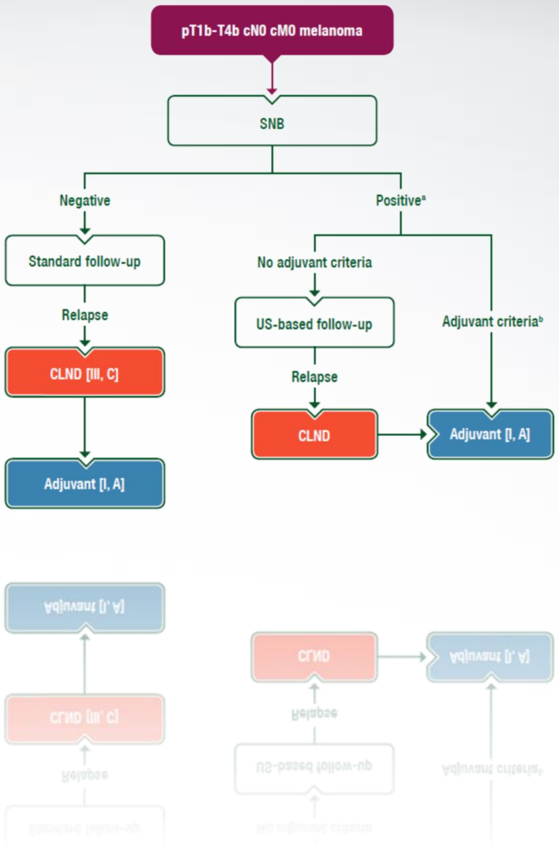
STOCK OWNERSHIP: None

Stage III Management Guidelines:

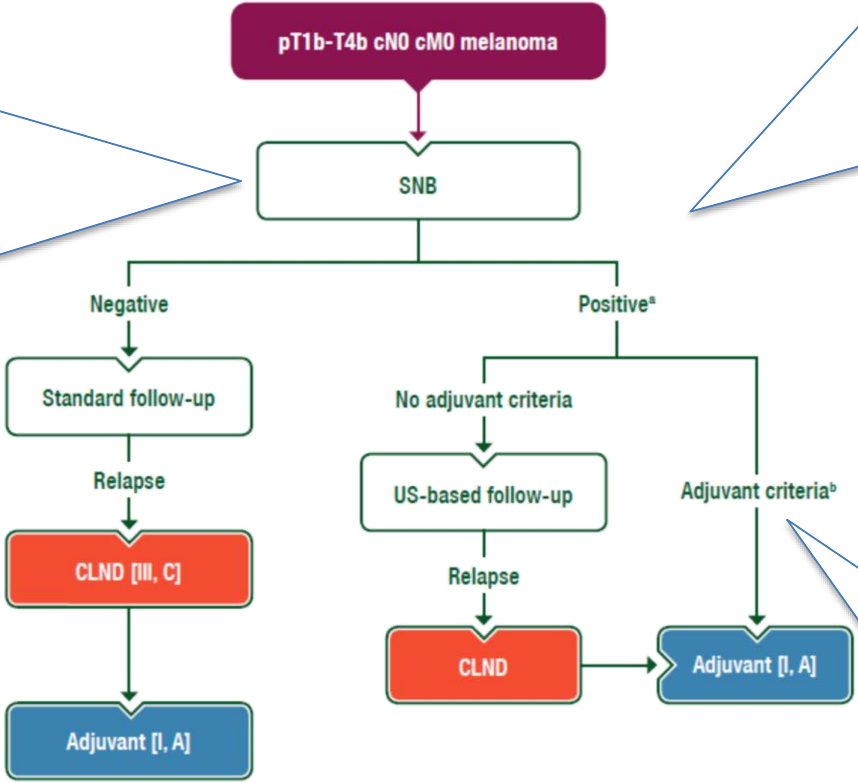
- SNB
- CLND
- Adjuvant treatment



Algorithm for stage I-III

Criteria for Sentinel Node Biopsy (SNB)

- SNB is recommended for staging in AJCC 8th edition stages pT1b (thickness >0.8 mm or <0.8 mm with ulceration) or higher [II,B][1].
- SNB is *not* recommended for stage pT1a (thickness <0.8 mm)[2].



No Complete Lymph Node Dissection (CLND) for SNB +

- For positive SNB patients, avoiding CLND is justified based on the results of the MSLT-II and DeCOG-SLT trials. The control arm of that trial is not standard observation, but US-based follow-up, which should be the strategy proposed to the patient [I, A].

Criteria for adjuvant:

- Patient with SNB deposit of more than 1 mm are candidate for adjuvant [I, A].

