Immunotherapies in melanoma: regulatory perspective

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Challenges for the approval of anti-cancer immunotherapeutic drugs
EMA-CDDF joint meeting, London 4-5 February 2016

disclaimers

- *the views presented are personal and may not be understood or quoted as being made on behalf of or reflecting the position of AEMPS, EMA or one of its committees or working parties*

- *data presented have been sourced from European Public Assessment Reports (EPARs) and published literature*

EU-approved immunotherapies in melanoma

- **ipilimumab:** YERVOY is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults

- **nivolumab:** OPDIVO as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults

- **pembrolizumab:** KEYTRUDA as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults

nivolumab dossier

OPDIVO as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults

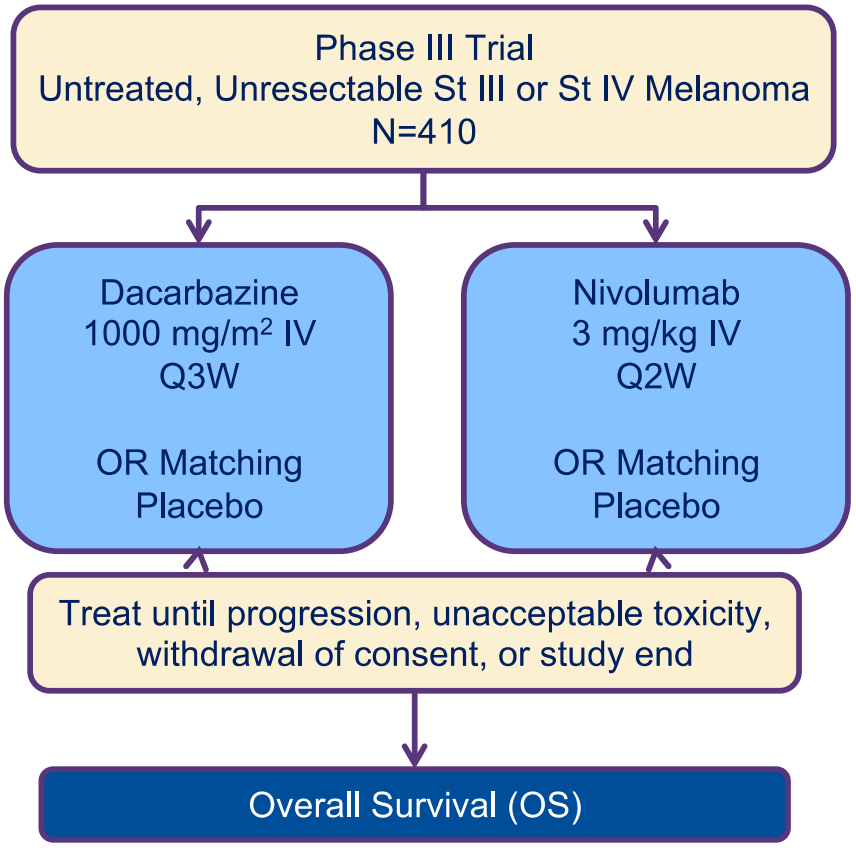
based on 2 pivotal phase 3 RCTs:

- **CheckMate 066**: nivolumab **vs. DTIC** in patients with **previously untreated**, unresectable or metastatic melanoma

- **CheckMate 037**: nivolumab vs. **physician's choice** (DTIC or carboplatin/paclitaxel) in advanced melanoma patients who have **progressed following anti-CTLA-4** therapy

CheckMate 066

Study CA209066: Phase III, Randomized, Double-Blind Study of Nivolumab vs. DTIC in Subjects with Previously Untreated, Unresectable or Metastatic Melanoma



Primary Endpoint

- OS in BRAF wild-type

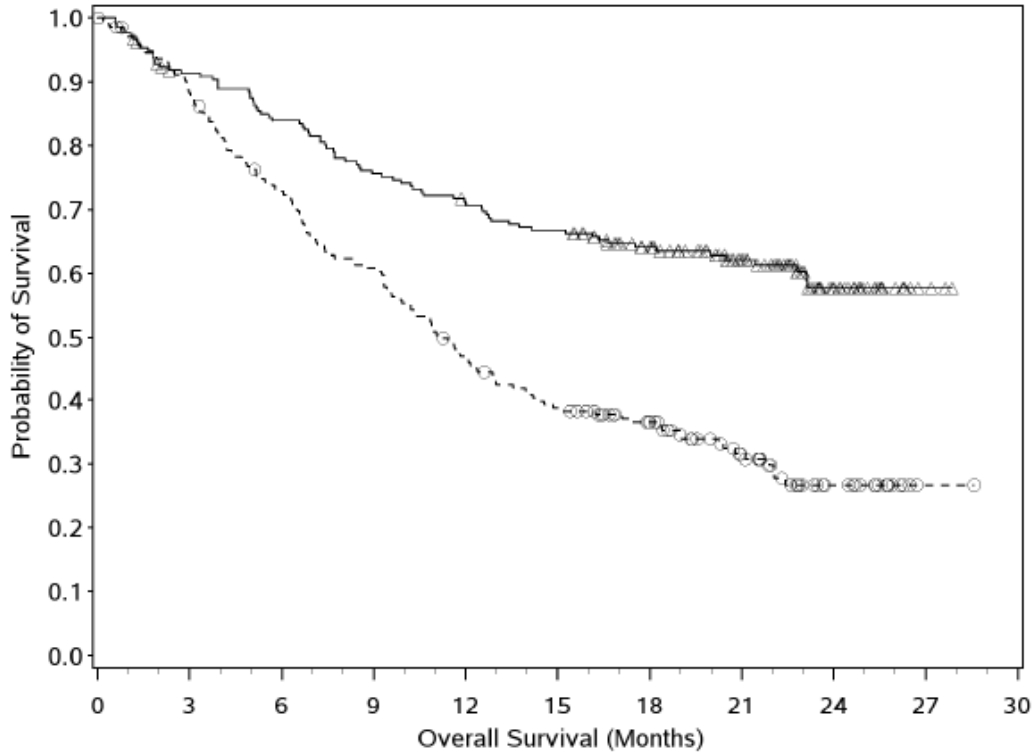
Secondary Endpoints

- PFS
- ORR
- PD-L1 as biomarker
- HRQoL

Key Eligibility Criteria

- Untreated, unresectable St III or St IV melanoma
- ECOG PS ≤1
- Known BRAF wild-type per regionally acceptable mutational status testing
- No identified, indeterminate, or unknown BRAF status
- Tumor tissue from an unresectable or metastatic site

CheckMate 066 (OS)



Number of Subjects at Risk

Nivolumab	210	186	171	154	143	135	111	81	30	4	0
Dacarbazine	208	179	146	122	92	76	60	38	16	1	0

Nivolumab (events : 80/210), median and 95% CI : N.A. (23.13, N.A.)

