Dr İbrahim Yıldız

MELANOMDA ADJUVAN VE NEOADJUVAN TEDAVİ

ACIBADEM ÜNİVERSİTESİ ATAKENT HASTANESİ

2015'sonrası farklı dönem

Approved drugs for the adjuvant therapy of stage III melanoma

Old Era (1996–2009)

- High-Dose Interferon (IFN)-α2b (US, EU), Low-Dose IFN-α2a (EU), pegylated IFN-α2b (US)

New Era (2015–2019) — **FDA approv**

• *Ipilimumab (US)[2]	HR_{RFS}(Ipilimumab vs. Placebo)=0.75	(2015)
• Nivolumab[3]	HR_{RFS}(Nivolumab vs. Ipilimumab)=0.65	(2017)
• *Dabrafenib plus Trametinib[4]	HR_{RFS}(Dab+Tra vs. Placebo)=0.47	(2018)
• *Pembrolizumab[5]	HR_{RFS}(Pembrolizumab vs. Placebo)=0.57	(2019)

* Trials performed in identical patient populations at high risk of relapse: IIIA >1mm; III

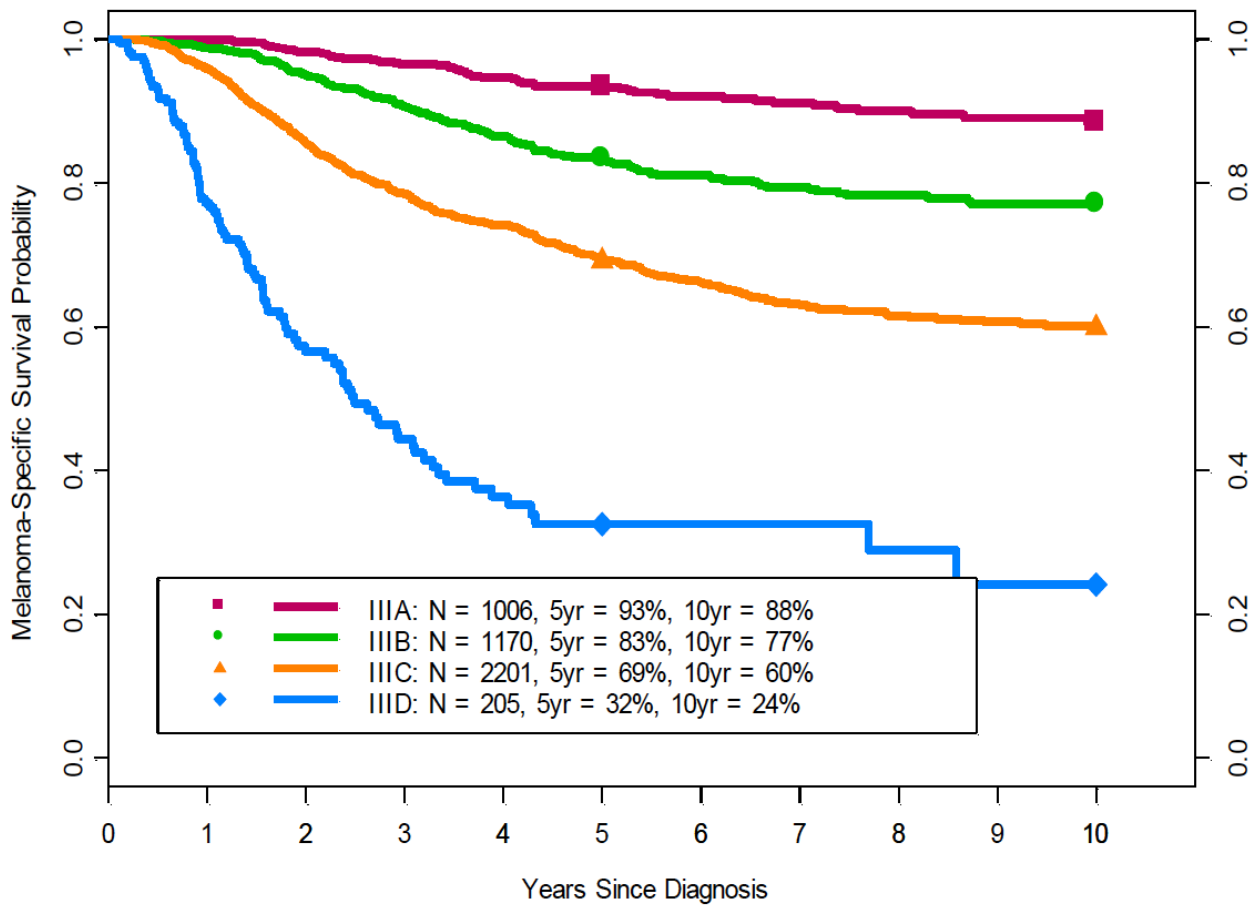
Stage III Melanoma (Regional Metastases)

Clinical Disease Spectrum

- Regional lymph nodes
  - occult (SLN +)
  - clinically apparent
- In-transit Disease (local, satellite, and in-transit)
  - dermal, epidermal-tropic, subcutaneous
  - extremity, trunk, Head and Neck

MSS according to Stage III Groups

8th Edition international melanoma database



- 4 stage groups
- Significant heterogeneity
- Substage stratification based on both T- and N-category criteria
  - Tumor thickness
  - Ulceration
  - # of Nodes and micro or macro disease
  - Microsat/ITM/satellites

Adjuvan tedavi tarihsel bakış..birçok ilaç denendi

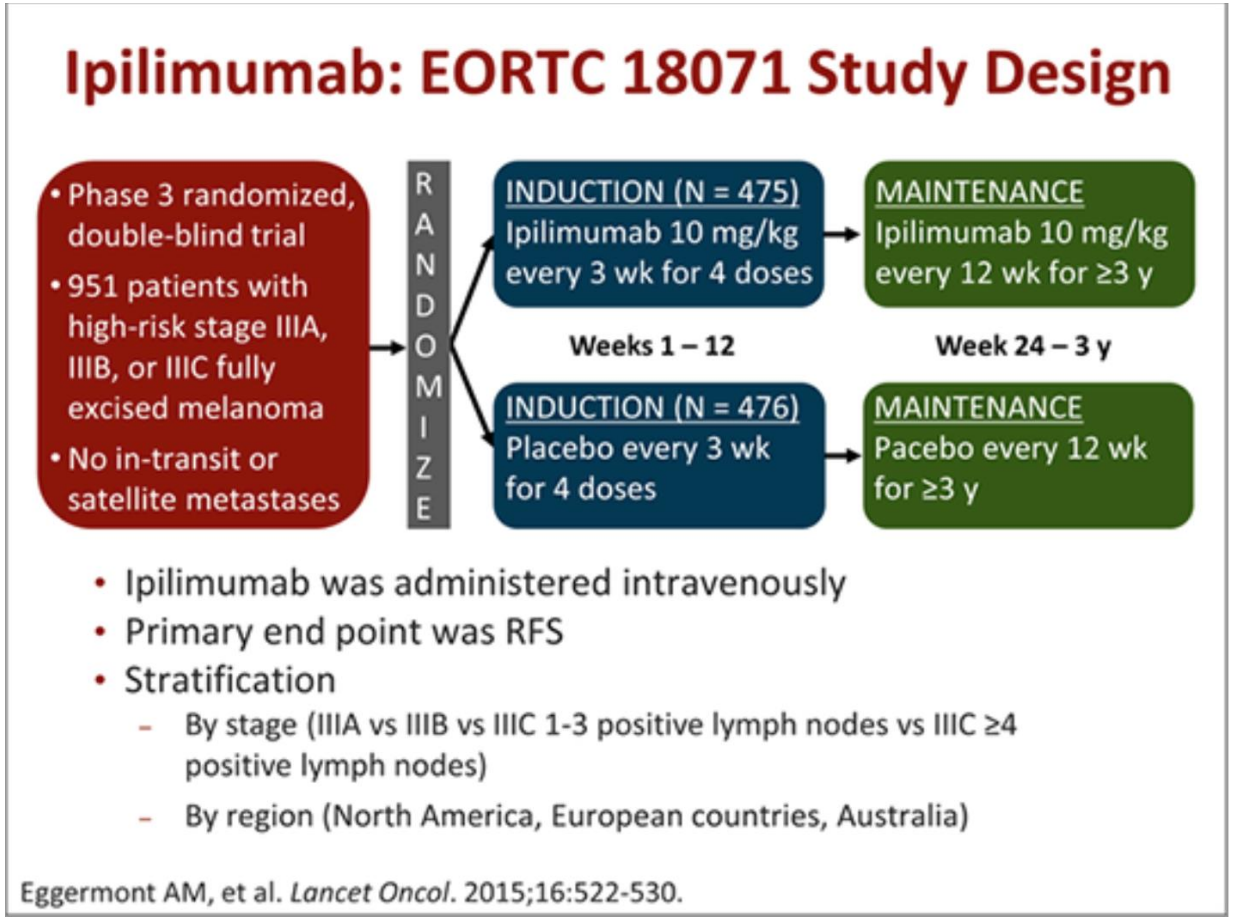
HD-IFN alfa: T4, N+, RFS+, 2 çalışmada OS yararı

Pegylated IFN: N+için RFS yararı+

Study	Stage	N	Regimen	Median Follow up (yr)	Impact on	
					RFS	OS
E1684	T4, N+	287	HD-IFN Vs. Observation	6.9	+	+
E1690	T4, N+	642	HD-IFN or LD-IFN vs. Observation	6.6	+	–
E1694	T4, N+	880	HD-IFN vs. GMK vaccine	2.1	+	+
EORTC 18991	N1,2	1256	Pegylated IFN vs. Observation	7.6	+	–

İpilimumab 10 mg/kg vs plasebo

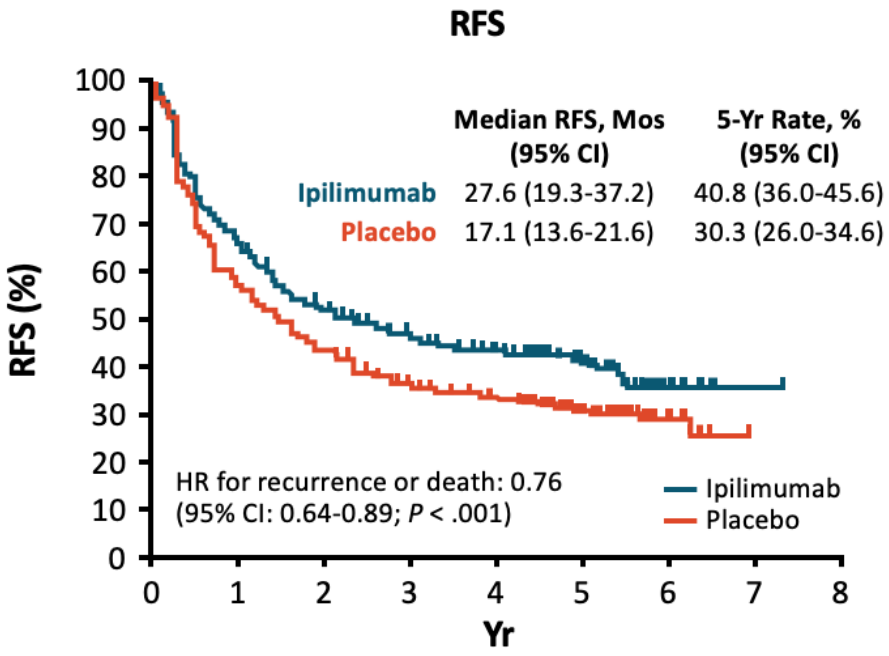
-ilk 3 ay **21 günde bir 4 doz**, ardından **3 yıl 3 ayda bir**

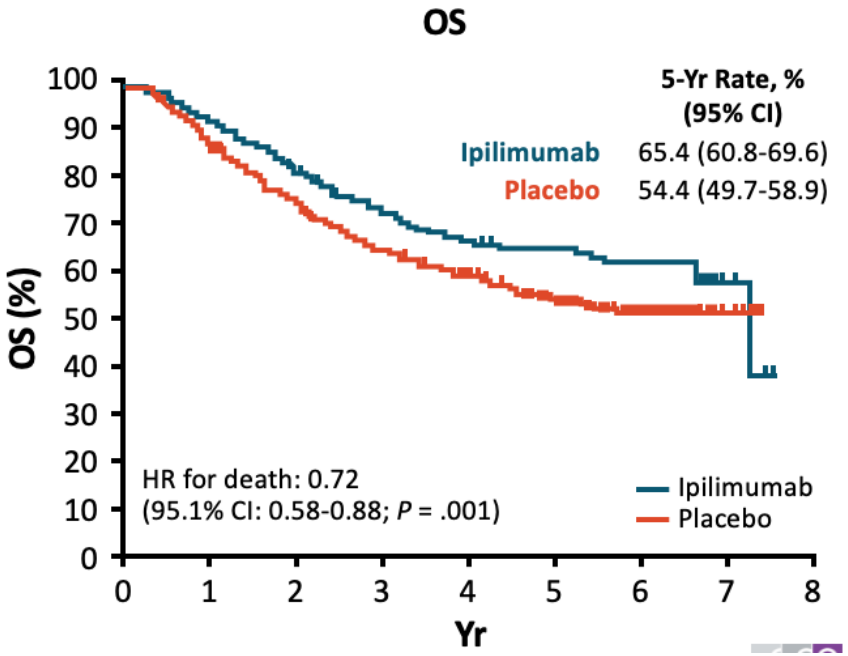


İpilumab>Plasebo(RFS-OS)

EORTC 18071: Phase III Trial of Ipilimumab 10 mg/kg vs Placebo in Stage III Melanoma

- Randomized, double-blind phase III trial of **ipilimumab** 10 mg/kg vs **placebo** as adjuvant therapy for stage III melanoma after surgical resection (N = 951)





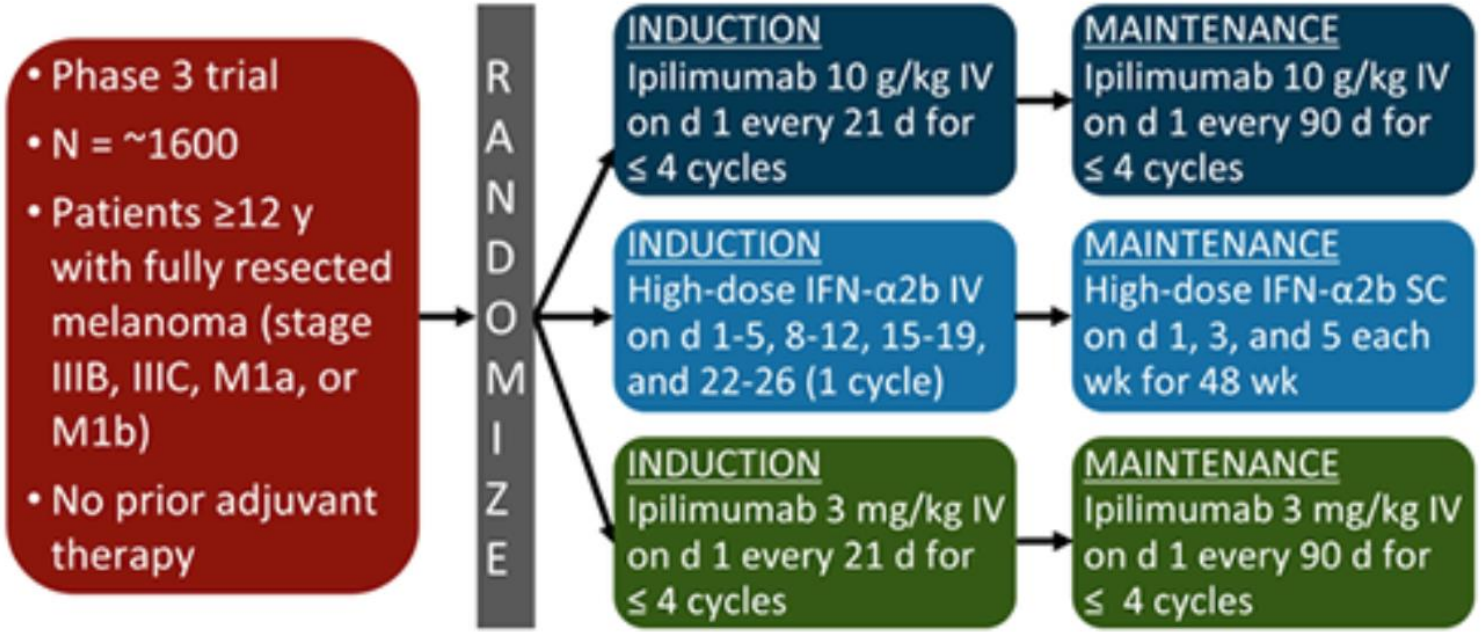
EORTC 18071: Safety

AEs, %	Ipilimumab (n = 471)	
	Any Grade	Grade 3/4
Any AE	98.7	54.1
Treatment-related AE	94.1	45.4
Treatment-related AE leading to d/c	**48.0**	32.9
Any immune-related AE	90.4	41.6

- Deaths due to treatment-related AEs
  - 5 patients (1.1%) in ipilimumab arm (3 colitis, 1 myocarditis, 1 multiorgan failure with Guillain-Barre syndrome)

İpi 10 mg/kg vs 3 mg/kg vs Yüksek doz IFN-alfa

US Intergroup E1609 Study Design

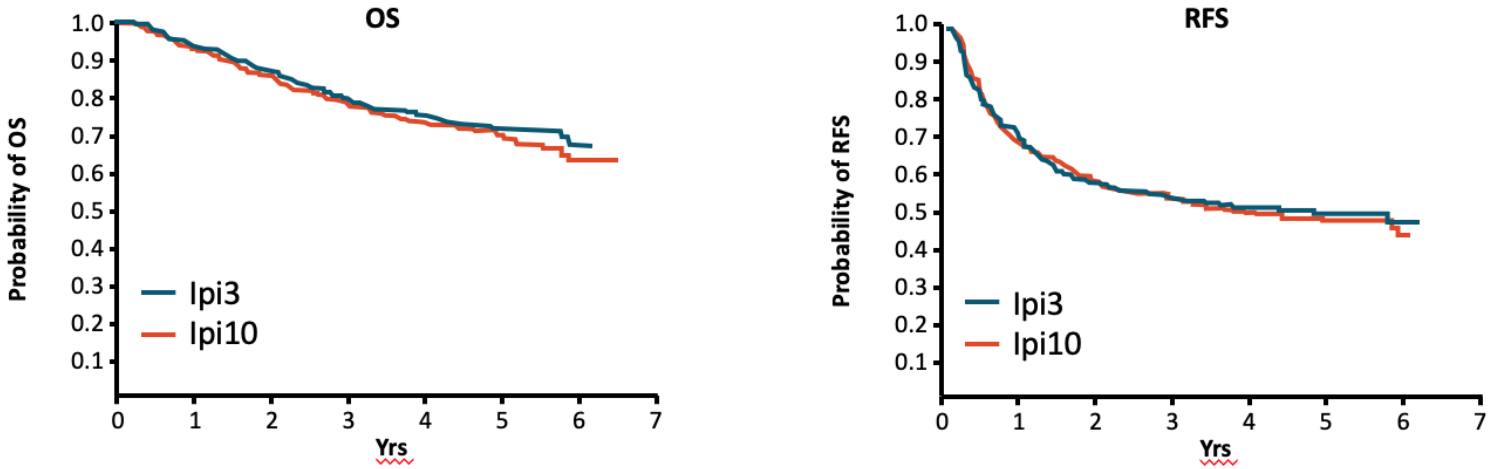


- Therapy continues until progression or drug intolerance
- Adult accrual for all treatment arms is complete (August, 2014)
- Co-primary end points: OS and RFS
- Other end points: quality-of-life and toxicity

Sonuç 1: İPİ 10 mg/kg vs İPİ 3 mg/kg

RFS ve OS her iki kolda **benzer, İPİ 10 daha toksik, ADJ önerisi İPİ3**

E1609: OS and RFS of Ipi3 vs Ipi10



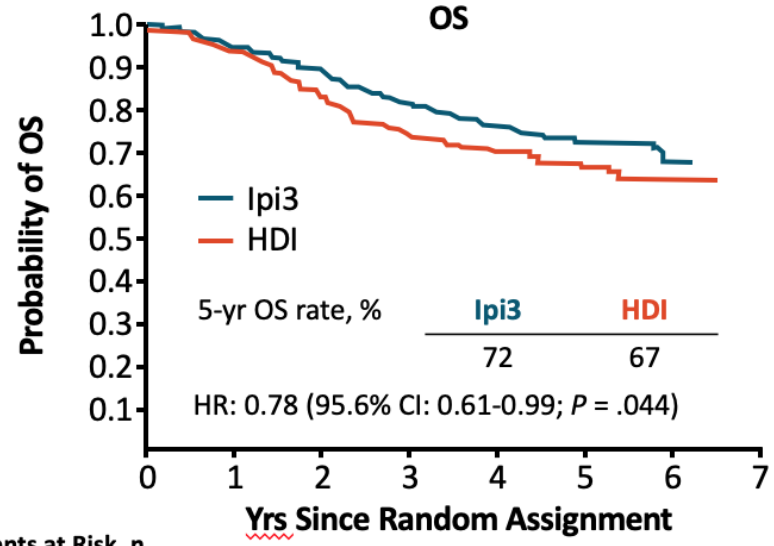
Event, %	Ipilimumab 3 mg/kg (n = 516)		Ipilimumab 10 mg/kg (n = 503)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Treatment-related AE	95.9	38.2	98.8	56.7
Treatment-related AE leading to d/c	34.9	25.0	54.1	42.9
Any immune-related AE	84.5	28.5	92.6	45.7
Grade 5 AE	0.6		1.6	

