



Adjuvant therapy versus watch-and-wait post surgery for stage III melanoma: a multicountry retrospective chart review

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Practice points

- As the treatment landscape for stage III melanoma evolves, it is important to have an understanding of the real-world patterns of use and impact of adjuvant therapy in the interferon (IFN) era.
- This analysis included 380 patients with stage III melanoma (as recorded in the patients' charts as part of the routine care) who underwent surgical resection in years 2011–2016 in three global regions, North America, South America and Europe: 251 (66%) were managed under a watch-and-wait approach and 129 (34%) received adjuvant therapy. In the latter group, 121 patients received IFN-based adjuvant therapy (IFN α 2b or pegylated IFN α 2b) and 8 received other systemic adjuvant therapies.
- The most widely cited reasons for using the watch-and-wait approach were patients' decision and physician's perception of poor tolerability of approved adjuvant therapies.
- Among patients who received adjuvant therapy, IFN α 2b was the most common treatment (85%). However, substantial variation was observed in IFN α 2b starting dose/schedule and 56% discontinued therapy.
- Despite the heterogeneity in treatment, patients who received adjuvant therapy had a significantly longer relapse-free survival (RFS) compared with patients managed with watch-and-wait (adjusted hazard ratio = 0.63; $p < 0.05$). Similar results were observed in a subset of patients only treated with IFN-based adjuvant therapy (RFS: adjusted hazard ratio = 0.57; $p < 0.01$).
- The results of this study offer valuable real-world evidence from melanoma centers regarding clinical challenges in the adjuvant setting; there is a need for improved adjuvant therapies to address the unmet need for more tolerable therapies with clearer efficacy benefits in both RFS and overall survival.

Aim: To describe treatment patterns among patients with stage III melanoma who underwent surgical excision in years 2011–2016, and assess outcomes among patients who subsequently received systemic adjuvant therapy versus watch-and-wait. **Methods:** Chart review of 380 patients from 17 melanoma centers in North America, South America and Europe. **Results:** Of 129 (34%) patients treated with adjuvant therapy, 85% received interferon α -2b and 56% discontinued treatment (mostly due to adverse events). Relapse-free survival was significantly longer for patients treated with adjuvant therapy versus watch-and-wait (hazard ratio = 0.63; $p < 0.05$). There was considerable heterogeneity in adjuvant treatment schedules and doses. Similar results were found in patients who received interferon-based adjuvant therapy. **Conclusion:** Adjuvant therapies with better safety/efficacy profiles will improve clinical outcomes in patients with stage III melanoma.

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Keywords: adjuvant therapy • interferon • melanoma • metastatic melanoma • nodal disease • stage III melanoma

Although cutaneous melanoma represents approximately 5% of skin cancers, it accounts for a considerable portion of skin cancer-related deaths [1,2]. In 2018, an estimated 287,723 individuals were diagnosed with cutaneous melanoma worldwide [3]. Over the last several decades, the global incidence of melanoma has increased 3–6% annually and is projected to continue to increase in coming years for both early and advanced stages [2,4,5,6,7].

Surgical excision remains the initial standard of care for patients with primary, node-negative melanoma [8,9,10]. Although surgical excision can greatly benefit patients, some patients experience relapse during their lifetime or face a higher risk of relapse that substantially increases with T substage following surgery [11]. A recent systematic review reported that patients with stage III disease had a 5-year relapse-free survival (RFS) $< 50\%$ [12,13]. Among patients with stage III disease, there is considerable variability among different stage III substages, regardless of the American Joint Committee on Cancer (AJCC) classification system used. A long-term follow-up of the international Phase III COMBI-AD trial reported 4-year RFS rates of 62%, 37% and 30% in the placebo arm for patients with stage IIIA, IIIB and IIIC melanoma, respectively, when using the 7th edition of the AJCC classification [14]; these rates became 71%, 40%, 33% and 18% for patients with stage IIIA, IIIB, IIIC and IIID, respectively, after the authors performed a *post hoc* analysis in which tumor stages were determined according to the 8th edition of the AJCC classification [15,16]. Adjuvant therapy has been shown to reduce the risk of relapse in many patients with locally and regionally advanced disease.