Dacarbazine (events : 139/208), median and 95% CI : 11.17 (9.56, 12.98)

Hazard Ratio (Nivolumab over Dacarbazine) and 95% CI (1): 0.43 (0.33, 0.57)

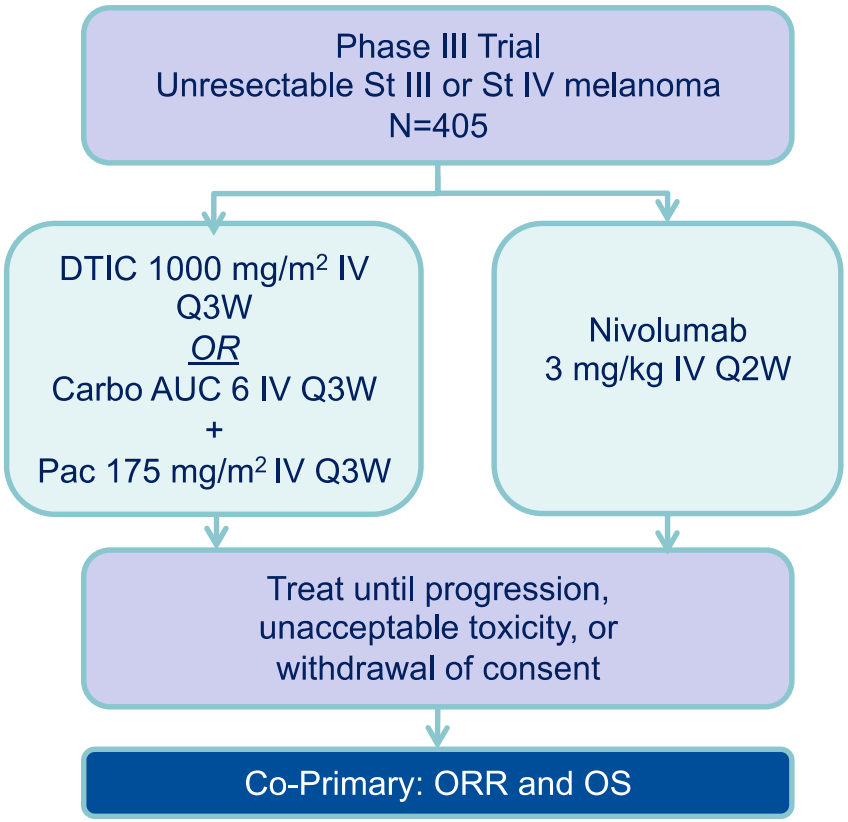
Stratified log-rank p-value: <0.0001

benefit shown vs DTIC

regardless of PD-L1 expression

CheckMate 037

- **Study CA209037: Phase III Study of Nivolumab vs. Physician's Choice (DTIC or Carboplatin/Paclitaxel) in Advanced Melanoma Patients who Have Progressed Following Anti-CTLA-4 therapy**



Co-Primary Endpoints and analysis:

- **ORR (IRC):** 120 nivolumab-treated subjects with a minimum of 6 months follow-up
- **OS:** All patients (286 events) comparative analysis

Secondary Endpoints

- PFS
- PD-L1 as a biomarker
- HRQoL

Key Eligibility Criteria

- Unresectable St III or St IV melanoma
- ECOG PS ≤1
- RECIST defined progression during or after ≤2 prior treatment regimens
  - BRAF WT: progressed post anti-CTLA-4 treatment
  - BRAF V600 Mutation Positive: progressed post-treatment with a BRAF inhibitor in addition to anti-CTLA-4 therapy
- Known BRAF status

* PD-L1 and BRAF status and prior anti-CTLA-4 best response were used as stratification factors

CheckMate 037 (ORR)

	Group A N=120	*Group B* N=47
Best overall response, n (%)		
Complete response (CR)	4 (3.3)	0
Partial response (PR)	34 (28.3)	5 (10.6)
Stable disease (SD)	28 (23.3)	16 (34.0)
Progressive disease (PD)	42 (35.0)	15 (31.9)
Unable to determine (UTD)	12 (10.0)	11 (23.4)
Not reported	0	0
Objective Response Rate (ORR), n (%)	**38 (31.7)**	**5 (10.6)**
95% exact CI[a]	(23.5, 40.8)	(3.5, 23.1)
ORR difference	**21.0**	
95% CI[b]	(6.8, 31.7)	

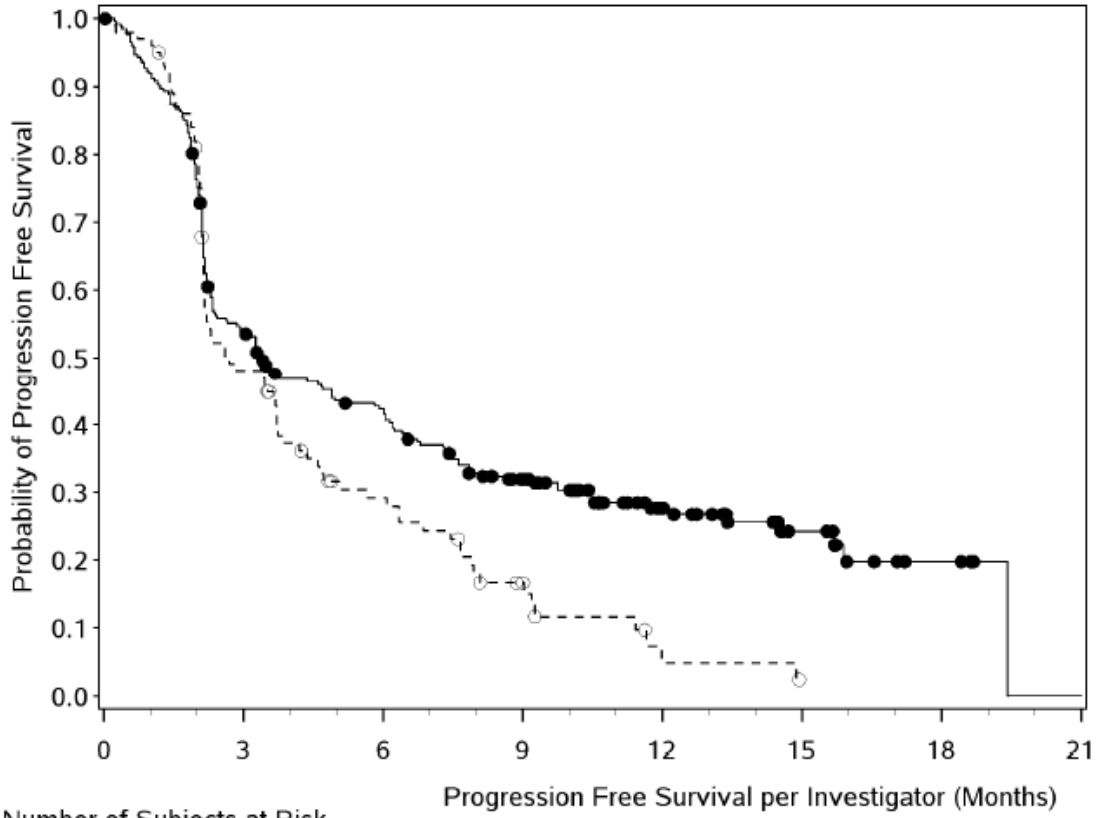
Column header counts and denominators are the number of treated subjects randomized as of 09/10/2013.

a. Clopper-Pearson confidence interval for the overall response rate in the group.

b. Newcombe Score confidence interval for the risk difference between Group A and Group B.

