SYSTEMIC THERAPY AND IMAGING SURVEILLANCE IN HIGH-STAGE MELANOMA PATIENTS DURING THE END OF LIFE: A RETROSPECTIVE COHORT STUDY

Pieter van Lith
S1230107

Examination committee
University of Twente
Prof. dr. S. Siesling
L. ter Weele – Nieuwenhuis, MSc
IKNL
Dr. ir. K. Schreuder
Dr. ir. M.W.J. Louwman

Faculty of Science and Technology
Master Thesis Health Sciences

Health Technology & Services Research (HTSR)
December 2020

IKNL Netherlands comprehensive cancer organisation

UNIVERSITY OF TWENTE.

Preface

As I write this preface, I realize that my time as a student at the University of Twente, since 2011, has really come to an end. As every chapter ends, a new one will follow, and I will continue to focus on my dream of becoming a doctor.

The completion of this thesis was only possible because of the support and commitment of many people around me. I would therefore like to thank some of them in particular.

First of all, I would like to thank Anouk Prins of the University of Twente, who made it possible for me to do this master's degree alongside my current medical studies and who has always guided and supported me. I would also like to thank my supervisors, first Lisette Nieuwenhuis for the last review. Sabine Siesling and Marieke Louwman for the guidance, insight and the years of knowledge and experience during this thesis. Last but not least, I would like to thank Kay Schreuder, who took a lot of time for my thesis and during – unfortunately forced – online sessions where we racked our brains on several parts of this thesis. I really appreciated your supervision. My last word of gratitude goes to my parents and my girlfriend for their support.

After completing this thesis, I can focus on my ultimate goal that I have had in mind since I was eleven years old, I will never give up.

Table of Contents

ABSTRACT

Introduction Melanoma is the most aggressive form of skin cancer and is the cause for 11% of all skin cancers. The incidence increased significantly in the period 1990-2019. In recent years, new systemic therapies have been developed that improve the survival of high-stage melanoma patients, but these systemic therapies are associated with high costs and potentially severe side effects. Therefore, it is very important to carefully consider its use towards the end of life in high-stage melanoma patients. Currently, very little is known about which factors are related to the use of systemic therapy and of diagnostic interventions for melanoma patients in the months before death. The aim of the current study is to examine which patient and tumor characteristics are associated with the use and timing of systemic therapies, and which imaging techniques are performed in high-stage melanoma patients during the end of life.

Methods A retrospective cohort study was performed analyzing patients with high-stage melanoma from the Netherlands Cancer Registry (NCR). From the 1st of July 2017 a melanoma high stage registration (MelaHS) was incorporated in the NCR. The study contained 476 patients with high-stage melanoma who were deceased between July 2017 till the end of 2019. Patient and tumor characteristics were summarized using descriptive statistics for types of systemic therapy (immune, targeted-, both or no therapy), also patients who started and ended with systemic therapy and types of imaging interventions were stratified according to certain time frames before death occurred. Significance was tested by using chi-square tests ($p < 0.05$).

Results Patients who received systemic therapy (N = 314; 66%) were younger (69 vs. 75,5 years), lived longer after diagnosis high-stage (5,9 vs. 2 months), were diagnosed with more metastases (5,3 vs. 2,8) had a 'good' performance status (ECOG 0 – 1; 70% vs. 24,1%) and had a BRAF mutation (56,7% vs. 21,6%) compared to non-systemic patients. Most patients who were treated systemically had received immune therapy (46,8%). Patients who were treated with both therapies (immune- and targeted therapy) were younger, had a 'good' performance status, lived longer since the primary high-stage diagnosis, irradiated and screened most often with mainly CT & MRI-scan compared to patients who received only immune- or targeted therapy. Patients who started with only immune therapy within 30 days before death had more elevated LDH levels (76,2% vs. 58,8%), compared to patients who started within 90 days before death, the same applies to only targeted treated patients but the difference was smaller. A 'good' performance status and a longer lifespan (0 – 30 = 1,9 months & 31 – 90 = 3,4 months) since the MelaHS inclusion was seen more in only immune treated patients, compared to patients who were treated with only targeted therapy with a shorter lifespan (0 – 30 = 0,8 months & 31 – 90 = 3 months) since the MelaHS inclusion and with mainly a 'poorer' performance status shortly before death. Most imaging surveillance was used on patients receiving both therapies.

Conclusion This study showed that age, performance status (ECOG), elevated LDH levels and a BRAF mutation were possible factors associated with the use and timing of systemic therapy in the period before death and which imaging techniques were used. A start with targeted therapy was used for potentially weaker and older patients, where immune treated patients (and combination of both) were younger and potentially stronger shortly before death. To start or end a systemic therapy is a complicated and often emotionally charged decision, where a well-informed assessment of both the harm and benefit of systemic therapy should be comprehensively considered, especially when the patient is nearing the end of life.

Introduction

Skin cancer is the most common form of cancer in the Netherlands, as it is responsible for approximately 52% of all cancers diagnosed.(1) Melanoma, arising by transformation of melanocytes, is the most aggressive type of skin cancer and it accounts for 11 percent of all skin cancer cases.(2) These transformed melanocytes divide rapidly and often penetrate the basement membrane, going further into the dermis, and eventually metastasize by invading blood and lymphatic vessels.(3)

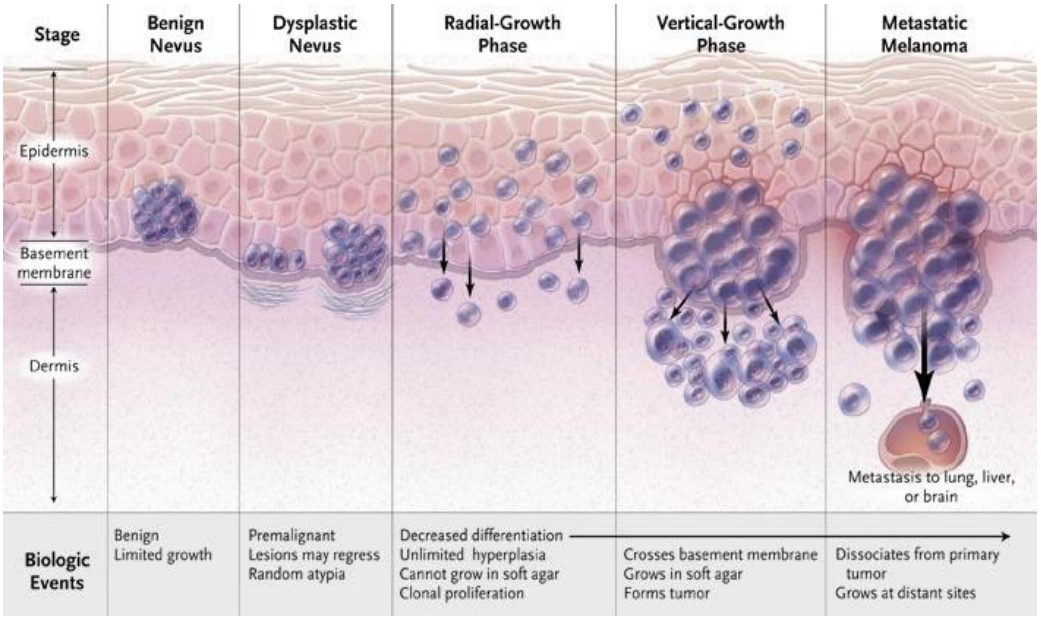

Figure 1: Biologic Events in the Progression of Melanoma(4)

The development of a melanoma is predominantly related to short-term intense UV-exposure and subsequent sunburn especially during the first 10 to 15 years of life; the use of sunbeds, the appearance of dysplastic neavi, a (family)history of cutaneous melanoma, phenotypic characteristics as light eye, hair and skin colour, presence of freckles and a high socioeconomic status.(5–7)

The Netherlands is one of the countries with the highest incidence of melanomas, which is probably due to better diagnostics.(8) In 2019, 7100 patients were diagnosed with melanoma in the Netherlands: 3500 were men (40,9 cases per 100.000) and 3600 women (41,5 cases per 100.000).(2) Almost 90 percent of the patients were diagnosed with an early stage melanoma (stage I or II) and the others (about 11%) were diagnosed with a high stage melanoma (stage III or IV).(9) Moreover, based on data from the Netherlands Cancer Registry (NCR), the number of new cases of melanoma increased significantly in the period 1990-2019, this was primarily due to changes in sun-related behaviour.(10) Overall, the 5- and 10-years relative survival of patients diagnosed with a melanoma in the years 2011 – 2015 and 2006 – 2010 is 91% and 86%, respectively.(9)