[1] Han *JCO* 2013; [2] Sondak ASCO Educational Book 2017

MSLT multicentre selective lymphadenectomy trial, US, ultrasound

Results from MSLT-II: no benefit to radical lymphadenectomy

The NEW ENGLAND JOURNAL of MEDICINE

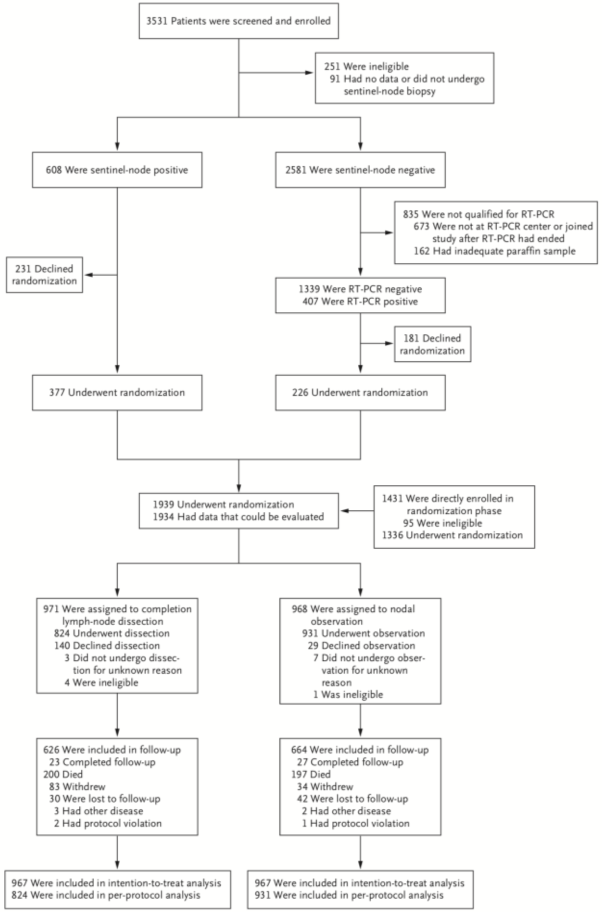
ESTABLISHED IN 1812 JUNE 8, 2017 VOL. 376 NO. 23

Completion Dissection or Observation for Sentinel-Node Metastasis in Melanoma

M.B. Faries, J.F. Thompson, A.J. Cochran, R.H. Andtbacka, N. Mozzillo, J.S. Zager, T. Jahkola, T.L. Bowles, A. Testori, P.D. Beitsch, H.J. Hoekstra, M. Moncrieff, C. Ingvar, M.W.J.M. Wouters, M.S. Sabel, E.A. Levine, D. Agnese, M. Henderson, R. Dummer, C.R. Rossi, R.I. Neves, S.D. Trocha, F. Wright, D.R. Byrd, M. Matter, E. Hsueh, A. MacKenzie-Ross, D.B. Johnson, P. Terheyden, A.C. Berger, T.L. Huston, J.D. Wayne, B.M. Smithers, H.B. Neuman, S. Schneebaum, J.E. Gershenwald, C.E. Ariyan, D.C. Desai, L. Jacobs, K.M. McMasters, A. Gesierich, P. Hersey, S.D. Bines, J.M. Kane, R.J. Barth, G. McKinnon, J.M. Farma, E. Schultz, S. Vidal-Sicart, R.A. Hoefer, J.M. Lewis, R. Scheri, M.C. Kelley, O.E. Nieweg, R.D. Noyes, D.S.B. Hoon, H.-J. Wang, D.A. Elashoff, and R.M. Elashoff

CONCLUSIONS

Immediate completion lymph-node dissection increased the rate of regional disease control and provided prognostic information but did not increase melanoma-specific survival among patients with melanoma and sentinel-node metastases. (Funded by the National Cancer Institute and others; MSLT-II ClinicalTrials.gov number, NCT00297895.)



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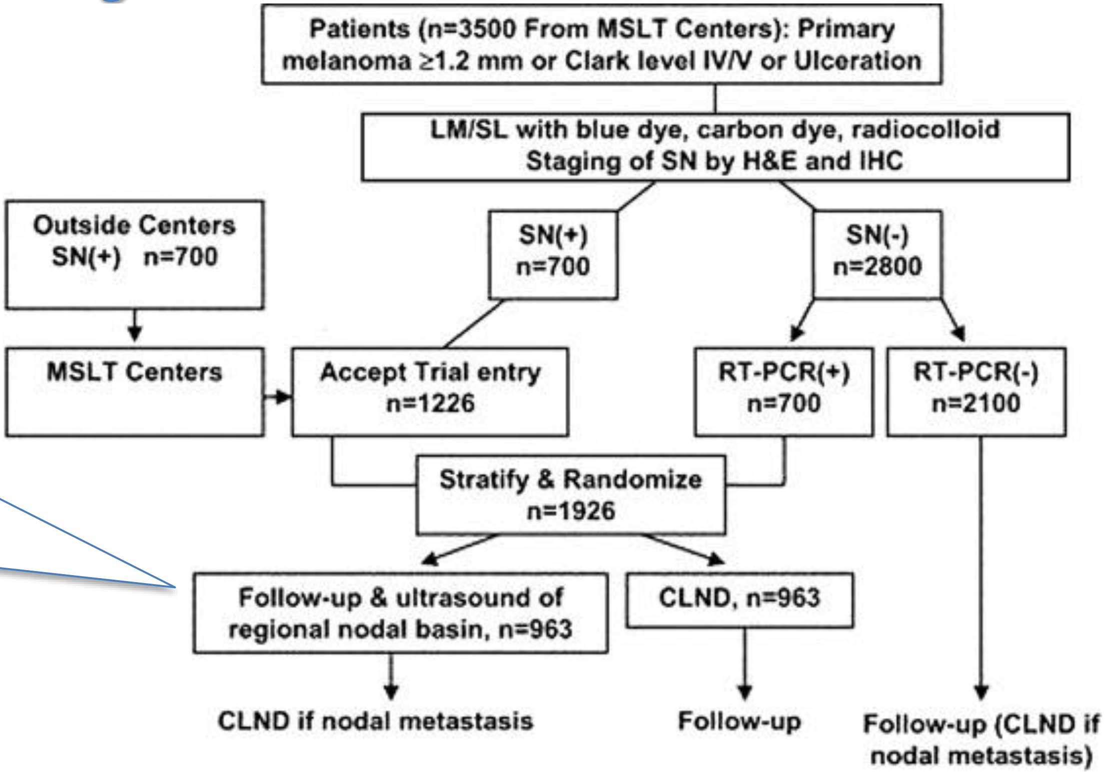
MSLT-II – Study design