CheckMate 037 (PFS)

Figure 4.3.2-2: Kaplan-Meier Plot of Progression-free Survival per Investigator in All Randomized Subjects - CA209037



Number of Subjects at Risk

NIVOLUMAB							
272	139	103	69	32	14	4	0
INVESTIGATOR'S CHOICE							
133	46	24	11	2	0	0	0

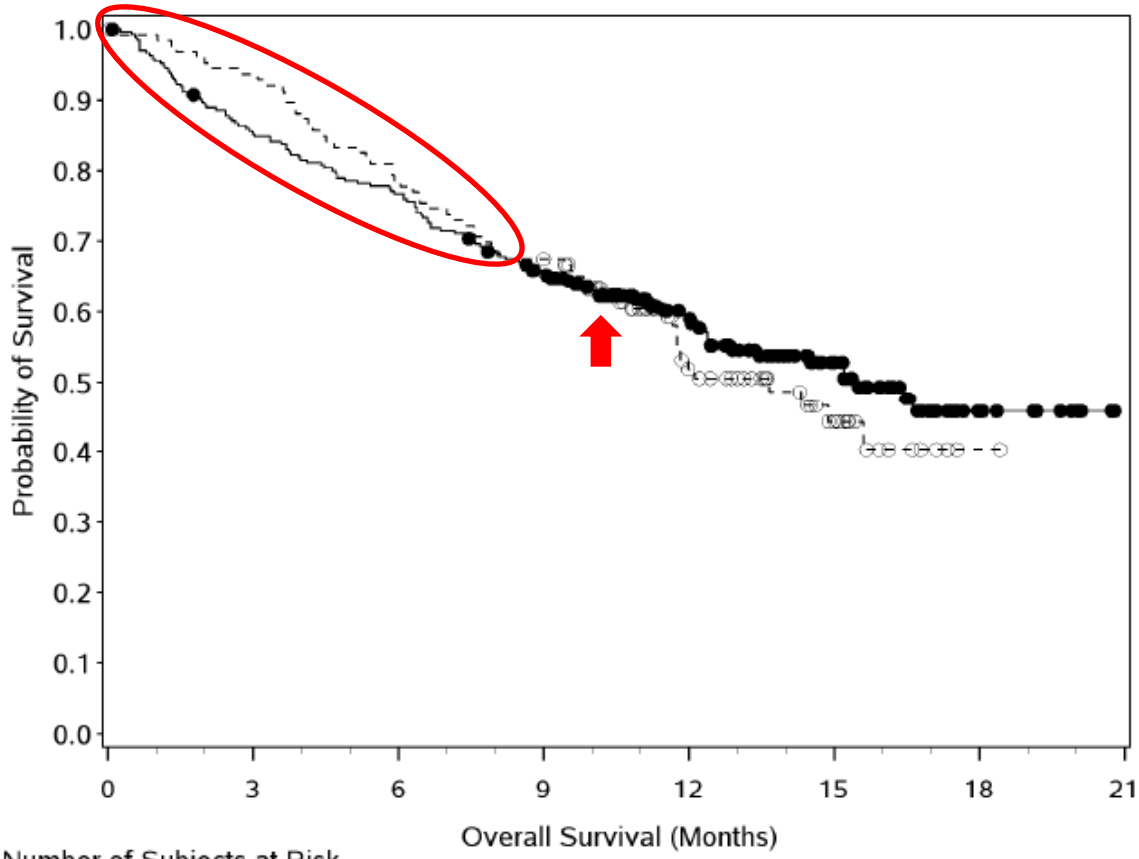
NIVOLUMAB (events : 187/272), median and 95% CI : 3.42 (2.43, 4.90)

INVESTIGATOR'S CHOICE (events : 85/133), median and 95% CI : 2.69 (2.17, 3.71)

Hazard Ratio (NIVOLUMAB over INV CHOICE) and 95% CI (1): 0.74 (0.57, 0.97)

CheckMate 037 (OS IA)

Figure 4.3.1.2-1: Kaplan-Meier Plot of Overall Survival in CA209037



Number of Subjects at Risk

NIVOLUMAB							
272	230	207	173	98	48	11	0
INVESTIGATOR'S CHOICE							
133	118	99	85	40	17	1	0

NIVOLUMAB (events : 121/272), median and 95% CI : 15.47 (12.39, N.A.)

INVESTIGATOR'S CHOICE (events : 61/133), median and 95% CI : 13.67 (11.50, N.A.)

Hazard Ratio (NIVOLUMAB over INV CHOICE) and 95% CI (1): 0.93 (0.68, 1.26)

