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Return to work after neoadjuvant versus adjuvant immunotherapy in stage III melanoma patients

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Abstract

Purpose Neoadjuvant immunotherapy in stage III melanoma has recently been shown to improve event-free and distant metastasis-free survival compared to adjuvant therapy. Pathologic response allows for subsequent personalization of surgery and omission/application of adjuvant therapy. We addressed the question whether neoadjuvant therapy allows an earlier and more to a more extent return to work in this curatively treated patient population.

Methods In this single-center retrospective analysis of patients participating at the Netherlands, we interviewed via the telephone 88 stage III melanoma patients treated with neoadjuvant versus adjuvant immunotherapy in regards of their stopping work during therapy, and when returning partially or fully to work.

Results Six, 12, and 24 months post start of therapy at least partially worked 80% versus 61%, 84% versus 73%, and 91% versus 82% in the neoadjuvant versus adjuvant groups. Full return to work was observed at 6 months in 52% versus 48%, at 1 year in 71% versus 52%, and at 2 years 82% versus 62%, respectively. Return to work (RTW) started in general in both groups after finishing the systemic therapies.

Conclusions Our data suggest that the manner of therapy (neoadjuvant versus adjuvant) and potentially its treatment duration might be major factors influencing the timing and extent of RTW.

Implications for Cancer Survivors A faster and full RTW is not only of importance for the patient's well-being and QoL, but has also a significant financial impact on patients and their families.

Keywords Stage III melanoma · Return to work after neoadjuvant vs adjuvant immunotherapy · Quality of life

Question: Is there a difference in regards of return to work (RTW) in patients with stage III melanoma patients whether they are treated with neoadjuvant or adjuvant checkpoint inhibition?

Findings: In this retrospective analysis, we found that patients treated with neoadjuvant immunotherapy return to work earlier and to a larger extent after stopping their work for therapy than adjuvant treated patients.

Meaning: Response-driven reduction in the extent adjuvant immunotherapy might improve patients' quality of life (QoL) and RTW and have a socioeconomic impact.

J. M. Lijnsvelt and Z. Lieveense shared authorship.

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Introduction

Melanoma is a common cancer diagnosed worldwide. Its incidence has increased over the last decades and continues to rise [1, 2]. Prior to modern adjuvant systemic therapies, the 5-year melanoma-specific survival was poor with 78%, 59%, and 40% overall survival (OS) for AJCC (7th edition) stage IIIA, IIIB, and IIIC melanoma patients, respectively [3, 4].

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Both, checkpoint inhibition with CTLA-4 (ipilimumab), and PD-1 blocking antibodies (nivolumab, pembrolizumab), as well as MAPK pathway targeting therapies (dabrafenib + trametinib), have shown to improve relapse-free survival (RFS) in stage III melanoma to a 50–60% RFS at 4 or 5 years [5–12].

Neoadjuvant immunotherapy in stage III melanoma has recently been shown to improve event-free survival as compared to 1 year adjuvant therapy. Six weeks of neoadjuvant combination immunotherapy induces even higher response rates, allowing frequently the omission of extensive surgery and adjuvant therapy [13, 14]. Only patients not responding to the short neoadjuvant therapy seem to be in need of extensive surgery and lymph node dissection (LND) and can benefit from additional 1 year adjuvant therapy [15]. These phase 2 data were recently confirmed in the phase 3 NADINA trial, which compared two cycles of neoadjuvant nivolumab plus ipilimumab versus 1 year adjuvant nivolumab. A statistically significant improved event-free survival (EFS) and distant metastasis-free survival (DMFS) was found at 12 months and at 18 months with hazard ratios of 0.32 and 0.37 in favor of the neoadjuvant arm, respectively. This trial incorporated a personalization of the adjuvant part, namely omitting any adjuvant therapy for patients achieving a major pathologic response (< 10% vital tumor after the neoadjuvant therapy) [16].

With the improvements in melanoma treatment and due to the rising incidence of melanoma, the number of long-term melanoma survivors is continuously increasing (<https://csn.cancer.org> and www.cancer.org) [1, 2]. Since melanoma is one of the most common cancers diagnosed in young adults, a considerable part of the melanoma patients and long-term melanoma survivors will be part of the working population (<https://doi.org/https://doi.org/10.1111/ddg.15560>) [3, 17].

