An integrated view on assuring quality for multimodal therapy in oncologic care

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5 Early switching of targeted therapy to immunotherapy; the road to long-term survival in LDH elevated advanced melanoma patients?

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ABSTRACT

Background: The clinical outcomes of advanced BRAF-mutant melanoma patients with elevated serum lactate dehydrogenase (LDH) remain very poor. The aim was to explore whether patients with normalized LDH after targeted therapy could benefit from subsequent immunotherapy.

Methods: Data from all BRAF-mutant metastatic melanoma patients with an initial elevated serum LDH (≥ 2x above the upper limit of normal) receiving first-line targeted therapy between 2012 and 2017 in The Netherlands were prospectively collected. Patients were stratified according to response status to targeted therapy and change of LDH at start of subsequent immunotherapy. Differences in overall survival (OS) between the subgroups were compared using log-rank tests.

Results: After a median follow-up of 22.1 months, median OS of the total study population (N=270) was 4.7 months (95% CI 4.3– 5.1). Of all patients receiving subsequent immunotherapy (N=65), survival from start of subsequent immunotherapy was significantly longer in patients who had normalized LDH and were still responding to targeted therapy compared to those with LDH that remained elevated (median OS not reached vs 0.9 months).

Conclusions: Introducing immunotherapy upon response to targeted therapy with normalization of LDH could be an effective strategy in obtaining long-term survival in metastatic melanoma patients with elevated serum LDH.

INTRODUCTION

Multiple effective systemic treatment options have emerged for patients with advanced BRAF-mutant melanoma over the last decade. Since the approval of the BRAF inhibitor vemurafenib [1] and the CTLA-4 antibody ipilimumab [2], combination therapy with a BRAF and MEK inhibitor [3] and treatment with anti-PD-1 antibodies as monotherapy [4] [5] or combined with a CTLA-4 antibody [6] have broadened the therapeutic arsenal for these patients. Combination therapy with a BRAF and MEK inhibitor has resulted in a median overall survival of over 2 years [7], while treatment with anti-PD-1 also concurrently showed significant improvements with 2-year survival rates of 55-58% [8]. Although long-term survival may be achieved in a subgroup of patients, there is still an unmet medical need for patients with unfavourable prognostic factors [9][7]. Elevated serum lactate dehydrogenase (LDH) level is a well-known marker for poor outcome and a strong negative predictor for response to immunotherapy and targeted therapy [7][8]. In previous reports substantially less activity was demonstrated in patients with elevated serum LDH of ≥2x upper limit of normal (ULN), with a median OS of 2.9 months after ipilimumab therapy [9] and 2.3 months after anti-PD1 therapy [10] compared to 14.7 months and 16.1 months for patients with normal LDH, respectively. Similarly, LDH has been shown to be one of the key predictors of survival for patients receiving targeted therapy [11]. Although the majority of BRAF mutant patients with elevated serum LDH respond to targeted therapy, responses are usually short-lived, with median progression-free survival shorter than 6 months for patients with LDH ≥2xULN compared to 17 months for the patients with normal LDH [7].

Targeted therapies are capable of inducing rapid anti-tumour responses associated with a decrease in LDH [7], which might enable immunotherapy to work more efficiently in patients with initial elevated serum LDH. Furthermore, BRAF and MEK-inhibition could facilitate immune responses in multiple ways. Preclinical data showed an increase in CD8+ T-cell recognition of tumour cells by inducing rapid upregulation of MHC class I surface expression in BRAF-mutant melanoma cells [12] [13]. These data support the potential of BRAF-inhibition to increase response rates to immunotherapy. Although this concept seems promising, clinical data supporting the approach of BRAF inhibitor induction treatment preceding immunotherapy in

patients with aggressive disease are lacking and little is known about which patients could benefit from induction treatment.
This prospective population-based study focuses on the clinical outcomes of BRAF mutant metastatic melanoma patients with baseline serum LDH of ≥2x ULN treated with first-line targeted therapy. The main objective of the study was to investigate whether the level of LDH and response status at the switch to immunotherapy was associated with survival.