CheckMate 037

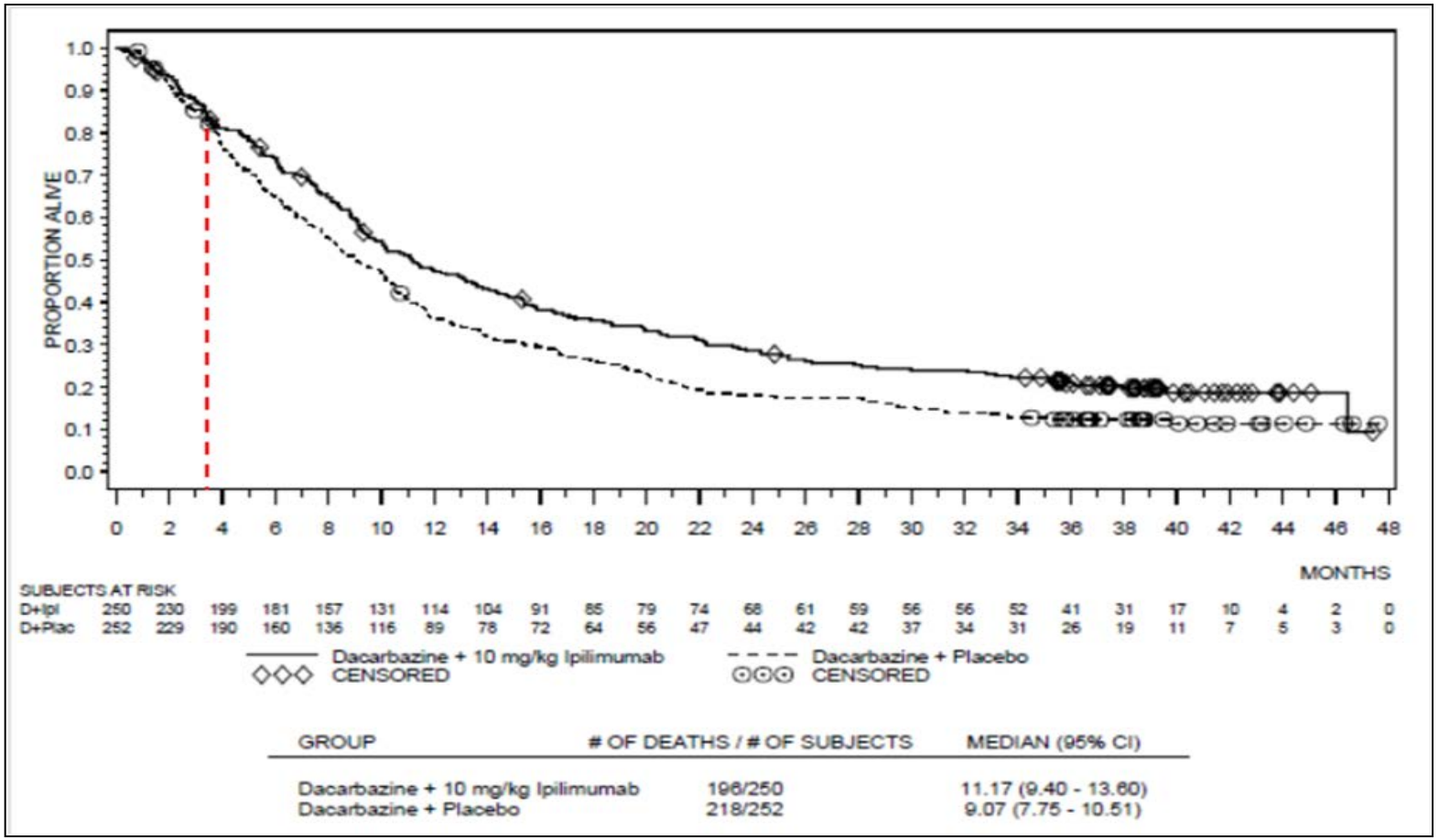
- antitumor activity (ORR)
- PFS benefit
- OS no benefit shown
- > deaths with nivolumab in first 6 months

WHY?

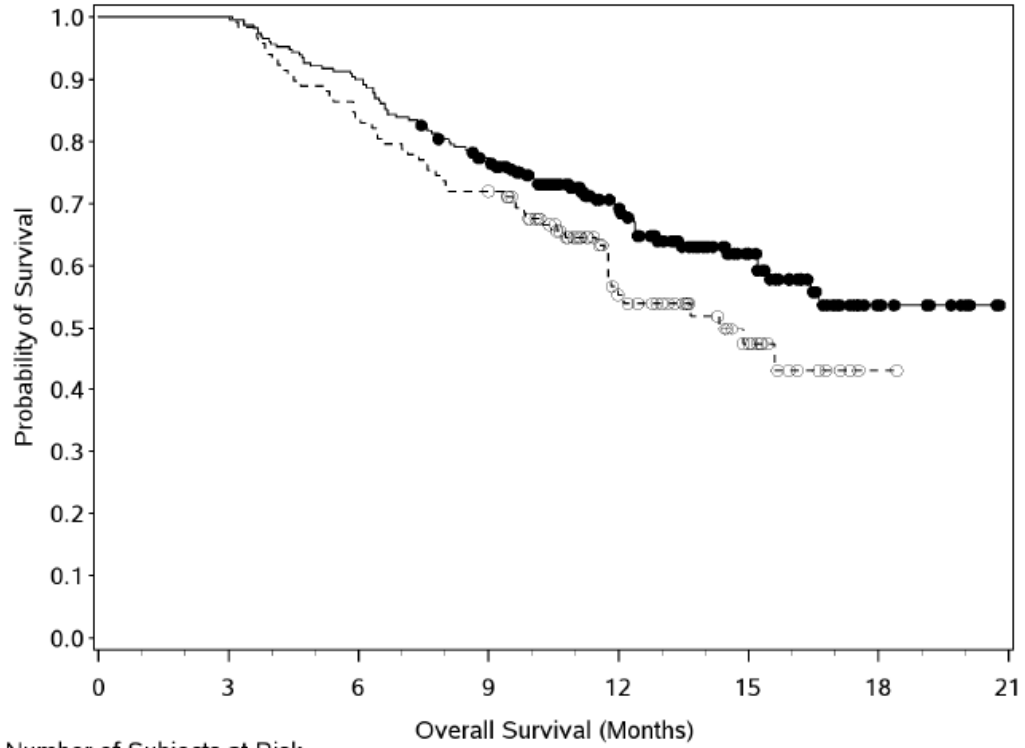
- onset of mechanism of action?
- imbalances in prognostic factors?

Onset mechanism of action

Study CA184024 (Ipi + DTIC vs DTIC)



CheckMate 037



Number of Subjects at Risk

NIVOLUMAB							
230	230	207	173	98	48	11	0
INVESTIGATOR'S CHOICE							
118	118	99	85	40	17	1	0

NIVOLUMAB (events : 81/230), median and 95% CI : N.A. (15.47, N.A.)

INVESTIGATOR'S CHOICE (events : 53/118), median and 95% CI : 14.32 (11.76, N.A.)

Hazard Ratio (NIVOLUMAB over INV CHOICE) and 95% CI (1): 0.69 (0.49, 0.98)

(1) from stratified Cox proportional hazard model using randomized arm as a single covariate.

Symbols represent censored observations.