Cancer treatment can cause somatic and psychological adverse effects which can heavily impact and disrupt the daily life of patients. Immunotherapy is known to cause immune-related adverse events (irAEs), including fatigue, diarrhea, pruritus, rash, colitis, nausea, asthenia, arthralgia, and endocrine disorders [17]. Fatigue, which is the most common irAE, has been identified as the main factor to be associated with no or a late return to work (RTW) [18, 19]. Some of these (long-term) adverse events can strongly affect the ability to work and therefore impact continuing or returning to work. Previous studies show that fatigue was the most self-reported reason for impaired RTW [20].

Unemployment can impact the daily structure and psychological well-being of patients. The workplace can offer a feeling of purpose beyond the illness and a renewed source of focus. It provides a sense of “normality” and a feeling of social belonging as it allows the patient to participate in society [21]. Therefore, work plays a role in establishing the patient’s identity and contributes to building social connections and meaningful relationships with others [22]. On the other hand,

discontinuation of work is associated with a decreased self-esteem and financial problems. At a larger scale, discontinuation of work of cancer patients has a societal and financial impact on enterprises and society through lower productivity, missing workers, and associated costs [21, 23–25].

We hypothesize that patients receiving a short period (6 weeks) of neoadjuvant immunotherapy will return to work earlier and to a greater extent than those receiving adjuvant immunotherapy (generally for 1 year). Therefore, the aim of this retrospective study is to investigate RTW of patients with stage III melanoma who received neoadjuvant ipilimumab + nivolumab versus patients who received adjuvant nivolumab.

Methods

Study population

This retrospective cohort study is a sub-cohort analysis of the AILEEN study (trial registration in the Netherlands, NL9198), an observational cohort study aiming at describing QoL of long-term surviving stage III and stage IV melanoma patients. In our sub-cohort analysis, we included all stage III melanoma patients treated with checkpoint inhibition at the Netherlands Cancer Institute. Patients agreeing in their informed consent to be contacted for further questions were telephone contacted and asked the following questions: (1) when after the surgery have you returned partial or fully working as at baseline, and (2) when fully returned to work if first worked partially. No further questions were asked, especially not whether the patients have done more physically work. Patients were treated in trials with neoadjuvant immunotherapy or with standard adjuvant immunotherapy. Only patients between 18 and 66 years old, being part of the working population (including voluntary work), with resectable stage III melanoma, and a World Health Organization (WHO) performance status score of 0 were included. Patients were excluded if they were retired or unemployed upfront start of the (neo)adjuvant therapy or if their ability to work was already impacted by other cancer treatments in the past. All patients signed the informed consent form and gave permission to be approached for follow-up research.

Patient treatment

In the neoadjuvant cohort, patients were treated with two cycles of neoadjuvant ipilimumab + nivolumab within the OpACIN-neo study and the PRADO extension cohort. Patients were screened and included (needed to be within 4 weeks) for OpACIN-neo between November 24, 2016, and June 28, 2018, and for PRADO between November 2018 and January 2020. All patients included in the neoadjuvant

cohort for this analysis here were treated between December 2016 and December 2019 [26, 27]. In OpACIN-neo, three different dosing schedules with ipilimumab + nivolumab were used, and all patients underwent a therapeutic lymph node dissection (TLND) of all lymph nodes in the region where the macroscopic metastasis was diagnosed. In the PRADO cohort, pathological response was assessed by a small surgical procedure removing one index lymph node (ILN), the largest lymph node metastasis, marked upfront the neoadjuvant therapy (e.g., by a magnetic marker) [28]. Only in case of pathologic non-response (pNR, > 50% vital tumor) or partial response (pPR, 10–50% vital tumor) after the neoadjuvant therapy a subsequent LND (removal of all remaining lymph nodes of that region) was performed and in case of pNR also adjuvant therapy started [17].

The adjuvant cohort consisted of patients treated with standard adjuvant immunotherapy with nivolumab 4-weekly starting between January 2019 and December 2020. Patients started either after having a melanoma-positive sentinel node (SN) after the sentinel node procedure (SNP) detecting the first draining lymph node of the primary melanoma, after satellite or in-transit metastases resection only, or in case of macroscopic disease, after LND with their adjuvant therapy.

