Title
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Publication Date
2016

DOI
10.1016/j.ejca.2015.09.013

Peer reviewed

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European Journal of Cancer xx (2015) 1–1

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Highlights

- Explorative analysis was performed of survival data from recent clinical trials in metastatic melanoma.
- Survival curves grouped by therapy strategy revealed a very high concordance.
- Kinase inhibitors (BRAF plus MEK) are similarly effective as immune checkpoint blockers (programmed-death-1 plus/minus CTLA-4) with regard to survival.
- Results have to be confirmed by prospective clinical trials including head-to-head comparisons.

http://dx.doi.org/10.1016/j.ejca.2015.09.013

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European Journal of Cancer xx (2015) 1–10

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Review

Survival of patients with advanced metastatic melanoma: The impact of novel therapies

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Received 17 September 2015; accepted 17 September 2015

KEYWORDS
Melanoma;
Therapy;
Kinase inhibitors;
Immune checkpoint blockers;
Survival

Abstract The survival of advanced metastatic melanoma has been greatly improved within the past few years. New therapeutic strategies like kinase inhibitors for BRAF-mutant melanoma and immune checkpoint blockers proved to prolong survival times within clinical trials, and many of them have already entered routine clinical use. However, these different treatment modalities have not yet been tested against each other, which complicate therapy decisions. We performed an explorative analysis of survival data from recent clinical trials. Thirty-five Kaplan–Meier survival curves from 17 trials were digitised, re-grouped by matching inclusion criteria and treatment line, and averaged by therapy strategy. Notably, the

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http://dx.doi.org/10.1016/j.ejca.2015.09.013

Please cite this article in press as: Ugurel S, et al., Survival of patients with advanced metastatic melanoma: The impact of novel therapies, European Journal of Cancer (2015), http://dx.doi.org/10.1016/j.ejca.2015.09.013

survival curves grouped by therapy strategy revealed a very high concordance, even if different agents were used. The greatest survival improvement was observed with the combination of BRAF plus MEK inhibitors as well as with Programmed-death-1 (PD1) blockers with or without cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) blockers, respectively, with these two treatment strategies showing similar survival outcomes. For first-line therapy, averaged survival proportions of patients alive at 12 months were 74.5% with BRAF plus MEK inhibitor treatment versus 71.9% with PD-1 blockade. This explorative comparison shows the kinase inhibitors as similarly effective as immune checkpoint blockers with regard to survival. However, to confirm these first trends for implementation into an individualised treatment of melanoma patients, data from prospective clinical trials comparing the different treatment strategies head-to-head have to be awaited.

1. Introduction

Systemic treatment of advanced metastatic melanoma has been an unmet medical need for decades. Chemotherapy with dacarbazine or other cytotoxic drugs resulted in median survival times of 7–9 months and no therapeutic regimen, either other chemotherapeutic agents, biochemotherapy, or immunotherapy proved to be superior to dacarbazine in terms of survival [1]. In these times, long-term survival of 5 years and more was only achieved in 5–10% of patients regardless of the specific therapy strategy used.

Recently, during the last few years, the treatment of metastatic melanoma has been rapidly evolving. Approximately 40–50% of metastatic cutaneous melanomas harbour a BRAF V600 mutation, constitutively activating the mitogen-activated protein kinase (MAPK) pathway [2]. The BRAF inhibitors vemurafenib and dabrafenib were developed to specifically target this driver mutation and further similar compounds like encorafenib are still under study [3,4]. Another target is the signalling molecule MEK downstream of BRAF, and its blockade can likewise inactivate the MAPK pathway [5]. Both, BRAF and MEK inhibitors showed superior activity in BRAF V600-mutated melanoma in comparison to dacarbazine, and led to a significantly increased progression-free (PFS) and overall survival (OS) in the respective patients. Even more efficacious is the combined inhibition of both targets, BRAF and MEK, and thus a simultaneous application of vemurafenib plus cobimetinib or dabrafenib plus trametinib led to a further prolongation of PFS and OS [6–9].

New immunotherapeutic approaches for metastatic melanoma are another promising approach, which developed simultaneously and in parallel to MAPK pathway inhibitors, resulting in two separate novel treatment strategies. Presently, targeting immune checkpoints, which normally terminate immune responses after antigen activation, is a main focus in the treatment of advanced melanoma. Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) is an immunomodulatory molecule that down-regulates T-cell-activation. Ipilimumab, a fully human monoclonal antibody that blocks CTLA-4 was the first successfully developed drug of a new class of therapeutics named immune checkpoint inhibitors. Long-term survival of up to 20% of treated patients has been reported with ipilimumab [10–12]. Programmed-death-1 (PD1) is another immune checkpoint target expressed on activated T-cells mediating immunosuppression. Its ligands PD-L1 (B7-H8) and PD-L2 (B7-DC) are expressed on many tumour cells, stroma cells and other cell types including leucocytes. The immunosuppressive action of the PD1 receptor is activated in the effector phase of the interaction between T lymphocytes and tumour cells, and the blockade of this receptor seems to be more effective towards T-cell-activation than CTLA-4 blockade. Nivolumab (BMS-936558) is a fully human IgG4 monoclonal antibody directed against PD1. Pembrolizumab (MK-3475) is a selective, humanised monoclonal IgG4-kappa anti-PD1 antibody. The efficacy of both agents was studied in advanced melanoma and other solid tumours [13–15]. Other PD-1 and PD-L1 inhibitors are also under evaluation.