Sonuç2: İpi 3 mg/kg vs HD IFN (OS)

5 yıllık takipte , HDI ile RFS benzer **ancak OS İpi 3 lehine** (%72 vs 67)

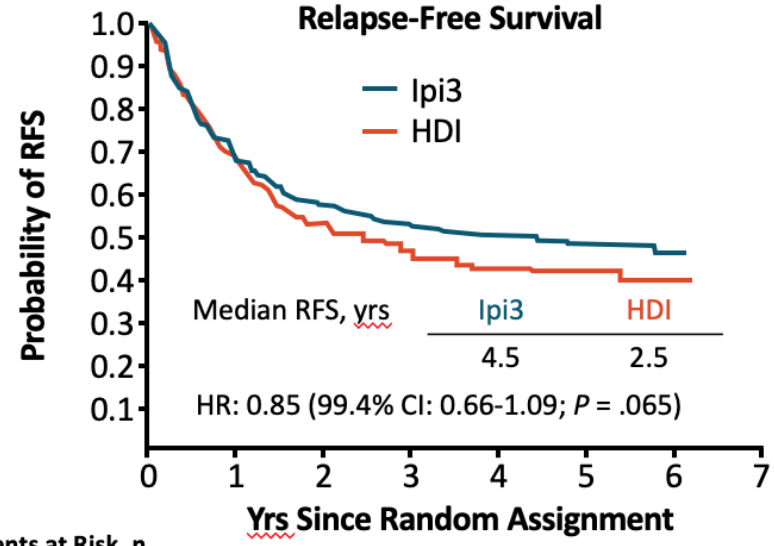
E1609: Adjuvant Ipi vs HDI in Resected High-Risk Melanoma: Survival Outcomes Ipi3 vs HDI

- Randomized, phase III study of adjuvant ipilimumab (3 mg/kg or 10 mg/kg) vs high-dose INF-α in high-risk, resected melanoma



Patients at Risk, n

HDI	528	393	343	297	252	103	16
Ipi3	523	475	429	380	309	114	17



Patients at Risk, n

HDI	528	281	208	171	128	40	5
Ipi3	523	336	267	225	178	57	8

ADJUVAN Anti-PD1

CheckMate 238

Patients with surgically-removed AJCC 7th Edition Stage IIIB/IIIc/IV melanoma

***Both trials required CLND and size of LN metastasis >1 mm

N = 906
R 1:1

Ipilimumab 10 mg/kg IV q3 weeks x4 and nivo placebo

Nivolumab 3 mg/kg IV q2 weeks x 1 year and ipi placebo

Primary Endpoint: RFS in ITT
Secondary Endpoints: OS, RFS based on PDL-1, safety, QoL

EORTC 1325/ Keynote 054

Patients with surgically-removed AJCC 7th Edition Stage IIIA-IIIC melanoma

N = 1019
R 1:1

Placebo

Pembrolizumab 200 mg IV q3 weeks x 1 year

Primary Endpoint: RFS in ITT
Secondary Endpoints: DMFS, safety, QoL

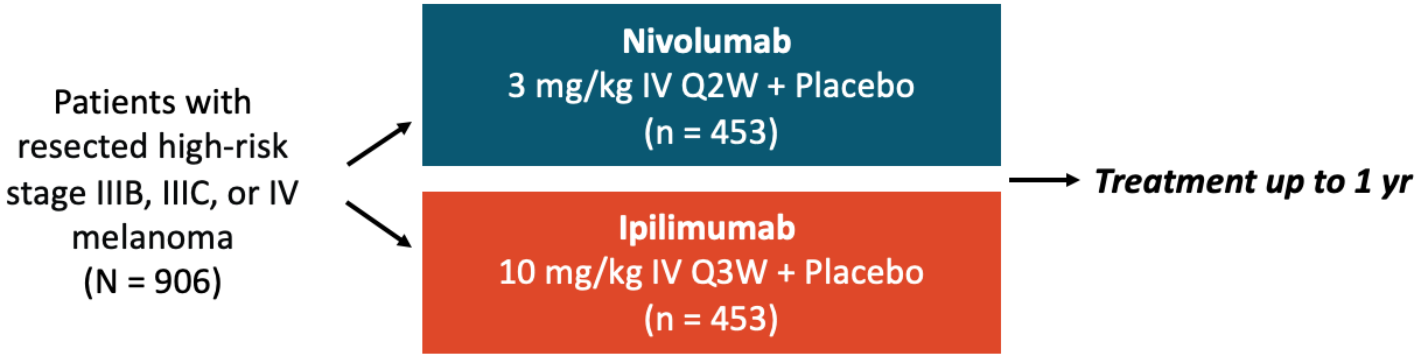
Weber J et al. *N Engl J Med*. 2017;377(19):1824-1835.
Eggermont AMM et al. *N Engl J Med*. 2018;378(19):1789-1801.

Nivo vs İPİ

N=906 hasta, faz 3, yüksek riskli (en az IIIB), evre IV:%18,BRAF+=%42,

CheckMate 238: Adjuvant Nivolumab vs Ipilimumab in High-Risk Melanoma

- Randomized, double-blind phase III trial



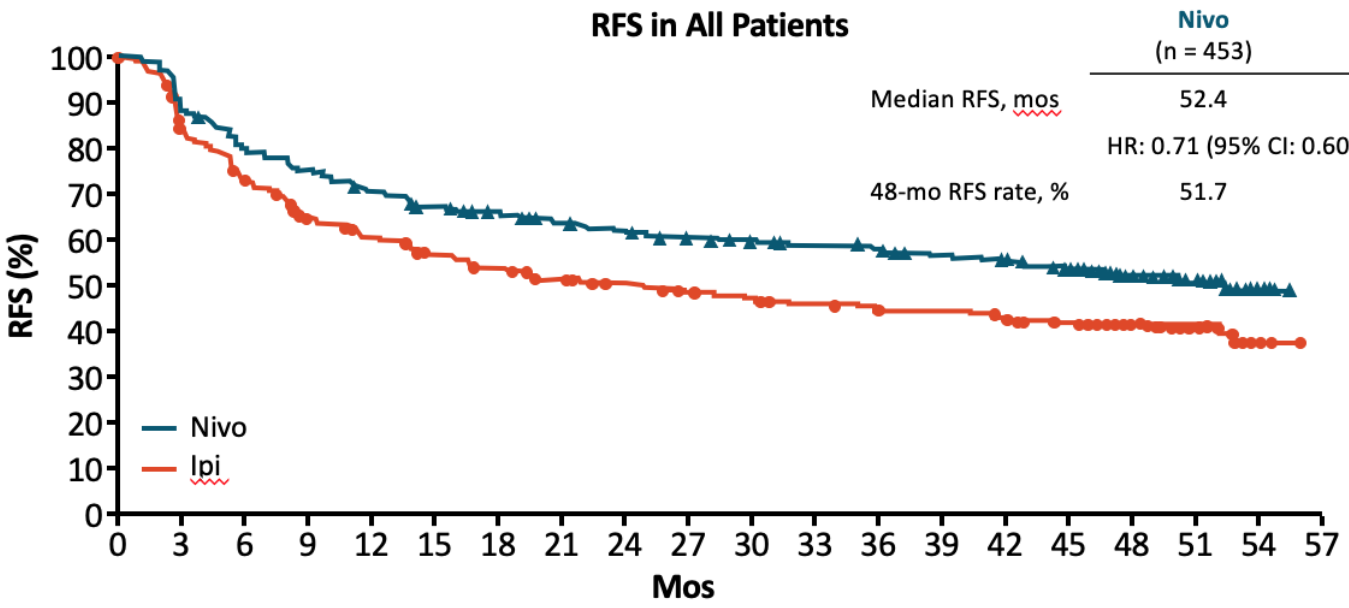
- Primary endpoint: RFS in ITT population
- Secondary endpoints: OS, safety, RFS by PD-L1 status, QoL
- Exploratory endpoint: DMFS

Nivo vs İPİ 10mg/kg: 48 aylık sonuç(esmo 2020)

-4-yıllık RFS: % 52 vs % 41, HR:0.71

-medyan RFS : 52.4 vs 24.1 ay

CheckMate 238: RFS in All Patients



	Nivo (n = 453)	Ipi (n = 453)
Median RFS, mos	52.4	24.1
HR: 0.71 (95% CI: 0.60-0.86; *P* = .0003)		
48-mo RFS rate, %	51.7	41.2

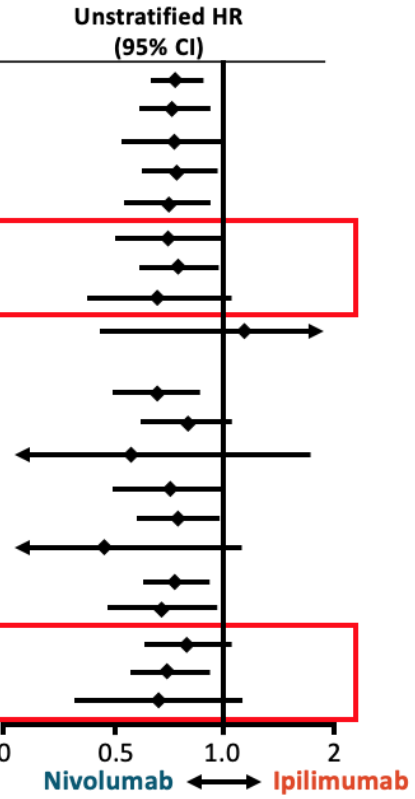
Patients at Risk, n

Nivo 3 mg/kg	453	395	354	332	311	293	283	271	262	250	245	240	233	224	218	206	147	37	11	0
Ipi 10 mg/kg	453	366	316	273	253	234	220	208	201	191	185	177	171	168	163	154	113	32	10	0

Nivo>ipi (RFS): PDL1 expresyonu ve BRAF durumundan bağımsız yarar var

CheckMate 238: RFS in Prespecified Groups

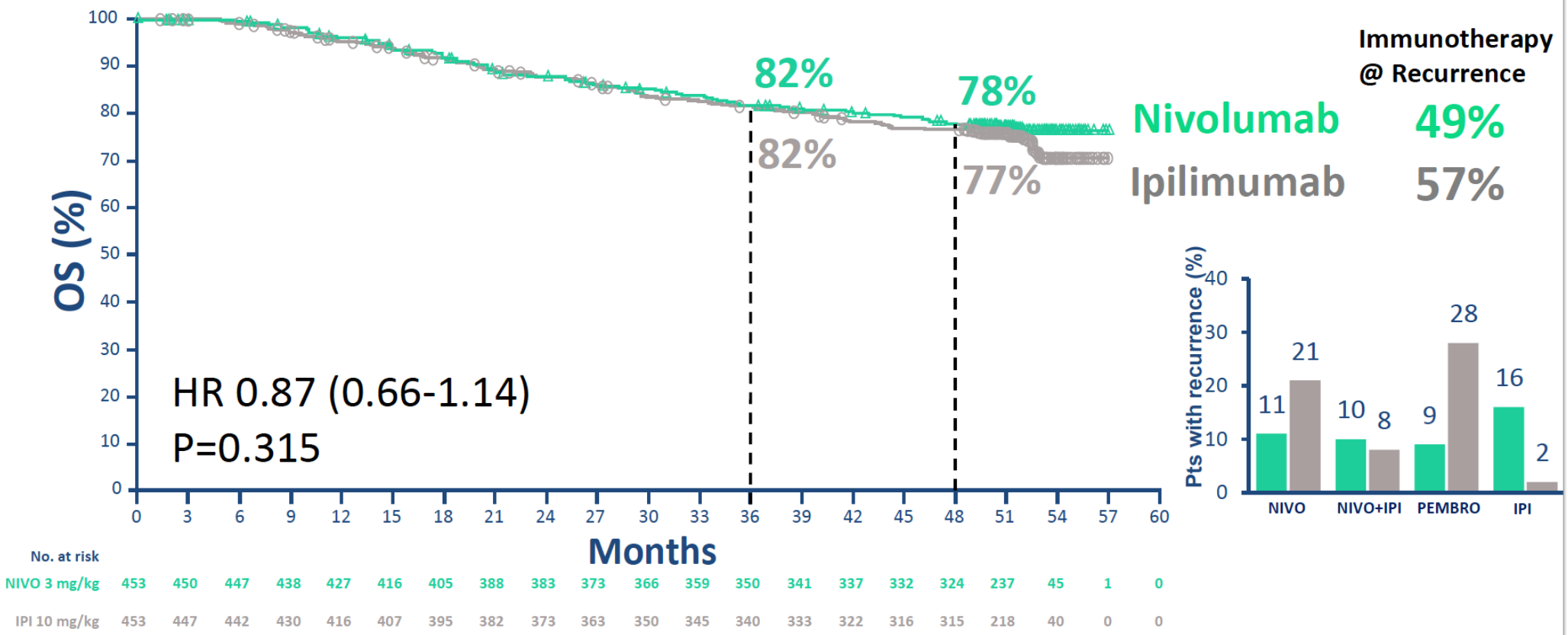
Subgroup		Events/Patients Nivo 3 mg/kg	Events/Patients Ipi 10 mg/kg	Unstratified HR (95% CI)
Overall	Overall	212/453	253/453	0.72 (0.60-0.86)
Age	< 65 yrs	146/333	180/339	0.72 (0.58-0.89)
	≥ 65 yrs	66/120	73/114	0.72 (0.51-1.00)
Sex	Male	129/258	155/269	0.74 (0.59-0.93)
	Female	83/195	98/184	0.69 (0.52-0.93)
Stage	IIIB	62/165	74/147	0.70 (0.50-0.98)
	IIIC	108/203	129/219	0.74 (0.57-0.96)
	IV M1a-M1b	32/62	42/66	0.65 (0.41-1.03)
	IV M1c	9/20	8/21	1.13 (0.44-2.93)
	Not reported	1/1	0/0	
Ulceration in stage III	Absent	80/201	115/213	0.65 (0.49-0.86)
	Present	85/155	81/137	0.79 (0.58-1.07)
	Not reported	5/15	7/16	0.55 (0.17-1.74)
Lymph node involvement in stage III	Microscopic	55/128	72/134	0.71 (0.50-1.00)
	Macroscopic	106/217	120/214	0.75 (0.58-0.97)
	Not reported	9/25	11/18	0.47 (0.19-1.13)
PD-L1 status	< 5%/indeterminate	157/300	182/299	0.74 (0.59-0.91)
	≥ 5%	55/153	71/154	0.67 (0.47-0.96)
BRAF status	Mutation	88/187	104/194	0.79 (0.60-1.05)
	No mutation	96/197	123/212	0.69 (0.53-0.91)
	Not reported	28/69	26/47	0.66 (0.38-1.12)



OS benzer…

-olay sayısı her iki kolda beklenenden az…

-İpi ile tedavi edilmiş hastalar daha çok ardışık tedavi aldı



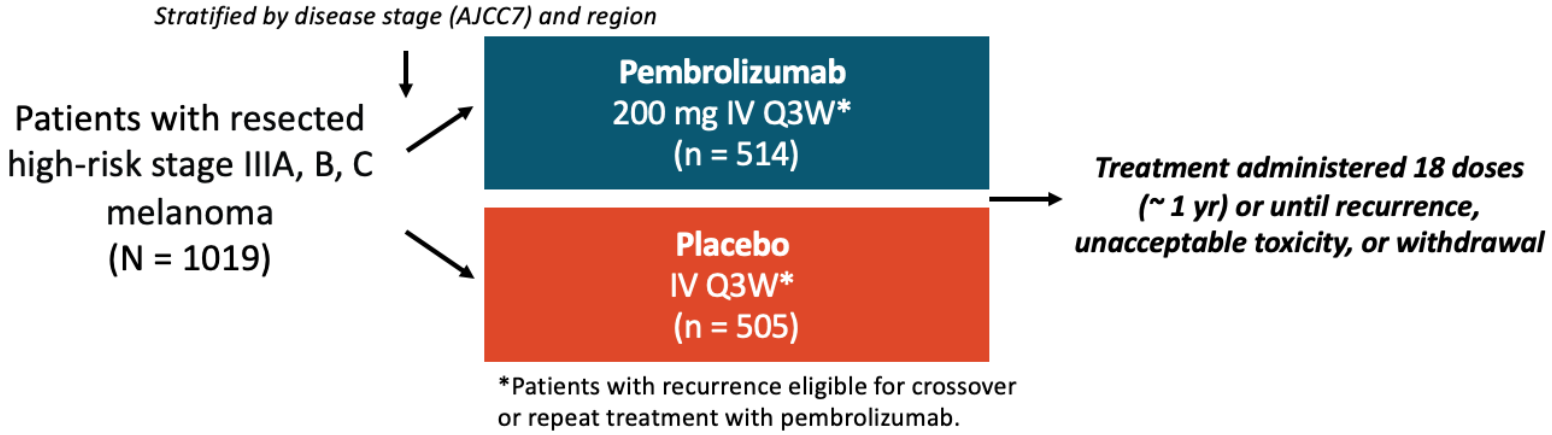
- 211 of 302 anticipated events (approximately 73% power)

Pembro vs Placebo,

N=1019, Pembro 200 mg, 3w, 18 kür

KEYNOTE-054: Adjuvant Pembrolizumab vs Placebo for Stage III Melanoma

- Randomized, double-blind phase III study



- Coprimary endpoints: RFS in ITT population, RFS in PD-L1+ subgroup
- Secondary endpoints: DMFS, OS, safety, QoL

EORTC
European Organisation for Research and Treatment of Cancer
The future of cancer therapy

Pembrolizumab versus placebo after complete resection of high-risk stage III melanoma: new recurrence-free survival results from the EORTC 1325-MG/Keynote 054 double-blinded phase 3 trial at 3-year median follow-up

Alexander MM Eggermont, MD, PhD,[1] Christian U Blank, MD, PhD,[2] Mario Mandala, MD,[3] Georgina V Long, MD, PhD,[4] Victoria Atkinson, MD,[5] Stéphane Dalle, MD,[6] Andrew Haydon, MD,[7] Andrey Meshcheryakov, MD,[8] Adnan Khattak, MD,[9] Matteo S Carlino, MD, PhD,[10] Shahneen Sandhu, MD,[11] Susana Puig, MD, PhD,[12] Paolo A Ascierto, MD,[13] Alexander van Akkooi, MD, PhD,[2] Clemens Krepler, MD,[14] Nageatte Ibrahim, MD,[14] Sandrine Marreaud, MD,[15] Michal Kicinski, PhD,[15] Stefan Suciu, PhD,[15] Caroline Robert, MD, PhD[16]

[1] Princess Máxima Center, Utrecht, the Netherlands; [2]Netherlands Cancer Institute – Antoni van Leeuwenhoek, Amsterdam, Netherlands; [3]Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy; [4]Melanoma Institute Australia, The University of Sydney, and Mater and Royal North Shore Hospitals, Sydney, Australia; [5]Princess Alexandra Hospital, University of Queensland, Brisbane, Australia; [6]HCL Cancer Institute, Cancer Research Center of Lyon, Lyon University, Lyon, France; [7]Alfred Hospital, Melbourne, Australia; [8]Federal State Budgetary Institution "Russian Oncology Scientific Centre named after N.N. Blokhin RAMS", Moscow, Russian Federation; [9]Fiona Stanley Hospital/University of Western Australia, Perth, Australia; [10]Westmead and Blacktown Hospitals, Melanoma Institute Australia and the University of Sydney, Australia; [11]Peter Maccallum Cancer Centre, Melbourne, Australia; [12]Hospital Clinic Universitari de Barcelona, Barcelona, Spain; [13]Istituto Nazionale Tumori IRCCS "Fondazione G. Pascale", Naples, Italy; [14]Merck & Co., Inc., Kenilworth, NJ, USA; [15]EORTC Headquarters, Brussels, Belgium; [16]Gustave Roussy Cancer Campus Grand Paris & University Paris-Saclay, Villejuif, France.