However, the survival rate of patients with melanoma strongly depends on the stage of the cancer at the time of diagnosis. Metastases in regional lymph nodes (stage III melanoma) or distant metastasis (stage IV melanoma) at time of diagnosis are associated with lower survival rates. Between 2010 and

2017, approximately 73% of patients diagnosed with stage III melanoma and only 22% of the patients diagnosed with stage IV were alive three years after initial diagnosis.(11,12)

In recent years, the diagnosis has been made at an earlier stage and other interventions, such as immune- and targeted therapy, have been increasingly used to improve the chances of survival in these patients. The introduction of immune- and targeted therapy resulted in important developments in the adjuvant treatment of high-stage melanoma, including the evolution of new classes of drugs (monoclonal antibodies, BRAF inhibitors, MEK inhibitors and anti-PD-1 antibodies). The results of the initial studies with these new therapies indicate that new modalities may be available as standard treatment in the future with significant and clinically meaningful improvements in survival rates.(13–17) These therapies have had a revolutionary impact in the treatment of advanced melanoma over the past 8 years.(18)

Since 2012, after being approved by the Dutch Association for Medical Oncology (*Nederlandse Vereniging voor Medische Oncologie* (NVMO), immune- and targeted therapy has become available in the Netherlands. Shortly after vemurafenib and ipilimumab, MEK inhibitors and anti-PD-1 antibodies became available in 2016. In 2018 the NVMO committee BOM (*Beoordeling van Oncologische Middelen)* approved both combination therapy with dabrafenib-trametinib and monotherapy nivolumab positive for the adjuvant treatment of high-stage melanoma.(19,20)

These new systemic therapies are associated with high costs and potentially serious side effects, for example heart and liver failure, endocrinological disorders and reduced kidney function.(21,22) Due to the side effects, high costs and a trend towards a rising aggressiveness of systemic therapy in the last months before death, it is important to carefully evaluate their use in high-stage melanoma patients towards the end of their lives.(23,24) In addition, surveillance imaging in systemically treated patients is relevant. Routine surveillance aims to support and reassure patients and clinicians to detect recurrence early so that appropriate treatment can be given in an optimal time frame or to avoid unnecessary further treatment as part of disease management.(25)

Currently, very little is known about which factors are related to the use of systemic therapy and imaging surveillance for high- stage melanoma patients in the months before death. A better understanding of the frequency and timing of end-of-life systemic therapy and the factors associated with its use, could enable us to improve the quality of end-of-life care for patients with high-stage melanoma. This knowledge into what happens to these patients in practice can be useful for optimizing patient care in the future. Therefore, the aim of the current study is to examine which patient and tumor characteristics are associated with the use and timing of systemic therapies and which medical imaging techniques (MRI, CT and/or PET scan) are performed in high-stage melanoma patients during the end of life.

Patient and methods

Data source

For this retrospective study data were obtained from the Netherlands Cancer Registry (NCR), which is hosted by the Netherlands Comprehensive Cancer Organisation (IKNL). Since 1989, the NCR registers data on patient-, tumor-, diagnostic-, and treatment characteristics of all Dutch cancer patients, obtained by data managers directly from patients' medical records. From the 1st of July 2017, a melanoma high-stage registration (MelaHS) has been incorporated in the NCR. In this registration both synchronous and metachronous advanced disease have been included, with additional items such as date of progression to high-stage diagnosis, mutation diagnostics, LDH (U/L), diagnostic imaging interventions, all treatment lines and follow up.

Study population

In total, 2206 patients were registered in the MelaHS registry and for the current study, only patients with high-stage melanoma who were deceased (from July 2017 till the end of June 2019) have been included (N = 476). These patients were diagnosed with a primary melanoma from 1st July 2017 and were classified as a high-stage melanoma (according to the TNM classification of Malignant Tumors (8th edition) according to the following criteria: Stage IV from 1st July 2017; inoperable stage IIIC/IIID from 1st July 2017; inoperable and operable stage IIIC/IIID from 1st July 2018; all stages IIIA/IIIB from 1st January 2019. Furthermore, patients were also included in case of primary melanoma before 1st July 2017, which eventually progressed to a high-stage melanoma (see Figure 2 for MelaHS inclusion).

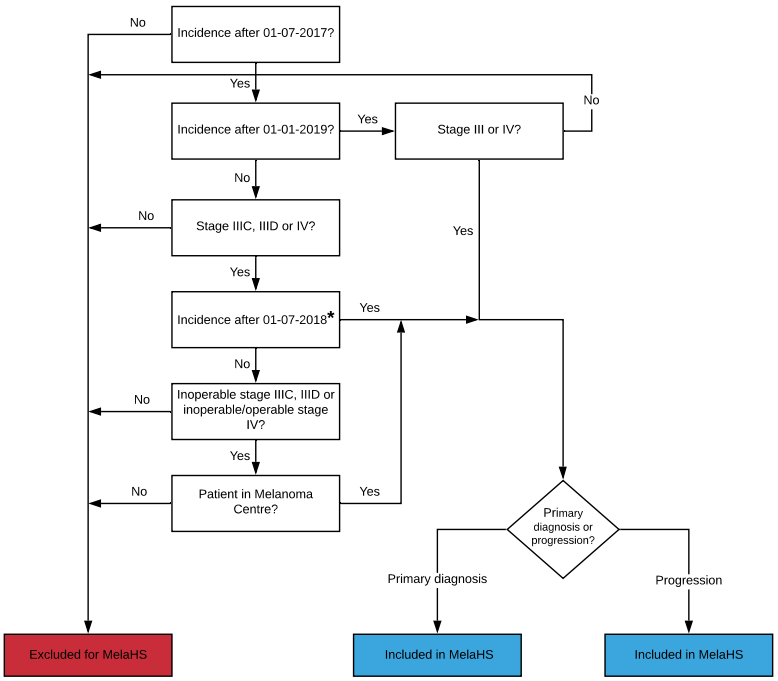

Figure 1: Inclusion criteria melanoma for MelaHS
**: Guideline change*

Data analysis

Patient and tumor characteristics were summarized using descriptive statistics presented as counts, row and column percentages, median and/or mean values. Initially different patient and tumor factors (median age, age group (≤40, 41-54, 55-64, 65-74, ≥75 years), gender, stage (TNM8 edition) and median survival time (time between diagnosis (primary and/or first inclusion MelaHS and death) were related to the period between primary diagnosis and first inclusion in the MelaHS registry (categories: (1) high-stage at time of primary diagnosis, (2) inclusion less or equal than 32 months after primary diagnosis and (3) more than 32 months after primary diagnosis. These intervals, and especially group 2 have been chosen because no patients had been diagnosed for a MelaHS inclusion before 1,8 months, other than during the primary diagnosis. In order to make a balanced distribution between the groups, a period shorter and longer than 32 months had been considered. Subsequently, these factors and topography, morphology (listed according to the classifications in the International Classification of Disease-Oncology (3th edition), elevated serum LDH levels, the Eastern Cooperative Oncology Group (ECOG) performance status, BRAF mutation (Positive, Negative, Unknown, Not tested), location of distant metastases and type of systemic therapy were assessed at the time of high-stage melanoma diagnosis. All these factors were also evaluated for patients treated with and without systemic therapy (immune and/or targeted), for systemically treated patients, where complications (≥ grade 3, based on guideline MelaHS registry) due to these therapies were also evaluated. The type of imaging surveillance (none, CT, MRI and/or PET) was categorized into 'single imaging' where patients only underwent one type of imaging (CT, MRI or PET), 'double imaging' where two different types of imaging were used (CT & MRI, MRI & PET or PET & CT), and patients who had undergone all types and no imaging (none) during the MelaHS inclusion. Thereafter, the percentages of imaging surveillance performed, and percentage of patients who started or ended with systemic therapies were stratified according to certain time frames before death occurred. The date of death was used as an index to define 5 observational intervals in order to include as many patients as possible from the register (30, 90, 180, 360 or 720 days before death). Also, differences in patient and tumor characteristics were assessed for specific time frames between last therapy and death (within 30 days and 31 till 90 days) and specified for patients who underwent only immune- or targeted therapy. Furthermore, patients who underwent both therapies and received within 90 days immune and/or targeted therapy and patients who have not received any of the aforementioned therapies before death are included. Significance was tested by using chi-square tests (p-values < 0.05 were considered to be significant). All analyses were conducted using STATA statistical analysis software, version 16.1 (StataCorp. 2019. Stata Statistical Software: Release 16.1. College Station, TX: StataCorp LLC, Texas, USA).