With regard to these new developments in the treatment of advanced melanoma, only few of these therapies have yet been compared to one another, and trials have not yet been conducted to evaluate the optimal sequence of therapies with rigorous, randomised designs. For BRAF-mutant patients, multiple therapy strategies with documented survival improvement exist from which to choose. However, there are no clear data as to which regimen should be administered in the first, second, or even third line, or whether there are patient characteristics or biomarkers helpful for treatment selection.

This work analyses selected clinical trials representative for the new treatment strategies in advanced melanoma and compares their survival outcome by digitisation of published Kaplan–Meier survival curves.

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Only prospective trials with similar inclusion and exclusion criteria were included. Compassionate use programmes were excluded. Data analysis is exploratory, does not include statistical testing, and comparisons are descriptive only. We intended to support current clinical decision-making in the individualised treatment of advanced metastatic melanoma while awaiting the conduct of definitive trials aimed at comparing individual and sequential treatment strategies.

2. Materials and methods

2.1. Search strategy and selection criteria

We searched PubMed from 1st January 2002 to 1st June 2015, with the algorithm "melanoma [Title] AND (vemurafenib OR PLX4032 OR dabrafenib OR GSK-2118436 OR LGX818 OR trametinib OR GSK-1120212 OR cobimetinib OR GDC-0973 OR ipilimumab OR MDX-010 OR tremelimumab OR CP-675,206 OR nivolumab OR MDX-1106 OR pembrolizumab OR MK-3475) AND clinical trial NOT review", and with the algorithm "(BRAF [ti] OR NRAS [ti]) AND melanoma [ti] AND survival", respectively. We also sourced relevant articles referenced by other papers and abstracts from clinical meetings held in the past 10 years. All papers were available in full text and were original articles or conference presentations published in English. Clinical trials included into this explorative survival analysis were phase III trials and large phase-I and -II trials. Only trials investigating therapy strategies of current interest were chosen for this comparison; thus, a clinical trial testing single-agent trametinib was omitted since MEK inhibitor monotherapy currently is not an option for the treatment of BRAF-mutated melanoma [5]. Comparator therapy arms confounded by cross-over to experimental arms were omitted from analysis due to a mixed therapeutic situation.

2.2. Description of survival curves

Kaplan–Meier survival curves for PFS and OS, respectively, were identified from the publications of the selected clinical trials, and subsequently scanned, extracted, and manually digitised using an interactive digitising software (DigitizeIt; http://www.DigitizeIt.de/). This software creates sampling points and allows curve construction by linear interpolation between these points. The accuracy of the manual digitisation depends on the quality of the graphical displays in the respective publications and on the zoom factors necessary for enlarging the displays. This method allows the construct of mean Kaplan–Meier curves by averaging selected groups of individual Kaplan–Meier plots. Weighted averaging is performed point-wise at the sampling points t_k from all individual Kaplan–Meier plots $\widehat{S}_i(t)$ in the group G by weighing with sample sizes n_i:

$$\widehat{S}(t_k) = \frac{\sum_{i \in G} n_i \widehat{S}_i(t_k)}{\sum_{i \in G} n_i}$$

2.3. Description of survival proportions

From each available Kaplan–Meier curve we calculated the proportion of patients free of disease progression at 6 months (6-months-PFS), and alive at 12 months (12-months-OS), respectively. For the estimation of variability we used a formula suggested by Peto [16] for an unbiased approximate estimate for the standard error (SE) for the survival distribution S(t):

$$SE_{Peto}[S(t)] = \left[\frac{S(t)(1-S(t))}{N - C(t)}\right]^{1/2}$$

C(t) equals the number of effectively censored data up to the time point t; N is the number of patients at study start. The empirical SE can be achieved by replacing S(t) by its empirical $\widehat{S}(t)$. A two-sided approximate confidence interval for S(t) can be based on a normal approximation and would thus read

$$\widehat{S}(t) \pm 1.96 \left[\frac{\widehat{S}(t)\left(1-\widehat{S}(t)\right)}{N - C(t)}\right]^{1/2}$$