The extent-of-surgery cohorts were divided into the following: (i) “no LND” cohort: patients undergoing either a satellite or in-transit metastases resection only, a sentinel node procedure (SNP) only, or patients with macroscopic disease undergoing index node (ILN) procedure only, or (ii) “LND” cohort: patients undergoing therapeutic lymph node dissection (TLND) after non response in the ILN in the neoadjuvant cohort or TLND upfront in the adjuvant cohort for macroscopic disease.

Data collection

Patients were one time telephone interviewed to obtain information about their date of partial RTW and date of full RTW. In addition, sociodemographic data and clinical information were obtained from patients’ medical health record. The data cutoff date was January 3, 2023. Partial RTW was defined as the moment patients returned to work to lower capacity and hours as prior to therapy after discontinuation of work. Full RTW was defined as the moment that patients returned to work to the same capacity and hours as prior therapy.

Statistical analysis

Time to partial RTW and time to full RTW were defined as time from start of treatment to at least partial RTW and full RTW, respectively. Different starting points were considered depending on treatment received: date of start of immunotherapy for the neoadjuvant group, while for patients

in the adjuvant group the date of SNP/LND was considered. Patients who did not RTW during follow-up were censored at the time of their telephone interview.

Baseline characteristics in the neoadjuvant cohort were compared to the adjuvant cohort using Fisher’s exact test for categorical variables and the Mann–Whitney *U*-test for continuous variables.

Survival estimates were obtained using the Kaplan–Meier method, and the cumulative incidences curves were obtained from these as one minus the Kaplan–Meier estimator of the survival function. Comparison of survival estimates at 6, 12, and 24 months was performed with a *z*-test using Greenwood’s formula for standard errors.

Neoadjuvant versus adjuvant immunotherapy cohorts and “LND” versus “no LND” cohorts were analyzed separately. Patients who only received a SNP (adjuvant cohort) or ILN resection (neoadjuvant cohort) were allocated to the “no LND” cohort. Median follow-up time was calculated using the reverse Kaplan–Meier method.

Univariable and multivariable Cox regression analyses were performed with potential variables associated with RTW: age, gender, marital status, education level, therapy, “LND” or “no LND” (modelled as a time-dependent covariate), and therapy (neoadjuvant or adjuvant). For full RTW, analyses adjusting for previous partial RTW as a time-dependent covariate were also performed. A non-linear association of age with RTW was explored using restricted cubic splines, and based on this, a cutoff of 50 years was used for dichotomization. Sensitivity analyses were performed modelling a constant effect of age up to 50 years and a linear trend after 50. Hazard ratios (HRs), 95% confidence intervals (CIs), and *P*-values were presented. Proportionality of hazards was assessed with a test for independence between scaled Schoenfeld residuals and time. Analyses were performed using SPSS Statistics (version 27) and R (version 3.5.1).

Results

Baseline characteristics

All 148 immunotherapy-treated patients participating in the AILEEN study were screened for eligibility, of whom 110 (74%) were enrolled and telephone interviewed between May and June 2022 (supplemental Fig. 1). Fifteen patients were excluded due to unemployment. Five patients were not reachable for the telephone interview. Two other patients were excluded because their workability was already impacted by other cancer treatments in the past. This resulted in a total sample of 88 patients.

The median time from start of treatment until the telephone interview was 33.0 and 40.9 months for adjuvant

and neoadjuvant patients, respectively. In the neoadjuvant cohort, more patients underwent LND, either before or after RTW, as compared to the adjuvant cohort (68% versus 46%, $P = 0.052$). However, LNDs occurring before RTW, which are considered for analysis of time to RTW, were similarly distributed between the neoadjuvant and adjuvant cohorts (41% versus 39% [$P = 1.00$], for partial RTW, and 48% versus 41% [$P = 0.67$], for full RTW, respectively). Five patients (11%) in the neoadjuvant cohort received adjuvant therapy after the neoadjuvant immunotherapy due to a pathological non-response, while all patients in the adjuvant cohort had received adjuvant therapy. Other characteristics were balanced between the neoadjuvant and adjuvant therapy cohorts (Table 1).

Work continuation and RTW

Baseline work continuation, final partial RTW, and final full RTW are displayed according to systemic therapy (neoadjuvant versus adjuvant) and extent of surgery (“no LND” versus “LND”) in Table 2. Disease relapse was not considered in the analysis, as this was only observed before RTW, in one adjuvant patient. More adjuvant patients continued work at baseline compared to neoadjuvant (36% versus 30%), but RTW was observed in less patients treated adjuvant (93% versus 98% at least partial RTW, 70% versus 84% full RTW).