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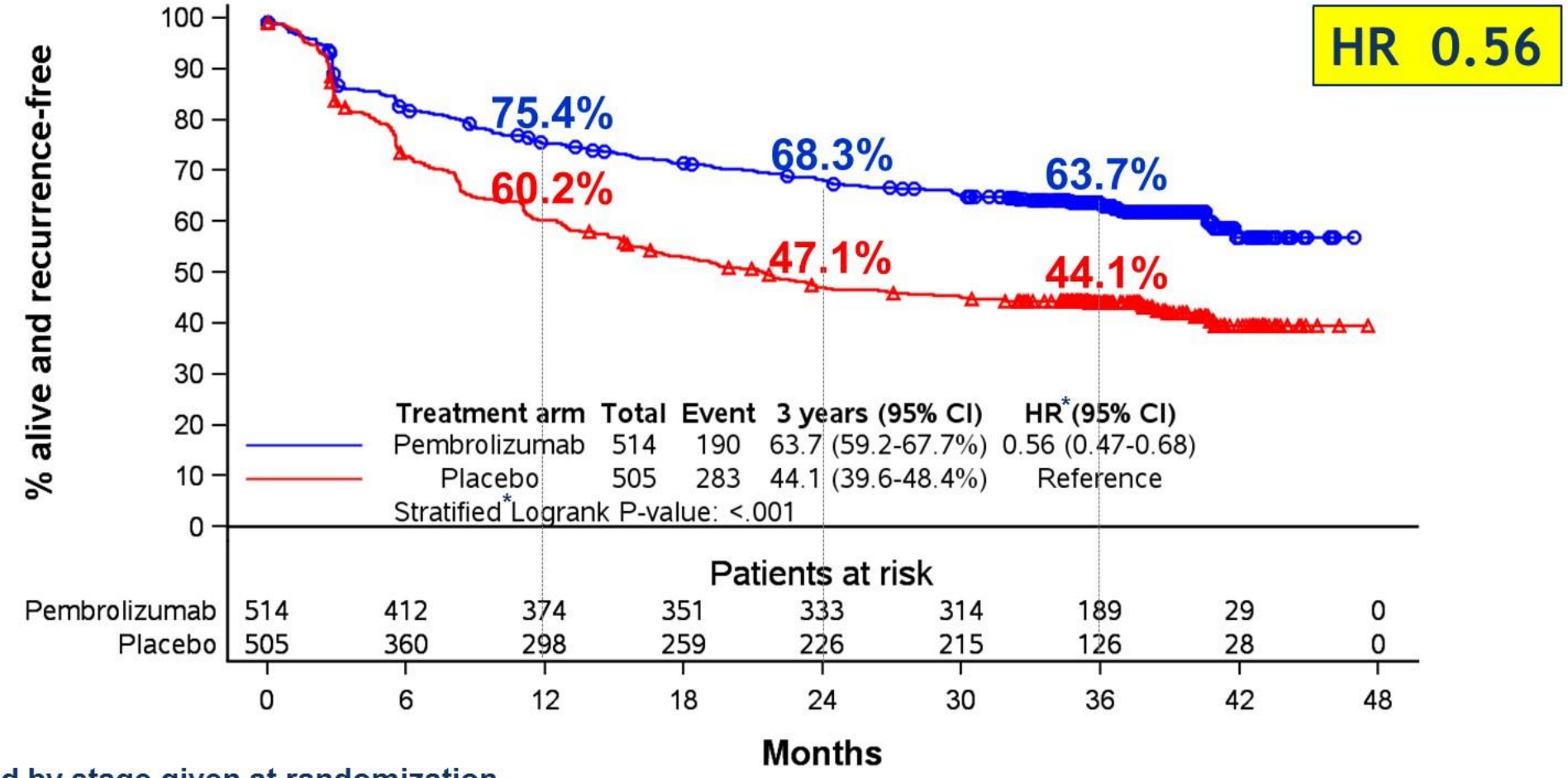
EORTC 1325/KEYNOTE-54: New RFS analysis (ASCO 2020)

- ***Cut-off date*** (30-Sep-2019); duration of follow-up: median **3** years; **473** RFS events



*Stratified by stage given at randomization

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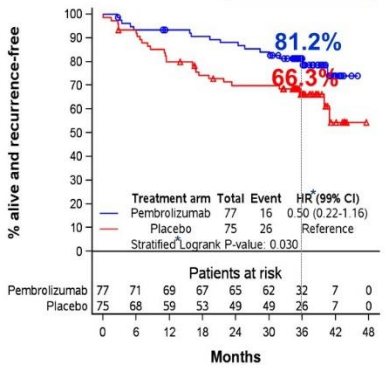
Recurrence-free survival according to AJCC-7 staging

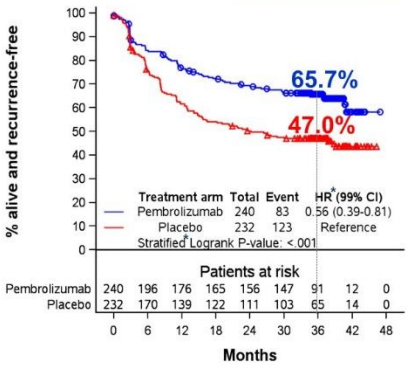
Stage IIIA (n=152)

HR 0.50



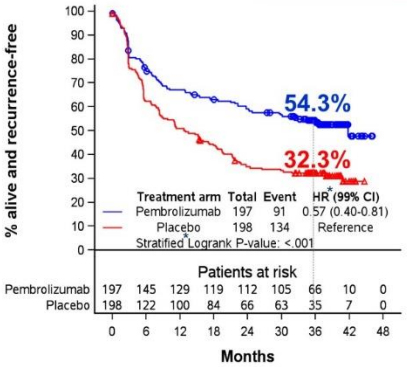
Stage IIIB (n=472)

HR 0.56



Stage IIIC (n=395)

HR 0.57

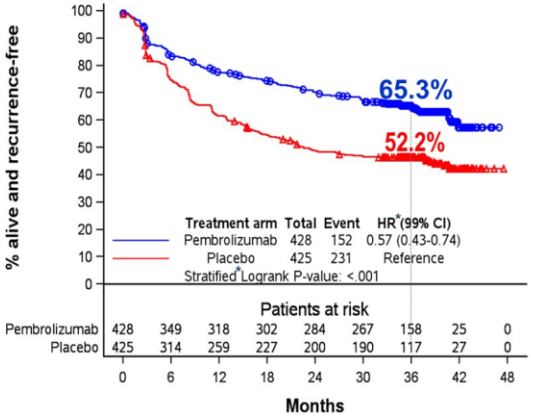


*Stratified by stage given at randomization

Recurrence-Free Survival according to PD-L1 expression

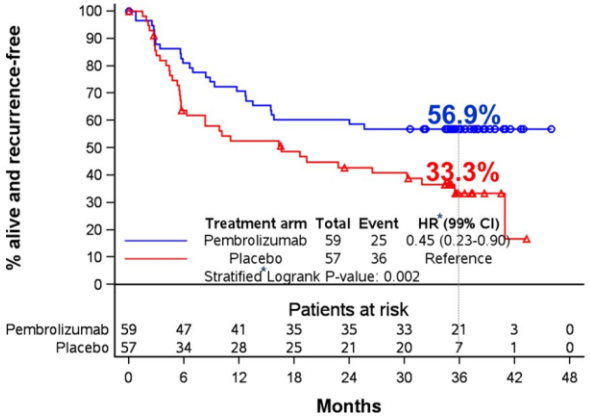
PD-L1 positive (n=853)

HR 0.57



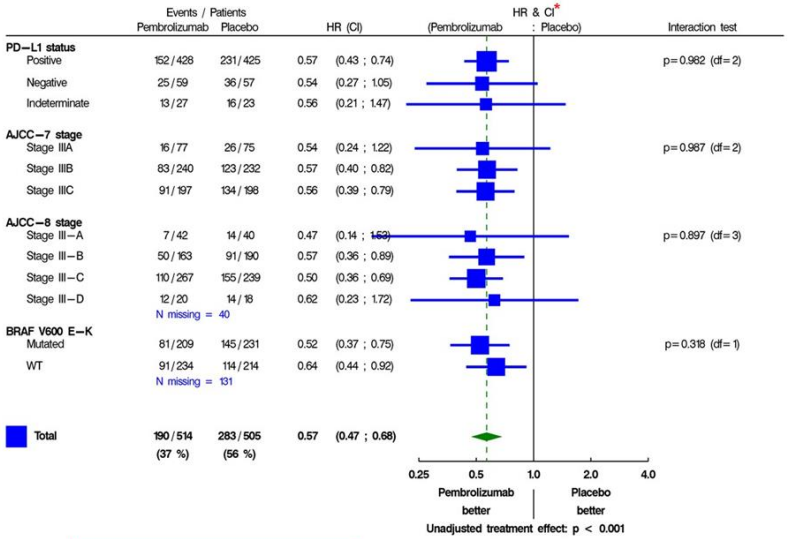
PD-L1 negative (n=116)

HR 0.45



*Stratified by stage given at randomization

Recurrence-free survival: Forest plot

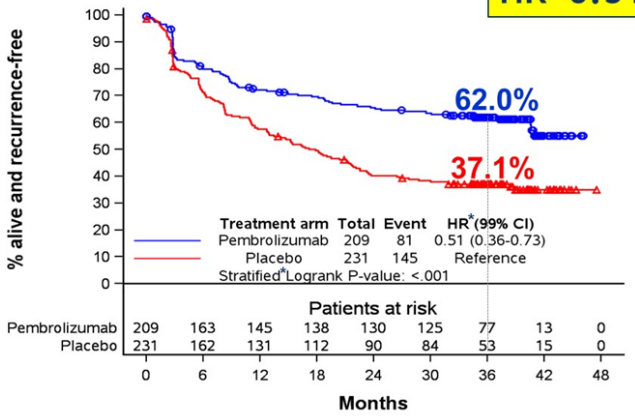


*95% CI for total, 99% CI for subgroups

Unstratified analysis by stage given at randomization

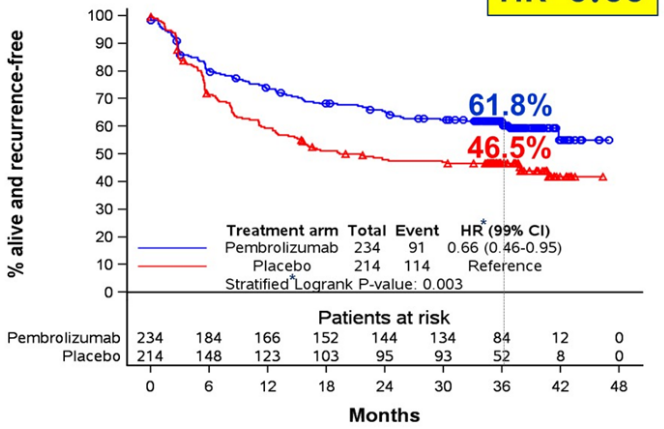
BRAF-mutated (n=440)

HR 0.51



BRAF-WT (n=448)

HR 0.66



*Stratified by stage given at randomization

yan etkiler

CheckMate 238 [1]				
AEs, %	Nivolumab (n = 452)		Ipilimumab (n = 453)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Any AE	96.9	25.4	98.5	55.2
TRAE*	85.2	14.4	95.8	45.9
▪ Fatigue	34.5	0.4	32.9	0.9
▪ Diarrhea	24.3	1.5	45.9	9.5
▪ Pruritus	23.2	0	33.6	1.1
▪ Rash	19.9	1.1	29.4	3.1
▪ Nausea	15.0	0.2	20.1	0
▪ Arthralgia	12.6	0.2	10.8	0.4
▪ Asthenia	12.6	0.2	11.7	0.9
▪ Hypothyroidism	10.8	0.2	6.8	0.4
TRAE leading to d/c	7.7	3.5	41.7	30.0

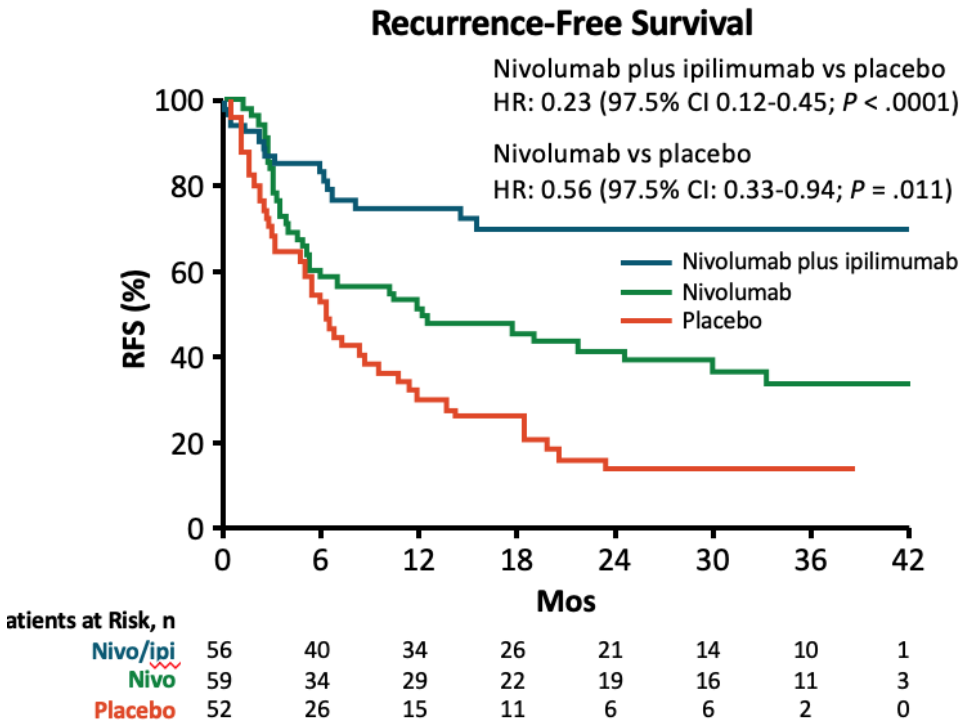
*Occurring in ≥ 10% of patients in the experimental arm.

KEYNOTE-054[2]				
AEs, %	Pembrolizumab (n = 509)		Placebo (n = 502)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Any AE	93.3	31.6	90.2	18.5
TRAE*	77.8	14.7	66.1	3.4
▪ Fatigue or asthenia	37.1	0.8	33.3	0.4
▪ Rash	16.1	0.2	10.8	0
▪ Pruritus	17.7	0	10.2	0
▪ Diarrhea	19.1	0.8	16.7	0.6
▪ Arthralgia	12.0	0.6	11.0	0
▪ Nausea	11.4	0	8.6	0
▪ Hypothyroidism	14.3	0	2.8	0
▪ Hyperthyroidism	10.2	0.2	1.2	0
TRAE leading to d/c	13.0	NR	1.6	NR

Rezekte evre 4 hastalar?

IMMUNED: Randomized, Phase II of Adjuvant Ipi3-Nivo1 vs Placebo and Nivo3 vs Placebo in Resected Stage IV Melanoma

- N = 167



Adverse Events n, %	Nivolumab plus ipilimumab (n = 55)		Nivolumab (n = 56)		Placebo (n = 51)	
	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4
Any AE	55 (100)	45 (82)	54 (96)	23 (41)	49 (96)	13 (25)
TRAE	53 (96)	39 (71)	47 (84)	15 (27)	28 (55)	3 (6)
TRAE to d/c	34 (62)	29 (53)	7 (13)	5 (9)	1 (2)	0

N=167,
2 yıllık RFS
nivo/ipi: **%70**
nivo:%42
plasebo: %14

TABLE 2: Recurrence-Free Survival in IMMUNED

	Nivolumab/ Ipilimumab (n = 56)	Nivolumab (n = 59)	Placebo (n = 52)
Median RFS	NR	12.4 months	6.4 months
Hazard ratio (95% CI) vs placebo	0.23 (0.13–0.41)	0.56 (0.36–0.88)	—
Hazard ratio (95% CI) vs nivolumab	—	0.40 (0.22–0.73)	—

CI = confidence interval; NR = not reached; RFS = recurrence-free survival.

ADJUVAN BRAF +/-MEK inh

BRIM 8

Patients with surgically-removed AJCC 7th Edition Stage IIC-IIIC BRAF V600 mutated melanoma

N = 498
R 1:1

Placebo

Vemurafenib 960 mg po BID x 1 year
Cohort 1: stage IIC-IIIB
Cohort 2: stage IIIC

Primary Endpoint: DFS
Secondary Endpoints: OS, DMFS, safety

Combi-AD

Patients with surgically-removed AJCC 7th Edition Stage IIIA-IIIC BRAF V600E/K melanoma, 1 mm size of LN deposit

N = 870
R 1:1

Placebo

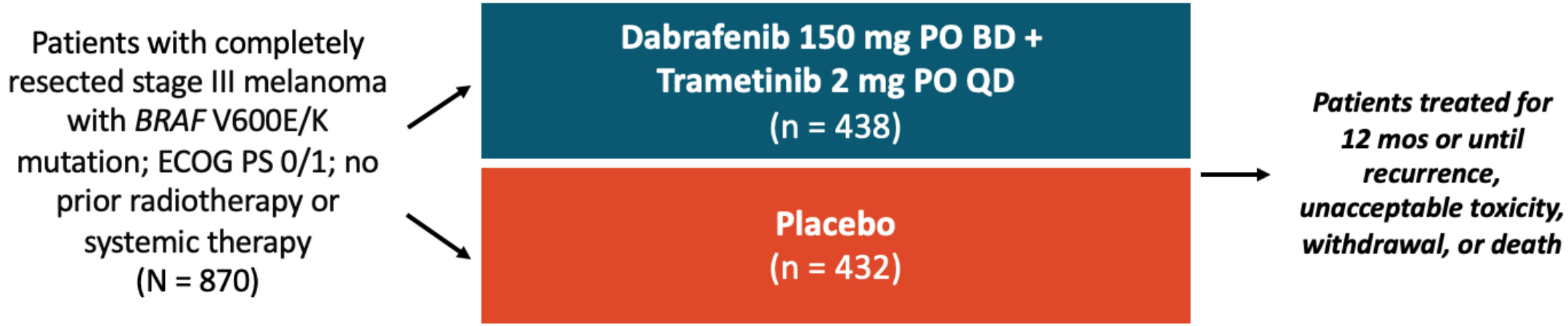
Dabrafenib 150 mg po bid
Trametinib 2 mg daily
for 1 year

Primary Endpoint: RFS
Secondary Endpoints: OS, DMFS, safety

Maio M et al. *Lancet Oncol*. 2018;19(4):510-520.
Long GV et al. *N Engl J Med*. 2017;377(19):1813-1823.

COMBI-AD: Adjuvant Dabrafenib + Trametinib for Stage III Melanoma With *BRAF* V600 Mutation

- Randomized, double-blind phase III study



- Primary endpoint: RFS
- Secondary endpoints: OS, DMFS, FFR, safety

Long-term benefit of adjuvant dabrafenib plus trametinib in patients with resected stage III *BRAF* V600-mutant melanoma: 5-year analysis of COMBI-AD

Axel Hauschild, Reinhard Dummer, Mario Santinami, Victoria Atkinson, Mario Mandalà, John M. Kirkwood, Vanna Chiarion Sileni, James Larkin, Marta Nyakas, Caroline Dutriaux, Andrew Haydon, Caroline Robert, Laurent Mortier, Jacob Schachter, Kohinoor Dasgupta, Eduard Gasal, Monique Tan, Georgina V. Long, Dirk Schadendorf, on behalf of the COMBI-AD Investigators

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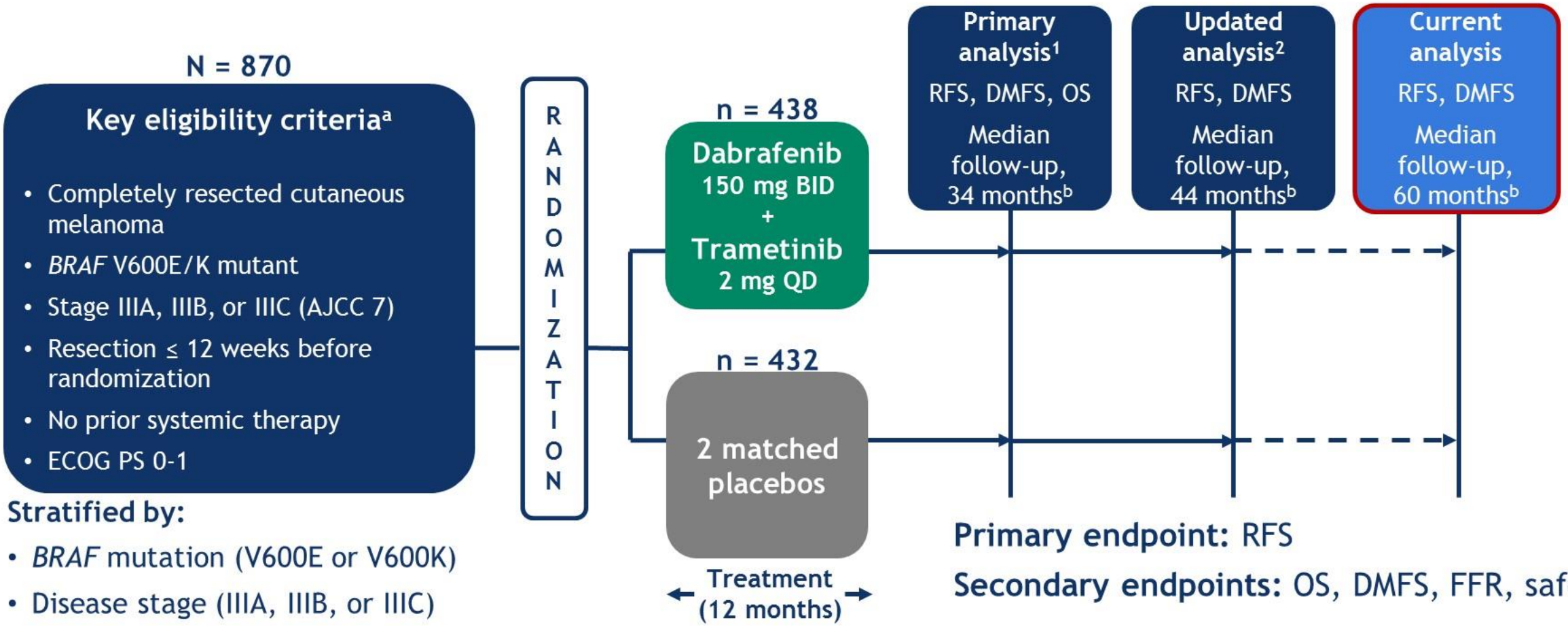
Study Design



Stratified by:

- *BRAF* mutation (V600E or V600K)
- Disease stage (IIIA, IIIB, or IIIC)

Primary endpoint: RFS

Secondary endpoints: OS, DMFS, FFR, safety

AJCC 7, American Joint Committee on Cancer Staging Manual, 7th edition; BID, twice daily; DMFS, distant metastasis-free survival; ECOG PS, Eastern Cooperative Oncology Group performance status; FFR, freedom from relapse; OS, overall survival; QD, once daily; RFS, relapse-free survival.