Results

Baseline patient and tumor characteristics

The baseline characteristics at primary diagnosis of melanoma are listed in Table 1. Patients who reached a high-stage melanoma more than 32 months after the primary diagnosis are younger (median 63 years; range 21 - 88), compared to patients who reached a high-stage at the time of primary diagnosis (median 71,5 years; range 24 - 96) or less than 32 months after the primary diagnosis (median 70 years; range 28 - 96).

In the group of patients who reached a high-stage more than 32 months after initial diagnosis, the proportion of men and women were more balanced (55,9% versus 44,1%) compared to high-stage at primary diagnosis (63,6% versus 36,4%) or less than 32 months after diagnosis (68,7% versus 31,3%).

The percentage of low-stage (stage I & II) patients at the time of the primary diagnosis is lower for patients with a shorter period of time (≤ 32 months, 62%) compared to patients with a longer period of time (> 32 months, 82%) between primary diagnosis and inclusion MelaHS. There were 3 patients with stage IV in group ≤ 32 months between primary diagnosis and MelaHS inclusion, these patients should already have been included in the MelaHS registration at the time of primary diagnosis.

Table 1 Baseline patient and tumor characteristics

N = 476	High-stage at time of primary diagnosis (MelaHS inclusion) N = 118	≤ 32 months* between primary diagnosis and MelaHS inclusion N = 179	> 32 months between primary diagnosis and MelaHS inclusion N = 179	*p*-Value
Age, *years*				0.15
Median	71,5	70	63	
Range	24 - 96	28 - 96	21 - 88	
Age group	N (%)	N (%)	N (%)	<0.001
≤ 40	7 (5,9%)	9 (5%)	14 (7,8%)	
41-54	10 (8,5%)	24 (13,4%)	43 (24%)	
55-64	18 (15,3%)	26 (14,5%)	39 (21,8%)	
65-74	40 (33,9%)	63 (35,2%)	57 (31,9%)	
≥ 75	43 (36,4%)	57 (31,9%)	26 (14,5%)	
Gender	N (%)	N (%)	N (%)	0.04
Male	75 (63,6%)	123 (68,7%)	100 (55,9%)	
Female	43 (36,4%)	56 (31,3%)	79 (44,1%)	
Stage	N (%)	N (%)	N (%)	<0.001
I	0 (0%)	30 (16,8%)	88 (49,2%)	
II	0 (0%)	81 (45,2%)	60 (33,5%)	
IIIA	0 (0%)	13 (7,3%)	11 (6,1%)	
IIIB	0 (0%)	14 (7,8%)	9 (5,0%)	
IIIC	16 (13,6%)	35 (19,5%)	6 (3,4%)	
IIID	4 (3,4%)	2 (1,1%)	0 (0%)	
IV	95 (80,5%)	3 (1,7%)	0 (0%)	
X	3 (2,5%)	1 (0,6%)	5 (2,8%)	
Months between first diagnosed melanoma and death				0.06
Median	4,3	19,5	69,0	
Range	0,1 - 18,3	3,5 - 46	32,8 - 488	

*: Patients ≤ 32 months between primary diagnosis and high-stage, excluded for patients with high-stage at time of primary diagnosis (MelaHS inclusion)

Baseline patient and tumor characteristics at high-stage melanoma

Table 2 demonstrates the patient and tumor characteristics at the time of high-stage diagnosis. The overall median age is 71 years and most of the patients were male (62,6%).

Superficial spreading melanoma was the most frequent subtype of melanoma (47,5%). Most of the patients had elevated serum lactate dehydrogenase (LDH) levels (55,5%) at the time of high-stage diagnosis. The majority of patients (54,4%) scored well on the performance status (ECOG 0 - 1). Molecular analysis of the activating mutation in the BRAF gene was performed in 90% (N = 426) and in 44,8% of these patients a BRAF mutation was confirmed (positive).

In total, 95,2% (N = 453) of the patients were diagnosed with distant metastases. Metastases in the respiratory system were most commonly diagnosed (63%), other frequently affected sites were the brain & nervous system (51%) and digestive system (49%).

In total, 314 patients (66%) received systemic therapy, including immune therapy (30,9%), targeted therapy (16,2%), and a combination of both (18,9%). The median survival time of all patients with high-stage melanoma was 4,6 months since diagnosis of high-stage.

Table 2 Baseline patient and tumor characteristics at high-stage melanoma	
	N = 476
	At high-stage melanoma (MelaHS)
Age, *years*	
Median	71
Range	24 - 97
Age group	**N (%)**
≤ 40	19 (4%)
41-54	59 (12,4%)
55-64	71 (14,9%)
65-74	157 (33%)
≥ 75	170 (35,7%)
Gender	**N (%)**
Male	298 (62,6%)
Female	178 (37,4%)
Topography	**N (%)**
Skin	401 (84,2%)
Unknown primary site	75 (15,8%)
Morphology	**N (%)**
Superficial Spreading Melanoma	226 (47,5%)
Nodular Melanoma	106 (22,3%)
Malignant Melanoma NOS	121 (25,4%)
Other	23 (4,8%)
Elevated serum LDH level (>250 U/L)	**N (%)**
No	177 (37,2%)
Yes	264 (55,5%)
Unknown	35 (7,3%)
ECOG performance status	**N (%)**
0	118 (24,8%)
1	141 (29,6%)
2	55 (11,6%)
3	41 (8,6%)
4	7 (1,5%)
Unknown	114 (23,9%)
BRAF mutation	**N (%)**
Positive	213 (44,8%)
Negative	199 (41,8%)
Unknown	14 (2,9%)
Not tested	50 (10,5%)
Distant Metastases	**N (%)**
No/Unknown	23 (4,8%)
Yes	453 (95,2%)
Location of distant metastases*	**%**
Respiratory system	63%
Connective/subcutaneous tissue & other soft tissue	26%
Bones, joints & joint cartilage	36%
Brain & nervous system	51%
Skin	8%
Lymph nodes	48%
Digestive system	49%
Other	36%
Systemic Therapy	**N (%)**
None	162 (34%)
Immune therapy	147 (30,9%)
Targeted therapy	77 (16,2%)
Both	90 (18,9%)
Months alive after diagnosed high-stage melanoma (MelaHS)	
Median	4,6
Range	0,1 - 23,4
*: Patients could have multiple sites of metastases	

Non-systemic therapy versus systemic therapy

Differences in patient, tumor and treatment characteristics between non-systemic and systemic treated patients are presented in Table 3. The patients who received systemic therapy were younger (69 versus 75,5 years), lived longer after diagnosis of high-stage melanoma (5,9 versus 2 months) and were diagnosed with more metastases (5,3 versus 2,8) compared to those not receiving the systemic treatment. Patients in the systemic therapy group were generally more likely to have a metastasis in a specific location than non-systemic patients, e.g. the respiratory system (69% versus 52%).
In the group of systemically treated patients the 'skin' (instead of an unknown primary site) was more commonly diagnosed as topography compared to the non-systemic patients (86,9% versus 79%). The percentage with ECOG 0 - 1 was higher in systemic treated patients compared to non-systemic patients, respectively 70% versus 24,1%. Patients with a BRAF mutation were more likely to receive systemic therapy (56,7% versus 21,6%), and 97,1% of the systemic treated patients will have been genetically tested. In addition, systemically treated patients were irradiated more often compared to the non-systemic group (43,3% versus 24,7%).