To account for the timing of RTW and adjust for clinical and demographic characteristics, including varying LND status over time, Cox regression analyses have been performed and discussed in the following section.

Analysis of time to at least partial RTW

No differences regarding partial RTW between neoadjuvant versus adjuvant treated patients (HR = 1.20, 95% CI 0.78–1.86, $P = 0.41$, Fig. 1A) were reported. See Supplemental Table 1 for more details. At 6 months, 80% of neoadjuvant treated patients worked at least partially compared to 61% treated adjuvant ($P = 0.039$). After 1 year, respectively, 84% versus 73% ($P = 0.060$) of the patients worked partially, and after 2 years 91% versus 82% ($P = 0.14$).

In univariable Cox regression analyses, patients with high education level were found to partially RTW earlier (HR = 1.65, 95% CI 1.01–2.71, $P = 0.047$). This effect remained statistically significant in a multivariable analysis (HR = 1.93, 95% CI 1.09–3.40, $P = 0.023$). Undergoing LND versus “no LND” did not lead to differences in partial RTW (HR = 0.97, 95% CI 0.60–1.58, $P = 0.91$). No sizeable differences between treatment cohorts were found (supplemental Table 1).

To correct for the imbalance in regards of patients continuing fully working at diagnosis (36% versus 30%

Table 1 Baseline and surgical characteristics

	Adjuvant ($N = 44$)	Neoadjuvant ($N = 44$)	Total ($N = 88$)	P value
Sex				0.831 ^[1]
Male	22 (50%)	24 (55%)	46 (52%)	
Female	22 (50%)	20 (46%)	42 (48%)	
Age				0.193 ²
N	44	44	88	
Median (Q1–Q3)	53 (48, 59)	52 (42, 56)	53 (44, 58)	
Mean (SD)	52 (9)	47 (12)	51 (11)	
Age (grouped)				0.829 ¹
> 50 years	27 (61%)	25 (57%)	52 (59%)	
≤ 50 years	17 (38%)	19 (43%)	36 (41%)	
Education level				0.218 ¹
Medium/low	30 (68%)	36 (82%)	66 (75%)	
High	14 (32%)	8 (18%)	22 (25%)	
Marital status				0.590 ¹
Living together with a partner	34 (77%)	37 (84%)	71 (80%)	
Living alone	10 (22%)	7 (16%)	17 (19%)	
Extent of surgery before RTW				1.000 ¹
No LND (SNP/ILN)	27 (61%)	26 (59%)	53 (60%)	
LND	17 (39%)	18 (41%)	35 (40%)	

Data are n (%), unless otherwise specified

ILN; index lymph node, IT; immunotherapy, LND; lymph node dissection, SNP; sentinel node procedure

^aEducation level was split into high (university education and higher professional education) and medium/low (vocational education or lower)

Table 2 Work status and treatment

	Neoadjuvant no LND (N = 23)	Adjuvant no LND (N = 26)	Neoadjuvant LND (N = 21)	Adjuvant LND (N = 18)	Total (N = 88)
Work change at baseline					
Continued work	13 (57%)	11 (42%)	0 (0%)	5 (28%)	29 (33%)
Reduced work	4 (1%)	4 (15%)	2 (10%)	3 (17%)	13 (15%)
Stopped work	6 (26%)	11 (42%)	19 (91%)	10 (56%)	46 (52%)
Only partial RTW					
Yes	10 (44%)	14 (54%)	20 (95%)	11 (61%)	55 (63%)
No	13 (57%)	12 (46%)	1 (5%)	7 (39%)	33 (38%)
At least partial RTW					
Yes	23 (100%)	25 (96%)	20 (95%)	16 (89%)	84 (96%)
No	0 (0%)	1 (4%)	1 (5%)	2 (11.1%)	4 (4.5%)
Full RTW					
Yes	22 (96%)	22 (85%)	15 (71%)	9 (50%)	68 (77%)
No	1 (4%)	4 (15%)	6 (29%)	9 (50%)	20 (23%)

Of note: Patients having partial RTW → LND → full RTW are considered as LND in the table, even though for partial RTW analyses they would be counted as not having LND, while for full RTW analyses they would be counted as having LND