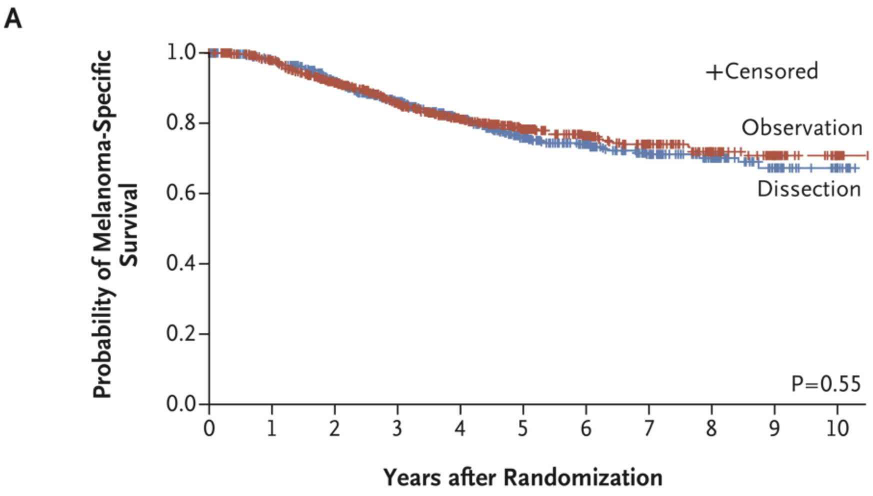
Important:

- The control arm is not simple clinical follow-up, but active US-based surveillance every 4 months!

CLND, complete lymph node dissection; H&E, hematoxylin & eosin staining; IHC, immunohistochemistry; LM, lymphatic mapping; MSLT, multicentre selective lymphadenectomy trial; RT-PCR, reverse-transcriptase-polymerase-chain-reaction; SL, sentinel lymphadenectomy; SN, sentinel node

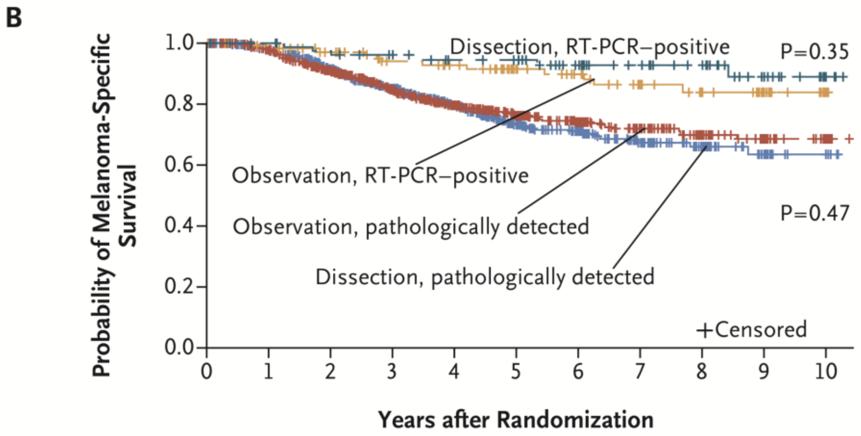
Faries, *NEJM* 2017

Results from MSLT-II: no benefit to radical lymphadenectomy



No. at Risk

	0	1	2	3	4	5	6	7	8	9	10
Dissection	824	759	654	510	389	275	191	128	83	39	13
Observation	931	856	734	564	425	304	217	151	95	55	13



No. at Risk

	0	1	2	3	4	5	6	7	8	9	10
Subgroup 1	744	682	581	441	326	214	144	92	53	21	6
Subgroup 2	820	751	639	482	348	241	163	109	64	34	8
Subgroup 3	80	77	73	69	63	61	47	36	30	18	7
Subgroup 4	111	105	95	82	77	63	54	42	31	21	5

Faries, *NEJM* 2017

RT-PCR, reverse-transcriptase-polymerase-chain-reaction

Overview of key adjuvant checkpoint blockade trials

Combo Phase III

Checkmate 915: Phase III, 900 pts
- Ipi 1 + nivo vs nivo
- Population: stage IIIB – D[c], IV
- Endpoint: RFS
- Accrual completed
- Results expected in 12/2020