Program Source: /gbs/prod/clin/programs/ca/209/037/csrfa02/rpt/ema/melanoma/20150325

Program Name: rg-ef-os-v01.sas 26MAR2015: 9:47:37

Kaplan-Meier of OS - all randomized subjects alive at month 3 - Checkmate 037

Prognostic factors

Frequency of death by arm for brain metastases and LDH dichotomised into two groups (0 to ≤ 3 Months and > 3 to ≤ 6 Months) – CheckMate 037

		Treated Subjects who Died ≤ 3 Months				Treated Subjects who Died >3 to ≤ 6 Months				All Randomized Subjects			
Baseline Factor		Nivo N = 38		Inv. Choice N = 5		Nivo N = 23		Inv. Choice N = 17		Nivo N = 272		Inv. Choice N = 133	
		n	%	n	%	N	%	n	%	n	%	n	%
Brain Mets	No	25	66%	4	80%	19	83%	13	76%	217	80%	115	86%
	Yes	13	34%	1	20%	4	17%	4	24%	55	20%	18	14%
LDH Category 1	≤ ULN	10	26%	2	40%	5	22%	8	47%	131	48%	77	58%
	> ULN	28	74%	3	60%	17	74%	9	53%	140	51%	46	35%
	UNK	0	0%	0	0%	1	4%	0	0%	1	0%	10	8%

Abbreviations: Inv = investigator; LDH = lactate dehydrogenase; Mets = metastasis; Nivo = nivolumab; ULN = upper limit of normal; UNK = unknown

- % patients brain mets that die ≤ 3 months: 23.6% vs 5.5% nivo vs chemo
- % patients brain mets that die 3-6 months: 9.5% vs 23.5% nivo vs chemo

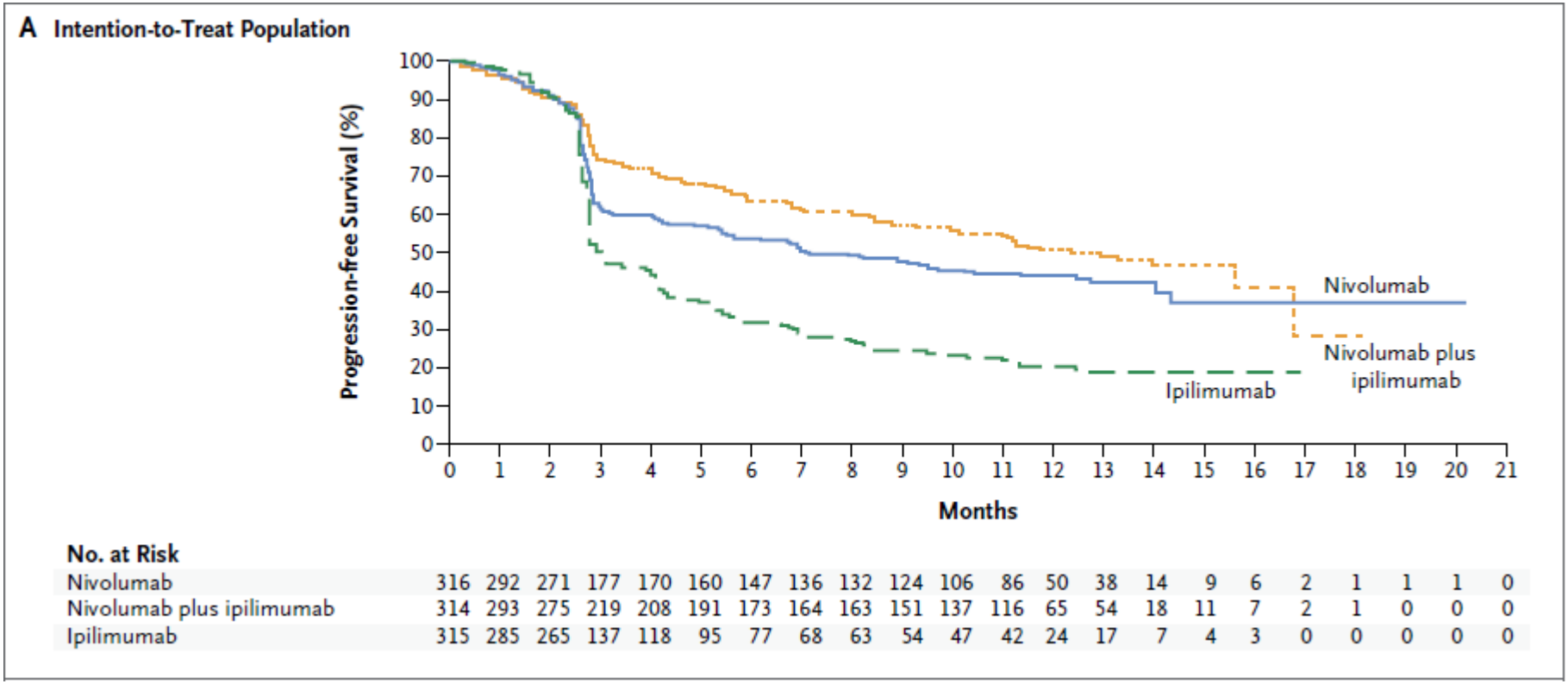
- % patients LDH > ULN that die ≤ 3 months: 20% vs 6.5% nivo vs chemo
- % patients LDH > ULN that die 6-3 months: 15.2% vs 20.9% nivo vs chemo

nivolumab + ipilimumab

- **CheckMate 067**: phase 3 double-blind RCT of **nivolumab or nivolumab + ipilimumab vs. ipilimumab** in subjects with **previously untreated** unresectable or metastatic melanoma

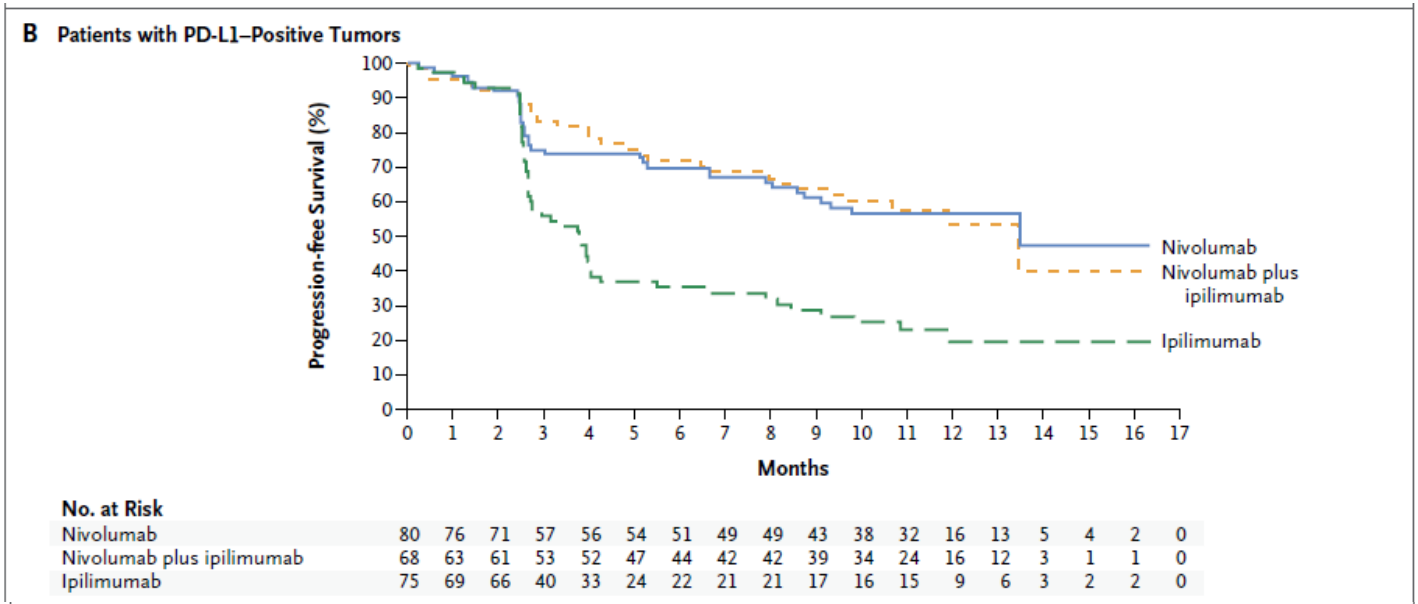
- Study CA209**069**: phase 2 double-blind RCT of **nivolumab + ipilimumab vs. ipilimumab** in subjects with **previously untreated**, unresectable or metastatic melanoma