[a] COMBI-AD is registered at ClinicalTrials.gov (NCT01682083). [b] Median follow-up shown is for the dabrafenib plus trametinib arm.

1. Long GV, et al. *N Engl J Med*. 2017;377:1813-1823; 2. Hauschild A, et al. *J Clin Oncol*. 2018;4:1382-1388.

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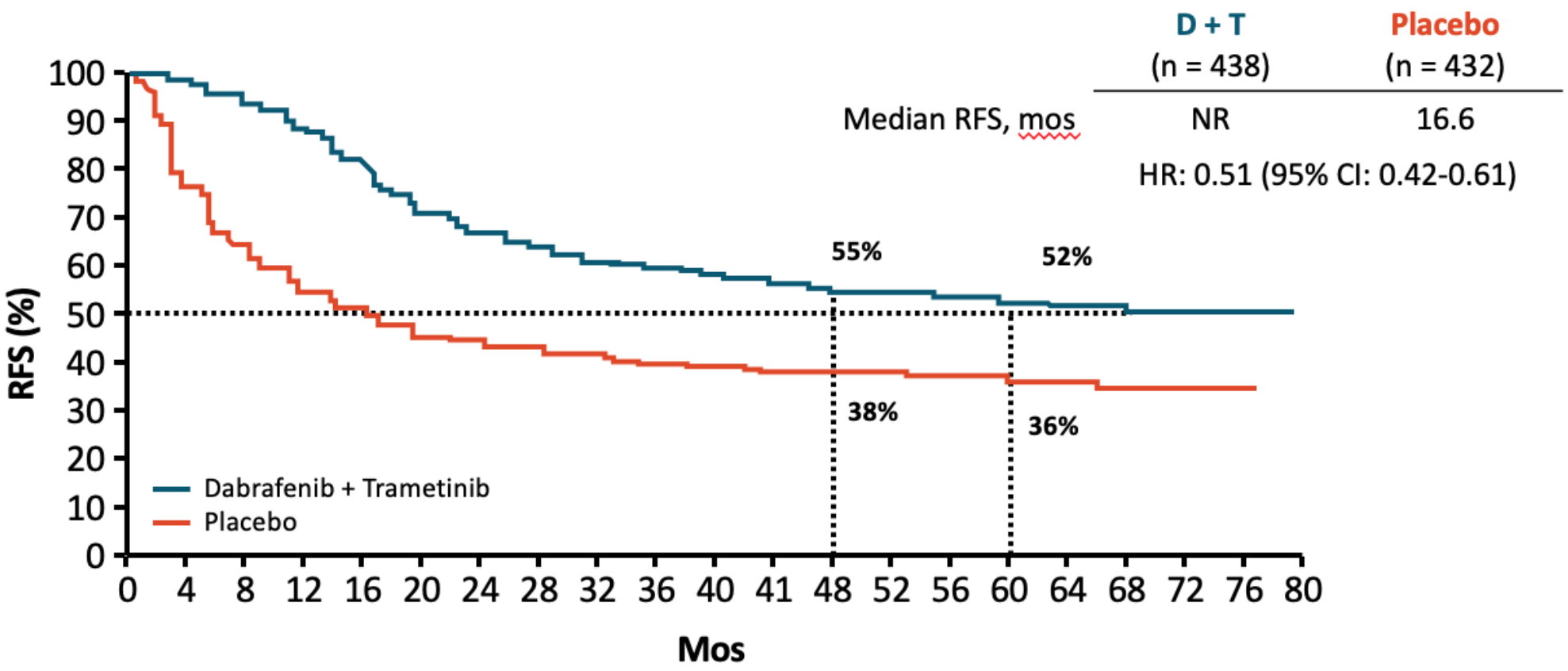
D+T vs plc : 60 aylık sonuç(ASCO 2020)

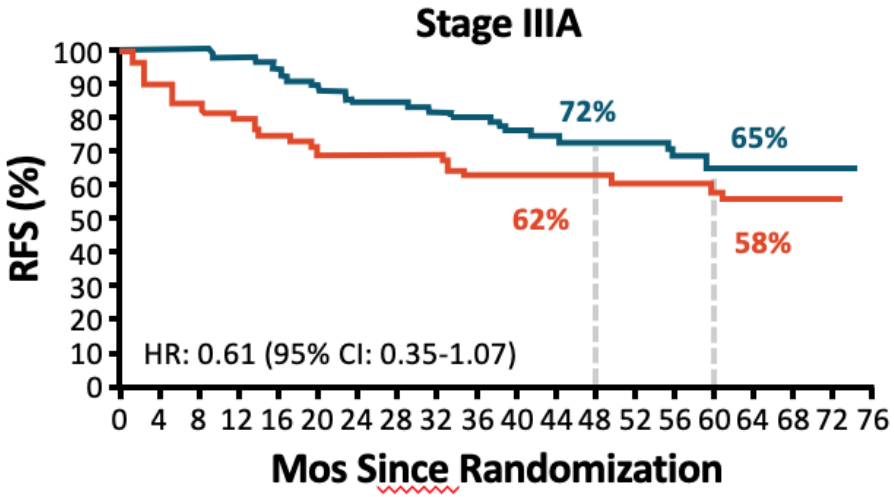
-5-yıllık RFS: % 52 vs % 36, HR:0.51
-medyan RFS : NR vs 16.6 ay, en belirgin yarar ilk 1 yılda

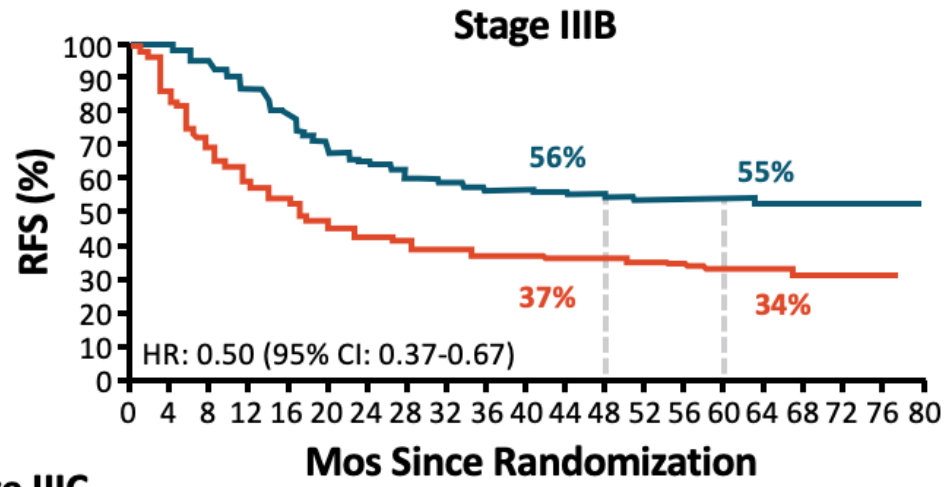


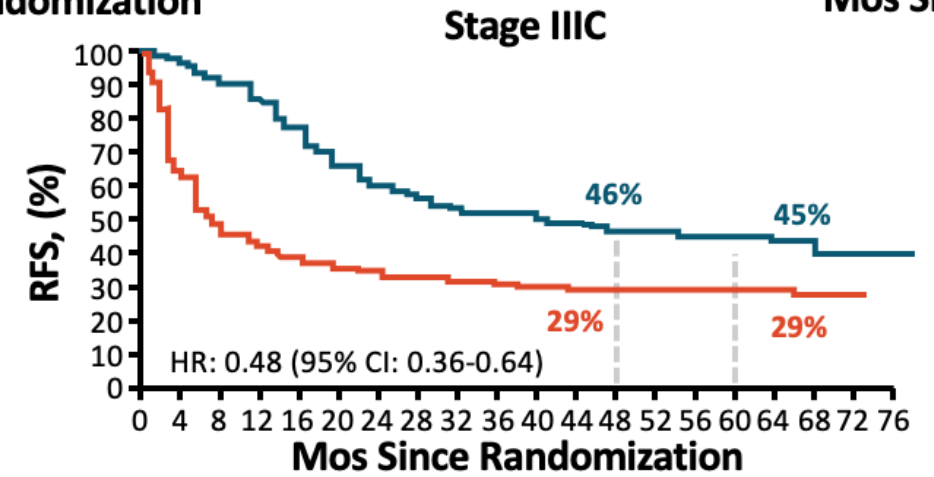
Patients at Risk, n

D + T	438	405	381	354	324	281	262	249	236	229	221	213	204	199	176	133	92	45	17	6	0
Placebo	432	322	263	219	199	178	168	164	157	147	143	139	136	133	121	99	69	35	13	1	0

COMBI-AD: RFS by AJCC 7 Stage







Dabrafenib + trametinib
Placebo

Dummer. NEJM. 2020;383:1139.

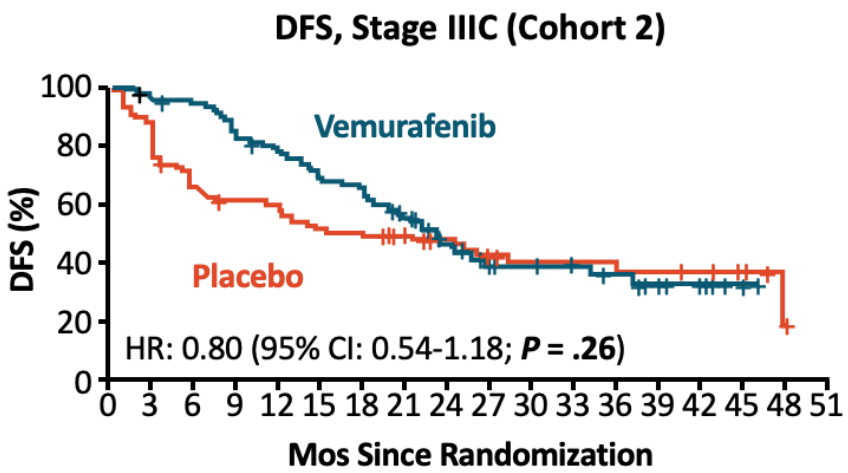
Slide credit: clinicaloptions.com

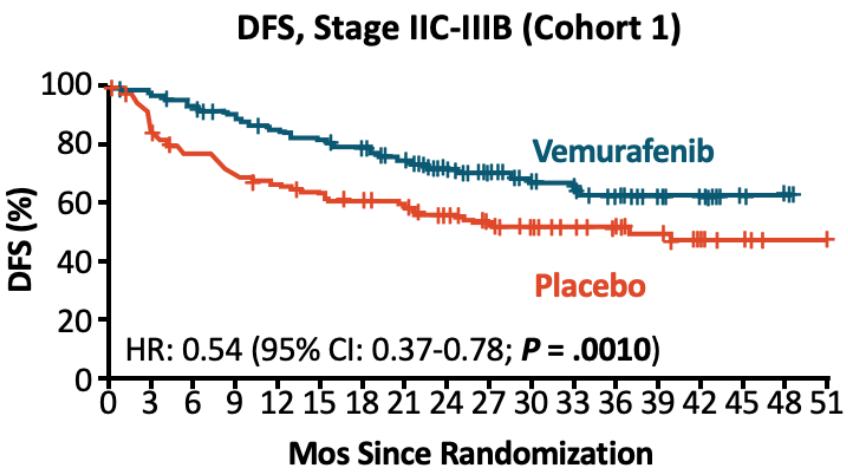
COMBI-AD: Safety Summary

AEs, %	Dabrafenib + Trametinib (n = 435)		Placebo (n = 432)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Any AE	97	41	88	14
▪ Pyrexia	63	5	11	< 1
▪ Fatigue	47	4	28	< 1
▪ Nausea	40	1	20	0
▪ Headache	39	1	24	0
▪ Chills	37	1	4	0
▪ Diarrhea	33	1	15	< 1
AEs leading to dose interruption	66	NA	15	NA
AEs leading to dose reduction	38	NA	3	NA
AEs leading to d/c of study regimen	26	NA	3	NA

BRIM8: Adjuvant Vemurafenib vs Placebo in Resected Stage III Melanoma

- Randomized, double-blind phase III study of adjuvant **vemurafenib** vs **placebo** for 1 yr in patients with resected stage IIC-IIIC, *BRAF* mutation–positive melanoma (N = 498)





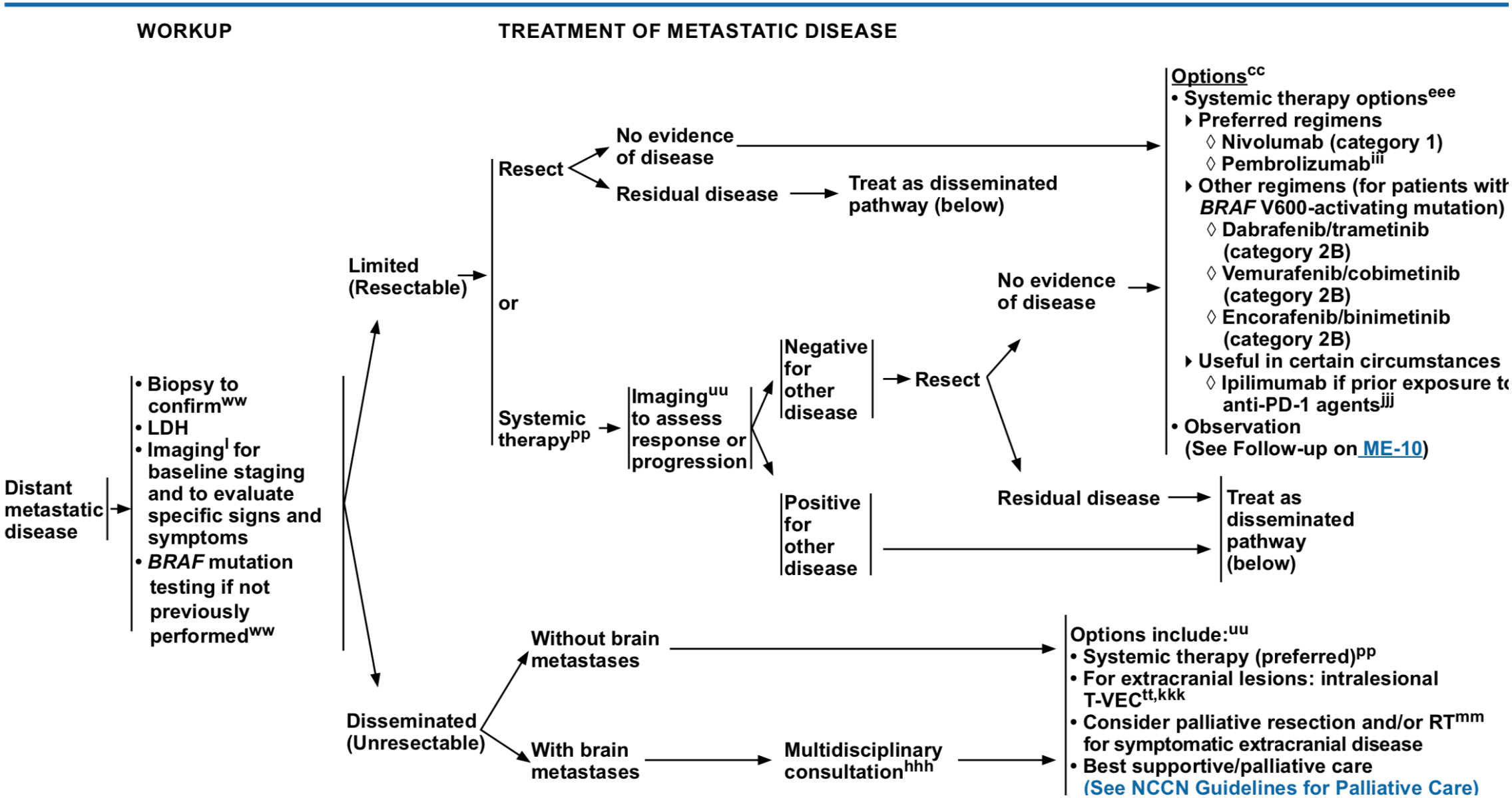
- Study did not meet overall primary endpoint due to lack of improvement in DFS in cohort 2

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2020
Cutaneous Melanoma

NCCN

CLINICAL/ PATHOLOGIC STAGE	WORKUP	PRIMARY TREATMENT	ADJUVANT TREATMENT
Stage III (clinically positive node[s])[y]	• Core biopsy or FNA preferred if feasible. If needle biopsy is not possible, incisional or excisional biopsy is acceptable • Imaging[l] for baseline staging and to evaluate specific signs or symptoms • *BRAF* mutation testing[z]	Wide excision of primary tumor[p] (category 1)[y] + therapeutic lymph node dissection (TLND)[kk]	Systemic therapy options:[cc] • Preferred regimens ▸ Nivolumab[ee] (category 1) ▸ Pembrolizumab[ee] (category 1) ▸ Dabrafenib/trametinib[jj] for patients with *BRAF* V600-activating mutation (category 1) and/or Locoregional therapy option: • Consider RT to nodal basin in selected high-risk patients based on location, size, and number of involved nodes, gross and/or histologic extracapsular extension[ll,mm] (category 2B) or Observation[cc]


WORKUP
TREATMENT OF METASTATIC DISEASE
Distant metastatic disease
• Biopsy to confirm[ww]
• LDH
• Imaging[l] for baseline staging and to evaluate specific signs and symptoms
• *BRAF* mutation testing if not previously performed[ww]
Limited (Resectable)
Resect
No evidence of disease
Residual disease
Treat as disseminated pathway (below)
or
Systemic therapy[pp]
Imaging[uu] to assess response or progression
Negative for other disease
Resect
No evidence of disease
Residual disease
Positive for other disease
Treat as disseminated pathway (below)
Options[cc]
• Systemic therapy options[eee]
Preferred regimens
◊ Nivolumab (category 1)
◊ Pembrolizumab[iii]
Other regimens (for patients with *BRAF* V600-activating mutation)
◊ Dabrafenib/trametinib (category 2B)
◊ Vemurafenib/cobimetinib (category 2B)
◊ Encorafenib/binimetinib (category 2B)
Useful in certain circumstances
◊ Ipilimumab if prior exposure to anti-PD-1 agents[jjj]
• Observation
(See Follow-up on ME-10)
Disseminated (Unresectable)
Without brain metastases
With brain metastases
Multidisciplinary consultation[hhh]
Options include:[uu]
• Systemic therapy (preferred)[pp]
• For extracranial lesions: intralesional T-VEC[tt,kkk]
• Consider palliative resection and/or RT[mm] for symptomatic extracranial disease
• Best supportive/palliative care
(See NCCN Guidelines for Palliative Care)

ORIGINAL ARTICLE

Adjuvant Dabrafenib plus Trametinib in Stage III *BRAF*-Mutated Melanoma

G.V. Long, A. Hauschild, M. S
V. Chiarion-Sileni, J. Larkin, M. Ny
L. Mortier, J. Schachter, D. Schadendo
B. Mookerjee, J. Legos, R. Keff

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV M

I. Weber, M. Mandala, M. Del Vecchio, H.I. Gogas, A.M. A

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

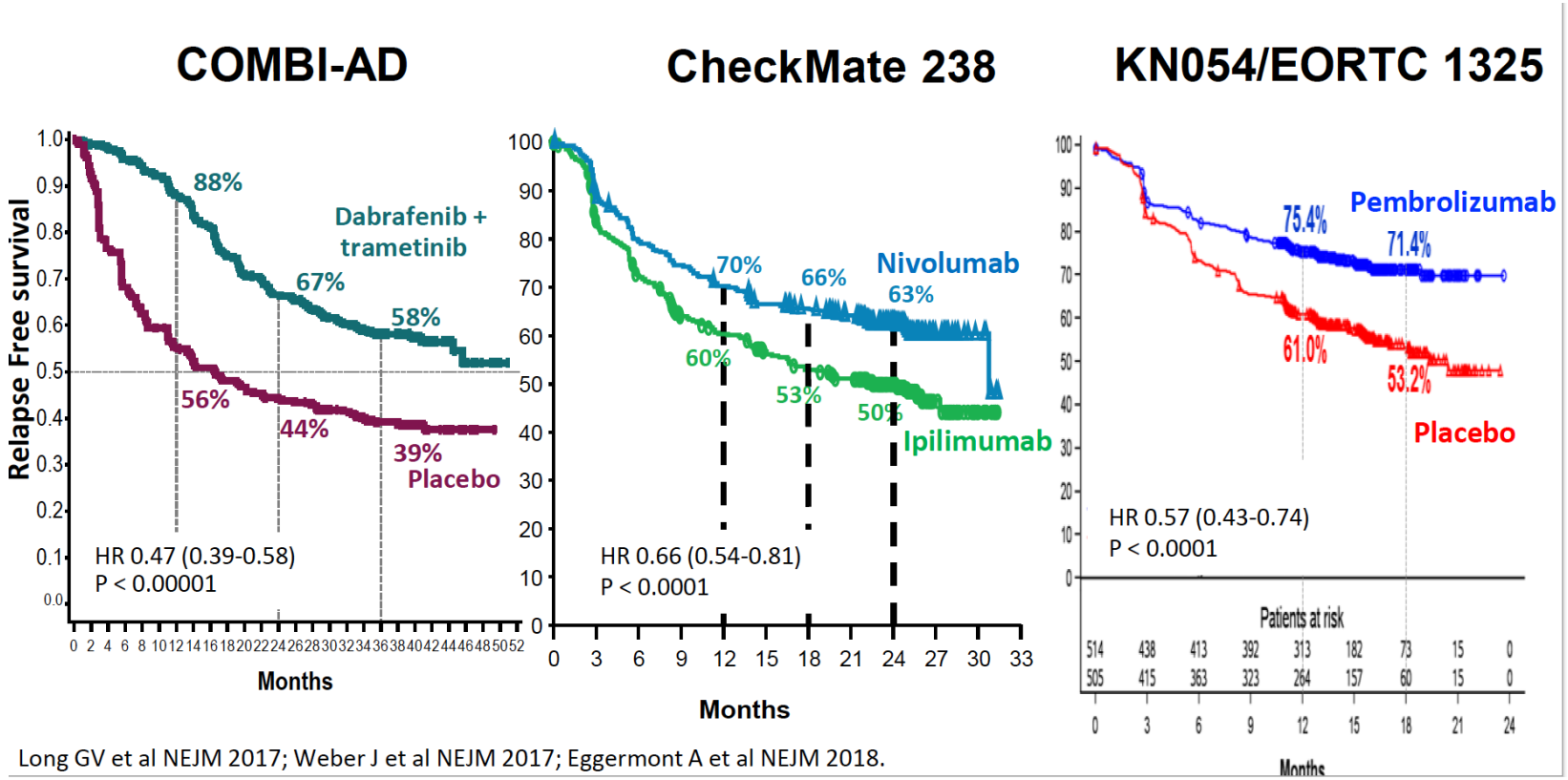
12 Months of Treatment

~50% reduction in risk of recurrence vs placebo

Piotr Rutkowski, M.D., Dirk Schadendorf, M.D., Ph.D., Rutger Koornstra, M.D.,
Leonel Hernandez-Aya, M.D., Michele Maio, M.D., Ph.D.,
Alfonsus J.M. van den Eertwegh, M.D., Ph.D., Jean-Jacques Grob, M.D., Ph.D.,
Ralf Gutzmer, M.D., Rahima Jamal, M.D., Paul Lorigan, M.D., Nageatte Ibrahim, M.D.,
Sandrine Marreaud, M.D., Alexander C.J. van Akkooi, M.D., Ph.D., Stefan Suciu, Ph.D.,
and Caroline Robert, M.D., Ph.D.