Single Agent Phase III

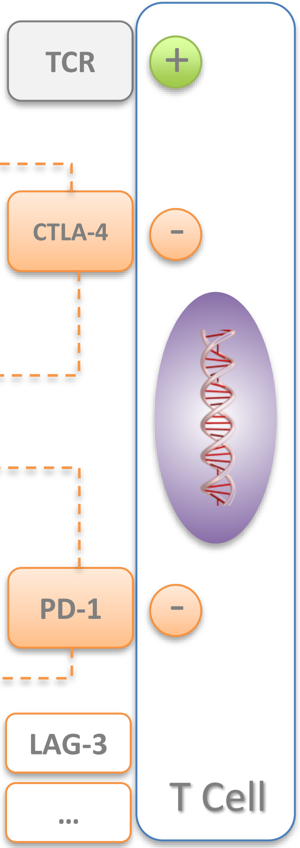
ECOG-1609[4]: Phase III, 1673 pts
- Ipi 10 vs ipi 3 vs HD INF-α2b
- Population: stage III B-C, IV M1a-b
- Endpoint: I, RFS & OS; II, QoL
- Adult accrual completed
- HR RFS/OS: 1.0[4]/NA

EORTC-18071[1]: Phase III, 951 pts
- Ipi 10 mg/kg vs placebo
- Population: stage III A[a]-C
- Endpoint: I, RFS; II, DMFS and OS
- mRFS/mOS: 28 vs 17 / 87 vs NR
- HR RFS/OS: 0.75/0.72

SWOG S1404: Phase III, 1378 pts
- Ipi 10 vs. pembro vs. HD IFN-α
- Population: stage IIIA (N2a) – C, IV
- Endpoint: OS/RFS in PD-L1+
- Accrual completed
- Results expected in 05/2020

Checkmate-238[2]: Phase III, 800 pts
- Ipi 10 mg/kg vs nivo 3 mg/kg
- Population: stage III B-C, IV NED
- Endpoint: I, RFS; II, OS
- mRFS/mOS: NA/NA
- HR RFS/OS: 0.65/NA

EORTC 1325[3,b]: Phase III, 1019 pts
- Pembro 200 mg vs placebo
- Population: stage III A[a]-C
- Endpoint: I, RFS; II, DMFS and OS
- mRFS/mOS: NA/NA
- HR RFS/OS: 0.57/NA



[1]Eggermont, *NEJM* 2016; [2]Weber, *NEJM* 2017; [3]Eggermont *NEJM* 2018; [4]Tarhini, ASCO 2017;Time in months, NA: Not Available, NR: Not Reached. [a] Excluding LN mets. < 1mm and in transit metastasis w/o nodal disease; [b] also Keynote-054; [c]AJCC 8th classification

Comparison of stage subgroup eligibility criteria

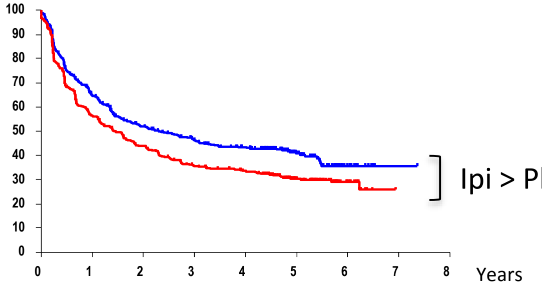
			Stage - AJCC 7^{th} Edition (All patients NED)				
	Study	**Design**	**IIC**	**IIIA**	**IIIB**	**IIIC**	**IV**
EMA/FDA NA/11.15	EORTC 18071	Ipilimumab 10 versus placebo		✓ SN > 1mm	✓	✓ no in transit mets	
EMA/FDA 12.18/02.19	EORTC 1325	Pembrolizumab versus placebo		✓ SN > 1mm	✓	✓ no in transit mets	
EMA/FDA 07.18/12.17	Checkmate 238	Ipilimumab 10 versus nivolumab			✓	✓	✓
	ECOG 1609	Ipilimumab 10 versus ipilimumab 3 versus HD INF-α2b			✓	✓	✓ M1a-b
	BRIM-8	Vemurafenib versus placebo	✓	✓ SN > 1mm	✓	✓	
EMA/FDA 08.18/04.18	COMBI-AD	Dabrafenib + trametinib versus placebo		✓ SN > 1mm	✓	✓	

AJCC, American Joint Committee on Cancer; EMA, European Medicines Agency; FDA, Food and Drug Administration; HD INF-α2b, high-dose interferon-α2b; NED, no evidence of disease; SN sentinel node.