Table 3 Non-systemic therapy versus Systemic therapy	N = 162	N = 314	
	Non-systemic therapy	Systemic therapy	*p*-Value
Age in years since high-stage melanoma			0.12
Median	75,5	69	
Range	39 - 97	24 - 92	
Months alive after diagnosed high-stage melanoma			0.06
Median	2	5,9	
Range	0,1 - 16,8	0,6 - 23,4	
Distant Metastases	**N (%)**	**N (%)**	0.001
No/Unknown	15 (9,3%)	8 (2,5%)	
Yes	147 (90,7%)	306 (97,5%)	
Total amount of metastases			<0.001
Mean	2,8	5,3	
Range	0 - 9	0 - 16	
Location of distant metastases	**%**	**%**	
Respiratory system	52%	69%	<0.001
Connective/subcutaneous tissue & other soft tissue	23%	27%	0.39
Bones, joints & joint cartilage	25%	42%	<0.001
Brain & nervous system	39%	57%	<0.001
Skin	3%	10%	0.01
Lymph nodes	35%	54%	<0.001
Digestive system	39%	54%	0.002
Other	26%	40%	0.002
Topography	**N (%)**	**N (%)**	0.02
Skin	128 (79%)	273 (86,9%)	
Unknown primary site	34 (21%)	41 (13,1%)	
ECOG performance status since high-stage melanoma	**N (%)**	**N (%)**	<0.001
0	14 (8,7%)	104 (33,1%)	
1	25 (15,4%)	116 (36,9%)	
2	19 (11,7%)	36 (11,5%)	
3	26 (16,1%)	15 (4,8%)	
4	6 (3,7%)	1 (0,3%)	
Unknown	72 (44,4%)	42 (13,4%)	
BRAF mutation	**N (%)**	**N (%)**	<0.001
Positive	35 (21,6%)	178 (56,7%)	
Negative	73 (45,1%)	126 (40,1%)	
Unknown	13 (8%)	1 (0,3%)	
Not tested	41 (25,3%)	9 (2,9%)	
Surveillance Imaging	**N (%)**	**N (%)**	<0.001
Single imaging			
Only CT	56 (34,6%)	84 (26,8%)	
Only MRI	14 (8,6%)	20 (6,4%)	
Only PET	2 (1,2%)	4 (1,3%)	
Double imaging			
CT & MRI	32 (19,7%)	141 (44,9%)	
MRI & PET	1 (0,6%)	5 (1,6%)	
PET & CT	3 (1,9%)	9 (2,9%)	
All imaging			
CT, MRI & PET	3 (1,9%)	20 (6,4%)	
None	51 (31,5%)	31 (9,9%)	
Radiotherapy	**N (%)**	**N (%)**	<0.001
Yes	40 (24,7%)	136 (43,3%)	
No	122 (75,3%)	178 (56,7%)	

Treatment characteristics

The type of therapy administered to high-stage systemically treated patients (N = 314) is shown in Table 4. In total, 147 (46,8%) patients were treated with immune therapy, 77 patients (24,5%) were treated with targeted therapy and 90 patients (28,7%) received both therapies. Patients who have undergone both therapies, although not statistically significant, were younger (median 62 years), lived longer since primary high-stage diagnosis (median 8,5 months), experienced the largest amount of metastases (mean = 7) and were irradiated most often (51,1%) compared to patients treated with only immune- or only targeted therapy.

Patients who received only immune- or targeted therapy had more 'single imaging' (only CT, MRI or PET) than patients who received both. For all therapies, 'double imaging' (CT & MRI, MRI & PET, or PET & CT) was most commonly used, with mainly a combination of CT & MRI-scan, especially patients receiving both therapies (64,5%), compared to immune- (36,7%) and targeted therapy (37,6%). However, in immune- and targeted therapy, more patients did not undergo any imaging intervention, 13,6% and 11,7% respectively, compared to the 'both therapies' group (2,2%).

The median duration of treatment was significantly longer in both therapies (5,9 months) than in immune- (1,4 months) and targeted therapy (2,7 months). Of all patients who were treated systemically, 18,5% had serious complications, the majority of which occurred in patients receiving both therapies (26,7%).

Table 4 Systemic Therapy, Immunetherapy, Targeted Therapy and Both	Systemic Therapy N = 314	Immune Therapy N = 147	Targeted Therapy N = 77	Both Therapies N = 90	*p*-Value
Age in years since high-stage melanoma					0.12
Median	69	71	68	62	
Range	24 - 92	24 - 90	33 - 92	27 - 85	
Months alive after diagnosed high-stage melanoma					0.33
Median	5,9	5	4,7	8,5	
Range	0,6 - 23,4	0,9 - 23,4	0,6 - 18,3	1,7 - 18	
Distant metastases	**N (%)**	**N (%)**	**N (%)**	**N (%)**	0.15
No/Unknown	8 (2,5%)	6 (4,1%)	2 (2,6%)	0 (0%)	
Yes	306 (97,5%)	141 (95,9%)	75 (97,4%)	90 (100%)	
Total amount of metastases					<0.001
Mean	5,3	4,5	4,7	7	
Range	0 - 16	0 - 12	0 - 16	1 - 15	
Total amount of metastases at primary high-stage diagnosis					0.66
Mean	3,2	2,9	3,5	3,3	
Range	0 - 9	0 - 7	0 - 9	0 - 9	
Location of distant metastases	**%**	**%**	**%**	**%**	
Respiratory system	69%	67%	70%	71%	0.74
Connective/subcutaneous tissue & other soft tissue	27%	22%	34%	29%	0.18
Bones, joints & joint cartilage	42%	41%	44%	43%	0.87
Brain & nervous system	57%	41%	64%	79%	<0.001
Skin	10%	8%	6%	17%	0.05
Lymph nodes	54%	49%	58%	60%	0.18
Digestive system	54%	53%	52%	58%	0.71
Other	40%	35%	36%	52%	0.03
Morphology	**N (%)**	**N (%)**	**N (%)**	**N (%)**	<0.001
Superficial Spreading Melanoma	158 (50,3%)	62 (42,2%)	41 (53,2%)	55 (61,1%)	
Nodular Melanoma	65 (20,7%)	34 (23,1%)	21 (27,3%)	10 (11,1%)	
Malignant Melanoma NOS	72 (22,9%)	33 (22,4%)	14 (18,2%)	25 (27,8%)	
Other	19 (6,1%)	18 (12,3%)	1 (1,3%)	0 (0%)	
Topography	**N (%)**	**N (%)**	**N (%)**	**N (%)**	0.55
Skin	273 (86,9%)	131 (89,1%)	66 (85,7%)	76 (84,4%)	
Unknown primary site	41 (13,1%)	16 (10,9%)	11 (14,3%)	14 (15,6%)	
BRAF mutation	**N (%)**	**N (%)**	**N (%)**	**N (%)**	<0.001
Positive	178 (56,7%)	19 (12,9%)	72 (93,5%)	87 (96,7%)	
Negative	126 (40,1%)	119 (81%)	5 (6,5%)	2 (2,2%)	
Unknown	1 (0,3%)	1 (0,7%)	0 (0%)	0 (0%)	
Not tested	9 (2,9%)	8 (5,4%)	0 (0%)	1 (1,1%)	
Surveillance Imaging	**N (%)**	**N (%)**	**N (%)**	**N (%)**	0.002
Single imaging					
Only CT	84 (26,7%)	43 (29,3%)	25 (32,5%)	16 17,8%)	
Only MRI	20 (6,4%)	13 (8,8%)	3 (3,9%)	4 (4,4%)	
Only PET	4 (1,3%)	1 (0,7%)	3 (3,9%)	0 (0%)	
Double imaging					
CT & MRI	141 (44,9%)	54 (36,7%)	29 (37,6%)	58 64,5%)	
MRI & PET	5 (1,6%)	3 (2,0%)	2 (2,6%)	0 (0%)	
PET & CT	9 (2,8%)	5 (3,4%)	1 (1,3%)	3 (3,3%)	
All imaging					
CT, MRI & PET	20 (6,4%)	8 (5,5%)	5 (6,5%)	7 (7,8%)	
None	31 (9,9%)	20 (13,6%)	9 (11,7%)	2 (2,2%)	
Radiotherapy	**N (%)**	**N (%)**	**N (%)**	**N (%)**	0.02
Yes	136 (43,3%)	67 (45,6%)	23 (29,9%)	46 (51,1%)	
No	178 (56,7%)	80 (54,4%)	54 (70,1%)	44 (48,9%)	
Months alive after latest systemic therapy					0.10
Median	0,8	1,1	0,4	0,7	
Range	0 - 14,6	0* - 14,6	0 - 11,4	0 - 8,9	
Months alive since start treatment					0.13
Median	4,3	3,0	3,7	7,2	
Range	0,1 - 23	0,2 - 23	0,1 - 17,8	1,2 - 17,6	
Duration of systemic therapy in months					<0.001
Median	3	1,4	2,7	5,9	
range	0 - 21,2	0 - 21,2	0* - 16,3	0,1 - 16,7	
Complication systemic therapy**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	0.03
Yes	58 (18,5%)	26 (17,7%)	8 (10,4%)	24 (26,7%)	
No	256 (81,5%)	121 (82,3%)	69 (89,6%)	66 (73,3%)	

*: Result contains 1 day

**: Based on the guideline MelaHS registration

Interventions before death occurred

The imaging interventions initiated, and the therapeutic interventions which started or ended within a number of days before death are shown in Table 5. A CT-scan (75,8%) was most often used in patients with high-stage melanoma, followed by the MRI-scan (50,2%) and PET-scan (9,9%) considering the complete MelaHS registry (0 – 720 days). In the last 30 days before death, almost 20% of the patients received a CT-scan, more than 7% received an MRI-scan whereas the PET-scan was scarcely used (0,4%). In the last 90 days, almost half of the patients (48,3%) had a CT-scan, more than 20% had an MRI and around 3% received a PET-scan. Between 31 and 90 days before death, the increase in imaging interventions was the largest compared to the other time intervals.