Presented by Georgina V Long @ProfGLongMIA

Tüm çalışmalarda RFS yararı

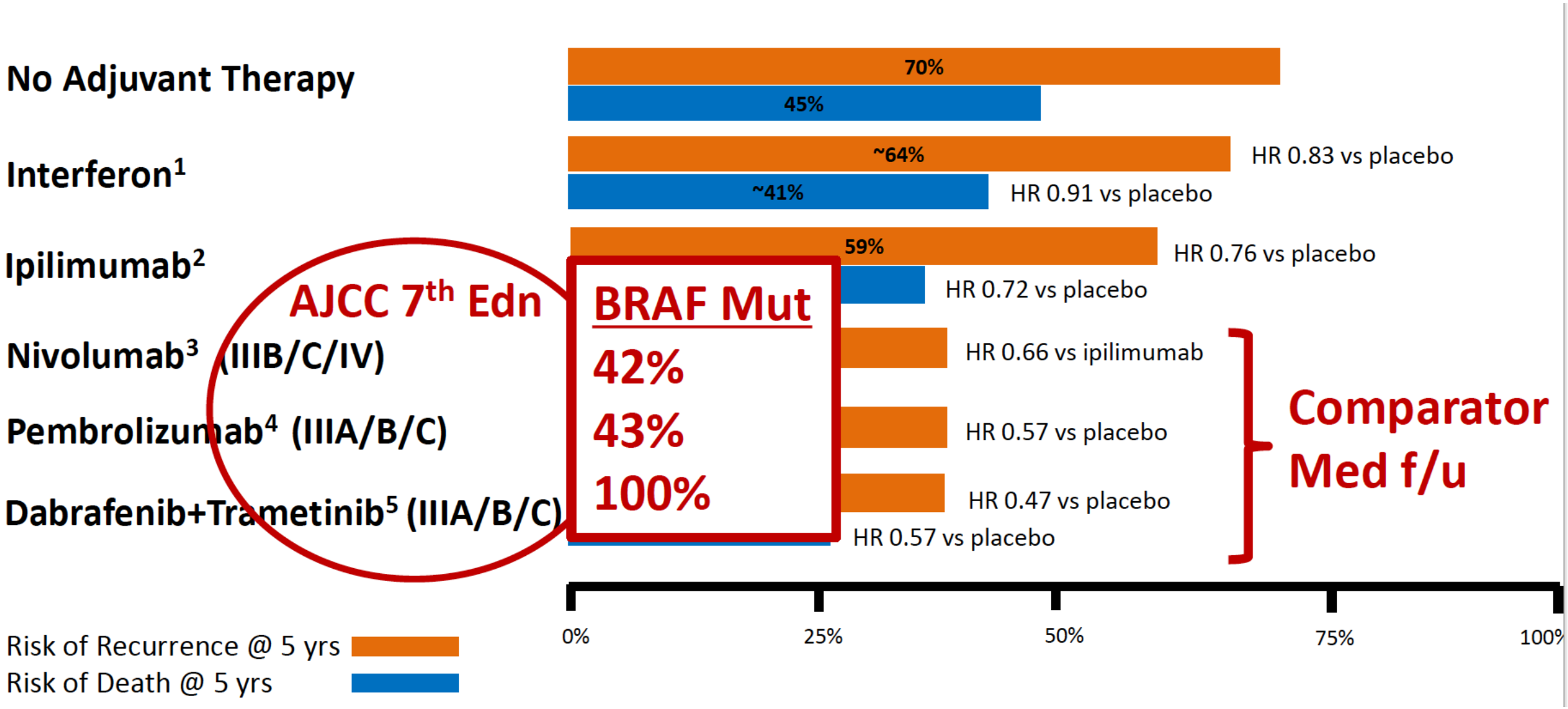


Long GV et al NEJM 2017; Weber J et al NEJM 2017; Eggermont A et al NEJM 2018.

Review > J Natl Cancer Inst. 2018 Jan 1;110(1). doi: 10.1093/jnci/djx133.

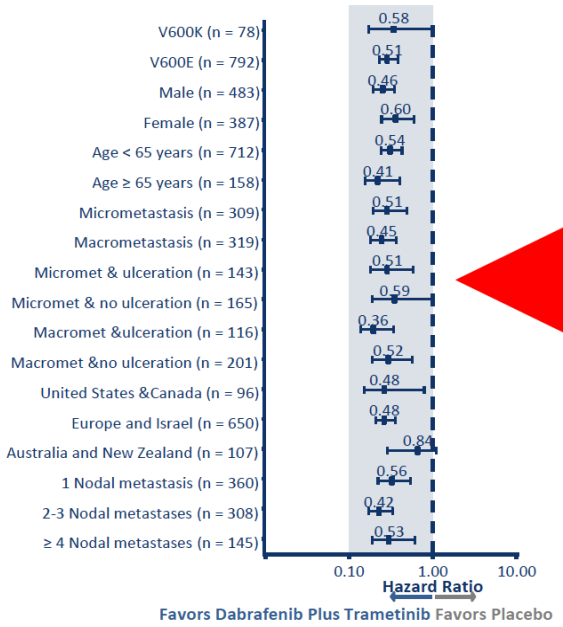
Relapse-Free Survival as a Surrogate for Overall Survival in the Evaluation of Stage II-III Melanoma Adjuvant Therapy

Conclusions: In high-risk stage II-III melanoma, RFS appeared to be a valid surrogate end point for OS for adjuvant randomized studies assessing interferon or a checkpoint inhibitor. In future similar adjuvant studies, a hazard ratio for RFS of 0.77 or less would predict a treatment impact on OS.

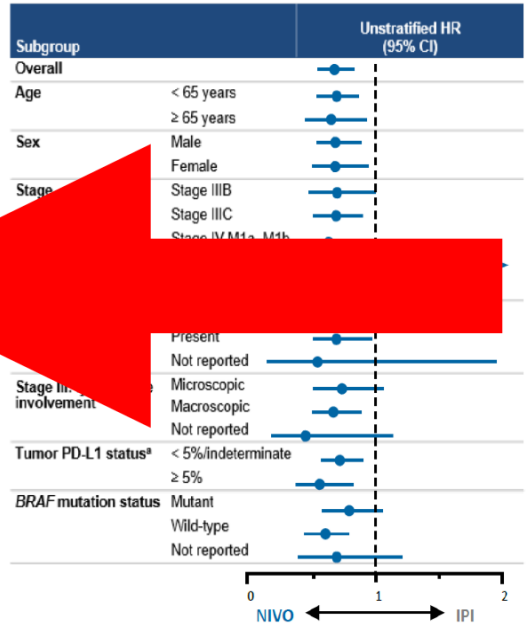

No Adjuvant Therapy
70%
45%
Interferon[1]
~64%
HR 0.83 vs placebo
~41%
HR 0.91 vs placebo
Ipilimumab[2]
59%
HR 0.76 vs placebo
HR 0.72 vs placebo
AJCC 7th Edn
BRAF Mut
Nivolumab[3] (IIIB/C/IV)
42%
HR 0.66 vs ipilimumab
Pembrolizumab[4] (IIIA/B/C)
43%
HR 0.57 vs placebo
Dabrafenib+Trametinib[5] (IIIA/B/C)
100%
HR 0.47 vs placebo
HR 0.57 vs placebo
Comparator
Med f/u
0%
25%
50%
75%
100%
Risk of Recurrence @ 5 yrs
Risk of Death @ 5 yrs

Yarar: Tüm risk gruplarında

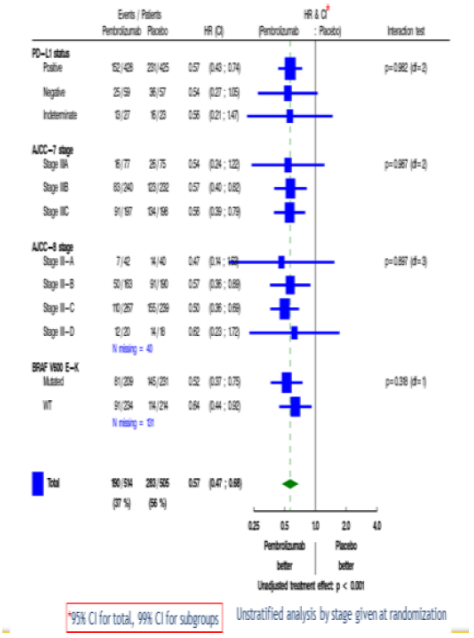
COMBI-AD



CheckMate 238



KN054/EORTC 1325



Long GV et al NEJM 2017; Weber J et al NEJM 2017; Eggermont A et al NEJM 2018.

Presented by Georgina V Long @ProfGLongMIA

Adjuvan Tedavide Toksisite Nedeniyle İlaç Bırakma Oranları

İpilimumab	%42.6
Nivolumab/ Pembrolizumab	%9.7 / %14
Dabrafenib+Trametinib	%26

Adjuvan Anti-PD1 ? D+T?

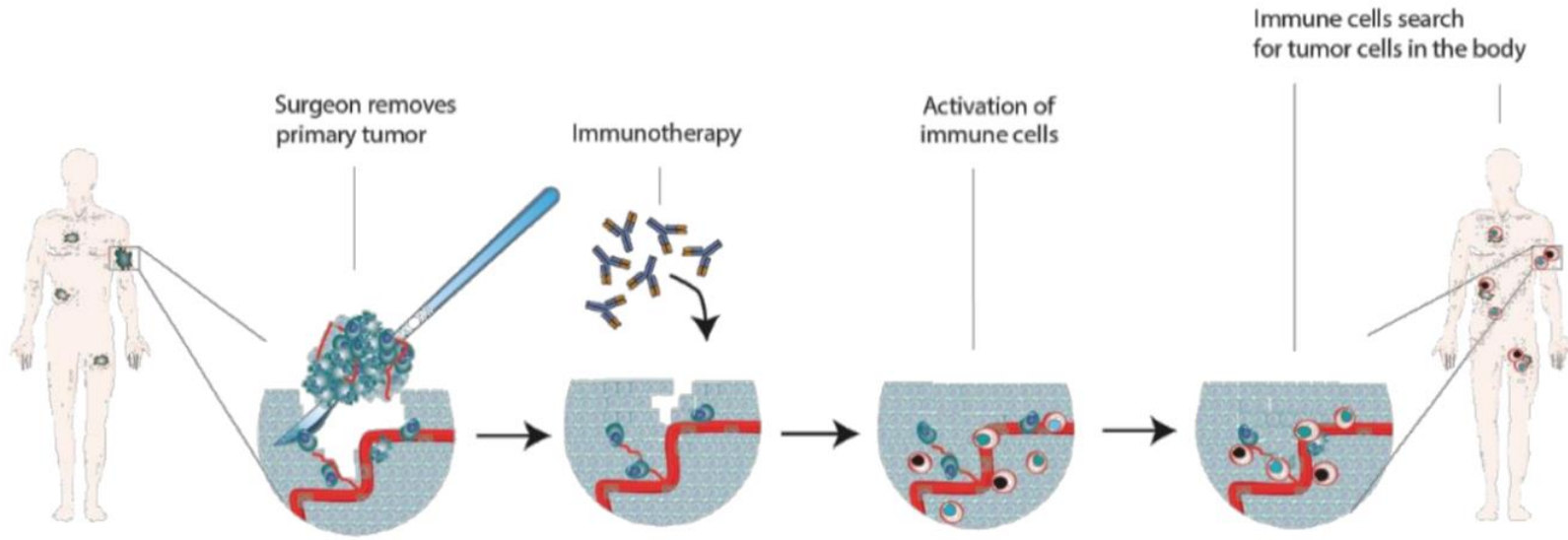
- Her iki tedavi yaklaşımları ile RFS ve uzun dönem sonuçlar çok benzer,
- *Bazı yayınlarda **düşük TMB, D+T kombinasyonundan daha çok yarar** ile ilişkili , diğer taraftan **yüksek TMB, anti-PD1 tercihi** için bir neden olabilir (hala experimental!)*
- Otoimmun hastalık, organ nakli, IV tedavi istemeyenlerde D+t tercih edilebilir. D+T çoğu yan etki kısa etkili
- Kardiak EF'si düşük ve retinal komorbititesi olanlara anti-PD1 tercih edilebilir, D+T'den farklı olarak anti-PD1 ilaçlar hipotiroidi ve artrit gibi kalıcı yan etkiler yapabilir

MALİGN MELANOMDA NEOADJUVAN TEDAVİ

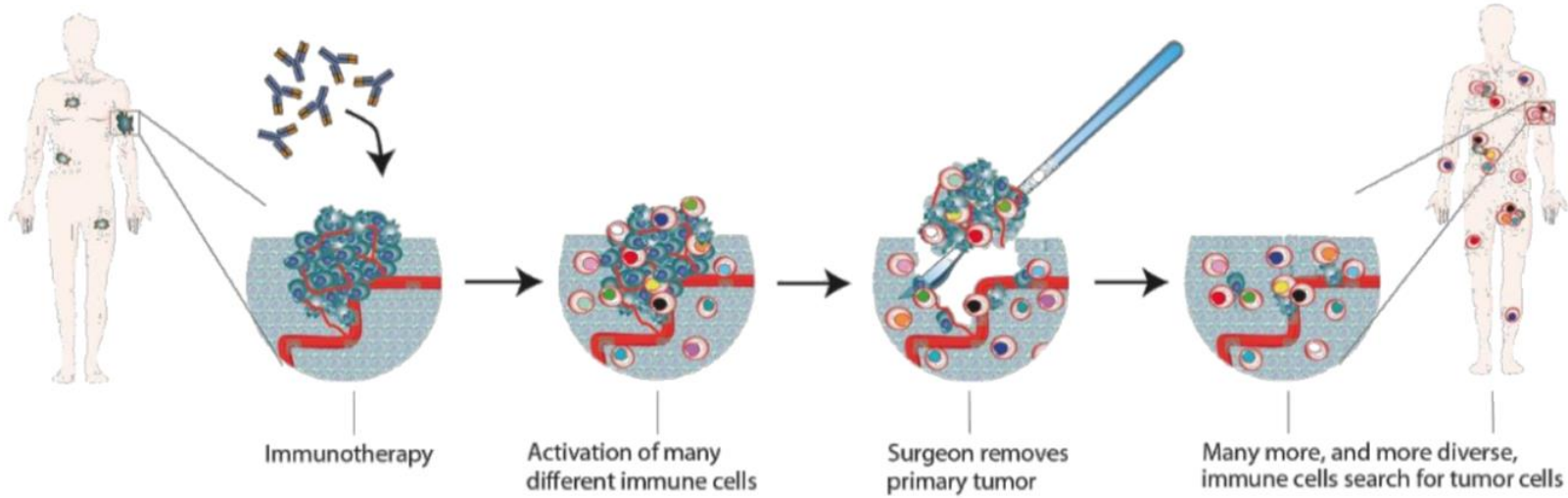
Neden neadjuvan?

- Tm'ü küçültmek…azalmış cerrahi mobidite(rezektabilite,lokal kontrol,organ koruma)
- Mikrometastazların ortadan kaldırılması ve uzak yayılımın önlenmesi
- Tedavi yanıtının patolojik materyalde objektif ölçümü ve adjuvan tedavinin kişiselleştirilmesi
- İnvivo tedaviye sensitivite testi, biospesmenlerde (kan ve tm örneği) tedavi yanıtı ve direnci ile bilgileri kolaylaştırmak, daha homojen bir populasonda daha kolay biomarkır çalışmaları ve ilaç çalışmaları
- Patolojik yanıtın uzun dönem DFS-OS için bir surrogate olabilir, özellikle yüksek riskli popülasyonun onkolojik sonuçlarını iyi leştirebilir
- IC tedavisi daha güçlü tm spesifik T hücre yanıtına neden olabilir?
- Sorunlar: yan etkiler cerrahiyi geciktirebilir, cerrahi şansı kaçırılabilir

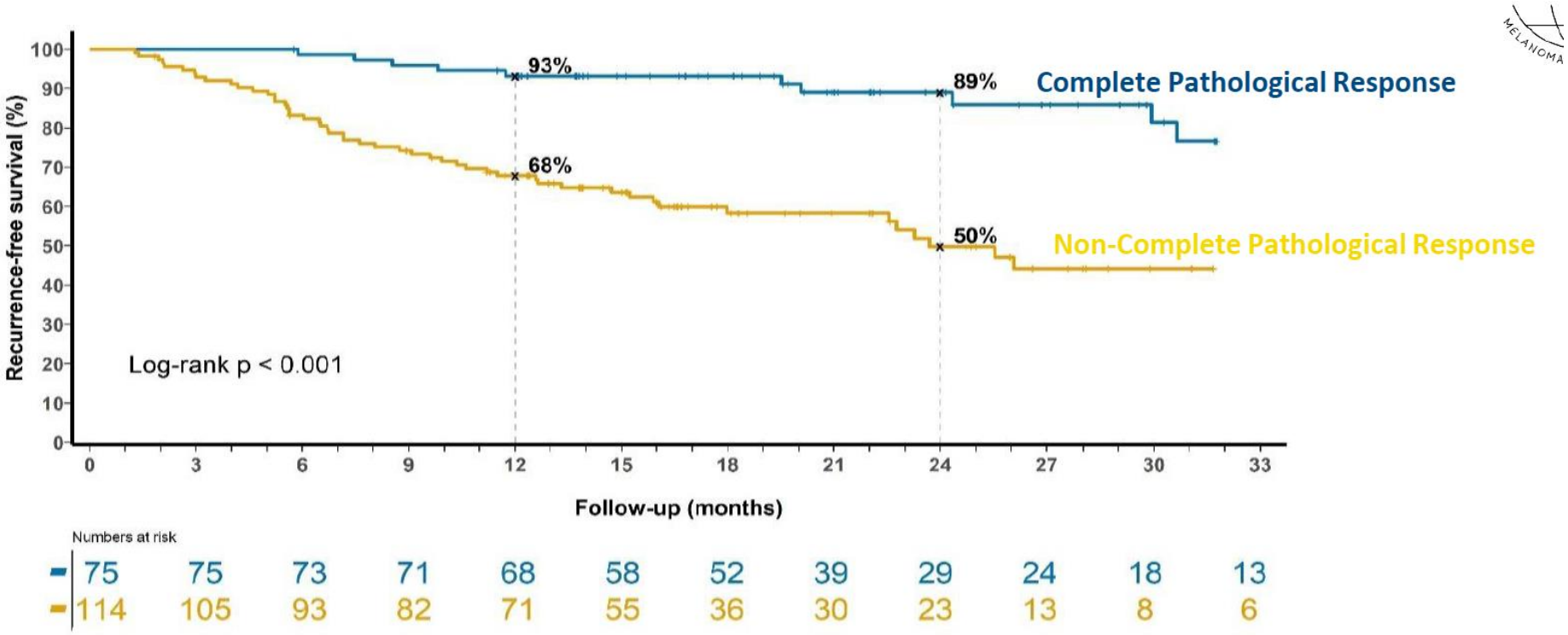
Adjuvant immunotherapy



Neoadjuvant immunotherapy



IO ve braf targeted ilaçlarla tedavi edilen evre 3 hastalarda PCR RFS için surrogate olabilir mi? POOL analiz