The number C(t) of censored data at 6 or 12 months, respectively, usually was not explicitly mentioned in the publications of the clinical trials selected for the present study. However, in the published Kaplan–Meier plots the number of patients at risk was provided at the bottom of each plot. These numbers were used for the calculation of variability in survival proportions. In some publications only the patient numbers at 4 and 8, but not at 6 months were given; here we interpolated linearly to estimate the number of patients at risk. The formula for the calculation of an upper boundary for the number of censored data C(t) based on the numbers r(t) at risk when N is the number of patients at study start (t = 6 or 12 months) is

$$N - \frac{r(t)}{\widehat{S}(t)} \geq C(t)$$

Using this approximation one can arrive at an upper bound for the SE

$$SE\left[\widehat{S}(t)\right] \leq \widehat{S}(t) \left[\frac{\left(1-\widehat{S}(t)\right)}{r(t)}\right]^{1/2}$$

This conservative approximation was used for the calculation of confidence intervals for PFS and OS at

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Table 1
Clinical trials testing new agents for the treatment of advanced metastatic melanoma.

Study name, reference and IDs	Phase, therapy line	Therapy arms, agents and dosage	Patient number	Median PFS	HR PFS (95% CI) p-value	% PFS at 6 month[a] (95% CI)	Median OS	HR OS (95% CI) p-value	% OS at 12 month[a] (95% CI)	Comments
Kinase Inhibitors										
Vemurafenib										
BRIM-2	Phase 2	Vemurafenib 960 mg bid	132	6.8 mo	n.d.	55.8 (46.9-64.7)	15.9 mo	n.d.	57.6 (48.9-66.4)	
Sosman 2012 (18) NCT00949702 / NP22657	2nd line									
BRIM-3	Phase 3	Vemurafenib 960 mg bid	337	5.3 mo	0.26 (0.20-0.33) p<0.001	57.1 (51.7-62.5)	[1]13.6 mo	0.37* (0.26-0.55) p<0.001	55.4 (50.0-60.8)	[1]censored at crossover
McArthur 2014 (3;19) NCT01006980 / NO25026	1st line	Dacarbazine 1000 mg/m^2 Q3W	338	1.6 mo		23.3 (18.9-27.6)	[1]9.7 mo	[1]0.70 (0.57-0.87) p=0.0008	46.6 (39.1-54.1)	*confounded by cross-over
Dabrafenib										
BREAK-2	Phase 2	Dabrafenib 150 mg BID	92 ([1]76; [2]16)	[1]6.3 mo [2]4.5 mo	n.d.	45.4 (34.5-56.4)	[1]13.1 mo [2]12.9 mo	n.d.	55.8 (45.0-66.6)	[1]BRAF V600E [2]BRAF V600K
Ascierto 2013 (20) NCT01153763 / 113710	1st / 2nd line									
BREAK-3	Phase 3	Dabrafenib 150 mg BID	187	5.1 mo [1]6.9 mo	0.30 (0.18-0.51) p<0.0001 [1]0.37 (0.23-0.57)	46.2 (33.7-58.8)	not reached [1]18.2 mo	0.61* (0.25-1.48) [1]0.76*	n.a.	*confounded by cross-over [1]updated at ASCO 2014
Hauschild 2012 (4) NCT01227889 / 113683	1st line	Dacarbazine 1000 mg/m^2 Q3W	63	2.7 mo [1]2.7 mo		19.6 (2.4-36.9)	not reached [1]15.6 mo*		n.a.	
Kinase Inhibitor Combinations										
Dabrafenib + Trametinib	Phase 1/2 1st / 2nd line	Dabrafenib 150 mg BID + trametinib 2 mg/d	54	9.4 mo	[1]0.39 (0.25-0.62) p<0.001	72.8 (60.4-85.2)	not reached [2]23.8 mo	n.d. [1,2]0.73* (0.43-1.24) p=0.24	n.a.	*confounded by cross-over [1]dabrafenib versus dabrafenib + trametinib 2mg/d [2]updated at ASCO 2014
Flaherty 2012b (6) NCT01072175 / 113220		Dabrafenib 150 mg BID + trametinib 1 mg/d	54	9.2 mo		64.1 (51.0-77.2)	not reached		n.a.	
		Dabrafenib 150 mg BID	54	5.8 mo		48.8 (35.1-62.5)	not reached [2]20.2 mo*		n.a.	
COMBI-D	Phase 3	Dabrafenib 150 mg BID + trametinib 2 mg/d	211	9.3 mo [1]11.0 mo	0.75 (0.57-0.99) p=0.03 [1]0.67 (0.53-0.84)	69.5 (63.1-76.0)	[1]25.1 mo	0.63 (0.42-0.94) p=0.02 [1]0.71 (0.55-0.92)	74.6 (68.4-80.7)	[1]updated at ASCO 2015
Long 2015 (8;21) NCT01584648 / 115306	1st line	Dabrafenib 150 mg BID + placebo	212	8.8 mo [1]8.8 mo	p<0.001	56.9 (49.9-63.9)	[1]18.7 mo	p=0.011	67.7 (61.2-74.1)	
COMBI-V	Phase 3	Dabrafenib 150 mg BID + trametinib 2 mg/d	352	11.4 mo	0.56 (0.46-0.69) p<0.001	70.5 (65.5-75.4)	not reached	0.69 (0.53-0.89) p=0.005	72.4 (66.5-78.4)	
Robert 2014c (7) NCT01597908 / 116513	1st line	Vemurafenib 960 mg bid	352	7.3 mo		53.6 (48.0-59.2)	17.2 mo		65.1 (58.3-71.9)	
coBRIM	Phase 3	Vemurafenib 960 mg bid + cobimetinib 60 mg/d	247	9.9 mo	0.51 (0.39-0.68) p<0.001	77.3 (70.8-83.7)	not reached	0.65 (0.42-1.00) p=0.046	78.7 (62.7-94.6)	
Larkin 2014b (9) NCT01689519 / GO28141	1st line	Vemurafenib 960 mg bid + placebo	248	6.2 mo		59.3 (51.6-67.0)	not reached		69.5 (53.1-85.9)	