In the last six months (180 days) of life, most patients started with immune therapy (33,8%), followed by radiotherapy (23,9%) and targeted therapy (21,0%). In the last 30 days before death, immune therapy was most often initiated (6,3%), compared to targeted- and radiotherapy (3,4% and 4,8% respectively). Of all therapies, even in the last 90 days before death, immune therapy was most frequently given (22,9%).

Just as for the imaging interventions, a relatively large number of patients started with a therapeutic intervention between 31 and 90 days before death, especially immune- and radiotherapy, compared to the other time intervals.

Table 5: Imaging and therapeutic interventions in days before death occurred

	0 - 30	0 - 90	0 - 180	0 - 360	0 - 720	0 - 30	31 - 90	91 - 180	181 - 360	361 - 720
Imaging interventions										
CT-scan	94 (19,7%)	230 (48,3%)	308 (64,7%)	350 (73,5%)	361 (75,8%)	94 (19,7%)	136 (28,6%)	78 (16,4%)	42 (8,8%)	11 (2,3%)
MRI-scan	34 (7,1%)	111 (23,3%)	170 (35,7%)	221 (46,4%)	239 (50,2%)	34 (7,1%)	77 (16,2%)	59 (12,4%)	51 (10,7%)	18 (3,8%)
PET-scan	2 (0,4%)	15 (3,2%)	25 (5,3%)	38 (8,0%)	47 (9,9%)	2 (0,4%)	13 (2,7%)	10 (2,1%)	13 (2,7%)	9 (1,9%)
Therapeutic Interventions										
Start immune therapy	30 (6,3%)	109 (22,9%)	161 (33,8%)	220 (46,2%)	237 (49,8%)	30 (6,3%)	79 (16,6%)	52 (10,9%)	59 (12,4%)	17 (3,6%)
End immune therapy	80 (16,8%)	170 (35,7%)	208 (43,7%)	231 (48,5%)	234 (49,2%)	80 (16,8%)	90 (18,9%)	38 (8%)	23 (4,8%)	3 (0,7%)
Start targeted therapy	16 (3,4%)	44 (9,2%)	100 (21,0%)	152 (31,9%)	167 (35,1%)	16 (3,4%)	28 (5,8%)	56 (11,8%)	52 (10,9%)	15 (3,2%)
End targeted therapy	106 (22,3%)	145 (30,5%)	158 (33,2%)	162 (34,0%)	162 (34,0%)	106 (22,3%)	39 (8,2%)	13 (2,7%)	4 (0,8%)	0 (0,0%)
Start radiotherapy	23 (4,8%)	72 (15,1%)	114 (23,9%)	163 (34,2%)	176 (37,0%)	23 (4,8%)	49 (10,3%)	42 (8,8%)	49 (10,3%)	13 (2,8%)
End radiotherapy	40 (8,4%)	101 (21,2%)	135 (28,4%)	164 (34,5%)	168 (35,3%)	40 (8,4%)	61 (12,8%)	34 (7,2%)	29 (6,1%)	4 (0.8%)

Number of days between therapy until death

In Table 6, patients are divided into different groups, based on the period between the start of last therapy and death. Patients who started with only immune- or only targeted therapy within 30 days before death were younger (64 years and 70 years, respectively), compared to patients who did not received systemic therapy at all (75,5 years). The same was applicable for patients treated within 90 days before death with only immune therapy (73 years) and only targeted therapy (65 years), even though the difference is smaller. The youngest patients (median 63 years) and oldest patients (median 75,5 years) were found in the group of patients treated with both therapies within 90 days before death and patients not receiving systemic therapy at all.

Patients who started with only immune therapy within 30 days before death had more elevated LDH levels compared to the patients who started within 90 days before death, 76,2% versus 58,8%. This proportion for elevated LDH was similar in the case of only targeted therapy, but the difference was smaller. Patients not receiving any systemic therapy, were characterized with lower percentages of elevated LDH levels, although it was notable that in 17,3% of these patients the LDH level have not been determined.

In general, patients with a good performance status (ECOG 0 – 1) had started with only immune therapy and patients with a poorer performance status (ECOG ≥ 2) started with only targeted therapy within 90 days until death. However, the amount of 'unknown' in only targeted therapy patients was relatively high compared to patients who had only received immune therapy. Furthermore, 72,1% of patients receiving both therapies had a good performance status (ECOG 0 – 1) at time of the primary high-stage diagnosis.

Patients who were treated with both therapies experienced the most metastases during their lifetime, i.e. more than 6 metastases on average, compared to the amount of metastases in patients who received only immune, or targeted therapy in the last 90 days of their life. For all groups of patients receiving systemic therapy, higher percentages of distant metastases were found compared to the patients not receiving therapy.

Patients receiving only targeted therapy within 90 days of death had a shorter lifespan from the MelaHS inclusion (0-30 = 0,8 months; 31-90 = 3 months), compared to patients receiving immunotherapy within 90 days of death (0-30 = 1,9 months; 31-90 = 3,4 months). Patients receiving both therapies lived for almost 6 months after the MelaHS inclusion; for patients not receiving systemic therapy, the median was 2 months.

Radiotherapy was used more frequently in patients who received immunotherapy than in patients who received targeted therapy. Furthermore, three out of four patients (75,3%) who did not receive systemic therapy were also not irradiated.

Patients who received immune- or targeted therapy within 30 days before death were mainly screened by a single scan (single imaging) during this period, with the CT-scan being the most frequent. More than one diagnostic intervention (double or all imaging) was performed more often in patients who received immune- and/or targeted therapy within 90 days before death. Almost one third (31,5%) of non-therapy patients had not undergone any diagnostic imaging.