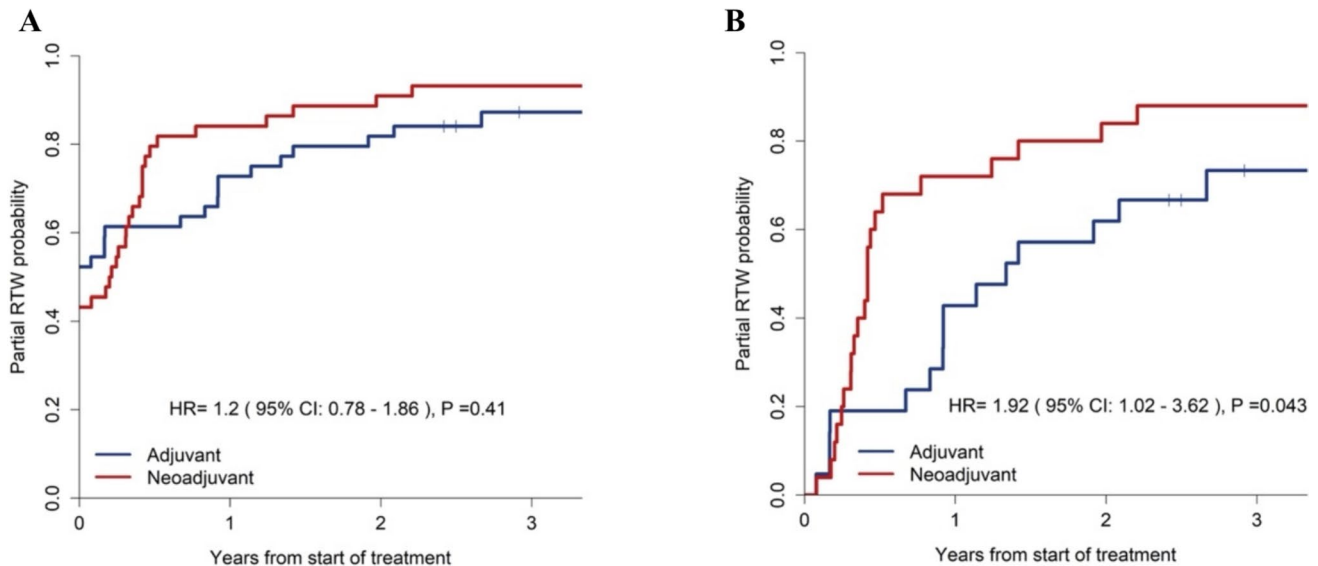


Fig. 1 Partial RTW, neoadjuvant versus adjuvant immunotherapy. **A** All patients and **B** excluding patients who at start of treatment continued with the same or lower capacity and hours as prior to therapy; RTW, return to work

in the adjuvant versus neoadjuvant cohort, respectively), we had pre-planned also an analysis of both cohorts for the subgroup of patients reducing their work at diagnosis before starting with any of the two treatment modalities. In that way, both cohorts effectively had a time to partial RTW equal to zero (19 neoadjuvant patients and 23 adjuvant patients, as seen in Table 2). In doing so, we now observed significant differences in partial RTW between the cohorts (neoadjuvant versus adjuvant HR = 1.92, 95% CI 1.02–3.62, $P = 0.043$, Fig. 1B).

Multivariable analyses indicated an earlier partial RTW for neoadjuvant versus adjuvant patients (HR = 2.25, 95% CI 0.98–5.17, $P = 0.057$), and for patients with higher education level versus medium/low (HR = 2.68, 95% CI 0.96–7.46, $P = 0.059$) (Supplemental Table 1). Given the difference in follow-up between neoadjuvant and adjuvant patients, sensitivity analyses truncating for both groups the time to at least partial RTW to the maximum follow-up for adjuvant patients led to similar results (data not shown).