Immune Checkpoint Inhibitors										
Ipilimumab										
Ipilimumab + dacarbazine vs dacarbazine Robert 2011 (11) NCT00324155 / CA184-024	Phase 3 1st line	Ipilimumab 10 mg/kg 4x Q3W + dacarbazine 850 mg/m^2 8x Q3W, thereafter Ipilimumab 10 mg/kg Q3M	250	2.8 mo	0.76 (0.63-0.93) p=0.006	31.7 (25.5-37.8)	11.2 mo	0.72 (0.59-0.87) p<0.001	47.4 (41.1-53.7)	
		Placebo 4x Q3W + dacarbazine 850 mg/m2 8x Q3W, thereafter Placebo Q3M	252	2.6 mo		22.7 (17.3-28.1)	9.1 mo		36.3 (30.3-42.3)	
Ipilimumab vs gp100 Hodi 2010 (12) NCT00094653 MDX010-20 / CA184-002	Phase 3 2nd line	Ipilimumab 3 mg/kg + gp100 vaccine 4x Q3W, thereafter re-induction possible	403	2.8 mo	[1]0.81 p<0.05 [2]0.64 p<0.001	15.8 (12.3-19.2)	10.0 mo	[1]0.68 (0.55-0.85) p<0.001 [2]0.66 (0.51-0.87) p=0.003	42.4 (37.4-47.3)	[1]Ipilimumab + gp100 *versus* gp100 [2]Ipilimumab *versus* gp100
		Ipilimumab 3 mg/kg + Placebo 4x Q3W, thereafter re-induction possible	137	2.9 mo		22.7 (15.7-29.7)	10.1 mo		44.1 (35.5-52.8)	
		Placebo + gp100 vaccine 4x Q3W, thereafter re-induction possible	136	2.8 mo		n.a.	6.4 mo		n.a.	
Tremelimumab										
Tremelimumab vs dacarbazine/temozolomide Ribas 2013 (22) NCT00257205 /A3671009	Phase 3 1st line	Tremelimumab 15 mg/kg 4x Q3M	328	n.d.	n.d.	n.a.	12.6 mo	0.88 p=0.13	52.2 (46.8-57.6)	
		Dacarbazine 1000 mg/m^2 Q3W or temozolomide 200 mg/m^2 d1-5 Q4W	327	n.d.		n.a.	10.7 mo		44.5 (39.2-49.8)	
Nivolumab										
Nivolumab Phase 1 Topalian 2014 (14) NCT00730639 / CA209-003	Phase 1 2nd line	Nivolumab 3 mg/kg Q2W	107	3.7 mo	n.d.	43.6 (33.5-53.8)	16.8 mo	n.d.	61.8 (51.8-71.7)	
CheckMate-066 Robert 2014a (23) NCT01721772 / CA209-066	Phase 3 1st line	Nivolumab 3 mg/kg Q2W + placebo Q3W	210	5.1 mo	0.43 (0.34-0.56) p<0.001	48.2 (40.7-55.7)	not reached	0.42 0.25-0.73 p<0.001	71.9 (60.7-83.0)	
		Placebo Q2W + dacarbazine 1000 mg/m^2 Q3W	208	2.2 mo		18.9 (12.6-25.2)	10.8 mo		41.5 (28.2-54.7)	
Pembrolizumab										
KEYNOTE-001 Robert 2014b (15) NCT01295827 / MK-3475-001	Phase 1 /2 1st / 2nd line	Pembrolizumab 2 mg/kg Q3W	89	5.0 mo	0.84 (0.57-1.23)	47.3 (35.8-58.8)	not reached	n.d.	57.1 (45.8-68.4)	
		Pembrolizumab 10 mg/kg Q3W	84	3.2 mo		38.5 (27.3-49.7)	not reached		63.1 (50.7-75.4)	
KEYNOTE-006 Robert 2015 (24) NCT01866319 / MK-3475-006	Phase 3 1st / 2nd line	Ipilimumab 3 mg/kg 4x Q3W	278	2.8 mo	0.58 (0.46-0.72) p<0.001 (ipilimumab vs pembrolizumab)	26.9 (19.9-33.9)	not reached	n.d.	58.1 (51.2-64.9)	
		Pembrolizumab 10 mg/kg Q2W	279	5.5 mo		47.7 (40.8-54.5)	not reached		73.6 (68.1-79.2)	
		Pembrolizumab 10 mg/kg Q3W	277	4.1 mo		46.6 (39.8-53.5)	not reached		68.3 (62.3-74.3)	
Immune Checkpoint Inhibitor Combinations										
CheckMate-067 Wolchok 2015 (25)	Phase 3 1st line	Nivolumab 3 mg/kg Q2W	313	6.9 mo	[1]0.57 (0.43-0.76) p<0.00001 [2]0.42	52.7 (46.8-58.6)	not reached	n.d.	n.a.	[1]Nivolumab versus