Med f/u 20.9 mo

Neoadjuvant Trial Landscape

Melanoma Institute Australia

NEOADJUVANT MELANOMA CONSORTIUM

51 neoadju trials listed on www.clinicaltrials.gov

2016 | 2017 | 2020 | 2021 | 2022 | 2023

NCT02303951
NEO-VC
Vem+cobi
2016

NCT02231775
COMBI-NEO
Dab + Tram
2017

NCT02434354
Pembro
April 2018

NCT02977052
Opacin-Neo
Nivo+Ipi
2018

NCT02339324
Pembro + HDIFNα2b
2018

NCT02858921
NeoTrio
D+T→Pem/D+T+Pem
2021

DON
ivo+/-Ipi

vOG 1801 Ph 2 Randomised
Neoadj vs Adj Pembro
2021

NCT01972347
NEO-COM
Da

pacin
Nivo+Ipi
2017

NCT02519322
Nivo +/- Ipi +/- LAG3
2019/2020

NCT01608594
Ipi + HDIFN α2b
2018

NCT02977052
PRADO
Nivo+Ipi; pCR → nil TLND
2020

NCT02858921
NeoPeLe
Lenvatinib+Pembro
2022

Ph 2
Randomised
Neoadj Ipi+nivo vs Adj Nivo
2023

Presented by Georgina V Long @ProfGLongMIA

Neoadjuvant plus adjuvant dabrafenib and trametinib versus standard of care in patients with high-risk, surgically resectable melanoma: a single-centre, open-label, randomised, phase 2 trial

Rodabe N Amaria*, Peter A Prieto*, Michael T Tetzlaff, Alexandre Reuben, Miles C Andrews, Merrick I Ross, Isabella C Glitza, Janice Cormier, Wen-Jen Hwu, Hussein A Tawbi, Sapna P Patel, Jeffrey E Lee, Jeffrey E Gershenwald, Christine N Spencer, Vancheswaran Gopalakrishnan, Roland Bassett, Lauren Simpson, Rosalind Mouton, Courtney W Hudgens, Li Zhao, Haifeng Zhu, Zachary A Cooper, Khalida Wani, Alexander Lazar, Patrick Hwu, Adi Diab, Michael K Wong, Jennifer L McQuade, Richard Royal, Anthony Lucci, Elizabeth M Burton, Sangeetha Reddy, Padmanee Sharma, James Allison, Phillip A Futreal, Scott E Woodman, Michael A Davies†, Jennifer A Wargo†

Neoadjuvant dabrafenib combined with trametinib for resectable stage IIIB–C *BRAF*^{V600} mutation-positive melanoma (NeoCombi): a single-arm, open-label, phase 2 trial

Georgina V Long, Robyn P M Saw, Serigne Lo, Omgo E Nieweg, Kerwin F Shannon, Maria Gonzalez, Alexander Guminski, Jenny H Lee, Hansol Lee, Peter M Ferguson, Robert V Rawson, James S Wilmott, John F Thompson, Richard F Kefford, Sydney Ch'ng, Jonathan R Stretch, Louise Emmett, Rony Kapoor, Helen Rizos, Andrew J Spillane, Richard A Scolyer, Alexander M Menzies

2 BRAF/MEK- and 4 anti–PD-1–based neoadjuvant trials published since 2018

nature medicine — LETTERS

Corrected: Author Correction; Publisher Correction

Neoadjuvant immune checkpoint blockade in high-risk resectable melanoma

Rodabe N. Amaria[1,10], Sangeetha M. Reddy[2,10], Hussein A. Tawbi[1], Michael A. Davies[1], Merrick I. Ross[3], Isabella C. Glitza[1], Janice N. Cormier[3], Carol Lewis[4], Wen-Jen Hwu[1], Ehab Hanna[4], Adi Diab[1], Michael K. Wong[1], Richard Royal[1], Neil Gross[4], Randal Weber[4], Stephen Y. Lai[4], Richard Ehlers[5], Jorge Blando[6], Denái R. Milton[6], Scott Woodman[1], Robin Kageyama[7], Daniel K. Wells[7], Patrick Hwu[1], Sapna P. Patel[1], Anthony Lucci[1], Amy Hessel[4], Jeffrey E. Lee[1], Jeffrey Gershenwald[1], Lauren Simpson[1], Elizabeth M. Burton[1], Liberty Posada[1], Lauren Haydu[1], Linghua Wang[8], Shaojun Zhang[8], Alexander J. Lazar[9], Courtney W. Hudgens[9], Vancheswaran Gopalakrishnan[3], Alexandre Reuben[3], Miles C. Andrews[3], Christine N. Spencer[8], Victor Prieto[9], Padmanee Sharma[6,10], James Allison[6], Michael T. Tetzlaff[8,9,11] and Jennifer A. Wargo[1,8,11]*

Neoadjuvant versus adjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma

Christian U. Blank[1,2*], Elisa A. Rozeman[1,2], Lorenzo F. Fanchi[2], Karolina Sikorska[2], Bart van de Wiel[4], Pia Kvistborg[2], Oscar Krijgsman[2], Marlous van den Braber[2], Daisy Philips[2], Annegien Broeks[4],

nature medicine — FOCUS | LETTERS

A single dose of neoadjuvant PD-1 blockade predicts clinical outcomes in resectable melanoma

Alexander C. Huang[1,2,3,4,5,6*], Robert J. Orlowski[1,7,8,9], Xiaowei Xu[4,5], Rosemarie Mick[3,4,6], Sangeeth M. George[7,10], Patrick K. Yan[2,3], Sasikanth Manne[2,3], Adam A. Kraya[1,4],

Identification of the optimal combination dosing schedule of neoadjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma (OpACIN-neo): a multicentre, phase 2, randomised, controlled trial

Elisa A Rozeman, Alexander M Menzies, Alexander C J van Akkooi, Chandra Adhikari, Caroline Bierman, Bart A van de Wiel, Oscar Krijgsman, Karolina Sikorska, Hannu Eriksson, Annegien Broeks, Johannes V van Thienen, Alexander D Guminski, Peter Meier-Hellmann, Anne Miek Koenen, Linda J Bosch, Kerwin Shannon, Lois M Pronk, Maria Gonzalez, Sydney Ch'ng, Lindsay C Spillane, Jonathan Stretch, Stijn Heimink, Harm van Tinteren, John B A G Haanen, Omgo E Nieweg, Willem M C Klop, Charlotte L Zuur, Robyn P M Saw,

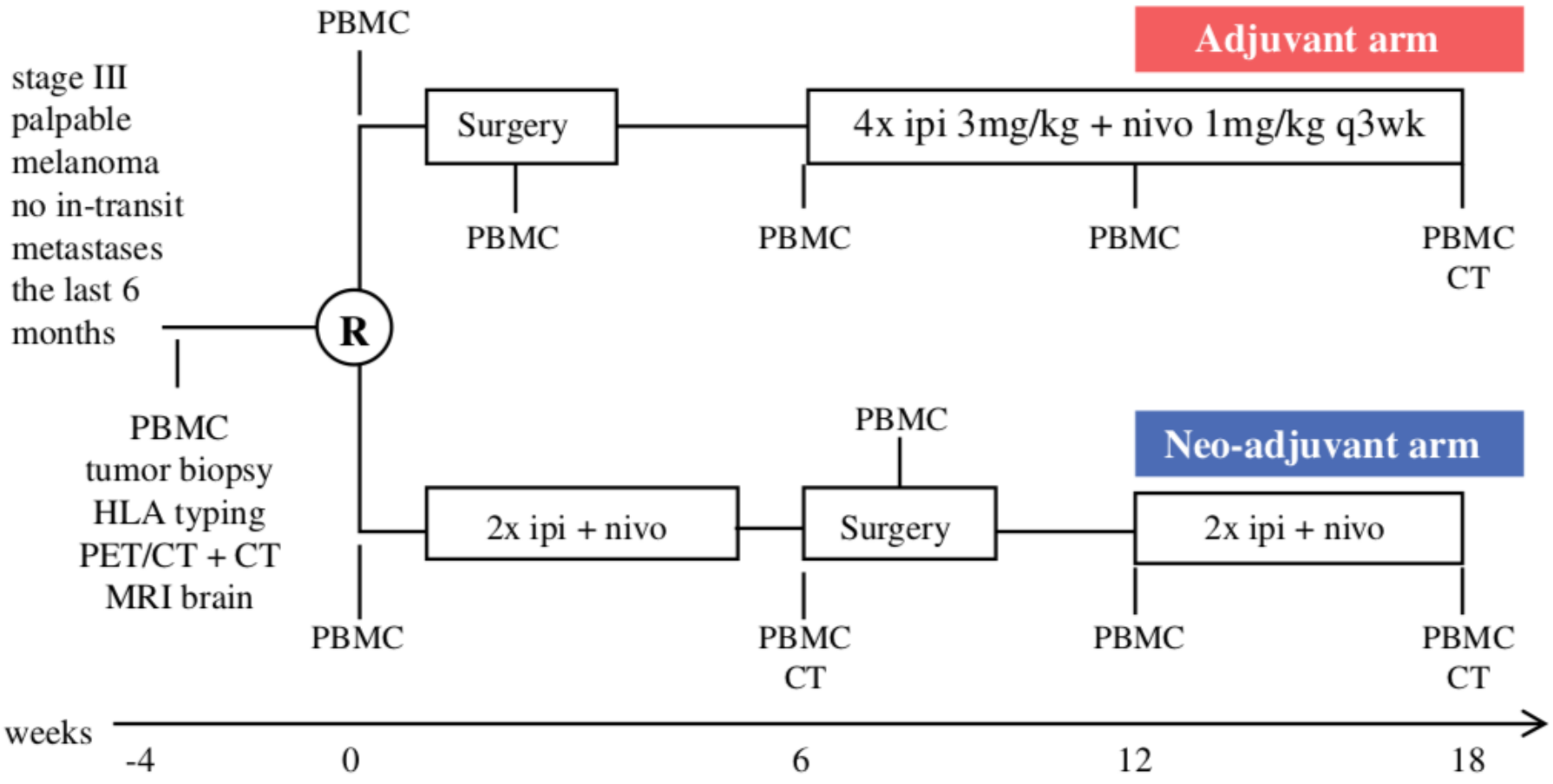
Neoadjuvan İO çalışmaları(tek ajan,kombine)

-evre3-4 hastalar, neo İO 2-3 ay verilmiş..

Trial	Population	Regimen	N	pCR (%)
Blank et al	Clinical III	I3N1 x2 – surgery – I3N1 x2	10	33
Amaria et al	Clinical III, resectable IV	A: Nivo x4 – surgery – Nivo x13 B: I3N1 x3 – surgery – Nivo x13	A: 12 B: 11	25 45
Huang et al	Clinical III, resectable IV	Pembro x1 – surgery – Pembro x17	30	19
Rozeman et al	Clinical III	A: I3N1 x2 – surgery B: I1N3 x2 – surgery C: Ipi x2 – Nivo x2 – surgery	A: 30 B: 30 C: 26	57

NEOADJUVAN VS ADJUVAN İPİ3+NİVO1: OPACIN Study

Blank ve ark, faz 1b, makroskopik erve III hastalar



- Esmo 2020 bu yıl 48.ay verileri sunuldu…ilk önemli çalışma
- Neoadjuvan kolda (N=10)
  - Patolojik yanıtlı: 7/9 (PCR=3 (%33), near PCR=4)….bunların hiçbirinde nüks yok
  - 2 yanıtsız , 1 değerlendirelemeyen…3’ünde nüks…1 hasta kaybedildi
- Adj kolda 4 hastada nüks,3 hasta kaybedildi
- Cerrahi sonrası 6.haftada neoadjuvan kolda dolaşımda daha fazla Tumor sfesifik T hücresi toplanabildi.
- Ancak rapor edilen **grade 3-4 YE: %90**
- Yanıt oranları beklenenden iyi olduğu için **OpaCIN-neo çalışması için öncü çalışma** oldu

Nivo vs I3N1: (Amaria ve ark), faz2,

A kolu(n=12): Nivox4—Cerrahi—NivoX13,

B kolu(n=11): I3N1X3---Cerrahi---NivoX13,

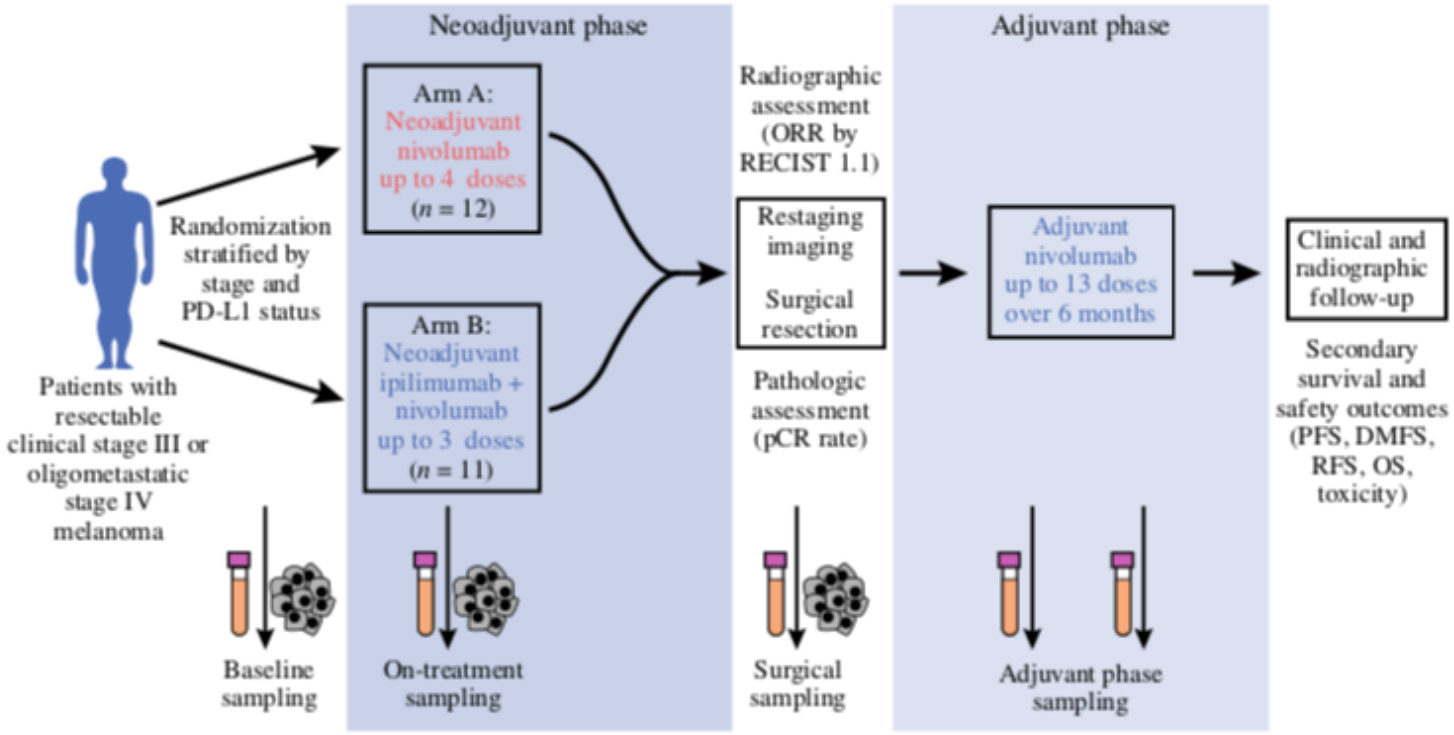
- A kolu

  -Nivo: 3 mg/kg, 2w

B kolu:

N: 1 mg/kg

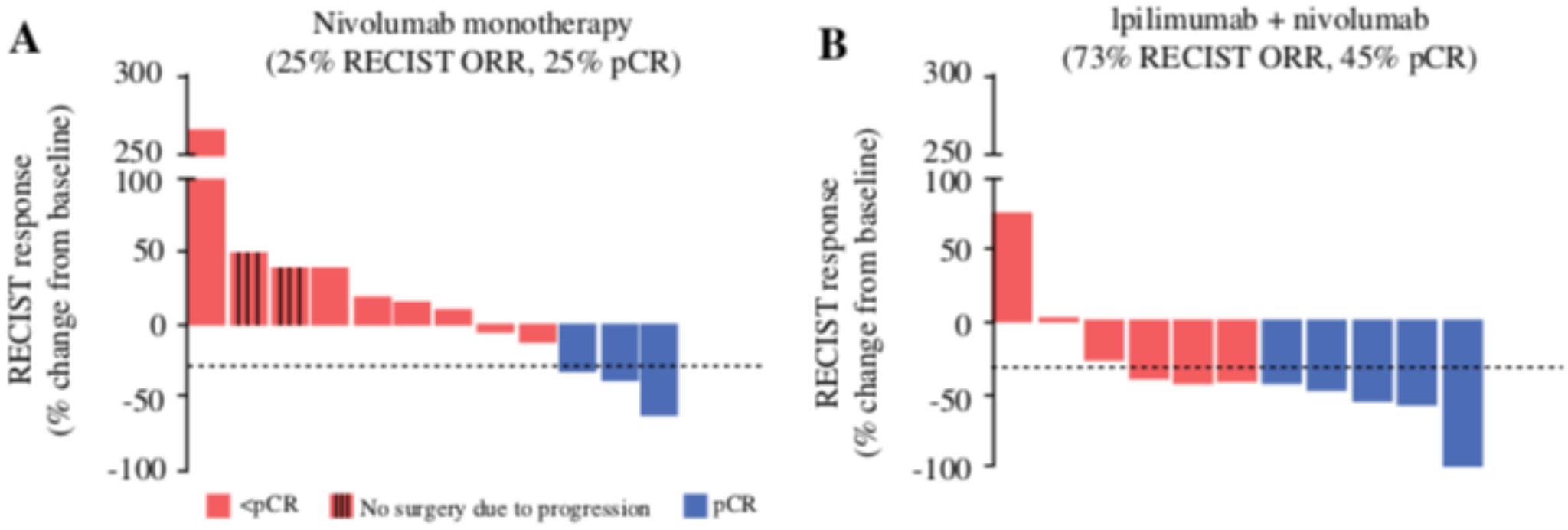
I: 3 mg/kg, 3w



Nivo 3 vs I3N1

A kolu(n=12): Nivo kolu: pCR:%25, Gr 3-4 YE:%8

B kolu(n=11): Kombine kol: pCR:%45 , **Gr 3-4 YE:%73**



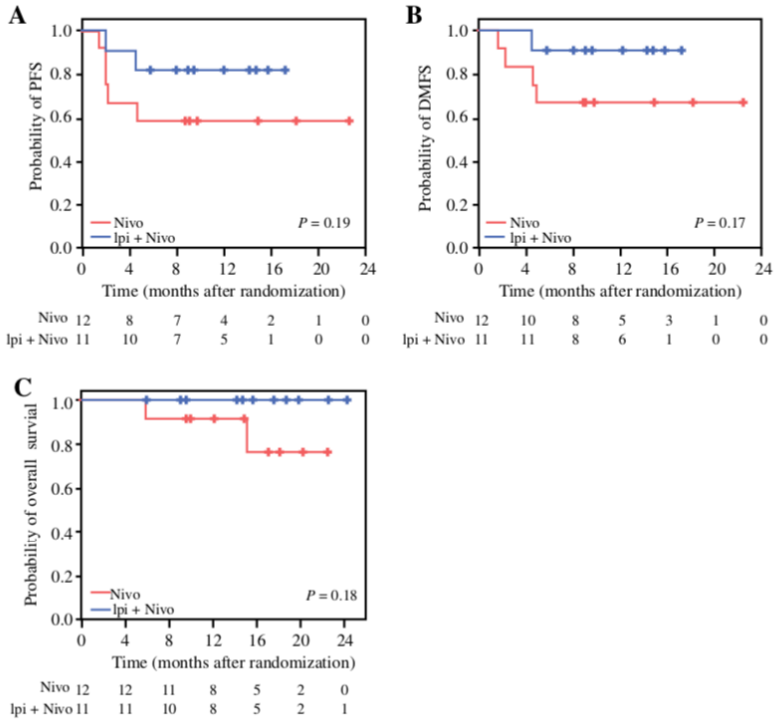
15 aylık FU sonuçlar;

-İpi-Nivo>Nivo; Ancak anlamlu uzun dönem fayda yok, **toksisite nedeniyle çalışma erken sonlandırıldı, (I3N1 TOKSİK)**