Table 6: Patient and tumor characteristics of different therapies and non-therapy before death							
	Only immune therapy		Only targeted therapy		Systemic therapy*	No therapy**	
	0 - 30 days until death	31 - 90 days until death	0 - 30 days until death	31 - 90 days until death	0 - 90 days until death	No systemic therapy until death	*p*-Value
	N = 21	N = 51	N = 11	N = 19	N = 43	N = 162	
Age at primary high-stage diagnosis							0.06
Median	64	73	70	65	63	75,5	
Range	30 - 82	42 - 90	63 - 89	39 - 89	31 - 79	39 - 97	
Gender	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	0.44
Male	14 (66,7%)	36 (70,6%)	8 (72,7%)	9 (47,4%)	27 (62,8%)	95 (58,6%)	
Female	7 (33,3%)	15 (29,4%)	3 (27,3%)	11 (57,9%)	16 (37,2%)	67 (41,4%)	
Elevated serum LDH level (>250 U/L) at primary high-stage diagnosis	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	0.01
No	5 (23,8%)	20 (39,2%)	1 (9,1%)	4 (21,1%)	14 (32,6%)	50 (30,8%)	
Yes	16 (76,2%)	30 58,8%)	9 81,8%)	14 (73,7%)	28 (65,1%)	84 (51,9%)	
Unknown	0 (0%)	1 (2%)	1 (9,1%)	1 (5,2%)	1 (2,3%)	28 (17,3%)	
ECOG Performance status at primary high-stage diagnosis	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	<0.001
0	4 (19%)	15 (29,4%)	1 (9,1%)	1 (5,2%)	15 (34,9%)	14 (8,6%)	
1	9 (42,9%)	23 45,1%)	4 (36,4%)	5 (26,3%)	16 (37,2%)	25 (15,4%)	
2	3 (14,3%)	7 (13,7%)	0 (0%)	4 (21,1%)	6 (14%)	19 (11,7%)	
3	2 (9,5%)	3 5,9%)	2 (18,1%)	2 (10,6%)	1 (2,3%)	26 (16,1%)	
4	0 (0%)	0 (0%)	0 (0%)	1 (5,2%)	0 (0%)	6 (3,7%)	
Unknown	3 (14,3%)	3 5,9%)	4 (36,4%)	6 (31,6%)	5 (11,6%)	72 (44,5%)	
Distant Metastases	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	0.27
No/Unknown	0 (0%)	4 (7,8%)	1 (9,1%)	1 (5,3%)	0 (0%)	15 (9,3%)	
Yes	21 (100%)	47 (92,2%)	10 (90,9%)	18 (94,7%)	43 (100%)	147 (90,7%)	
Total amount of metastases							<0.001
Mean	3,9	4,3	3,2	4,5	6,5	2,8	
Amount of metastases at primary high-stage diagnosis							
Mean	3	3,1	2,7	3,8	3,7	2,4	0.04
Location of distant metastases							
Respiratory system	71%	65%	73%	74%	72%	52%	0.07
Connective/subcutaneous tissue & other soft tissue	19%	22%	18%	37%	42%	23%	0.12
Bones, joints & joint cartilage	38%	49%	27%	26%	44%	25%	0.01
Brain & nervous system	57%	39%	27%	68%	79%	39%	<0.001
Skin	0%	8%	9%	0%	14%	3%	0.04
Lymph nodes	29%	45%	45%	68%	63%	35%	0.003
Digestive system	76%	49%	55%	63%	60%	39%	0.005
Other	38%	35%	18%	42%	47%	26%	0.1
Time in months between primary and high-stage diagnosis							0.12
Median	23,1	12,6	21,2	14,8	17,8	12,6	
Range	0 - 160,9	0 - 262,3	0 - 85,7	0 - 77,5	0 - 149,7	0 - 486,3	
Months between high-stage diagnosis and death							0.12
Median	1,9	3,4	0,8	3	5,8	2	
Range	0,9 - 14,5	1,4 - 10,8	0,6 - 5,3	1,5 - 8,3	1,7 - 15	0,1 - 16,8	
Radiotherapy	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	0.03
Yes	10 (47,6%)	21 (41,2%)	1 (9,1%)	5 (26,3%)	17 (39,5%)	40 (24,7%)	
No	11 (52,4%)	30 58,8%)	10 90,9%)	14 (73,7%)	26 (60,5%)	122 (75,3%)	
Surveillance Imaging							
Single imaging							<0.001
Only CT	10 (47,6%)	14 (27,4%)	8 (72,7%)	7 36,9%)	9 (20,9%)	56 (34,6%)	
Only MRI	3 (14,3%)	4 (7,8%)	0 (0%)	0 (0%)	1 (2,3%)	14 (8,6%)	
Only PET	0 (0%)	1 (2%)	0 (0%)	1 (5,2%)	0 (0%)	2 (1,2%)	
Double imaging							
CT & MRI	7 (33,3%)	16 (31,4%)	2 (18,2%)	6 (31,6%)	26 (60,5%)	32 (19,7%)	
MRI & PET	0 (0%)	2 (3,9%)	0 (0%)	1 (5,2%)	0 (0%)	1 (0,6%)	
PET & CT	0 (0%)	1 (2%)	0 (0%)	1 (5,2%)	3 (7%)	3 (1,9%)	
All imaging							
CT, MRI & PET	0 (0%)	3 5,9%)	0 (0%)	0 (0%)	3 (7%)	3 (1,9%)	
None	1 (4,8%)	10 (19,6%)	1 (9,1%)	3 (15,9%)	1 (2,3%)	51 (31,5%)	

*: Patients who received both therapies during MelaHS and received within 90 days before death immune and/or targeted therapy

**: Patients who not received immune or targeted therapy from high-stage diagnosis till death

Discussion

This study, of 476 patients with high-stage melanoma, showed that patient and tumor characteristics such as age, performance status (ECOG), elevated LDH levels and having a BRAF mutation were possible factors associated with the use and timing of systemic therapy shortly before death. In terms of surveillance imaging, the CT-scan has been most commonly used in the last 90 days of life, where one out of five patients received a scan 30 days before death.

High-stage melanoma is a disease associated with a poor prognosis. Prior to the introduction of immune- and targeted therapy for metastatic melanoma(22), chemotherapy (e.g., dacarbazine) was the standard systemic therapy for patients with metastatic melanoma.(26) However, this was of limited therapeutic benefit for these patients,(27,28) but the high response rates of recently introduced systemic therapies gave these patients a raised level of expectation.

The proportion of men in this study was higher. However, melanoma is more common in women(1), but the disease – in terms of survival – is generally worse in men.(29,30) As the time between primary diagnosis and MelaHS increases, the men/women ratio became more balanced. A possible reason for this difference could lie in the behavioural pattern of women, giving them a higher rate of survival, as they are more likely to enter the healthcare system than men.(31) If high-stage melanoma was present at the time of the primary diagnosis (MelaHS), these patients were older than patients who were not in a high-stage at the initial diagnosis. A possible explanation for the disproportionate increase in incidence among older people is that they have benefited less from public health campaigns than young people.(32,33)

At the time of the MelaHS inclusion, 95% had a metastasis, in which the respiratory system was most affected. This is supported by the study of Damsky *et al.*, where metastasis is most common in the lungs, and sites such as brain, bones and intestines, which are detected later in the disease progression.(34) Two thirds of these patients who had received systemic therapy, were younger and lived almost twice as long since the MelaHS inclusion than non-systemic treated patients, although the median survival time of systemic treated patients was less than half a year.

Significantly fewer patients with an unknown primary site had been treated systemically in the last months before death. Studies have shown that the outcome of unknown primary site patients was poorer when treated systemically than in known primary site patients, therefore a decision has been made not to start these systemic therapies.(35) However, this may also be due to the fact that these patients were diagnosed later, and the disease was already too progressive. Patients in this study with a BRAF mutation also appear to have been more likely to receive systemic treatment in the last months before death, mainly due to the fact that targeted therapy was intended for BRAF positive patients

and previous studies have shown that this therapy has improved progression-free and overall survival.(36)

Patients who received both therapies were younger, more often had a BRAF mutation, the duration of treatment and survival were longer, received more radiotherapy and were most often screened with mainly a combination of CT & MRI, compared to patients who received only immune- or targeted therapy during the end of life. A possible explanation could be that these patients received both therapies shortly before death due to their younger age and ECOG performance status. Therefore, making these patients more resistant to the severe side effects and their impact on the quality of life. Also having a BRAF mutation, could have led to a decision to apply both therapies rather than only immune therapy.(22)

In terms of surveillance imaging, the CT scan has been most widely used considering the entire MelaHS registration, including patients in the last 90 days of life. Eventually, one out of five patients received a scan 30 days before death. A possible explanation, in view of the high costs and potential serious side effects, could be that patients should be periodically monitored with new imaging during adjuvant systemic treatment to avoid unnecessary further treatment.(38)

Immune therapy was most commonly started shortly before death. Three months before death almost one in four of all patients still started with this therapy, where in the last 30 days before death 6% of all patients received this therapy for the first time. It is difficult to draw a specific conclusion here, perhaps that the clinician and the patient overestimated their chances, with the aim of nonetheless using immune therapy to prolong the survival time, improving symptom control and sustaining hope, to the detriment of the quality of life during the end of life. Interestingly, targeted therapy was the longest lasting treatment in the last months until death, which was probably due to the fact that this therapy was more tolerable than immune therapy.(36)

Differences in patient and tumor characteristics were found in patients who had been treated differently in the last months before death. This study indicates that age and possibly the ECOG performance status were factors in determining whether a patient is still eligible for systemic therapy. Patients who started with only immune therapy shortly before death (within 30 days) were younger, compared to patients who started therapy within 90 days or patients who did not received any therapy at all. Possible explanations are that these new therapies are associated with potentially severe side effects, bearing in mind that older patients tend to be less fit, have comorbidities and the quality of life in the end of life must be taken into account.(14,36) However, some studies have shown that elderly people had similar reactions to systemic therapy compared with their younger counterparts and that the ECOG performance status was therefore an important tool of eligibility for systemic therapy.(39,40)

Patients who received a systemic therapy shortly before death (within 30 days) were more likely to have elevated LDH levels than patients who started within 90 days. Research also showed that when LDH was elevated, this correlates with deteriorated survival and the long-term benefit of systemic therapy was unlikely for patients with elevated LDH and was used to guide patient selection for this therapy.(42,43)

In particular, patients who had started with only targeted therapy within 90 days before death had more elevated LDH levels, had a poor performance score (ECOG ≥ 2), had a shorter life expectancy since the MelaHS inclusion and were older when they started the therapy within 30 days before death compared to patients who had started with only immune therapy within 90 days before death, which was not unexpected. First, this therapy, as aforementioned, was more tolerable than immune therapy. Second, easier to manage and thirdly, their effectiveness was quickly visible and clinically assessable, mainly in reducing cancer-related symptoms, therefore more often used in patients who were very ill.(22,44) However, it was remarkable that some patients received only immune therapy this close before death (within 30 days), even though it takes longer to become effective, has more severe side effects and is very expensive.(22)

To our knowledge, this is the first study aimed at identifying the utilization of immune and targeted therapy, and different diagnostic imaging in high-stage melanoma patients shortly before death occurred. Some additional limitations of this study should be noted. First, this research has been conducted on a particular selection of patients. Patients have only been included with a diagnosis in a certain period of time and they must have died before a certain date. If this study is followed up in two years' time, it might not have the same result, because there was a relatively large amount of 'unknown' data. Second, there is a possible selection bias , as data from a single large melanoma centre were absent in this study, therefore this study may not fully represent the population with high-stage melanoma in the Netherlands (13 out of 14 centres). Thirdly, there was no data available on certain factors such as patient preferences, quality of life index and which clinician per patient. Prospective studies could further examine these factors.