METHODS

Data: the Dutch Melanoma Treatment Registry (DMTR)

Data was retrieved from the Dutch Melanoma Treatment Registry (DMTR), a prospective population-based registry that was set-up to monitor the safety and effectiveness of the new drugs in real-world clinical practice and to assess the quality of melanoma care in the Netherlands. The DMTR contains information on baseline patient and tumour characteristics, local and systemic treatment modalities, treatment-related adverse events (grade 3 or 4 according to common terminology criteria for adverse events (CTCAE) version 4) and clinical outcomes of all patients with unresectable stage IIIc or IV melanoma. A detailed description of the DMTR was published previously [14].
In compliance with Dutch regulations, the DMTR was approved by the medical ethical committee and was not subject to the Medical Research Involving Human Subjects Act. Patients were offered an opt-out option.

Patients

All patients with BRAF-mutant unresectable or metastatic (stage IIIC or stage IV) cutaneous melanoma or with a BRAF-mutant melanoma of unknown primary with a baseline serum LDH of ≥2x above the upper limit of normal (ULN) who received targeted therapy (either monotherapy with a BRAF inhibitor or combination therapy with BRAF and MEK inhibitors) between July 1st 2012 and June 30th 2017 were included (follow-up data cut-off was November 5th 2017). The ULN was defined at 250 U/L. Patients with prior systemic treatment for metastasized disease were excluded to avoid bias of on going activity of previous systemic agents.

Statistical analysis

Time to next treatment (TTNT) and overall survival (OS) with corresponding two-sided 95% confidence intervals (CI) for medians were analysed using the Kaplan-Meier method. For the overall study population, TTNT was determined from the start of targeted therapy to the start of subsequent systemic therapy or death from any cause. Patients who were still on treatment were censored at time of analysis. OS was defined as the time from start of targeted therapy to the date of death from any cause. Patients alive at time of analysis were censored. Follow-up time was calculated from start date of targeted therapy using the inverse Kaplan-Meier method [15].

The main objective of the study was to investigate whether the response to targeted therapy and level of serum LDH at start of subsequent immunotherapy affects survival. For this analysis, OS was defined from start of subsequent immunotherapy to the date of death from any cause. Patients were stratified according to LDH at start of subsequent immunotherapy (< ULN, >1 to < 2x ULN, ≥2x ULN) and tumour response after treatment of targeted therapy according to Response Evaluation Criteria in Solid Tumors (RECIST). OS was compared between the subgroups using log-rank tests. Multivariable Cox proportional hazard model was applied to identify prognostic factors at start of subsequent immunotherapy associated with OS. Backward stepwise selection was performed to eliminate non-influential variables from the multivariable model. The following factors at start of immunotherapy were entered in the model: gender, age, ECOG PS (0,1 and ≥2), serum LDH (<1x ULN, 1-2x ULN, ≥2x ULN), number of organ sites involved counted as any organ with at least one metastasis (<3 *vs* ≥ 3), brain metastases (no brain metastases, asymptomatic, symptomatic), RECIST response on targeted therapy. Statistical significance was defined as a two-sided p value <0.05.

All statistical analyses were performed in PASW Statistics version 20 (SPSS Inc. Chicago, IL).

RESULTS

Overall study population

A total of 4043 unresectable stage IIIC or IV melanoma patients were registered in the DMTR between July 1st 2012 and June 30th 2017 (Supplemental Figure 1). Of

Table 1. Patient and treatment characteristics of study population

	N=270 (%)
Median age, years (IQR)	60 (59-88)
Age in categories	
<50	67 (25)
50-59	65 (24)
60-69	79 (29)
≥70	59 (22)
Gender	
Male	163 (60)
Female	107 (40)
ECOG PS	
0	63 (23)
1	78 (29)
≥2	99 (37)
Unknown	30 (11)
Median baseline LDH (IQR)	815 (613-1396)
Nubmer of organ sites involved	
<3	49 (18)
≥3	195 (72)
Unknown	26 (10)
Brain metastases	
No	186 (69)
Asymptomatic	24 (9)
Symptomatic	43 (16)
Unknown	17 (6)
Type of targeted therapy	
BRAFi monotherapy	205 (76)
BRAFi + MEKi	65 (24)
Type of subsequent immunotherapy	
Ipilimumab	23 (9)
Anti-PD1	29 (11)
Ipilimumab & nivolumab	14 (5)