Key efficacy landmarks in the adjuvant setting of melanoma

EORTC 18071[1]

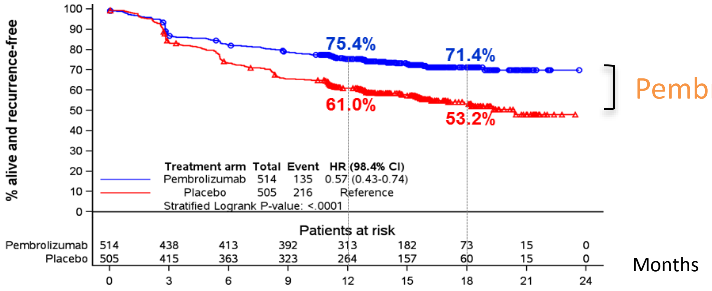
- Ipilimumab 10 mg/kg vs placebo,
- Stage IIIA-C; RFS HR 0.76, OS HR 0.72



Ipi > Pbo

EORTC 1325

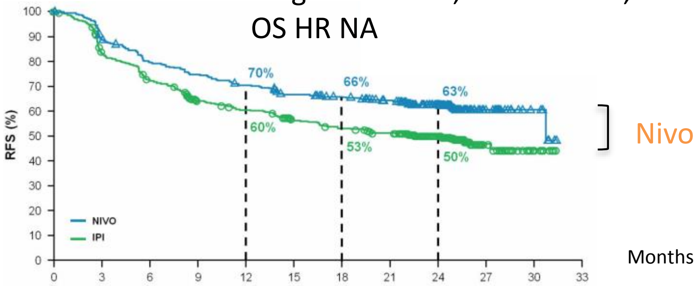
- Pembrolizumab vs placebo,
- Stage IIIA-C; RFS HR 0.57, OS HR NA



Pembro > Pbo

Checkmate 238

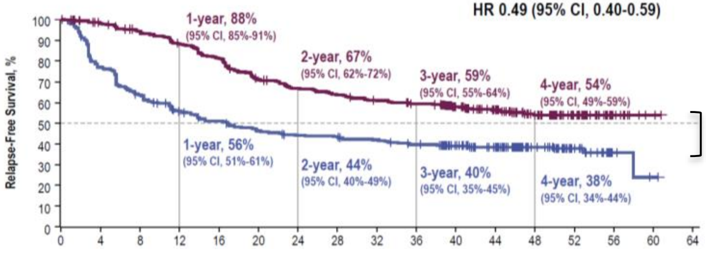
- Ipilimumab 10 mg/kg vs nivolumab,
- Stage IIIB-C + IV; RFS HR 0.66, OS HR NA



Nivo > Ipi

COMBI-AD

- Dabrafenib + trametinib vs placebo
- Stage IIIA-C; RFS HR 0.49, OS HR 0.57



D+T > Pbo

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[1]Eggermont, *NEJM* 2016; [2]Eggermont *NEJM* 2018; [3]Weber, *NEJM* 2017 & ASCO 2019; [4]Long, *NEJM* 2017 & ESMO 2018

Current adjuvant options shown in orange

Adjuvant in melanoma: important data are still missing!

EMA/FDA NA/11.15

EMA/FDA 12.18/02.19

EMA/FDA 07.18/12.17

EMA/FDA 08.18/04.18

		Efficacy data		
Study	**Design**	**HR RFS**	**HR DMFS**	**HR OS**
EORTC 18071[1]	Ipilimumab 10 mg versus placebo	0.76	0.76	0.72
EORTC 1325[2]	Pembrolizumab versus placebo	0.57	*0.53*[6]	NA
Checkmate 238[3]	Ipilimumab 10 versus nivolumab	0.65	*0.73*[7]	NA
ECOG 1609	Ipilimumab 10 versus ipilimumab 3 versus HD INF-α2b	1.0	NA	NA
BRIM-8[4]	Vemurafenib versus placebo	0.54 (IIC-IIIB) 0.8 (IIIC)	NA	NA
COMBI-AD[5]	Dabrafenib + trametinib versus placebo	0.47	0.51	0.57

Stage III patients from these trials were required to have complete lymph node dissection!

How do we integrate those results in a post MSLT-2/ DeCOG[8,9] trial era?

[1]Eggermont, *NEJM* 2016; [2]Eggermont *NEJM* 2018; [3]Weber, *NEJM* 2017; [4]Maio, Lancet Oncol 2018; [5]Long, *NEJM* 2017; [6]Preliminary, Eggermont, AACR 2018; [7]Exploratory; [8]Faries, NEJM 2017; [9]Leiter, Lancet 2016; Time in months;

Data not randomised head to head, should not be compared directly
DMFS, distant metastasis-free survival; EMA, European Medicines Agency; FDA, Food and Drug Administration; HD INF-α2b, high-dose interferon-α2b; NA, not available

Overview of PFS outcome per stage subgroup:

EMA/FDA NA/11.15

EMA/FDA 12.18/02.19

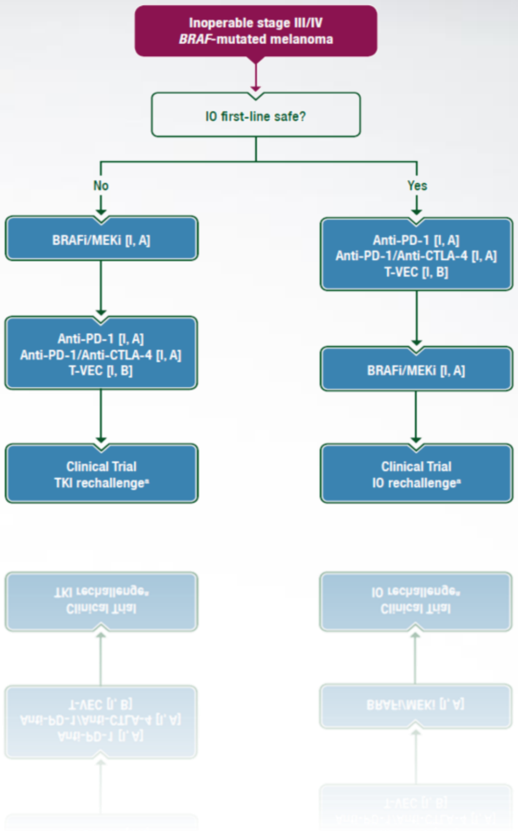
EMA/FDA 07.18/12.17

EMA/FDA 08.18/04.18

		Stage - AJCC 7th Edition (All patients NED)				
Study	**Design**	**IIC**	**IIIA**	**IIIB**	**IIIC**	**IV**
EORTC 18071[1]	Ipilimumab 10 mg versus placebo		SN > 1mm, HR 0.98	HR 0.75	HR 1.00, 1-3 n HR 0.48, ≥ 4 n	
EORTC 1325[2]	Pembrolizumab versus placebo		SN > 1mm, HR 0.38	HR 0.58	HR 0.58	
Checkmate 238[3]	Ipilimumab 10 versus nivolumab			HR 0.68	HR 0.68	HR 0.66 M1a/b, *HR 0.78 M1c*[2]
ECOG 1609	Ipilimumab 10 versus ipilimumab 3 versus HD INF-α2b			HR NA	HR NA	M1a-b, HR NA
BRIM-8[4]	Vemurafenib versus placebo	HR 0.0-NE	SN > 1mm, HR 0.52	HR 0.63	HR 0.8	
COMBI-AD[5]	Dabrafenib + trametinib versus placebo		SN > 1mm, HR 0.44	HR 0.50	HR 0.45	

Data not randomized head to head, should not be compared directly; [1]Eggermont, *NEJM* 2016; [2]Eggermont *NEJM* 2018; [3]Weber, *NEJM* 2017; [4]Maio, Lancet Oncol 2018; [5]Long, *NEJM* 2017;

Stage IV Management Guidelines:
- Immunotherapies
- Targeted therapies



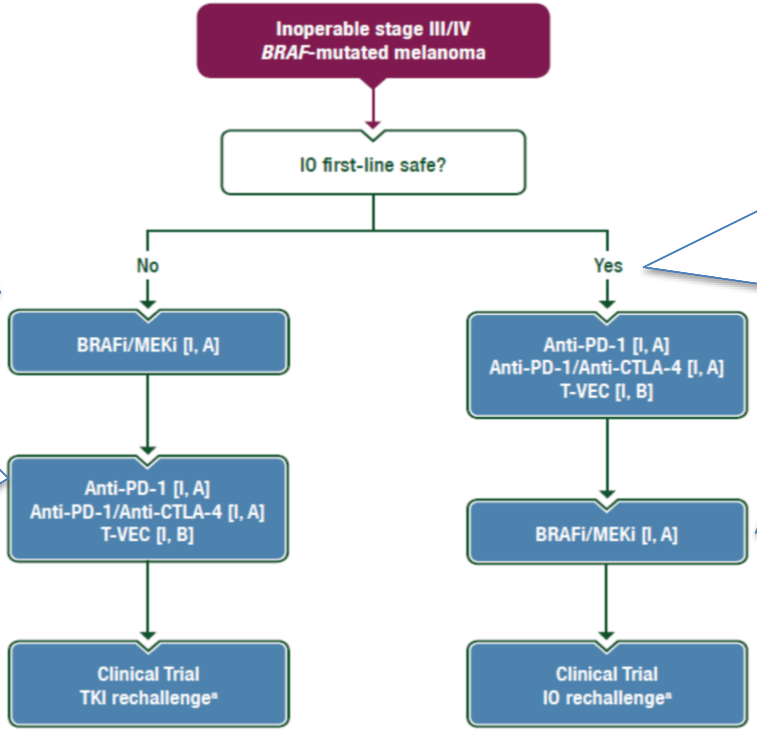
Algorithm for inoperable stage III-IV

First line TKI is limited to selected patients

- Rapidly evolutive disease, need for quick response, no time to allow safe delivery of 1st line IO

IO rechallenge can be an option in selected patients

- In retrospective series, ipilimumab or ipilimumab+nivolumab shows around 20% ORR after PD-1 failure



First line IO is the preferred option if safe

- Unless the status of the patient does not allow for safe delivery of first line IO, PD-1 based therapies are the preferred options