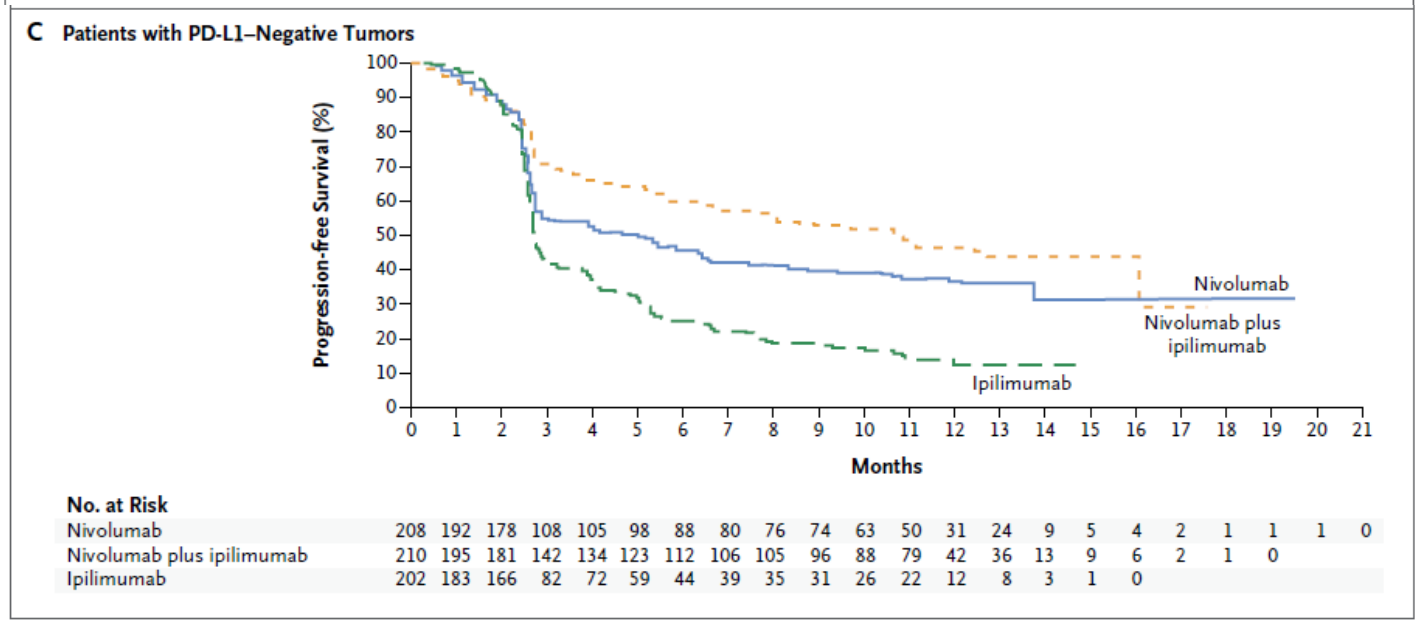
CheckMate 067



Treatment Arm	Median PFS mo (95% CI)	HR (95% CI) vs Ipi	HR (95% CI) vs Nivo
Nivo + Ipi (n = 314)	11.5 (8.9-16.7)	0.42 (0.31-0.57)*	0.74 (0.60-0.92)†
Nivo (n = 316)	6.9 (4.3-9.5)	0.57 (0.43-0.76)*	–
Ipi (n = 315)	2.9 (2.8-3.4)	–	–

PD-L1 expression?





CheckMate 067 (ORR)

PD-L1 Positive			
	Nivolumab alone (N=80)	**Nivolumab plus Ipilimumab (N=68)**	**Ipilimumab alone (N=75)**
Objective response†			
No. of patients (% [95% CI])	46 (57.5 [45.9–68.5])	49 (72.1 [59.9–82.3])	16 (21.3 [12.7–32.3])
Estimated odds ratio (95% CI)§	5.03 (2.44–10.37)	10.41 (4.63–23.40)	---
PD-L1 Negative			
	Nivolumab alone (N=208)	**Nivolumab plus Ipilimumab (N=210)**	**Ipilimumab alone (N=202)**
Objective response†			
No. of patients (% [95% CI])	86 (41.3 [34.6–48.4])	115 (54.8 [47.8–61.6])	36 (17.8 [12.8–23.8])
Estimated odds ratio (95% CI)§	3.25 (2.05–5.13)	5.90 (3.71–9.38)	---

† Best overall response was assessed by the investigators with the use of RECIST v1.1.

§ Relative to ipilimumab alone.

disconnection between ORR and PFS?

Questions to be resolved

1. **Survival benefit in CheckMate 037**
    - Longer survival?
    - PD-L1 expression?
    - Chemotherapy preferable in some patients?

2. **combination ipi + nivo (Checkmate 067)**
    - Better than nivolumab alone?
    - Disconnection ORR-PFS?
    - What about OS?
    - PD-L1 expression as biomarker?