Historically, the main adjuvant treatment for resected high-risk melanoma has been high-dose interferon α -2b (IFN α 2b) [8]. Results from the pivotal trial that led to its approval in 1995 showed a 5-year RFS rate of 37% among treated patients versus 26% among those untreated after surgical resection [17]. In the same study, the overall survival (OS) was 46% among treated patients versus 37% for untreated [17]. However, conclusive evidence of the benefit of IFN α 2b on RFS and OS has been lacking since the publication of that study. For example, high-dose IFN α 2b did not consistently or significantly improve OS across studies [17,18,19]. Similarly, the subsequently developed pegylated derivative (i.e., pegylated IFN α 2b [pegIFN α 2b]; approved in 2011 in the USA [20]) significantly extended RFS, but not OS [21,22]. Moreover, concerns regarding the toxicity associated with these therapies, particularly IFN α 2b, led to a high variability in its practical use [17,23]. These inconsistent clinical trial results may limit the use of IFN (IFN α 2b or pegIFN α 2b) among patients at highest risk of relapse [24]. Furthermore, there is a scarcity of real-world studies regarding the use of adjuvant therapies such as IFN and associated patient outcomes, which could provide a benchmark for the more recently approved adjuvant therapies. These new therapies hold the prospect of improving treatment efficacy, including both RFS and OS, and also of reducing toxicity compared with IFN-based therapies [25].

Examples of recent therapies include immune checkpoint inhibitors nivolumab (approved in the USA [26] in 2017 and Europe [27] in 2018) and pembrolizumab (approved in the USA [28] in 2019 and Europe [29] in 2018) as well as ipilimumab (approved in the USA [30] in 2015) in addition to the small molecule inhibitors dabrafenib plus trametinib (targeted therapies; approved in 2018 the USA [31,32] and Europe [33,34]) for *BRAF*V600-mutated tumors, which represent the most common type of mutation. Despite these changes, assessing the impact of adjuvant therapy during the IFN era may still provide meaningful insights about the potential benefits and challenges associated with recently approved adjuvant treatments.

The present study was conducted to describe real-world treatment patterns among patients with melanoma who underwent surgical excision in years 2011–2016, and assess clinical outcomes among those who subsequently received systemic adjuvant therapy versus watch-and-wait. The analysis aimed to provide a global perspective of these measurements across eight countries in North America, South America and Europe.

Materials & methods

Data source & study design

In this multicountry, retrospective, center-based chart review study, participating physicians were recruited from 17 melanoma treatment centers or hospitals in North America (Canada and the USA), South America (Argentina and Brazil), and Europe (France, Germany, Spain and the UK). Using a standardized case report form, data abstractors (e.g., physicians, nurse practitioners) extracted de-identified patient-level information (i.e., patient characteristics, treatments and outcomes) for patients who satisfied inclusion criteria from July 2017 to July 2018. Each data abstractor contributed information for 2–50 patient charts.

The date of the first surgical resection for stage III cutaneous melanoma was defined as the index date. By design, all patients had stage III surgery before 1 January 2011 as well as ≥ 24 months from the index date to the date of chart abstraction (i.e., 24 months of potential follow-up). Study outcomes (patterns of adjuvant therapy, relapses, deaths) were evaluated from the index date until the earliest among death and date of chart abstraction (follow-up period).

Study sample & study cohorts

To be included in this study, patients were required to meet the following criteria: diagnosis of resectable stage III cutaneous melanoma (as recorded in the patients' charts as part of the routine care; patients presenting with initial resectable lymph node recurrence after a diagnosis of stage I or II melanoma were eligible); ≥ 18 years of age on the date of the diagnosis of stage III cutaneous melanoma; (3) evidence of complete surgical resection of stage III cutaneous melanoma after 1 January 2011; have ≥ 24 months of clinical follow-up history following surgical resection, with the exception of deceased patients for whom follow-up until death was required.

Patients were excluded if they had any evidence of incomplete surgical resection as initial surgery for stage III cutaneous melanoma; received a diagnosis of any other type of malignancy before being diagnosed with stage III cutaneous melanoma, unless the patient was disease free of other types of malignancy for ≥ 5 years prior to the diagnosis of stage III cutaneous melanoma; received adjuvant treatment for melanoma in a clinical trial setting.