(*continued on next page*)

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Table 1 (*continued*)

Study name, reference and IDs	Phase, therapy line	Therapy arms, agents and dosage	Patient number	Median PFS	HR PFS (95% CI) p-value	% PFS at 6 month[a] (95% CI)	Median OS	HR OS (95% CI) p-value	% OS at 12 month[a] (95% CI)	Comments
NCT01844505 / CA209-067		Ipilimumab 3 mg/kg + nivolumab 1 mg/kg 4x Q3W, thereafter nivolumab 3 mg/kg Q2W	313	11.5 mo	(0.31-0.57) p<0.00001 [3]0.74 (0.60-0.92)	62.8 (57.1-68.5)	not reached		n.a.	Ipilimumab [2]Nivolumab +Ipilimumab versus Ipilimumab
		Ipilimumab 3 mg/kg + placebo 4x Q3W, thereafter placebo Q2W	311	2.9 mo		52.7 (46.8-58.6)	not reached		n.a.	[3]Nivolumab +Ipilimumab versus Nivolumab
CheckMate-069	Phase 2	Ipilimumab 3 mg/kg	95	not	0.40 (0.23-0.68)	67.7	not	n.d.	n.a.	
Postow 2015 (26) NCT01927419 / CA209-069	1st line	+ nivolumab 1 mg/kg 4x Q3W, thereafter nivolumab 3 mg/kg Q2W		reached	P<0.001	(56.4-78.9)	reached			
		Ipilimumab 3 mg/kg + placebo 4x Q3W, thereafter placebo Q2W	47	4.4 mo		31.6 (14.5-48.6)	not reached		n.a.	

Data were taken from publications of the respective clinical trials, besides a. a, proportions of patients free of disease progression at six months, and alive at twelve months, respectively, were calculated from Kaplan-Meier survival curves as described in Materials and Methods. Abbreviations: OS, overall survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; mo, months; n.d., not done and/or not reported in publication; n.a., not applicable.

distinct time points (6 and 12 months, respectively). In cases with more than one Kaplan–Meier curve available for a certain treatment strategy group, separated by first or second line, we also calculated a mean and confidence interval according to the random effects assumption [17].

3. Results

3.1. Explorative analysis of survival outcomes

Thirty-five Kaplan–Meier curves for either PFS or OS or both were available from the publications of 17 clinical trials selected by the above mentioned criteria (Table 1 and Supplementary Table 1) [3,4,6–9,11,12,14,15,18–26]. After digitisation, the survival curves were newly grouped and displayed by treatment line (first-line versus second or later lines) and therapy strategy (chemotherapy, single-agent BRAF inhibitor therapy, combination BRAF plus MEK inhibitor therapy, CTLA-4 inhibitor therapy, PD1 inhibitor therapy, combination CTLA-4 plus PD1 inhibitor therapy), respectively (Supplementary Figs. 1 and 2), to allow a head-to-head explorative comparison. Trials including first- as well as second-line therapy were grouped as second-line trials.

Grouping of digitised Kaplan–Meier survival curves by therapy strategy showed a high concordance between the single survival curves within each group (Supplementary Figs. 1 and 2). This high concordance was found even in therapy strategy groups containing different agents, e.g. for CTLA-4 inhibitors (ipilimumab, tremelimumab), PD1 inhibitors (nivolumab, pembrolizumab), and BRAF inhibitors (vemurafenib, dabrafenib), respectively. Weighted averaging of survival curves was performed within each group as described above and displayed separately for first-line therapies as well as for later therapy lines (Fig. 1). For first-line therapy strategy groups, averaged survival proportions (percentages of PFS at 6 months and OS at 12 months, respectively) were calculated and displayed in Supplementary Table 2.