IQR = interquartile range; ECOG PS = Eastern Cooperative Oncology Group performance status; BRAFi = BRAF-inhibitor; MEKi= MEK inhibitor

these, 270 BRAF-mutant advanced melanoma patients with a baseline serum LDH of ≥2x ULN received first-line targeted therapy and were included for analyses. Baseline characteristics are shown in Table 1. The median age was 60 years and the majority of patients were male (60%). Median serum LDH was 815 U/L (IQR 613-1396). Thirty seven percent of patients had an ECOG PS of ≥2 and most patients had ≥3 organ sites involved (72%). The majority of patients received BRAF monotherapy (76%). BRAF monotherapy was administered up to August 2016. Combination therapy with a BRAF- and MEK inhibitor was increasingly being used since October 2015 and was the only administered therapy in 2017. Median follow-up was 22.1 months (95% CI 14.8- 29.5) and 228 patients (84%) died during follow-up. At time of analysis, 93% of patients discontinued treatment with targeted therapy, due to disease progression (63%), toxicity (10%) and death (10%), planned in advance (7%), patient's choice (2%), other (4%) and unknown (4%).

Median OS was 4.7 months (95% CI 4.3– 5.1) (Figure 1). Survival rates at 6 months and 1 year were 37% (95%CI 31-43) and 12% (95% CI 8-16), respectively.

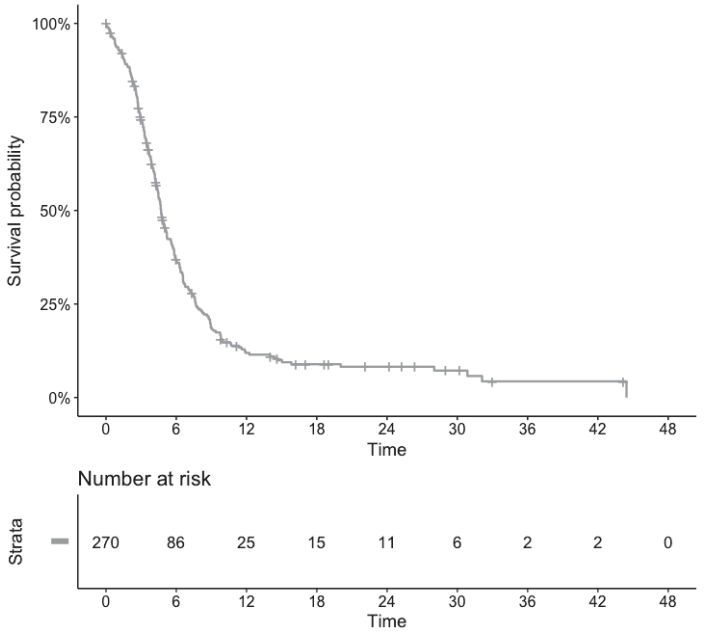

Figure 1. Overall survival of study population.

Table 2. Patient and treatment characteristics at start of subsequent immunotherapy

	N=65 (%)
Median age, years (min-max)	56 (16-77)
Age in categories	
<50	18 (28)
50-59	17 (26)
60-69	18 (28)
≥70	12 (18)
Gender	
Male	43 (66)
Female	22 (34)
ECOG PS	
0	12 (18)
1	37 (57)
≥2	7 (11)
Unknown	9 (14)
Number of organ sites involved	
<3	11 (17)
≥3	48 (74)
Unknown	6 (9)
Brain metastases	
No	46 (71)
Asymptomatic	9 (14)
Symptomatic	7 (11)
Unknown	3 (3)
Type of targeted therapy	
BRAFi monotherapy	41 (63)
BRAFi + MEKi	24 (37)
Serum LDH	
<ULN	19 (29)
≥1 to <2 x ULN	27 (42)
≥2 x ULN	19 (29)
Response on targeted therapy	
Partial response	7 (11)
Stable disease	6 (9)
Progressive disease	52 (80)

ECOG PS = Eastern Cooperative Oncology Group performance status; BRAFi = BRAF-inhibitor; MEKi= MEK inhibitor. LDH= lactate dehydrogenase, ULN=upper limit of normal.