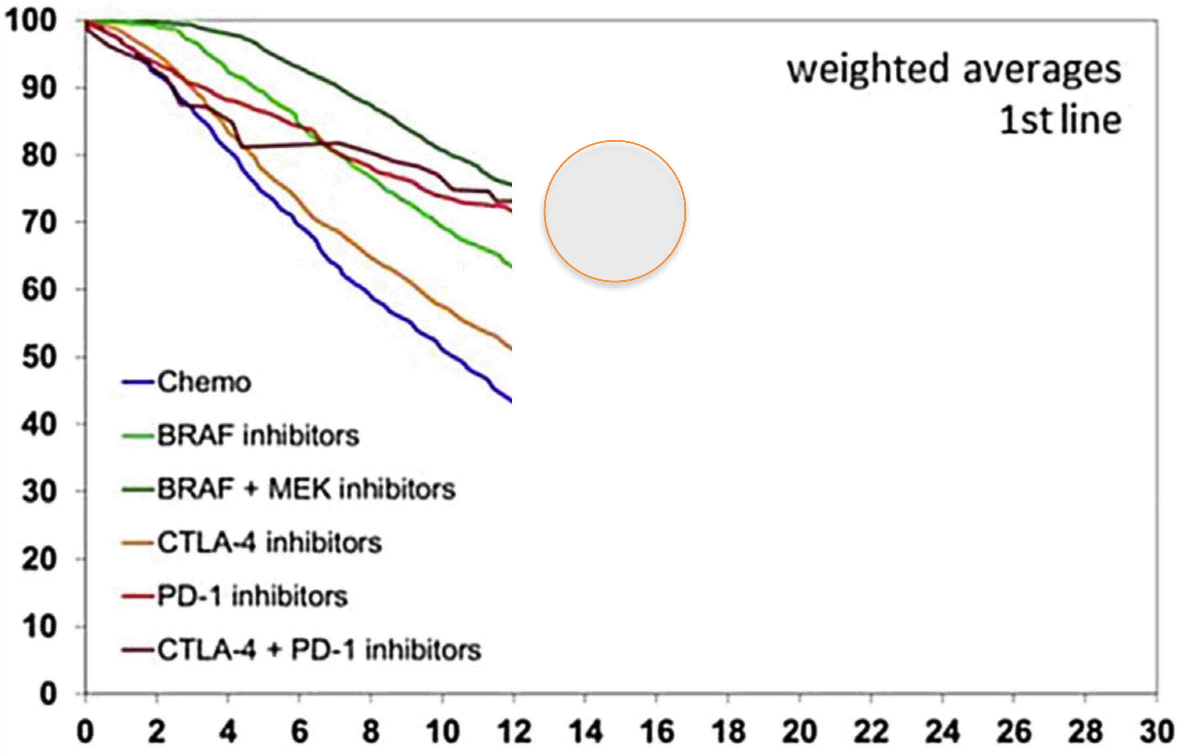
BRAF/MEKi are the preferred second line option

- Cave: toxicity!
  Long half life of checkpoints inhibitors!

Ref. Cutaneous melanoma; ESMO Clinical practice guidelines for diagnosis, treatment, follow-up 2019

BRAFi, BRAF inhibitor; CTLA-4, cytotoxic T lymphocyte-associated antigen 4; IO, immuno-oncology; MEKi, MEK inhibitor; ORR, overall response rate; PD-1, programmed cell death 1;TKI, tyrosine kinase inhibitor; T-VEC, talimogene laherparepvec

Low level of evidence points to IO as the first line choice



- Targeted therapies provide better early outcome…
- … but immuno-oncology curves are crossing at around 14 months[1] …
- … and the difference seems to increase with time

[1] Ugurel, *EJC* 2017

Guidelines for patients failing adjuvant treatment?

Owen, ASCO 2019

Melanoma Institute Australia

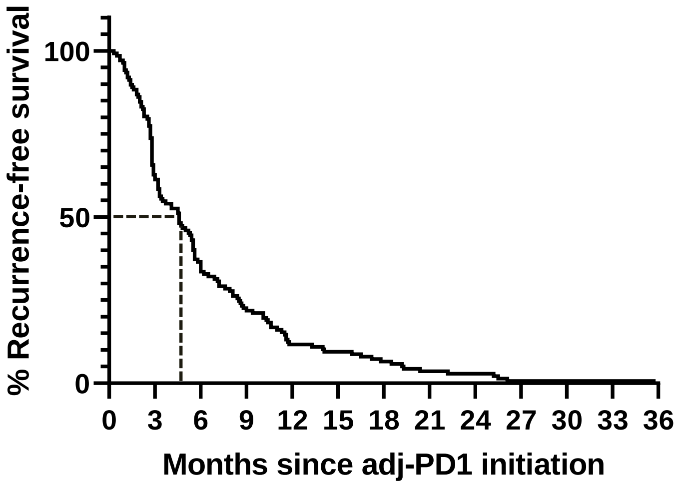
A multicenter analysis of melanoma recurrence following adjuvant anti-PD1

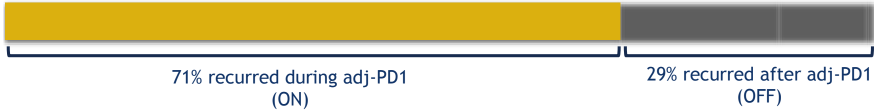
Carina Owen, James MG Larkin, Alexander N Shoushtari, Matteo S Carlino, Christian U Blank, Belinda Lee, Joanna Mangana, Victoria Atkinson, Michael Millward, Farzana Zaman, Arissa Young, Muhammad Adnan Khattak, Sapna P Patel, Christoph Hoeller, Peter Hersey, Dharmisha Chauhan, David J Palmieri, Serigne Lo, Alexander M Menzies, Georgina V Long