3.2. Survival with MAPK pathway inhibitors

Mean survival curves obtained by weighted averaging revealed the combination treatment with BRAF plus MEK inhibitors clearly superior to BRAF inhibition alone in first-line treatment PFS and OS as well as in second-line or later PFS (Fig. 1A–C). The proportions of patients free of disease progression at 6 months were 71.6% with BRAF plus MEK inhibition compared to 56.0% with BRAF inhibition alone; the proportions of patients alive at 12 months were 74.5% compared to 64.4% (Supplementary Table 2). Second-line or later OS data for BRAF plus MEK inhibitor combination

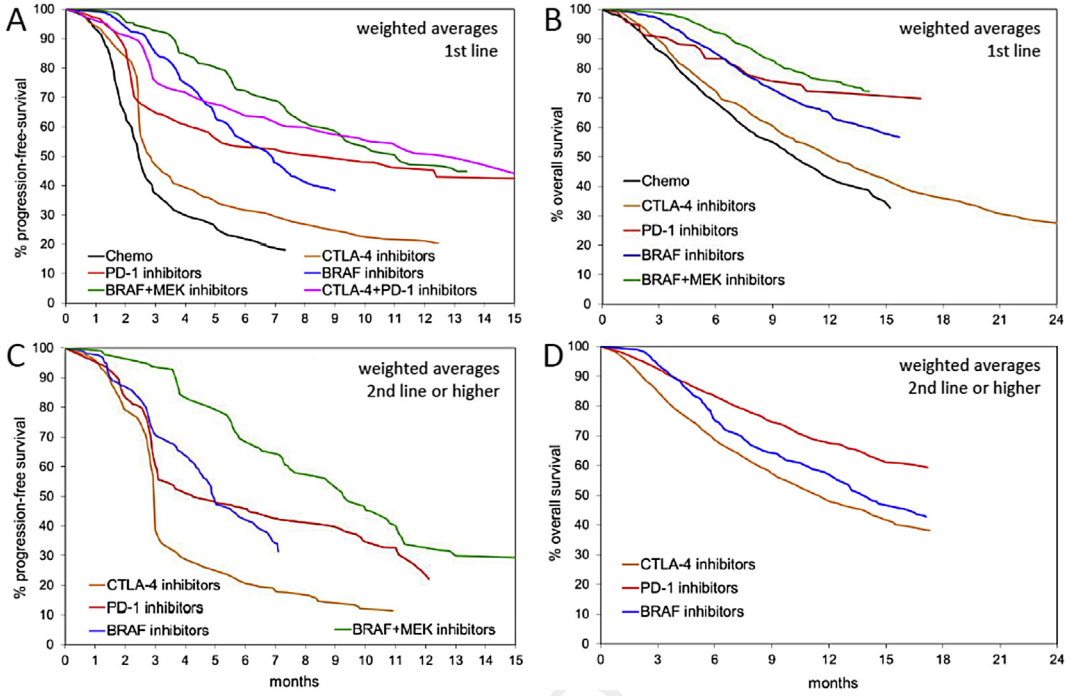

Fig. 1. Mean survival curves created by weighted averaging of digitised Kaplan–Meier survival curves of melanoma patients treated in selected clinical trials. Weighted averaging was performed as described in Materials and methods, and displayed by therapy strategy (chemotherapy, single-agent BRAF inhibitor therapy, combination BRAF plus MEK inhibitor therapy, CTLA-4 inhibitor therapy, PD1 inhibitor therapy, combination CTLA-4 plus PD1 inhibitor therapy) as PFS (A, C) and OS (B, D), in first-line (A, B) and second or later lines (C, D), respectively. PFS, progression-free survival; OS, overall survival; CTLA-4, cytotoxic T-lymphocyte-associated antigen-4; PD1, programmed-death-1.

therapy were not available at the time point of this analysis (Fig. 1D). BRAF inhibitor monotherapy led to better survival outcomes than chemotherapy in first-line treatment PFS (proportions of patients free of disease progression at 6 months 56.0% versus 22.1%; Supplementary Table 2) and OS (proportions of patients alive at 12 months 64.4% versus 42.2%; Supplementary Table 2) (Fig. 1A, B). In second-line or later therapy settings no chemotherapy arms were used in recent clinical trials; thus no survival data were available for the PFS and OS explorative analysis (Fig. 1C, D).