Post-A measures nivolumab

1. Post-authorisation efficacy study (PAES): The MAH should submit the final Study report for study CA209037: a Randomized, Open-Label, Phase 3 Trial of nivolumab vs Investigator's Choice in Advanced (Unresectable or Metastatic) Melanoma Patients Progressing Post Anti-CTLA-4 Therapy.	The final clinical study report should be submitted by 30th June 2016
4. The value of biomarkers to predict the efficacy of nivolumab should be further explored, specifically:	
1. To continue the exploration of the optimal cut-off for PD-L1 positivity based on current assay method used to further elucidate its value as predictive of nivolumab efficacy. These analyses will be conducted in Studies CA 209037 and CA209066 in patients with advanced melanoma.	30th September 2015
2. To further investigate the value biomarkers other than PD-L1 expression status at tumour cell membrane level by IHC (e.g., other methods / assays, and associated cut-offs, that might prove more sensitive and specific in predicting response to treatment based on PD-L1, PD-L2, tumour infiltrating lymphocytes with measurement of CD8+T density, RNA signature, etc.) as predictive of nivolumab efficacy. These additional biomarker analyses are occurring in the context of Study CA209-038 and Study CA209-066.	30th September 2017
3. To further investigate at post-approval the relation between PDL-1 and PDL-2 expression in Phase 1 (CA209009, CA209038 and CA209064).	31st March 2017
4. To further investigate the associative analyses between PDL-1 and PDL-2 expression conducted in Study CA209-066.	31st December 2017
5. To further investigate at post-approval the possible change in PD-L1 status of the tumour during treatment and/or tumour progression in Studies CA209-009, CA209-038 and CA209-064.	30th September 2017

pembrolizumab dossier

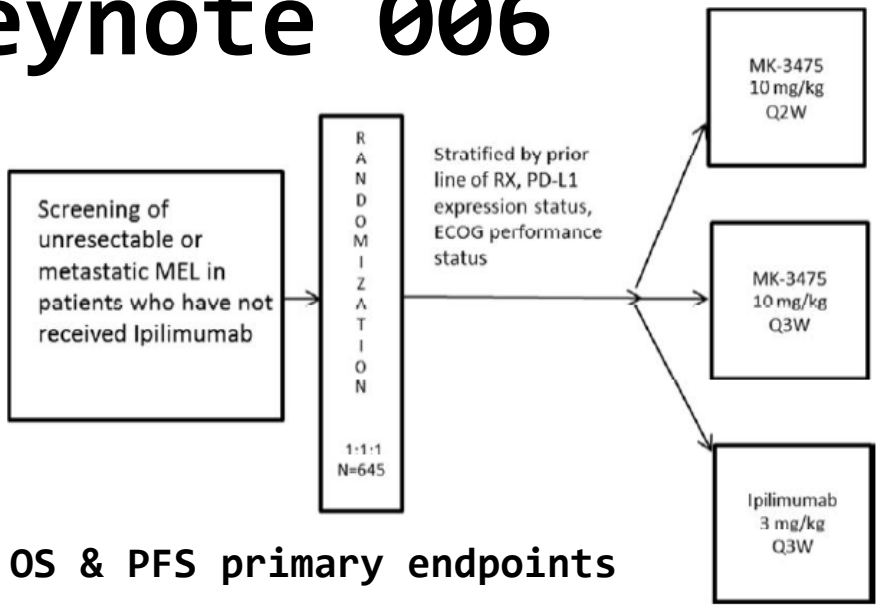
KEYTRUDA as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults

- KEYNOTE-**006**: Phase 3 RCT in **ipilimumab-naïve**, comparing pembro 10 mg/kg **Q2W** vs. pembro 10 mg/kg **Q3W** vs. **ipilimumab**

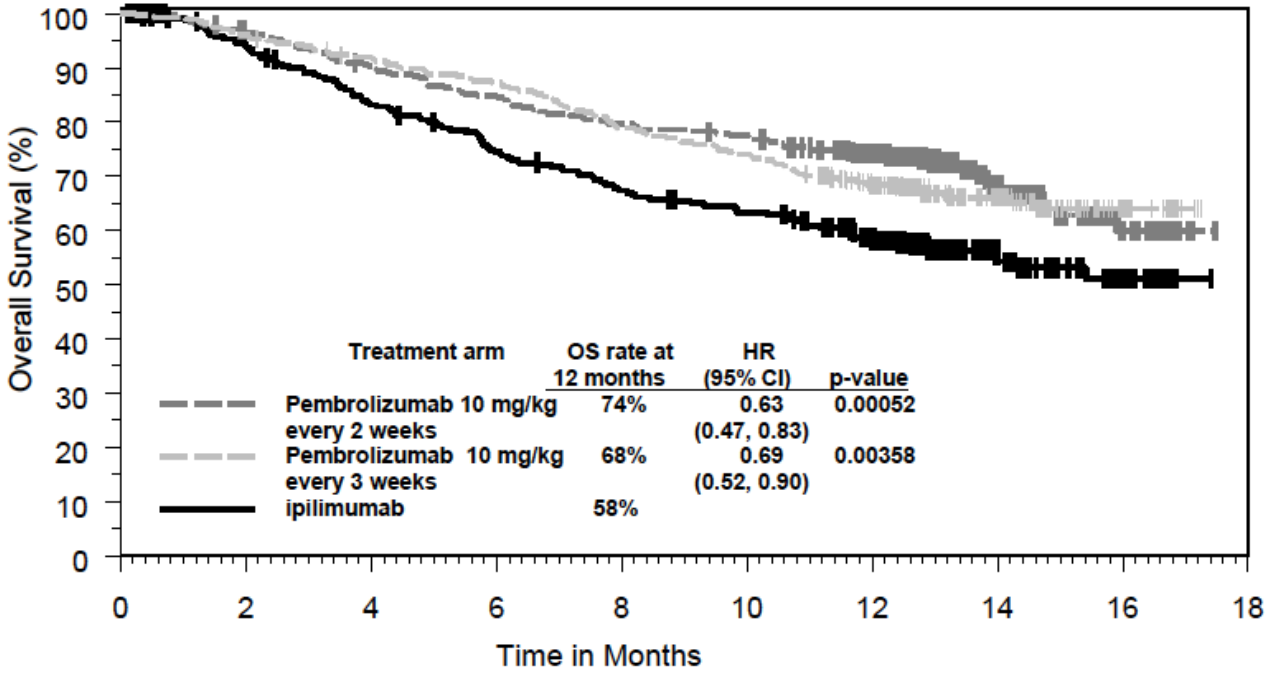
- KEYNOTE-**002**: Phase 2 RCT in **previously treated** (with ipilimumab and if BRAFm+ a BRAFi or MEKi), comparing pembro 2 mg/kg **Q3W** vs. pembro 10 mg/kg **Q3W** vs. **chemo**

- KEYNOTE-**001**: open-label study in naïve and previously-treated with ipilimumab