Patients were classified into one of two cohorts based on the therapy received after complete surgical resection of stage III cutaneous melanoma and before a relapse. Those who initiated systemic adjuvant therapy in this latter period were included in the adjuvant therapy cohort, while remaining patients were included in the watch-and-wait cohort. Supplementary analyses were performed to assess study outcomes among patients who specifically received an IFN-based adjuvant therapy.

Study measures & outcomes

Patient characteristics that were assessed at the index date included demographics (e.g., age, sex), country of residence, insurance coverage (e.g., public vs private), employment status (e.g., full time, part time, voluntary), days from stage III melanoma diagnosis to surgical resection, and characteristics of stage III melanoma (i.e., substage, tumor thickness, ulceration/mitosis, lymph node involvement, primary location of melanoma; [Table 1](#)). Additional characteristics included *BRAFV600* testing and *BRAFV600* mutation status (e.g., type of mutation). Treatment patterns (e.g., type of adjuvant therapy, dose increases, dose decreases, dose interruptions, add-on therapy) and reasons for treatment discontinuation (e.g., adverse events) were also assessed after the index date and before the first relapse. Physician rationale (e.g., physician reasons for prescribing adjuvant therapy or preferring watchful waiting or other therapies) was described. RFS and OS post-index dates were assessed in patients with adjuvant therapy versus watch-and-wait. All study measures and outcomes were evaluated for the overall study population (all patients with stage III tumor) and in subgroups of patients with stage IIIA, IIIB and IIIC melanoma, based on the AJCC 7th edition [14].

Statistical analyses

Descriptive analyses were performed using means, medians and standard deviations (SD) to summarize continuous variables, and frequencies and percentages for categorical variables. Time-to-event (i.e., RFS and OS) outcomes were

Table 1. Patient baseline characteristics.

Baseline characteristics	All patients N = 380	Adjuvant therapy [‡] N = 129	Watch-and-wait [§] N = 251	p-value [¶]
Demographics				
Country of residence N, (%)				< 0.001 [†]
– Argentina	20 (5.3)	0 (0.0)	20 (8.0)	
– Brazil	8 (2.1)	7 (5.4)	1 (0.4)	
– Canada	15 (3.9)	12 (9.3)	3 (1.2)	
– France	67 (17.6)	17 (13.2)	50 (19.9)	
– Germany	120 (31.6)	31 (24.0)	89 (35.5)	
– Spain	80 (21.1)	46 (35.7)	34 (13.5)	
– UK	10 (2.6)	1 (0.8)	9 (3.6)	
– USA	60 (15.8)	15 (11.6)	45 (17.9)	
Age at index date (years)				
– Mean ± SD [median]	57.2 ± 14.2 [57]	52.9 ± 11.6 [52]	59.3 ± 14.9 [61]	< 0.001 [†]
– 65 years or older, N (%)	127 (33.4)	22 (17.1)	105 (41.8)	< 0.001 [†]
Males, N (%)	211 (55.5)	73 (56.6)	138 (55.0)	0.849
Insurance coverage at the time of stage III melanoma, N (%)[#]				
Public insurance plan only	265 (69.7)	95 (73.6)	170 (67.7)	0.284
Private insurance plan only	42 (11.1)	12 (9.3)	30 (12.0)	0.544
Mix of public/private insurance plan	9 (2.4)	5 (3.9)	4 (1.6)	0.303
Unknown	64 (16.8)	17 (13.2)	47 (18.7)	0.221
Employment status at the time of stage III melanoma, N (%)				
Full time	160 (42.1)	67 (51.9)	93 (37.1)	0.008 [†]
Part time	17 (4.5)	6 (4.7)	11 (4.4)	1
Voluntary work	2 (0.5)	1 (0.8)	1 (0.4)	1
Sick leave	5 (1.3)	3 (2.3)	2 (0.8)	0.445
Unemployed	23 (6.1)	10 (7.8)	13 (5.2)	0.442
Early retirement	2 (0.5)	1 (0.8)	1 (0.4)	1
Normal retirement	99 (26.1)	16 (12.4)	83 (33.1)	< 0.001 [†]
Other (e.g., disabled, student)	7 (1.8)	2 (1.6)	5 (2.0)	1
Unknown	65 (17.1)	23 (17.8)	42 (16.7)	0.901
Comorbidity				
CCI				
– Mean ± SD [median]	2.3 ± 0.8 [2]	2.2 ± 0.6 [2]	2.4 ± 0.9 [2]	0.002 [†]
– CCI ≤2, N (%)	292 (76.8)	112 (86.8)	180 (71.7)	0.001 [†]
Tumor stage at initial diagnosis, N (%)				
Stage I	64 (16.8)	11 (8.5)	53 (21.1)	< 0.001 [†]
Stage II	146 (38.4)	54 (41.9)	92 (36.7)	
Stage III	145 (38.2)	61 (47.3)	84 (33.5)	
Unknown	25 (6.6)	3 (2.3)	22 (8.8)	
Stage III characteristics				
Substage at stage III diagnosis, N (%)				0.157
[†] Statistical significance at the 5% level. [‡] The adjuvant therapy cohort was defined as patients who received systemic therapy following initial surgery for stage III (but prior to relapse). [§] The watch-and-wait cohort was defined as patients who did not receive any systemic therapy following initial surgery for stage III (i.e., watch-and-wait/observation) (prior to relapse). [¶] Statistical comparisons between the adjuvant therapy and watch-and-wait cohorts were performed using Wilcoxon rank-sum tests for continuous variables and Chi-square tests for categorical variables. [#] Other type of plan and no insurance plan categories for insurance coverage at the time of stage III melanoma are not shown, as no patient in the study sample was included in either of these categories. ^{††} During the follow up period, a relapse (loco-regional, unresectable/metastatic, or secondary primary melanoma) was observed for 168 patients (43 in adjuvant therapy cohort and 125 in watch-and-wait cohort). CCI: Charlson Comorbidity Index; N: Sample size; SD: Standard deviation.				