3.3. Survival with immune checkpoint blockers

PD-1 inhibitors revealed a better survival outcome than CTLA-4 inhibitors in all therapy settings, first-line PFS and OS as well as second-line or later PFS and OS, as obtained by weighted averaging (Fig. 1A–D). For the first-line setting, the proportions of patients free of disease progression at 6 months were 51.0% with PD-1 inhibitors compared to 31.0% with CTLA-4 inhibitors; the proportions of patients alive at 12 months were 71.9% compared to 50.1% (Supplementary Table 2). PD-1 plus CTLA-4 inhibitor combination therapy showed better survival data than PD-1 inhibitors alone in first-line PFS (proportions of patients free of disease progression at 6 months 63.8% versus 51.0%, Supplementary Table 2; Fig. 1A). For all other therapy settings up to now no survival data have been available for this combination (Fig. 1B–D). CTLA-4 inhibition resulted in an improved survival compared to chemotherapy, at least for first-line treatment PFS and OS (Fig. 1A, B). The proportions of patients free of disease progression at 6 months were 31.0% with CTLA-4 inhibition versus 22.1% with chemotherapy; the proportions of patients alive at 12 months were 50.1% versus 42.2% (Supplementary Table 2). For the second-line setting, no survival data under chemotherapy were available (Fig. 1C, D).

3.4. Comparison of survival with MAPK pathway inhibitors and immune checkpoint blockers

In first-line therapy, weighted averaging revealed superior survival curves for the MAPK pathway blockade with BRAF plus MEK inhibitor combination therapy compared to immune checkpoint blockade with PD-1 inhibitors alone (PFS, OS; Fig. 1A, B) or in combination with CTLA-4 (PFS; Fig. 1A). The proportions of patients free of disease progression at 6 months were 71.6% with BRAF plus MEK inhibition compared to 63.8% with CTLA-4 plus PD-1 inhibition and 51.0% with PD-1 inhibition alone, respectively (Supplementary Table 2). This superiority of BRAF plus MEK

Please cite this article in press as: Ugurel S, et al., Survival of patients with advanced metastatic melanoma: The impact of novel therapies, European Journal of Cancer (2015), http://dx.doi.org/10.1016/j.ejca.2015.09.013

inhibition versus immune checkpoint blockers is clearly visible during the first year after onset of treatment, thereafter curves are crossing and the survival outcomes of these treatment strategies roughly equal. Accordingly, the proportions of patients alive at 12 months were 74.5% with BRAF plus MEK inhibitor treatment versus 71.9% with PD-1 blockade (Supplementary Table 2).

In the second-line setting, weighted average PFS curves revealed a superiority of BRAF plus MEK inhibitor combination therapy compared to PD-1 inhibition (Fig. 1C). For OS in this setting, up to now no data are available for the combination therapy (Fig. 1D). Survival under BRAF inhibitor monotherapy was superior to that under CTLA-4 inhibition. This difference in survival was more obvious in the first-line setting (Fig. 1A, B) than in the second or later lines (Fig. 1C, D). PFS and OS under BRAF inhibitor monotherapy is superior to that under PD-1 inhibitor therapy within the first 6 months of first-line therapy (Fig. 1A, B). After this time period, survival curves cross, and PD-1 inhibitor therapy reveals a better long-term survival compared to BRAF inhibition. In the second-line or later setting, weighted average survival curves of both treatment strategies, BRAF and PD-1 inhibitor monotherapy, run equally during the first 3–6 months of treatment (Fig. 1C, D). Thereafter, PD-1 inhibition clearly shows superior long-term survival in both, PFS and OS, as compared with single-agent BRAF inhibition.

4. Discussion

A tremendous improvement in the survival of advanced metastatic melanoma patients has been achieved by the recently developed therapy strategies of kinase inhibitors as well as immune checkpoint blockers. In this regard, combination regimens of BRAF and MEK inhibitors proved to be superior to single-agent regimens with BRAF inhibitors. Within the group of immune checkpoint blockers, the first head-to-head comparative trials (KEYNOTE-006; CheckMate-067) demonstrated the PD-1 inhibitors to prolong survival as compared to CTLA-4 inhibition with ipilimumab [24]. Moreover, for PFS the combination treatment with PD1 inhibitors plus ipilimumab tends to be superior to PD1 inhibition alone, at least in certain patient subgroups (CheckMate-067; CheckMate-069) [26]. For OS there are no data yet available for evaluation.

However, there still are no data available from clinical trials testing BRAF and/or MEK inhibitors head-to-head with checkpoint blockers. In this regard, our presentation of Kaplan–Meier survival curves grouped by matching inclusion criteria, and superimposed by weighted averaging shows clear and informative trends. Using this methodology, we found that the combination of BRAF plus MEK inhibitors provides very similar results in terms of survival as PD1 inhibition as a single-agent or in combination with ipilimumab. These two treatment strategies, BRAF plus MEK inhibition and PD1 plus or minus CTLA-4 inhibition, were superior to all other therapy modalities investigated. Interestingly, this superiority became evident in PFS and OS in the first-line as well as in second and later-line settings. The second best survival curves resulted from single-agent BRAF inhibitor therapies, which were clearly inferior to BRAF plus MEK inhibitor combinations, and also to PD1 inhibitors, respectively. The poorest survival was observed with single-agent ipilimumab and with any type of chemotherapy, respectively, with ipilimumab showing slightly better results than chemotherapy.