Analysis of time to full RTW

Again when including all patients (also the ones not stopping working at all at diagnosis, no statistical differences were observed in regards of full time return to work (HR 1.36, 95% CI 0.84–2.21, $P = 0.21$, Fig. 2A). At 6 months, 52% of patients treated with neoadjuvant therapy fully returned to work as compared to 48% ($P < 0.0001$) of the patients treated with adjuvant immunotherapy. After 1 year, this was 71% versus 52% ($P = 0.0078$), and at two years, 82% versus 62% ($P = 0.06$) of the patients worked fully. As seen with partial RTW, earlier full RTW was observed for patients with high education level compared to medium/low in univariable (HR = 1.79, 95% CI 1.06–3.01, $P = 0.028$) and multivariable analyses (HR = 2.04, 95% CI 1.14–3.65, $P = 0.016$). In multivariable analyses, an advantage of the neoadjuvant cohort over the adjuvant cohort seemed to be indicated (HR = 1.61, 95% CI 0.96–2.69, $P = 0.073$), which was not found in univariable analyses (Supplemental Table 2). When again excluding the patients who at start of treatment continued with the same capacity and hours as prior to therapy, effectively having a time to full RTW equal to zero (13 neoadjuvant patients and 16 adjuvant patients, as seen in Table 2), differences in time to full RTW were still observed favoring the neoadjuvant cohort (HR = 2.12, 95% CI 1.09–4.12, $P = 0.027$; Fig. 2B) and high education level (HR = 1.27, 95% CI 1.27–4.89, $P = 0.0079$) in univariable analyses. These differences remained strong in multivariable analyses (neoadjuvant versus adjuvant HR = 3.73, 95% CI 1.63–8.56, $P = 0.0019$; high versus medium/low education level HR = 4.03, 95% CI 1.69–9.64, $P = 0.0017$) (Supplemental Table 2).

Having already partially returned to work, added to the multivariable model as a time-dependent covariate, decreased the time to full RTW (HR = 6.74, 95% CI 2.82–16.12, $P < 0.0001$), and led to similar conclusions in the comparison between neoadjuvant versus adjuvant cohorts (HR = 2.51, 95% CI 1.14–5.54, $P = 0.022$). Sensitivity analyses truncating time to full RTW as in partial RTW analyses led to very comparable results.

Discussion

This retrospective cohort study is, to our knowledge, the first study to investigate partial and full RTW of patients with stage III melanoma receiving neoadjuvant and/or adjuvant immunotherapy. Our data indicate that patients who received neoadjuvant immunotherapy might have higher partial and full RTW rates compared to patients who received adjuvant immunotherapy. Neoadjuvant treated patients had a higher rate of work discontinuation, but there was a tendency that they returned to work faster than adjuvant treated patients.

Considering the retrospective character of this work, we applied several multivariable analyses to exclude sample bias and confounding factors. We found that neoadjuvant therapy was an independent factor for faster and to a higher percentage partial and full RTW. Especially the extent of surgery, which is often lower in neoadjuvant approaches, did not seem to be a confounding factor for the differences we observed between neoadjuvant and adjuvant treated patients.

In addition, in the multivariable analyses, age, gender, and marital status were not significantly associated with