Patients with subsequent immunotherapy

A total of 65 patients (24%) received subsequent immunotherapy. Anti-PD1 (44%) was most often administered, followed by ipilimumab (35%) and a combination of ipilimumab & nivolumab (21%). Baseline characteristics at start of subsequent immunotherapy are shown in Table 2. Median follow up from start of subsequent immunotherapy was 15.0 months (95% CI 5.7- 24.4).

Outcomes were stratified according to LDH at start of subsequent immunotherapy and tumour response after targeted therapy. Table 3 shows the median OS and 6-months survival rates, calculated from start of subsequent immunotherapy.

Patients with a normalized LDH who had a partial response to targeted therapy (BRAF monotherapy: n=5, combination therapy with BRAF and MEK inhibitor: n=1) had the best survival from start of immunotherapy (median OS and 6-months survival rate not reached). These patients had an original LDH level at start of targeted therapy between 541- 690 U/L. Median duration of targeted therapy before switching to immunotherapy was 2.4 months (95%CI 2.2-2.7).

All patients who had an elevated LDH at start of immunotherapy had progressed on targeted therapy (n=44). Median duration of targeted therapy before switching to

Table 3. Kaplan-Meier estimates of time to next treatment, median overall survival, and 6 months survival rates at start of subsequent immunotherapy, according to serum LDH at start of subsequent immunotherapy and tumour response after targeted therapy

Serum LDH at start IT	Response on targeted therapy	Deaths/ No. of patients	Median OS (95% CI), mo	6 mo survival rate (95% CI), %
<ULN				
	PR	0/6	NR	NR
	SD	4/5	8.8 (0-20.9)	60 (17-100)
	PD	7/8	4.4 (2.4-6.3)	29 (0-62)
≥1 to <2x LN[a]				
	PD	19/25	2.7 (1.9-3.6)	22 (5-39)
≥2 x ULN				
	PD	16/19	0.9 (0.3-1.7)	17 (0-34)

LDH= lactate dehydrogenase, ULN=upper limit of normal, IT = immunotherapy, TTNT = time to next treatment, OS = overall survival, mo = months, NR = not reached, PR = partial response, SD = stable disease, PD = progressive disease.

[a] Due to low numbers of patients with stable disease (N=1) and partial response (N=1) in this subgroup, these patients were excluded from analyses

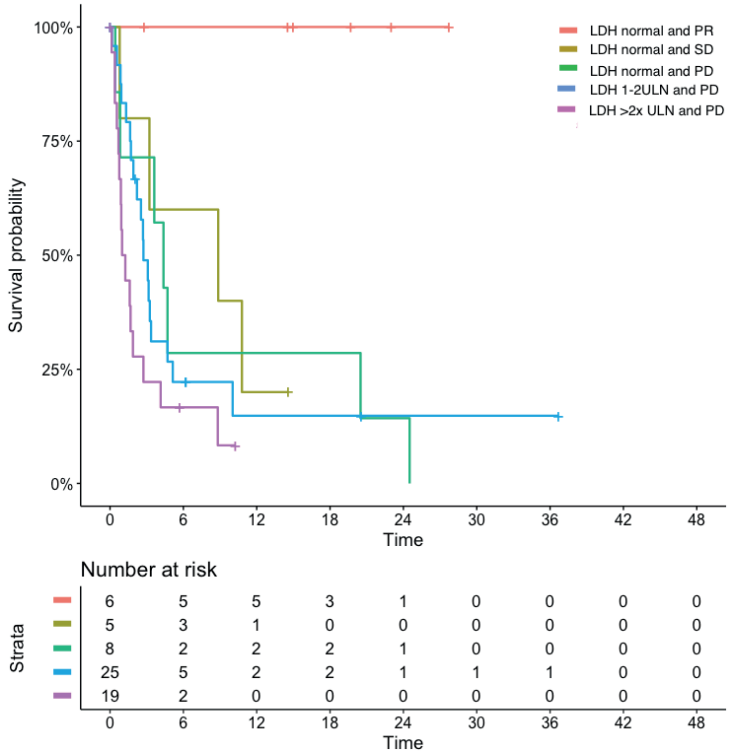

Figure 2. Kaplan Meier curves of overall survival at start of subsequent immunotherapy, according to serum LDH at start of subsequent immunotherapy and tumour response after targeted therapy.

immunotherapy was 5.8 months (95%CI 4.7-6.9). Patients who started second-line immunotherapy with LDH ≥2x ULN had the worst outcomes with a median OS of 0.9 months (95%CI 0.3-1.7) and 6-months survival rate of 17% (95%CI 0-34). The survival curves demonstrate significant survival differences between the normalized LDH group with partial response compared to the other subgroups (Figure 2).