Importantly, due to the rapid development of new therapeutics, times of study conduct are of high probability to impact survival outcomes in melanoma patients. In specific, the availability of subsequent treatments which could prolong OS differed during the last years; e.g. many BRAF inhibitor trials were conducted before PD1 blockers became available. It should also be noted, that long-term follow-up data are only available for ipilimumab to indicate that the same 20% of patients alive at 3 years are alive at 5 years and beyond [10]. This longevity of benefit has yet to be established for PD-1 or BRAF inhibitor-based treatments. Since the clinical use of ipilimumab started much earlier than that of PD1 blockers, long-term survival data for anti-PD1 of 3 years and longer are not yet available.

Finally, it should be noted, that the results of this descriptive comparative analysis have to be interpreted with caution. In general, the inclusion criteria of the different trials were similar (no active or untreated brain metastases, no ocular primary, ECOG performance state 0 or 1), Supplementary Table 1. However, differences in these criteria were present, such as a different definition of brain metastasis control or the possibility to treat beyond progression. These deviations between trials may have led to different patient selections, and thus may have influenced patient's survival outcomes. Additionally, the percentages of patients with poor prognostic markers like elevated serum LDH, impaired overall performance status, or higher M category, differed significantly between trials even if their inclusion criteria were similar (Supplementary Table 1). Due to the descriptive nature of the comparisons done by us, no statistical tests were applied.

The conclusions drawn from clear differences between survival curves resulting from different treatment strategies allow a first preliminary transfer into the routine clinical setting of decision-making in advanced metastatic melanoma patients. Notably, the survival curves taken from single clinical trials and grouped by

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distinct therapy strategies revealed a very high concordance, even if different agents were used. However, to confirm these first trends for implementation into an individualised treatment of melanoma patients, data from prospective clinical trials comparing the different treatment strategies head-to-head have to be awaited. From our perspective, this explorative comparison showing the combination of BRAF and MEK kinase inhibitors as similarly effective as PD1 immune checkpoint blockade towards survival, although of limited validity, highlights the good performance of the targeted therapy approach based on BRAF kinase inhibitors in advanced melanoma. This is of special importance in the current times where immunotherapy dominates the therapeutic field of advanced melanoma.

Authors' contributions

Selma Ugurel: literature search, figures, data analysis, data interpretation, writing.
Joachim Röhmel: figures, data analysis, data interpretation, writing.
Paolo A. Ascierto: data interpretation, writing.
Keith T. Flaherty: data interpretation, writing.
Jean Jacques Grob: data interpretation, writing.
Axel Hauschild: data interpretation, writing.
James Larkin: data interpretation, writing.
Georgina V. Long: data interpretation, writing.
Paul Lorigan: data interpretation, writing.
Grant A. McArthur: data interpretation, writing.
Antoni Ribas: data interpretation, writing.
Caroline Robert: data interpretation, writing.
Dirk Schadendorf: data interpretation, writing.
Claus Garbe: literature search, figures, data analysis, data interpretation, writing.

Conflict of interest statement

Selma Ugurel: relevant financial activities (Medac, BMS, Merck, Roche).
Joachim Röhmel: none.
Paolo A. Ascierto: relevant financial activities (BMS, Roche, Merck, Ventana, Amgen, Novartis).
Keith T. Flaherty: relevant financial activities (BMS, Merck, Novartis, Roche).
Jean Jacques Grob: relevant financial activities (BMS, Merck, Novartis, Roche).
Axel Hauschild: relevant financial activities (Amgen, BMS, Celgene, Eisai, GSK, MedImmune, Mela Sciences, Merck, Novartis, OncoSec, Roche).
James Larkin: relevant financial activities (BMS, Merck, Novartis, Roche).
Georgina V. Long: relevant financial activities (Amgen, BMS, GSK, Novartis, Merck, Roche, Provectus).
Paul Lorigan: relevant financial activities (BMS, Merck, Novartis, Roche).
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Caroline Robert: relevant financial activities (Roche, GSK, Novartis, Amgen, BMS and Merck).
Dirk Schadendorf: relevant financial activities (Roche, GSK, Novartis, BMS, Merck, Amgen, Boehringer Ingelheim, Leo).
Claus Garbe: relevant financial activities (Roche, GSK, Novartis, BMS, Merck).

Role of the funding source

No funding source to declare.

Ethics committee approval

Not applicable.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejca.2015.09.013.

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