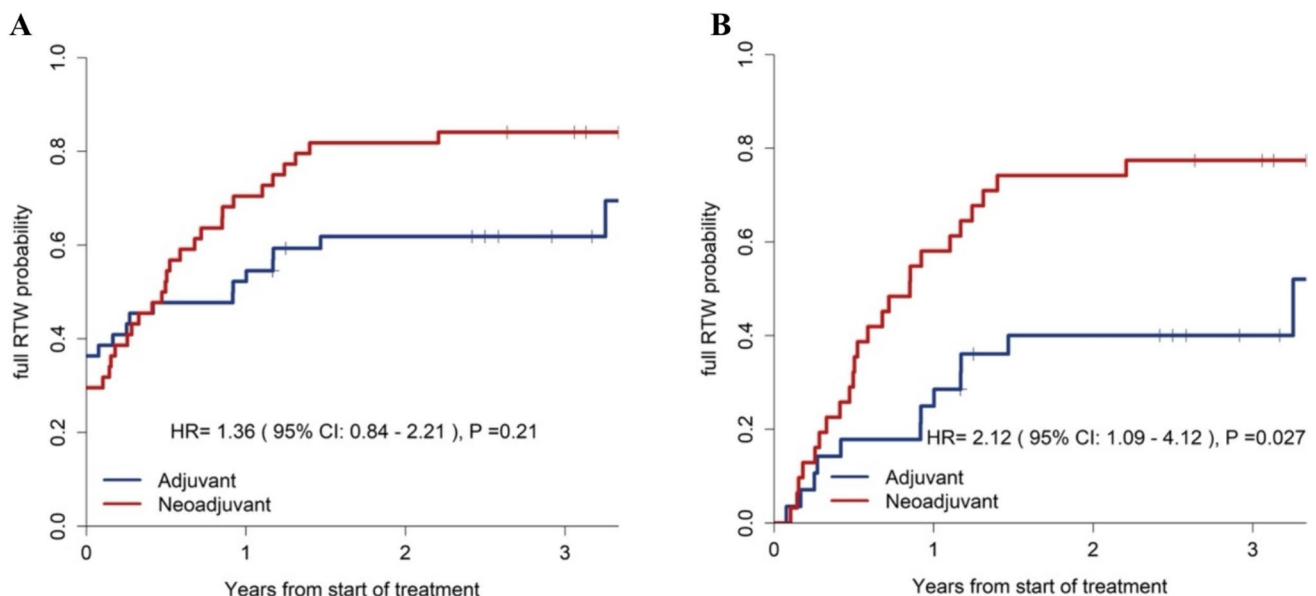


Fig. 2 Full RTW, neoadjuvant versus adjuvant immunotherapy. **A** All patients and **B** excluding patients who at start of treatment continued with the same capacity and hours as prior to therapy; RTW, return to work

time to partial and full RTW. Educational level was also not associated with partial RTW, but was well associated with full RTW.

No immunotherapy-focused RTW analyses have been published so far, but reviews on RTW after chemotherapy indicate a wide range of RTW rates of 30 to 94% in cancer patients. Comparison is further hindered by different definitions of RTW and the different contexts in which RTW rates were registered [29]. Our findings are in line with a study in the Netherlands, which reported a full RTW rate of 73% of cancer survivors as compared to the 77% full RTW rate we report in our total cohort here [30].

We know from former trials that patients treated with neoadjuvant combination therapy experience a higher rate of adverse events compared to patients treated with adjuvant nivolumab alone, but this does not seem to affect the RTW [16, 31].

Despite of the extent of surgery being a strong factor to influence QoL as shown in our previous PRADO trial, in which patients who only underwent the ILN procedure had significantly lower surgical adverse events (e.g., pain, seroma, and lymph edema), better long-term physical functioning scores, and lower long-term fatigue scores [32], in our analysis here, surgery did not have an impact on RTW.

The higher rates of RTW in neoadjuvant treated patients might be at first sight explained by the reduction of tumor burden and therefore reduced postoperative complications and morbidity [32–34]. However, in stage III melanoma, the tumor burden reduction has no influence on the extent of surgery. Patients who received neoadjuvant immunotherapy were treated in experimental studies, which could explain the higher rates of baseline work discontinuation. Patients could have quit work more often, not knowing what to expect. However, they seem to return to work fast after starting the treatment. Adjuvant treated patients had a delay in RTW and started to RTW after 12 months, which co-incidences with the end of their adjuvant treatment. RTW for neoadjuvant treated patients also seems to correlate with the end of their treatments. Thus, duration of therapy seems to be an important factor as well. However, in our cohort, these sub-cohorts are too small to draw conclusive conclusions.

With the low cohort size, our retrospective study is limited in its statistical power, and we often observed only numerical patterns. Also, due to its retrospective character with the patients being interviewed on when returning to work, the study might be biased on the remembrance of the patients. Secondly, this study does not include a deeper qualitative understanding of the experiences, decision-making, feelings, and thoughts of the patients, and also not of the extent of physical work the patients were doing. Also a

potential influence of the covid period cannot be excluded. Further research should be conducted with a larger cohort of patients from of different period to research whether the reported results can be confirmed. In about 2–3 years, this will be possible using the NADINA cohorts [16]. A larger sample will also allow for more substantiated results that can be generalized to the larger patient population. Additionally, further qualitative research could be conducted to gain a better understanding of the reasons (e.g., psychosocial factors or physical factors such as fatigue) for not returning to work for different patient groups.

In conclusion, our work is the first study that investigated RTW in stage III melanoma receiving cancer immunotherapy. Our data suggest that the manner of therapy (neoadjuvant versus adjuvant) and potentially the treatment duration might be major factors influencing RTW. Neoadjuvant immunotherapy allowing omitting adjuvant therapy in responders and potentially the knowledge of a favorable pathologic response allow a faster and higher rate of RTW. A faster and full RTW is not only of importance for the patient's well-being and QoL, but has also a significant financial impact on patients and their families, employers, and society.

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Author contribution Z. Lievense, E Albers, JM Lijnsvelt; data collection and writing M Lopez; Statisticus L vd Poll en C Blank; supervisors.

Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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