Escapes on or following adjuvant PD-1 blockade

- Data are are just emerging on this new patient population[1]
- No guidelines exist yet
- Aspects will be addressed in an upcoming ESMO Melanoma Consensus paper

Characteristic	N	%
Stage (AJCC 8th)		
IIIA	6	4%
IIIB	42	31%
IIIC	66	49%
IIID	5	4%
IV	17	12%
Adjuvant Tx		
Nivo	58	43
Pembro	39	29
Niv/ipi	20	15
Niv +/- ipi	19	14





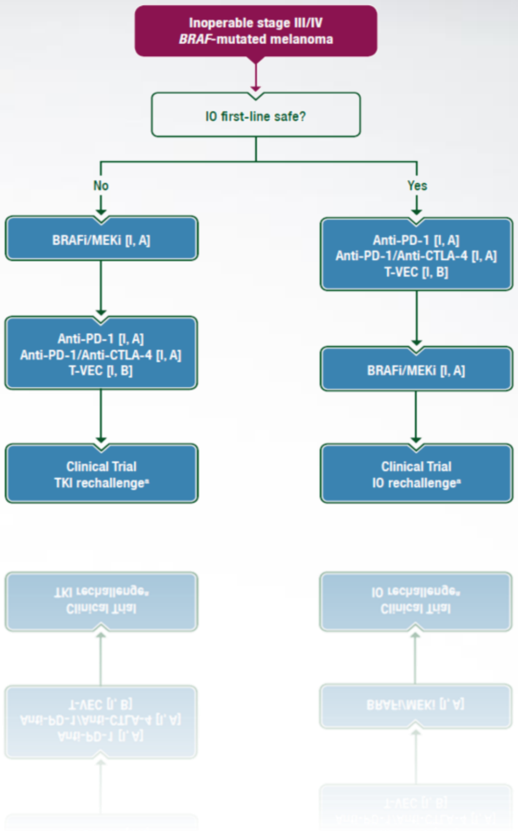
[1] Owen, ASCO 2019

Efficacy of 1st line metastatic treatment in adjuvant PD-1 failures[1]

Timing of initial recurrence	Systemic treatment	N	CR/PR	SD	PD	ORR
ON adj-PD1	Ipilimumab +/-anti-PD1	33	**8**	5	20	24%
	BRAF/MEKi	23	**18**	5	0	78%
	Anti-PD1 + novel agent	9	**1**	1	7	11%
	Anti-PD1	6	**0**	1	5	0%
OFF adj-PD1	Ipilimumab +/-anti-PD1	5	**2**	0	3	40%
	BRAF/MEKi	10	**9**	0	1	90%
	Anti-PD1 + novel agent	1	**0**	0	1	0%
	Anti-PD1	5	**2**	1	2	40%

[1] Owen, ASCO 2019

Stage III and IV Melanoma Management: still a lot of unsolved questions!



The new ESMO *guidelines* will be complemented by a ESMO *consensus paper*

ESMO Melanoma Clinical Practice Guidelines - 2019 Edition

- Evidence based guidelines with
  - Level of Evidence (LoE)
  - Grade of Recommendation (GoR)
- Based on
  - Primary clinical data from clinical trials and meta-analyses
- Awaiting publication in *Annals of Oncology* September 2019

ESMO Consensus Conference Paper – 2019 Edition

- Consensus recommendation from an expert panel
  - Level of agreement among panelists on predetermined key questions
- Based on
  - Immature / insufficient clinical data
  - Clinical experience / expertise

- Publication expected late 2019 / early 2020

Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

O. Michielin[1], A. van Akkooi[2], P. Ascierto[3], R. Dummer[4] & U. Keilholz[5], on behalf of the ESMO Guidelines Committee*

[1]Department of Oncology, University Hospital Lausanne, Lausanne, Switzerland; [2]Department of Surgical Oncology, Netherlands Cancer Institute – Antoni van Leeuwenhoek, Amsterdam, the Netherlands; [3]Istituto Nazionale Tumori IRCCS Fondazione "G. Pascale", Napoli, Italy; [4]Department of Dermatology, Skin Cancer Centre, University Hospital Zürich, Zürich, Switzerland; [5]Charité Comprehensive Cancer Centre, Charité-Universitätsmedizin Berlin, Berlin, Germany.

*Correspondence to: ESMO Guidelines Committee, ESMO Head Office, Via Ginevra 4, CH-6900 Lugano, Switzerland; E-mail: clinicalguidelines@esmo.org

†Approved by the ESMO Guidelines Committee: February 2002, last update July 2019. This publication supersedes the previously published version—Ann Oncol 2015; 26 (Suppl 5): v126-v132.

Awaiting Publication in *Annals of Oncology*

THANK YOU FOR YOUR ATTENTION!

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