After backward multivariable selection, only LDH at start of second-line immunotherapy and response to targeted therapy retained in the final model (Table 4). In particular, normal LDH was significantly associated with survival (HR 0.38 95%CI 0.16-0.94). No significant differences were found between characteristics at start of second-line immunotherapy according to response status to immunotherapy (data not shown).

Table 4. Multivariable Cox regression analysis after backward stepwise selection associated with overall survival using baseline characteristics at start of immunotherapy.

	OS HR (95% CI)	*P*
Response on targeted therapy		
PR	0.24 (0.05-1.07)	0.061
SD	0.64 (0.23-1.77)	0.391
PD	reference	
LDH level at start of immunotherapy		
<ULN	0.38 (0.16-0.94)	0.036
≥1 to <2 x ULN	0.50 (0.25-1.02)	0.058
≥2 x ULN	reference	

LDH= lactate dehydrogenase, ULN=upper limit of normal, IT = immunotherapy, OS = overall survival, HR = hazard ratio, PR = partial response, SD = stable disease, PD = progressive disease.

DISCUSSION

These real-world data support previous reports of the poor prognosis of advanced melanoma patients with elevated serum LDH. At the same time, these data provide a potential strategy to improve clinical outcomes. In our cohort of metastatic melanoma patients with baseline serum LDH of ≥ 2x ULN treated with first-line BRAF(/MEK) inhibitors, median OS was significantly longer in patients who started second-line immunotherapy with normalized LDH and still responding to initial targeted therapy compared to those with elevated LDH at start of immunotherapy. Our data suggest that introducing immunotherapy upon response to targeted therapy with normalization of LDH could be an effective strategy in obtaining long-term survival in patients with initial elevated serum LDH.

The median OS of 4.7 months of the overall study population confirms previous data that clinical outcomes remain poor in this subgroup of patients [9] [10] [16]. Patients who received subsequent immunotherapy with LDH ≥ 2x ULN at start of immunotherapy are unlikely to benefit from immunotherapy with a median OS of 0.9 months and a 6-months survival rate of 17%.

The exact role of LDH is not completely elucidated. It could simply be a marker of more aggressive disease that requires rapid anti-tumour responses [9]. The delayed

tumour responses generally observed with immunotherapies might therefore take too long for these patients to benefit. Moreover, tumour metabolism is characterized by the conversion of pyruvate into lactate, even in the presence of sufficient oxygen. Preclinical data demonstrated that tumour cells producing high levels of lactic acid disturb the function of cytotoxic T lymphocytes, thereby negatively influencing the potency of an immune response [17] [18].

Interestingly, our data showed that patients who switch to immunotherapy with normalized LDH while still responding to targeted therapy have a real chance of long-term survival. After a median follow-up of 15 months, median OS was not reached and survival was significantly longer compared to the other subgroups. Moreover, targeted therapy was given as an 'induction' therapy with a median duration of only 2.4 months, suggesting that sequential treatment with an early switch to immunotherapy in this subgroup could result in durable outcomes. Although promising, baseline LDH values of these patients did not exceed 690 U/L (<3x ULN). Patients with extremely high LDH values of >3x ULN at baseline might not be good candidates for this strategy. It should also be noted that only a small proportion of patients received this treatment strategy (n=6; 2%). However, the majority of our study population received BRAF monotherapy as first-line targeted therapy. The emergence of combination therapy with a BRAF and MEK inhibitor for this subgroup of patients might lead to a greater proportion of patients with response to targeted therapy and normalisation of LDH. A 3-year follow-up pooled analysis of phase III trials with BRAF and MEK inhibitor combination therapy showed promising results with 50% partial response in patients with initial LDH ≥ 2x ULN [19].