-Ama monoterapi ile neoadjuvanda erken progresyon

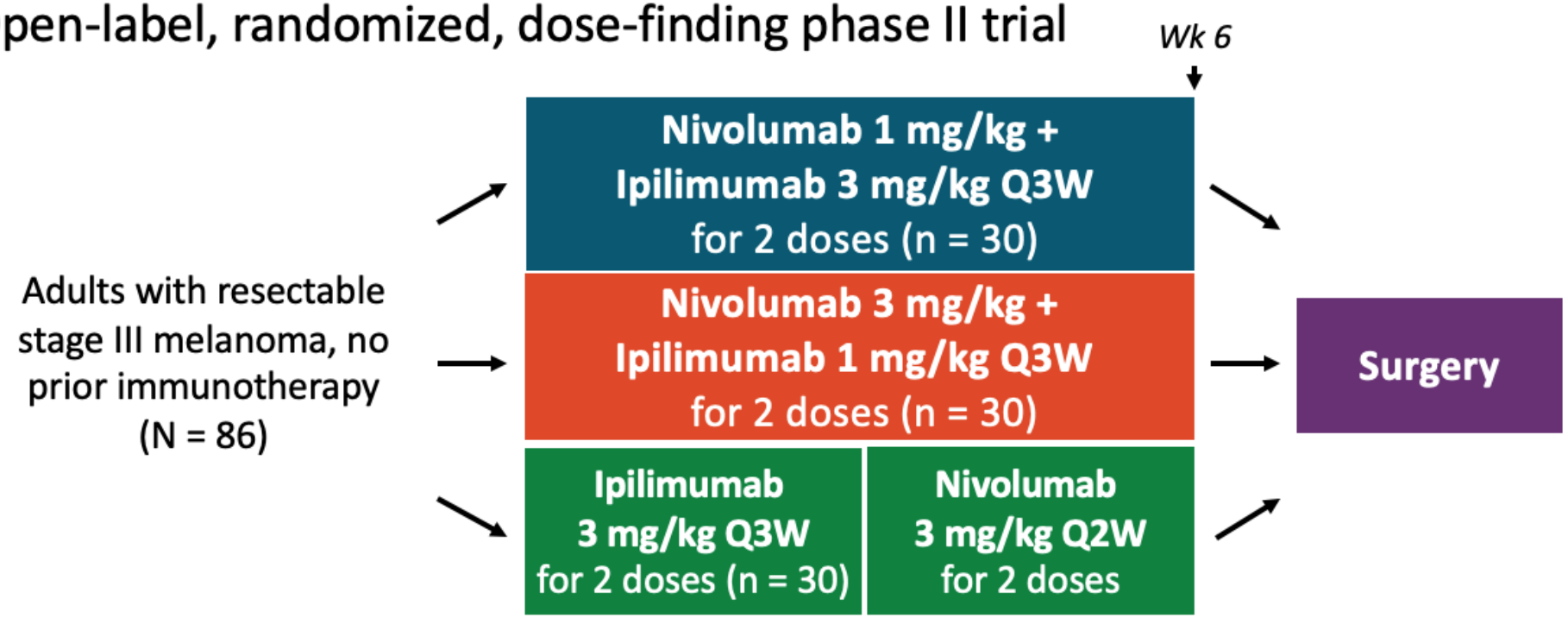
-yüksek TMB olması yanıt ile ilişkili, patolojik yanıtlılarda T hücre klonalitesi artmış

-



OpACIN-NEO:faz 2, n=86

- Open-label, randomized, dose-finding phase II trial

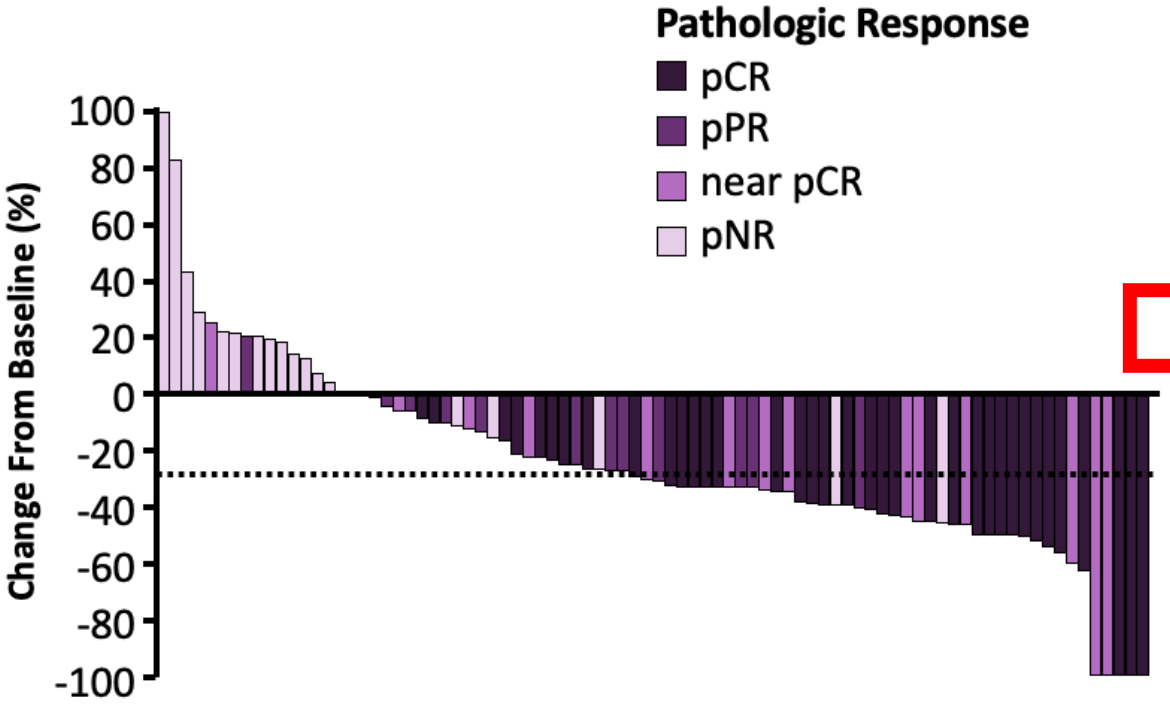


- Primary endpoints: safety, response rate, RFS
- Median follow-up: 8.3 mos

Düşük doz **ipi (1 mg/kg) and nivo (3 mg/kg)** ile

-yüksek ORR(%80) ve PCR(%57)

-Kabul edilebilir toksisite: Gr 3-4 %20



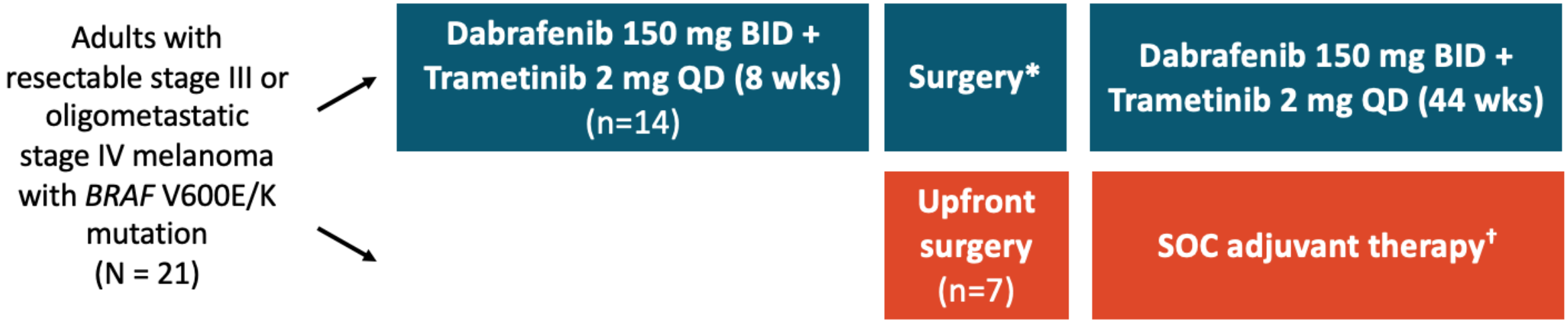
Pathologic Response: Central Review

Response, n (%)	Nivo 1 mg/kg + Ipi 3 mg/kg (n = 30)	Nivo 3 mg/kg + Ipi 1 mg/kg (n = 30)	Ipi 3 mg/kg Then Nivo 3 mg/kg (n = 26)
Overall	24 (80)	23 (77)	17 (65)
▪ pCR	14 (47)	17 (57)	6 (23)
▪ Near pCR	7 (23)	2 (7)	6 (23)
▪ pPR	3 (10)	4 (13)	5 (19)
▪ pNR	6 (20)	7 (23)*	8 (31)
▪ NE	-	-	1 (4)†

*n = 1, only palliative resection of largest lymph node. †Surgery not performed due to toxicity; patient had a radiologic CR.

Combi-Neo: Neoadjuvant/Adjuvant Dabrafenib + Trametinib for Patients With Advanced Melanoma

- Single center, open-label, randomized phase II trial

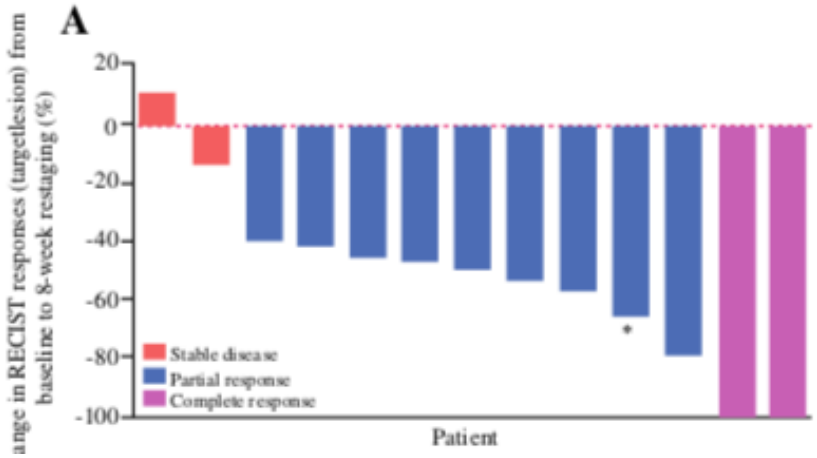


- Primary endpoint: EFS at 12 mos

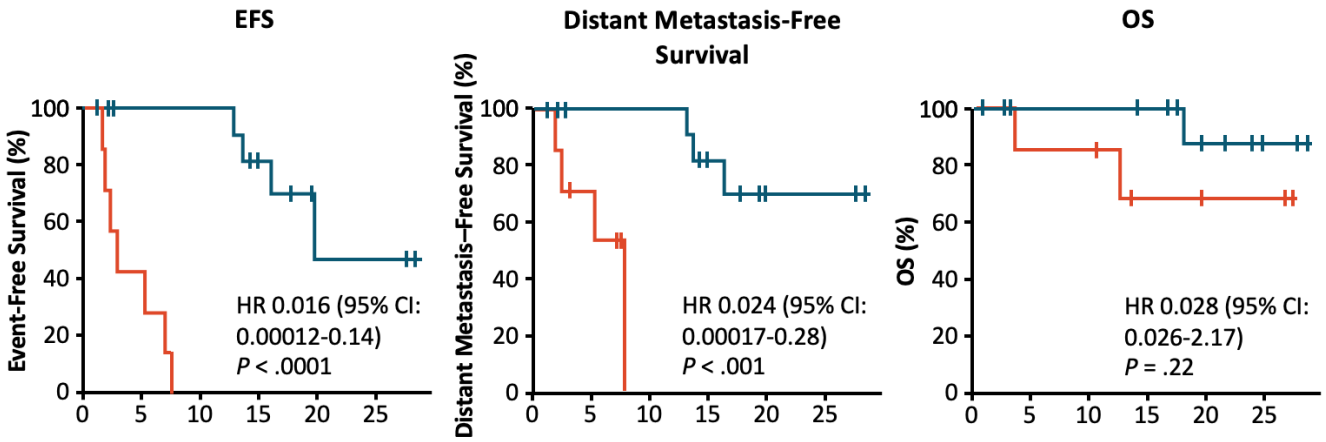
Neoadjuvan ve adjuvan dabrafenib+trametinib ? A kolu(n=14): D+TX 2 ay..cerrahi..adj D+T 44 w B kolu (n=7): cerrahi+SOC(Tedavisiz)

- Faz 2
- Rezektabl evre III ve oligometastatik BRAF mutant hastalar dahil edildi
- Neoadjuvan kolunda: %58 pCR, %17 patolojik parsiyel yanıt
- Medyan EFS: 19.7 vs 2.9 ay kombinasyon lehine
- PCR olanlarda uzun dönem RFS daha iyi
- Çalışma neadjuvan tedavi yararı nedeniyle erken sonlandırıldı

Neoadjuvant Systemic Therapy (NAST) for Stage 3 Melanoma Patients



Combi-Neo: Survival



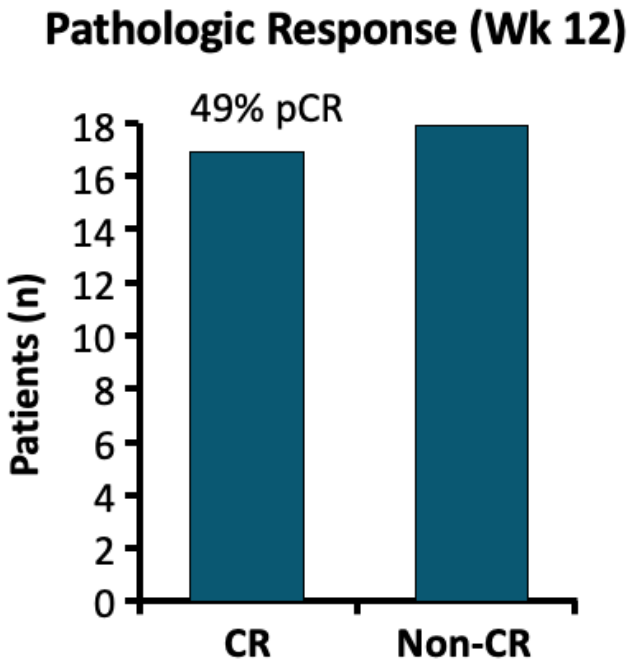
Median EFS for SOC: 2.9 mos
Median EFS for neoadjuvant D + T: 19.7 mos

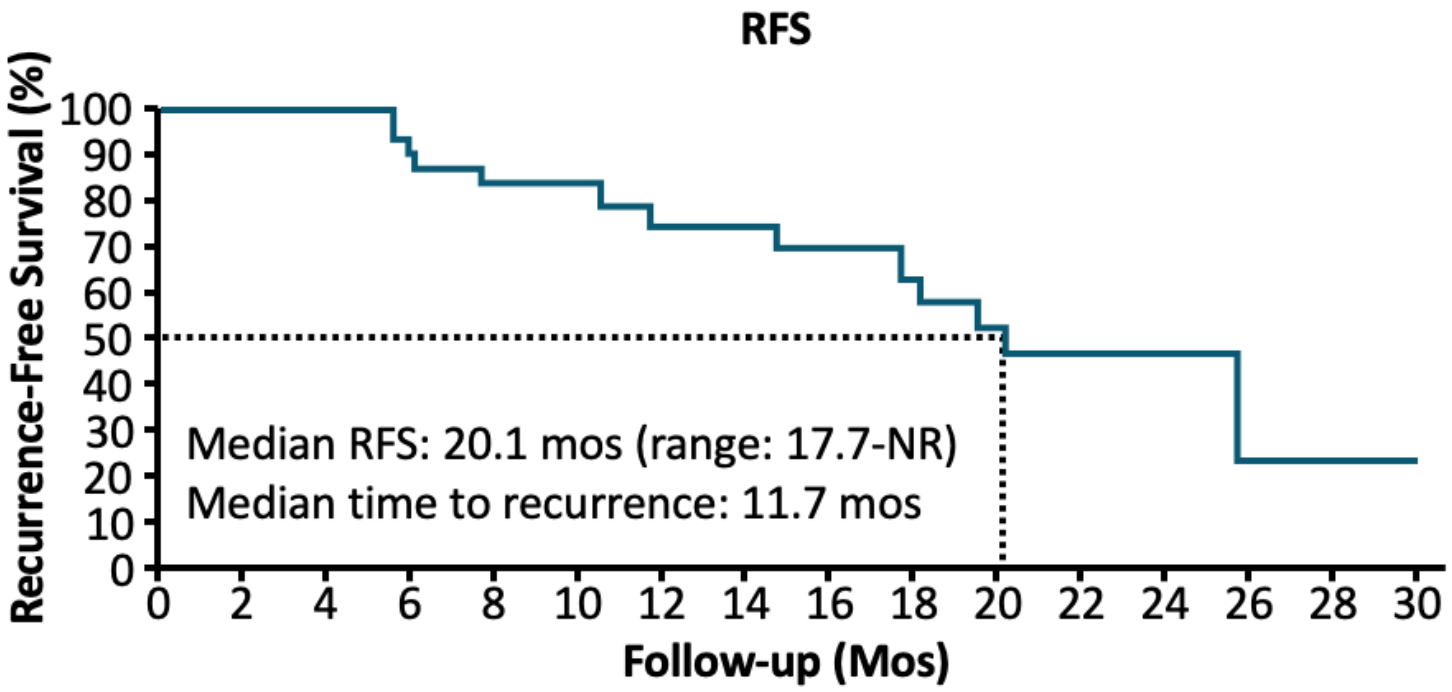
AustralianNeoadjuvan D+T?
-**D+Tx3 ay**..cerrahi....adj D+T 40 w

- Rezektabl evre IIIC BRAF mutant, Faz 2 tek kollu çalışma (N=35)
- pCR:17/35(%49), 18 hastada pPR
- Neoadjuvan tedavi sırasında progresyon hiçbir hastada yoktu
- Hastaların yarısında neoadjuvan tedavi cerrahiyi kolaylaştırmış.
- Median 12 aylık takipte 12 hastada (%36) rekürrens meydana geldi (4'ü adjuvan tedavi alırken).
- pCR olan **17 hastadan 8'i cerrahiden median 30 ay sonra nüksetti**(pCR'a rağmen yarısı nüksetmiş)

Australian Neoadjuvant/Adjuvant Dabrafenib + Trametinib for Patients With Stage III Melanoma

- Open-label phase II trial of neoadjuvant/adjuvant **dabrafenib + trametinib** in patients with resectable stage IIIB-C *BRAF* V600 mutation–positive melanoma (N = 35)





First safety and efficacy results of PRADO

A phase 2 study of Personalized Response-driven surgery and Adjuvant therapy after neoadjuvant ipilimumab and nivolumab in resectable stage III melanoma

CU Blank, ILM Reijers, T Pennington, JM Versluis, RPM Saw, EA Rozeman, E Kapiteijn, AAM van der Veldt, KPM Suijkerbuijk, GAP Hospers, WMC Klop, K Sikorska, JA van der Hage, DJ Grünhagen, A Spillane, RV Rawson, BA van de Wiel, AM Menzies, ACJ van Akkooi and GV Long

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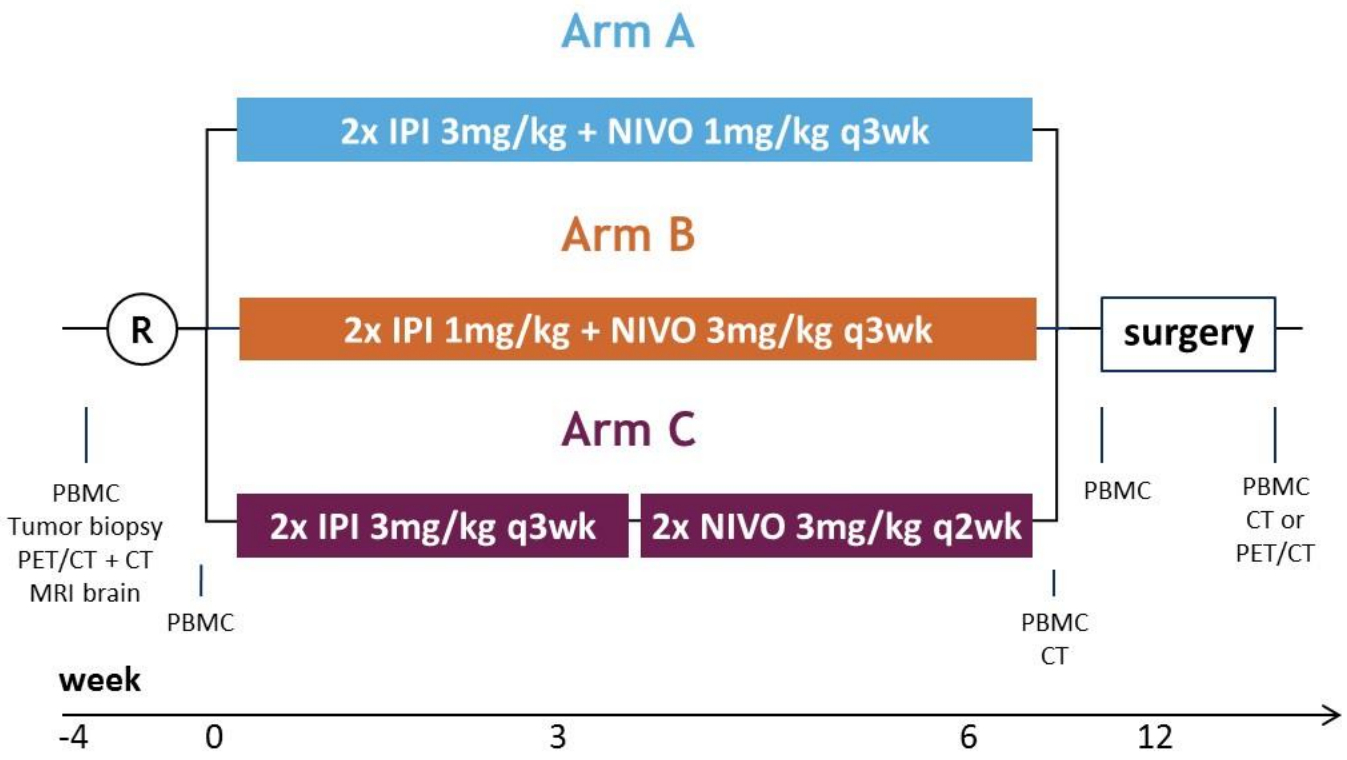
The OpACIN-neo study identified neoadjuvant IPI 1 mg/kg + NIVO 3 mg/kg as the optimal treatment scheme