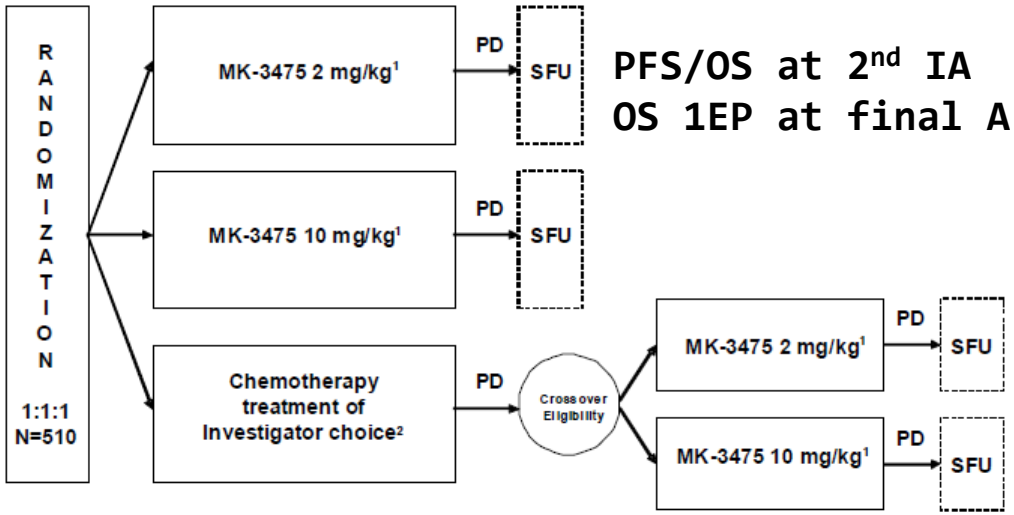
Keynote 006



OS & PFS primary endpoints

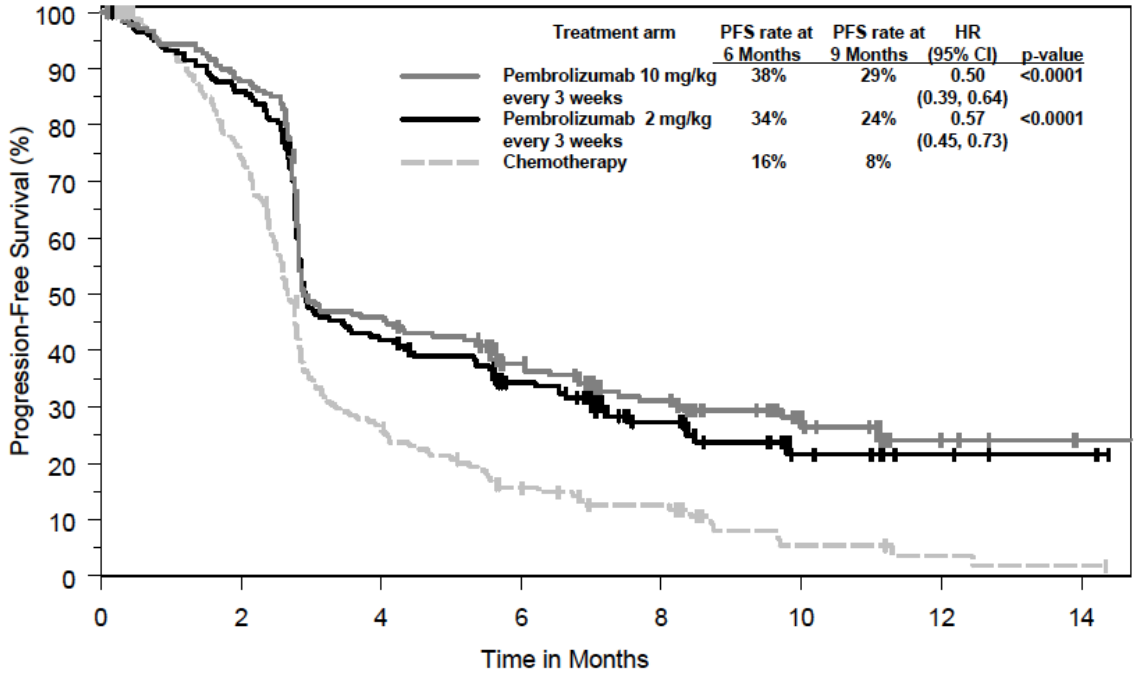


Keynote 002



PFS/OS at 2nd IA
OS 1EP at final A

[1] MK-3475 dose assignments are blinded to Investigators, patients, and Sponsor.
[2] Options: Carboplatin plus Paclitaxel, Carboplatin alone, Paclitaxel alone, Dacarbazine, or Temozolomide
PD = Progressive Disease
SFU = Survival Follow-up
Crossover is permitted at Week 12 or beyond.



PD-L1 expression?

KEYNOTE 006

95% CI

OS
- HR 0.56 (0.43, 0.73) PD-L1+
- HR 0.95 (0.56, 1.62) PD-L1-

PFS
- HR 0.53 (0.43, 0.65) PD-L1+
- HR 0.73 (0.47, 1.11) PD-L1-

ORR
- 37% vs. 12% PD-L1+
- 18% vs. 11% PD-L1-

KEYNOTE 002

95% CI

PFS
- HR 0.52 (0.39, 0.68) PD-L1+
- HR 0.60 (0.38, 0.94) PD-L1-

ORR
- 26% & 23% vs. 4% PD-L1+
- 15% & 11% vs. 8% PD-L1-

Questions to be resolved

1. **Survival benefit in KEYNOTE 002**
   - PD-L1 expression?
   - BRAF status?
   - Optimal dose?

2. **KEYNOTE 006**
   - Final results
   - PD-L1 expression?

Post-A measures

1. Post-authorisation efficacy study (PAES): The MAH should submit the final study report for study P002: Randomized, Phase II Study of MK-3475 versus Chemotherapy in Patients with Advanced Melanoma – Final Study Report	1Q 2017
2. Post-authorisation efficacy study (PAES): The MAH should submit the final study report for study P006: A Multicenter, Randomized, Controlled, Three-Arm, Phase III Study to Evaluate the Safety and Efficacy of Two Dosing Schedules of MK-3475 Compared to Ipilimumab in Patients with Advanced Melanoma – Final Study Report	1Q 2017
3. Post-authorisation efficacy study (PAES): In order to confirm the benefit in BRAF V600 mutant and in PD-L1 negative patient subgroups at the recommended dose, the MAH should provide updated analyses from Study P001 and P002: • Updated efficacy data in subgroups comparing 2 vs 10 mg/kg Q3W from the P002 final analysis. • Efficacy data in subgroups comparing the 2 vs 10 mg/kg Q3W from P001, using the data cut-off date of 18-Oct-2014 from Parts B2 and D of P001 by dose level.	1Q 2017 3Q 2015
4. The value of biomarkers to predict the efficacy of pembrolizumab should be further explored, specifically: Although PD-L1 status is predictive of response in advanced melanoma patients, durable responses have been observed in PD-L1 negative patients. Additional biomarkers other than PD-L1 expression status by IHC (e.g. PD-L2, RNA signature, etc.) predictive of pembrolizumab efficacy should be investigated together with more information regarding the pattern of expression of PD-L1 obtained in the ongoing melanoma studies (P001, P002 and P006): • Comparison between PD-L1 IHC staining in archival tissue vs newly obtained • Comparison of PD-L1 IHC between pre and post treatment tumor tissues • Data on the Nanostring RNA gene signature • IHC staining for PD-L2 • Data on RNA and proteomic serum profiling • Data on Immune cell profiling (peripheral blood)	1Q 2017

Thank you!

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