The value of sequencing targeted therapy prior to immunotherapy in patients with initial elevated LDH has not been investigated thus far. Previous retrospective reports revealed that normalization of LDH while on targeted therapy was a strong feature of ipilimumab cycle completion [20] [21]. Another report on 101 advanced melanoma patients with decreased serum LDH after BRAF inhibitor treatment who were fit enough to complete all courses of ipilimumab had a significantly longer OS compared to those who did not (median OS 12.7 months *vs* 1.2 months) [22].
The real benefit of induction treatment with combined BRAF- and MEK-inhibition in patients with elevated LDH is currently investigated in multiple prospective ran-

domized trials. In the Netherlands, the phase II COWBOY study (NCT02968303) comparing BRAF- and MEK-inhibitor induction treatment with vemurafenib and cobimetinib followed by ipilimumab and nivolumab or upfront immunotherapy in advanced melanoma patients with elevated serum LDH is currently recruiting. Another trial, the EORTC EBIN study (NCT03235245), will compare ipilimumab and nivolumab upfront versus the same treatment preceded by induction therapy with encorafenib and binimetinib in advanced melanoma patients, irrespective of LDH level. One of the arms of the three-arm phase II SECOMBIT study (NCT02631447) will assess whether an induction treatment with encorafenib plus binimetinib of 8 weeks before combination immunotherapy might help potentiate an immunotherapeutic response. Guidelines are not conclusive on this issue and the abovementioned trials are currently recruiting. Our results may therefore be of added value to medical oncologists while awaiting these trial results.

It would be interesting to investigate survival differences between patients who started second-line immunotherapy with normalized LDH and response to initial targeted therapy vs responders who stayed on targeted therapy. The 3-year follow-up pooled analysis of phase III trials with BRAF and MEK inhibitor combination therapy showed that patients with initial elevated LDH levels that normalized at 6 months could have long-term benefit with a 3-years survival rate of 41% [19]. Unfortunately, this could not be assessed with our data, as we have no information of LDH level during follow-up of patients who stayed on targeted therapy.

Given the observational design of this analysis, we cannot rule out confounding by indication or selection bias. However, its multicentre design attenuates this potential selection bias. Furthermore, observational studies are more susceptible to registration bias. To ensure high-quality data, data managers were extensively trained and supervised by oncologists [14]. Another limitation is the small number of patients of the subgroup analyses. The conclusions drawn need validation in prospective randomized trials. Lastly, other clinical parameters such as lymphocyte counts and CRP level that have also been associated with patient outcome after immunotherapy were not registered in our database and could therefore not be included in this study [18].

In conclusion, our population-based study suggests immunotherapy upon response to targeted therapy with normalization of LDH may be beneficial in this group of patients with generally a poor prognosis. Nevertheless, randomized trials are needed to assess the real benefit of sequential treatment of targeted therapy and immunotherapy in patients with elevated serum LDH.

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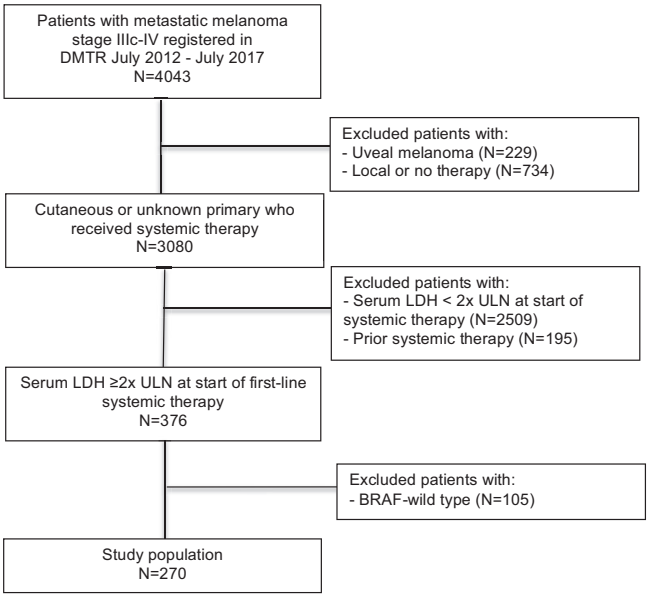
APPENDICES



Supplementary Figure 1. Flowchart of study population

Part III

Assuring quality focusing on patient centred outcomes