	Grade 3-4 toxicity	Pathologic Response
Arm A	40%	80%
Arm B	20%	77%
Arm C	50%	65%

Rozeman et al., Lancet Oncology, 2019

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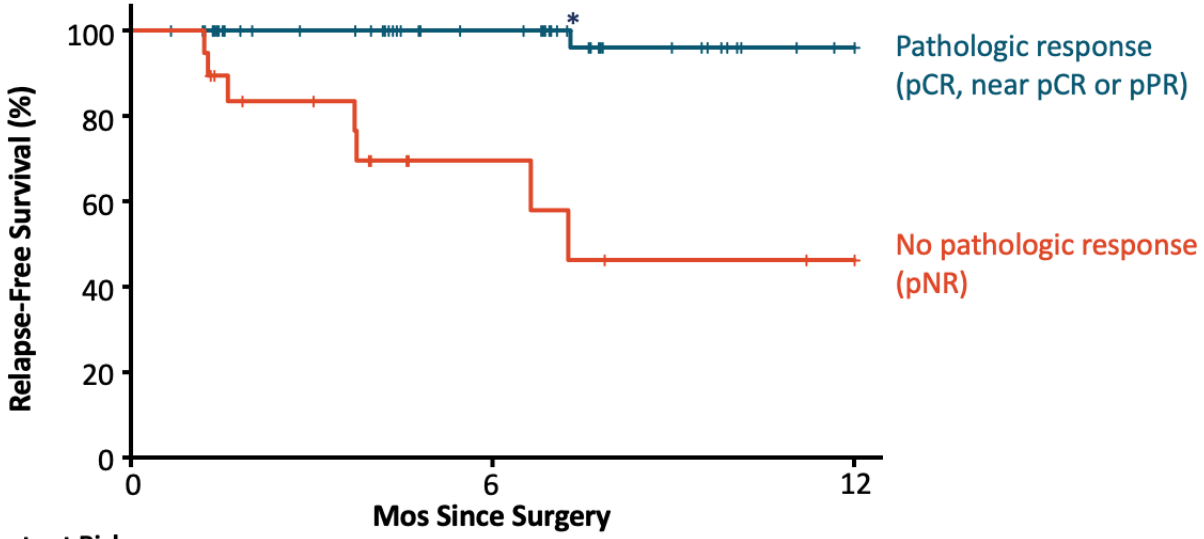
Dosing in Arm A, B, and C based on data from Blank, et al. Nat Med 2018, Long, et al. Lancet Oncol 2017, Meerveld-Eggink et al. Ann Oncol 2017

2 yıllık izlemde patolojik yanıtlı hastalarda(PCR-near pCR-pPR) sadece 1/64 (%2) hastada relaps var

OpACIN-Neo: RFS According to pCR



Patients at Risk, n			
Response	64	34	10
No Response	19	6	2

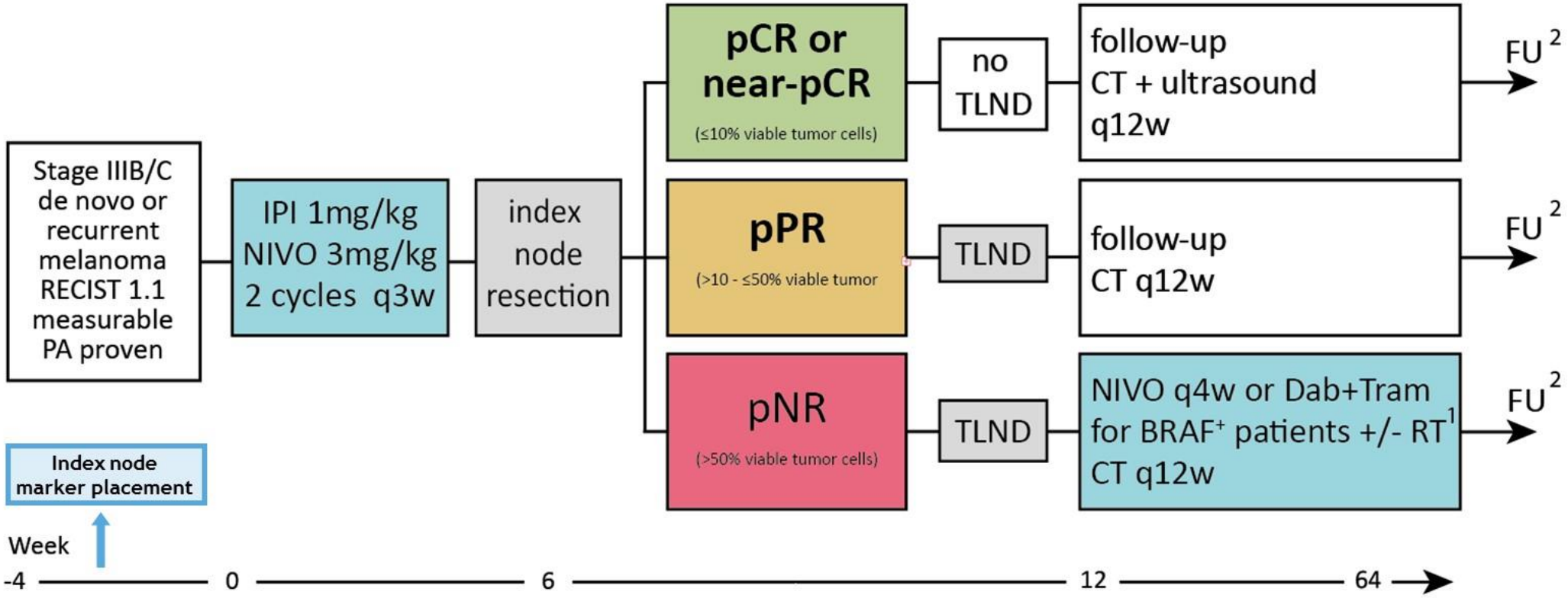
*One patient who achieved a pCR had died due to complications of an immune-related encephalitis without signs of melanoma relapse.

Rozeman. ESMO 2018. Abstr LBA42.

Slide credit: clinicaloptions.com

PRADO: study design

Personalized Response-driven Adjuvant therapy after Combination of Ipilimumab and Nivolumab in stage IIIB/C melanoma



TLND = therapeutic lymph node dissection

1. Adjuvant radiotherapy according to patient's and physician's decision.
2. According to institutes standard.

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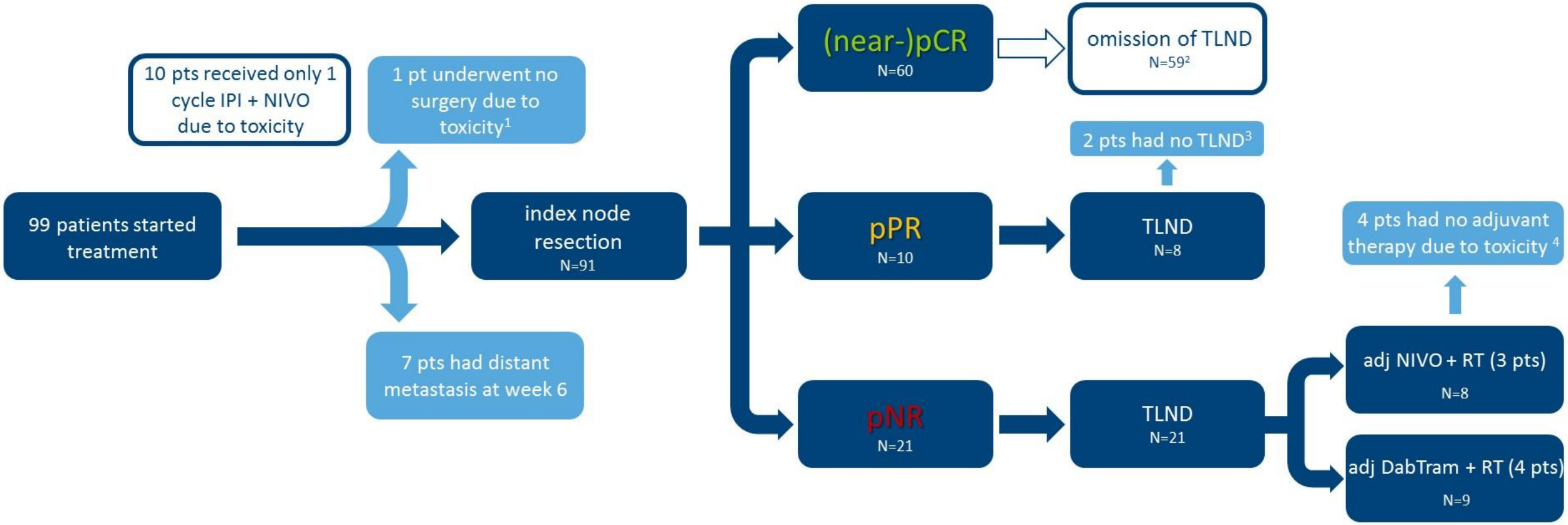
Study profile



Week 0 — 3 — 6 — 9 — 12 →

1. One patient developed a myelitis transversa-like syndrome leading to constipation and colon perforation. This patient had a radiologic response.
2. One patient had surgery despite achieving a near-pCR due to unfavorable pathologic features in the index node.
3. Two patients did not want to undergo a CLND after achieving a pPR.
4. All patients were BRAF wildtype and did not receive adjuvant nivolumab due to an immunotherapy-related colitis, cholangitis, myocarditis and arthritis.

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Baseline characteristics

	Total cohort (n=99)
Age, median (range)	58 (19-85)
Gender, male	65 (66)
WHO PS, 0	
T stage at diagnosis	
T1a/b	
T2a/b	
T3a/b	
T4a/b	
Tx	
Unknown primary	
Positive nodes on baseline PE	
1	
2-3	
>3	
Ulceration, yes	
BRAF V600E/K mutation, posi	

Patients per Institute

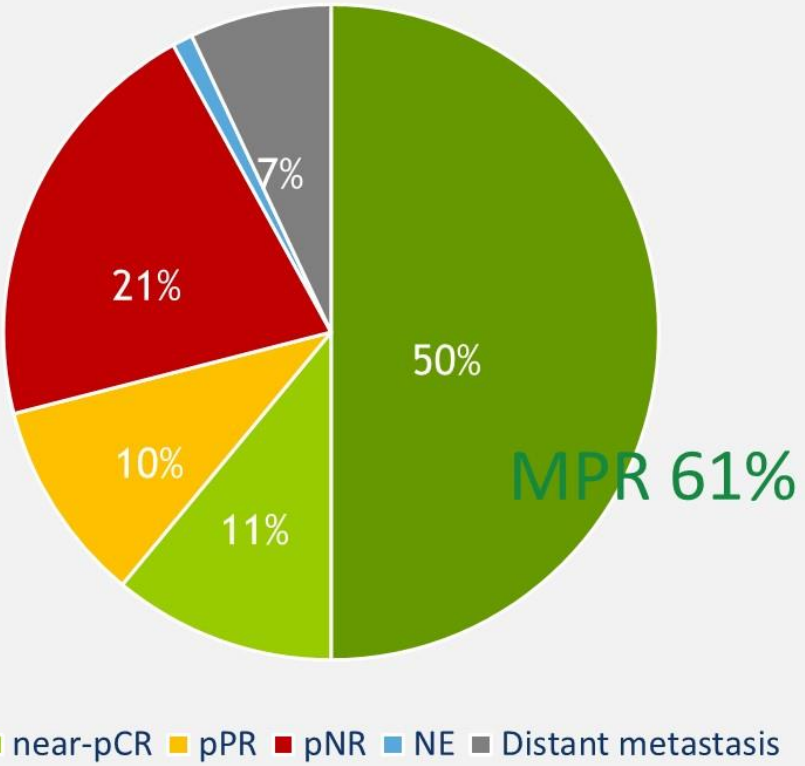
PRADO	Total cohort (n=99) [1]
pRR	70 (71%)
pCR	49 (50%)
Near-pCR	11 (11%)
pPR	10 (10%)
pNR	21 (21%)
Not evaluable [2]	1 (1%)
Distant metastases	7 (7%)

PRADO	Total cohort (n=99)
ORR	45 (45%)
CR	14 (14%)
PR	31 (31%)
SD	38 (38%)
PD	13 (13%)
Not done [1]	3 (3%)

Change from baseline (%)

1. 3 patients did not have a week 6 CT-scan due toxicity.

Pathologic and Radiologic Response



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Immune-related AEs within the first 12 weeks

Adverse event	All grade (%)	Grade 3-4 (%)	Adverse event	All grade (%)	Grade 3-4 (%)
Any adverse event	**96 (97)**	**22 (22)**	Serum lipase increased	8 (8)	3 (3)
Fatigue	54 (55)	–	Dry skin	7 (7)	–
Rash	47 (47)	3 (3)	Fever	7 (7)	–
Pruritus	27 (27)	–	Colitis	6 (6)	4 (4)
Alanine aminotransferase increased	22 (22)	7 (7)	Creatine kinase increased	6 (6)	1 (1)
Hyperthyreoidism	22 (22)	–	Dry eye	6 (6)	–
Diarrhea	21 (21)	5 (5)	Dyspnea	5 (5)	–
Aspartate aminotransferase increased	20 (20)	5 (5)	Serum amylase increased	4 (4)	1 (1)
Nausea	18 (18)	1 (1)	Myocarditis	2 (2)	2 (2)
Dry mouth	16 (16)	–	Ggt increased	2 (2)	1 (1)
Hypothyreoidism	16 (16)	–	Cholangitis	1 (1)	1 (1)
Arthralgia	15 (15)	–	Confusion	1 (1)	1 (1)
Headache	13 (13)	1 (1)	Myelitis transversa-like syndrome	1 (1)	1 (1)
Myalgia	10 (10)	–			
Infusion related reaction	8 (8)	–			

Adverse events that occurred in ≥ 5 patients or were grade 3-4 are displayed in the table

Sadece index lenf nodu prosedürü uygulananlarda yaşam kalitesi skorları daha İYİ

Surgery-related adverse events

p<0.001

	Total cohort (n=96)[1]		Index node procedure only (n=63)[2]		Subsequent TLND (n=31)	
Adverse event	All grade (%)	Grade 3 (%)	All grade (%)	Grade 3 (%)	All grade (%)	Grade 3 (%)
Any adverse event	**52 (54)**	**6 (6)**	**26 (41)**	**–**	**25 (81)**	**6 (19)**
Seroma	30 (31)	–	17 (27)	–	13 (42)	–
Wound infection	11 (11)	3 (3)	4 (6)	–	7 (23)	3 (10)
Lymphedema	7 (7)	–	2 (3)	–	5 (16)	–
Wound dehiscence	6 (6)	–	1 (1)		5 (16)	–
Fever	3 (3)	–	–	–	3 (10)	–
Wound complication	1 (1)	1 (1)	–	–	1 (3)	1 (3)
Difficulty mobilizing	1 (1)	1 (1)	–	–	1 (3)	1 (3)
Dizziness	1 (1)	1 (1)	–	–	1 (3)	1 (3)
Postoperative hemorrhage	1 (1)	1 (1)	–	–	1 (3)	1 (3)

1. One patient did not undergo surgery because of toxicity, 2 patients because of distant metastases.
2. Two patients had an additional small surgery to remove 1-3 lymph nodes and were therefore excluded from the surgical subgroup analysis.

Adverse events that occurred in ≥3 patients or were grade 3-4 are displayed in the table

Summary and conclusion

- PRADO **confirms the high pathologic response rate and safety** observed previously in OpACIN-neo arm B (ipilimumab 1mg/kg + nivolumab 3mg/kg)
  - Pathologic response rate = **71%**
  - Grade 3-4 irAE rate = **22%** in the first 12 weeks
- The radiologic response underestimates the pathologic response, but radiologic assessment has an added value in identifying patients progressing to stage IV disease pre-surgically
- TLND was omitted in 59 (**60%**) patients
- Index lymph node-only surgery reduced the surgical morbidity
  - Surgical-related adverse events in **41%** of patients with index node procedure only versus **81%** in patients with TLND
- Index LN only patients show **higher quality of life scores**
- First EFS and RFS data is planned to be presented at ESMO 2020

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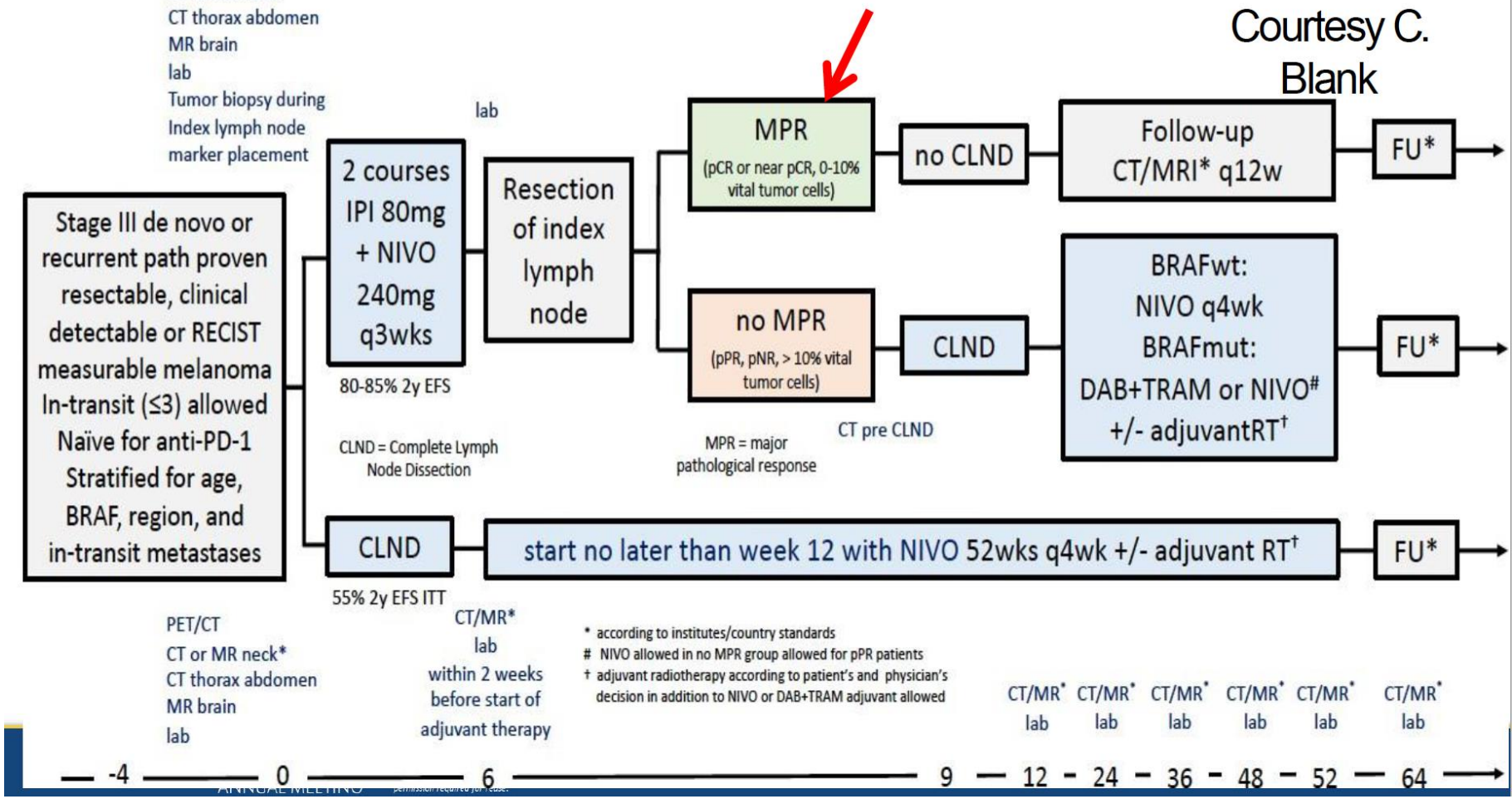
NEO vs ADJ

Phase 3 trial comparing response driven neo-adjuvant combination of ipilimumab + nivolumab versus adjuvant nivolumab (NADINA)

(368 pts, EFS at 2y 60% -> 75%, alpha one sided, 0.05, power 80%)

Courtesy C. Blank



özet

- Historik olarak ele alındığında IFN ve İPİ önemli toksisiteye sahiptir ve hafif RFS ve/veya OS yararı var, klavuzlardan çıkartıldı
- **Nivo>ipi…**RFS'de iyileşme ve daha düşük toksisite
- **Pembro>Plasebo'dan** üstün…RFS
- **Dabrafenib-tremetinib>plasebo'dan** üstün…RFS (BRAF+ hastalarda)
  - Bu 3 tedavi güncel klavuzlarda ktg1 önerilmekte
- Neoadjuvan tedavi; klavuzlarda net öneri yok ama ilgi çeken bir alan.
  - Kombine IO: %40-50 pCR, I1N3 optimal rejim (2-3 kür), pCR olanlarda RFS iyi
  - Nivo monoterapisi .%20 pCR, ancak progresyon riski
  - D+T : pCR:%50