However, in spite of the possible limitations, an important strength of this study is the use of data from the Netherlands Cancer Registry (NCR) with an additional registration (MelaHS) that includes nationwide data of Dutch patients diagnosed with high-stage melanoma. Data in the NCR is uniformly and independently gathered by trained data managers, who also operate according to the same guidelines. In addition, high-stage patients outside the melanoma centres and/or who did not receive any treatment, are included in the registry. This increases the validity of the results and provides a good reflection of daily practice.

Conclusion

In conclusion, this study showed that mainly younger patients, patients with a good performance status, having a BRAF mutation and the elevated level of LDH are possible factors related to the choice of starting these systemic interventions shortly before death. Therefore, routine diagnostic imaging has an important role to play in order to continue to systematically monitor high-stage melanoma patients more frequently and to reconsider the survival prospects of individual patients on the basis of this intervention.

Targeted therapy could be said to be used for potentially weaker and older patients (if BRAF mutated) and immunotherapy (and combination of both) for younger and potentially healthier patients, yet – as mentioned in the discussion – there are differences that are difficult to explain. The trajectory of patients with metastatic melanoma is by definition uncertain and the time until death can hardly be predicted. For patients with metastatic melanoma whose potential for long-term survival is limited due to the advanced nature of the disease, the quality of life and potential benefits of systemic therapy for the time remaining should be considered repeatedly.

To start or end a systemic therapy is a complicated and often emotionally charged decision, especially when the patient is approaching the end of life. This decision must be made by a well-informed assessment of both the risks and benefits by the clinician and the patient. Therefore, the advice is based on shared-decision making, in which the clinician informs the patient about the treatment possibilities to prolong life, but also discusses possible risks including serious side effects and deterioration of quality of life, so that the patient can make an informed decision.

Understanding end of life facilitates complex end of life decision making. That is why we urgently need to develop well-defined and demarcated guidelines for starting and ending systemic therapies for high-stage melanoma patients in the last months of life.

References

1. Integraal Kankercentrum Nederland. Huidkanker - IKNL [Internet]. Iknl.Nl. Available from: https://www.iknl.nl/kankersoorten/huidkanker
2. Integraal Kankercentrum Nederland. Incidentie huidkanker IKNL [Internet]. Available from: https://www.iknl.nl/kankersoorten/huidkanker/registratie/incidentie
3. Mescher L. Skin | Junqueira's Basic Histology: Text and Atlas, 15e [Internet]. 15th ed. 15e. 2018. Available from: https://accessmedicine-mhmedical-com.proxy-ub.rug.nl/content.aspx?bookid=2430&sectionid=190285972
4. Miller AJ, Mihm MC. Melanoma. N Engl J Med [Internet]. 2006 Jul 6;355(1):51–65. Available from: http://www.nejm.org/doi/abs/10.1056/NEJMra052166
5. Gandini S, Sera F, Cattaruzza MS, Pasquini P, Picconi O, Boyle P, et al. Meta-analysis of risk factors for cutaneous melanoma: II. Sun exposure. Eur J Cancer [Internet]. 2005 Jan;41(1):45–60. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15617990
6. Thomas NE, Edmiston SN, Alexander A, Millikan RC, Groben PA, Hao H, et al. Number of nevi and early-life ambient UV exposure are associated with BRAF-mutant melanoma. Cancer Epidemiol Biomarkers Prev. 2007 May 1;16(5):991–7.
7. Schadendorf D, van Akkooi ACJ, Berking C, Griewank KG, Gutzmer R, Hauschild A, et al. Melanoma. Vol. 392, The Lancet. Lancet Publishing Group; 2018. p. 971–84.
8. Integraal Kankercentrum Nederland. Europese verschillen in incidentie en sterfte melanoom [Internet]. 2019. Available from: https://www.iknl.nl/nieuws/2019/europese-verschillen-in-incidentie-en-sterfte-mela
9. Schreuder K, de Groot J, Hollestein L, Louwman M. Huidkanker in Nederland [Internet]. 2019. 25–25 p. Available from: https://iknlsawebprod.blob.core.windows.net/mediacontainer/iknl/media/pdfs/kankersoorten/iknl_huidkanker-in-nl_rapport_nkr.pdf
10. IKNL. Huidkanker | Cijfers & Context | Trends | Volksgezondheidenzorg.info [Internet]. 2019. Available from: https://www.volksgezondheidenzorg.info/onderwerp/huidkanker/cijfers-context/trends#node-trend-nieuwe-gevallen-melanoom
11. IKNL. NKR Cijfers - Overleving, Stadium bij diagnose, TNM 7e editie (2010-2017) [Internet]. [cited 2020 Oct 29]. Available from: https://www.iknl.nl/nkr-cijfers
12. Gershenwald JE, Scolyer RA, Hess KR, Sondak VK, Long G V., Ross MI, et al. Melanoma staging: Evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin [Internet]. 2017 Nov 1;67(6):472–92. Available from: http://doi.wiley.com/10.3322/caac.21409
13. Flaherty KT, Puzanov I, Kim KB, Ribas A, McArthur GA, Sosman JA, et al. Inhibition of mutated, activated BRAF in metastatic melanoma. N Engl J Med. 2010 Aug 26;363(9):809–19.
14. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010 Aug 19;363(8):711–23.
15. Longo C, Pampena R, Lallas A, Kyrgidis A, Stratigos A, Peris K, et al. Adjuvant therapy for cutaneous melanoma: a systematic review and network meta-analysis of new therapies. J Eur Acad Dermatology Venereol [Internet]. 2020 May 6;34(5):956–66. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/jdv.16074
16. Wolchok JD, Chiarion-Sileni V, Gonzalez R, Rutkowski P, Grob J-J, Cowey CL, et al. Overall Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. N Engl J Med [Internet]. 2017 Oct 5;377(14):1345–56. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1709684
17. Conic RRZ, Knackstedt R, Sussman TA, Rambhia S, Damiani G, Funchain P, et al. Utilization and impact of immunotherapy in stage IV melanoma using the National Cancer Database. Melanoma Res [Internet]. 2020;30(4):376–85. Available from:

https://pubmed.ncbi.nlm.nih.gov/32404731/
18. Samuel E, Moore M, Voskoboynik M, Shackleton M, Haydon A. An update on adjuvant systemic therapies in melanoma. Melanoma Manag [Internet]. 2019 Nov 1;6(3):MMT28. Available from: /pmc/articles/PMC6891936/?report=abstract
19. Eskens F, Wymenga A, Beerepoot L, NVMO-commissie BOM. Adjuvant nivolumab bij stadium IIIb, IIIc of IV melanoom na volledige chirurgische resectie. Med Oncol [Internet]. 2018 Dec;9(21):53–6. Available from: https://medischeoncologie.nl/jaargangen/2018/9-dec/adjuvant-nivolumab-bij-stadium-iiib-iiic-of-iv-melanoom-na-volledige-chirurgische-resectie-2.html
20. Eskens F, Wymenga A, Beerepoot L, NVMO-commissie BOM. Adjuvant dabrafenib in combinatie met trametinib bij stadium III melanoom. Med Oncol [Internet]. 2018 Dec;9(21):47–50. Available from: https://medischeoncologie.nl/jaargangen/2018/9-dec/adjuvant-dabrafenib-in-combinatie-met-trametinib-bij-stadium-iii-melanoom-2.html
21. Leeneman B, Uyl-De Groot CA, Aarts MJB, Van Akkooi ACJ, Van Den Berkmortel FWPJ, Van Den Eertwegh AJM, et al. Healthcare costs of metastatic cutaneous melanoma in the era of immunotherapeutic and targeted drugs. Cancers (Basel) [Internet]. 2020 Apr 1;12(4):1003. Available from: /pmc/articles/PMC7225943/?report=abstract
22. van Zeijl MCT, van den Eertwegh AJ, Haanen JB, Wouters MWJM. (Neo)adjuvant systemic therapy for melanoma [Internet]. Vol. 43, European Journal of Surgical Oncology. W.B. Saunders Ltd; 2017. p. 534–43. Available from: https://pubmed-ncbi-nlm-nih-gov.proxy-ub.rug.nl/27453302/
23. Ho TH, Barbera L, Saskin R, Lu H, Neville BA, Earle CC. Trends in the aggressiveness of end-of-life cancer care in the universal health care system of Ontario, Canada. J Clin Oncol [Internet]. 2011 Apr 20;29(12):1587–91. Available from: /pmc/articles/PMC3082976/?report=abstract
24. Cheung MC, Earle CC, Rangrej J, Ho TH, Liu N, Barbera L, et al. Impact of aggressive management and palliative care on cancer costs in the final month of life. Cancer [Internet]. 2015 Sep 15;121(18):3307–15. Available from: https://onlinelibrary.wiley.com/doi/10.1002/cncr.29485
25. DIeng M, Khanna N, Nguyen MTH, Turner R, Lord SJ, Menzies AM, et al. Cost-effectiveness analysis of PET/CT surveillance imaging to detect systemic recurrence in resected stage III melanoma: Study protocol. BMJ Open [Internet]. 2020 Nov 5;10(11):37857. Available from: http://bmjopen.bmj.com/
26. Yang AS, Chapman PB. The History and Future of Chemotherapy for Melanoma [Internet]. Vol. 23, Hematology/Oncology Clinics of North America. NIH Public Access; 2009. p. 583–97. Available from: /pmc/articles/PMC3904102/?report=abstract
27. Lui P, Cashin R, Machado M, Hemels M, Corey-Lisle PK, Einarson TR. Treatments for metastatic melanoma: Synthesis of evidence from randomized trials [Internet]. Vol. 33, Cancer Treatment Reviews. Cancer Treat Rev; 2007. p. 665–80. Available from: https://pubmed-ncbi-nlm-nih-gov.proxy-ub.rug.nl/17919823/
28. Eigentler TK, Caroli UM, Radny P, Garbe C. Palliative therapy of disseminated malignant melanoma: A systematic review of 41 randomised clinical trials. Vol. 4, Lancet Oncology. Lancet Publishing Group; 2003. p. 748–59.
29. el Sharouni MA, Witkamp AJ, Sigurdsson V, van Diest PJ, Louwman MWJ, Kukutsch NA. Sex matters: men with melanoma have a worse prognosis than women. J Eur Acad Dermatology Venereol [Internet]. 2019 Nov 1;33(11):2062–7. Available from: https://pubmed-ncbi-nlm-nih-gov.proxy-ub.rug.nl/31246315/
30. Joosse A, De Vries E, Eckel R, Nijsten T, Eggermont AMM, Hölzel D, et al. Gender differences in melanoma survival: Female patients have a decreased risk of metastasis. J Invest Dermatol [Internet]. 2011;131(3):719–26. Available from: https://pubmed-ncbi-nlm-nih-gov.proxy-ub.rug.nl/21150923/
31. Hajdarevic S, Schmitt-Egenolf M, Brulin C, Sundbom E, Hörnsten Å. Malignant melanoma:

gender patterns in care seeking for suspect marks. J Clin Nurs [Internet]. 2011 Sep 1;20(17–18):2676–84. Available from: http://doi.wiley.com/10.1111/j.1365-2702.2011.03788.x
32. Schuurman MS, Hollestein LM, Bastiaannet E, Posthuma EFM, van Akkooi AJC, Kukutsch NA, et al. Melanoma in older patients: declining gap in survival between younger and older patients with melanoma. Acta Oncol (Madr) [Internet]. 2020 Jan 2;59(1):4–12. Available from: https://pubmed-ncbi-nlm-nih-gov.proxy-ub.rug.nl/31347929/
33. Aitken JF, Youlden DR, Baade PD, Soyer HP, Green AC, Smithers BM. Generational shift in melanoma incidence and mortality in Queensland, Australia, 1995–2014. Int J Cancer [Internet]. 2018 Apr 15;142(8):1528–35. Available from: https://pubmed.ncbi.nlm.nih.gov/29105744/
34. Damsky WE, Rosenbaum LE, Bosenberg M. Decoding melanoma metastasis [Internet]. Vol. 3, Cancers. Multidisciplinary Digital Publishing Institute (MDPI); 2011. p. 126–63. Available from: /pmc/articles/PMC3756353/?report=abstract
35. Utter K, Goldman C, Weiss SA, Shapiro RL, Berman RS, Wilson MA, et al. Treatment outcomes for metastatic melanoma of unknown primary in the new era: A single-institution study and review of the literature. Oncol [Internet]. 2017 Sep 1;93(4):249–58. Available from: /pmc/articles/PMC5617794/?report=abstract
36. Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med [Internet]. 2011 Jun 30;364(26):2507–16. Available from: /pmc/articles/PMC3549296/?report=abstract
37. Federatie Medisch Specialisten. Melanoom - Aanvullend onderzoek/rol PET CT in follow-up - Richtlijn - Richtlijnendatabase [Internet]. Richtlijnen. 2016. Available from: https://richtlijnendatabase.nl/richtlijn/melanoom/melanoom_-_locoregionale_ziekte/melanoom_-_aanvullend_onderzoek_rol_pet_ct_in_follow-up.html
38. Federatie Medisch Specialisten. Melanoom - Adjuvante systemische behandeling na initiële behandeling - Richtlijn - Richtlijnendatabase [Internet]. Richtlijnen. 2019. Available from: https://richtlijnendatabase.nl/richtlijn/melanoom/melanoom_-_locoregionale_ziekte/melanoom_-_adjuvante_systemische_behandeling_na_initi_le_behandeling.html#tab-content-starting-question
39. Sileni VC, Pigozzo J, Ascierto PA, Grimaldi AM, Maio M, Di Guardo L, et al. Efficacy and safety of ipilimumab in elderly patients with pretreated advanced melanoma treated at Italian centres through the expanded access programme. J Exp Clin Cancer Res [Internet]. 2014 Apr 4;33(1):30. Available from: /pmc/articles/PMC3996509/?report=abstract
40. Azam F, Latif MF, Farooq A, Tirmazy SH, Alshahrani S, Bashir S, et al. Performance Status Assessment by Using ECOG (Eastern Cooperative Oncology Group) Score for Cancer Patients by Oncology Healthcare Professionals. Case Rep Oncol [Internet]. 2019 Sep 1;12(3):728–36. Available from: https://pubmed.ncbi.nlm.nih.gov/31616281/
41. Maltoni M, Caraceni A, Brunelli C, Broeckaert B, Christakis N, Eychmueller S, et al. Prognostic factors in advanced cancer patients: Evidence-based clinical recommendations - A study by the steering committee of the european association for palliative care. J Clin Oncol [Internet]. 2005;23(25):6240–8. Available from: https://pubmed.ncbi.nlm.nih.gov/16135490/
42. Agarwala SS, Keilholz U, Gilles E, Bedikian AY, Wu J, Kay R, et al. LDH correlation with survival in advanced melanoma from two large, randomised trials (Oblimersen GM301 and EORTC 18951). Eur J Cancer [Internet]. 2009 Jul;45(10):1807–14. Available from: https://pubmed.ncbi.nlm.nih.gov/19419855/
43. Kelderman S, Heemskerk B, Van Tinteren H, Van Den Brom RRH, Hospers GAP, Van Den Eertwegh AJM, et al. Lactate dehydrogenase as a selection criterion for ipilimumab treatment in metastatic melanoma. Cancer Immunol Immunother [Internet]. 2014 Mar 8;63(5):449–58. Available from: https://link-springer-com.proxy-ub.rug.nl/article/10.1007/s00262-014-1528-9
44. Delaye M, Scotte F, Voisin-Saltiel S, Pavliuc E, Vigouret-Viant L, Dauchy S, et al. Using targeted

therapies at the end of life. BMJ Support Palliat Care [Internet]. 2020 Aug 27 23];bmjspcare-2020-002529. Available from: https://spcare.bmj.com/content/early/2020/08/27/bmjspcare-2020-002529