Table 1. Patient baseline characteristics (cont.).

Baseline characteristics	All patients	Adjuvant therapy [‡]	Watch-and-wait [§]	p-value [¶]
	N = 380	N = 129	N = 251	
– Stage IIIA	146 (38.4)	55 (42.6)	91 (36.3)	
– Stage IIIB	168 (44.2)	58 (45.0)	110 (43.8)	
– Stage IIIC	66 (17.4)	16 (12.4)	50 (19.9)	
Lymph node involvement, N (%)				0.070
– Yes	377 (99.2)	126 (97.7)	251 (100.0)	
– No	0 (0.0)	0 (0.0)	0 (0.0)	
– Unknown	3 (0.8)	3 (2.3)	0 (0.0)	
Tumor ulceration or mitoses $\geq 1/\text{mm}^2$, N (%)				0.274
– Absent	207 (54.5)	63 (48.8)	144 (57.4)	
– Present	145 (38.2)	56 (43.4)	89 (35.5)	
– Unknown	28 (7.4)	10 (7.8)	18 (7.2)	
Tumor thickness, N (%)				0.153
– ≤ 1 mm	39 (10.3)	10 (7.8)	29 (11.6)	
– 1.01–2.0 mm	95 (25.0)	39 (30.2)	56 (22.3)	
– 2.01–4.0 mm	106 (27.9)	28 (21.7)	78 (31.1)	
– >4.0 mm	112 (29.5)	42 (32.6)	70 (27.9)	
– Unknown	28 (7.4)	10 (7.8)	18 (7.2)	
Primary location of melanoma, N (%)				0.154
– Legs	132 (34.7)	45 (34.9)	87 (34.7)	
– Back	81 (21.3)	37 (28.7)	44 (17.5)	
– Trunk	69 (18.2)	22 (17.1)	47 (18.7)	
– Arms	54 (14.2)	16 (12.4)	38 (15.1)	
– Head	28 (7.4)	5 (3.9)	23 (9.2)	
– Other	12 (3.2)	3 (2.3)	9 (3.6)	
– Unknown	4 (1.1)	1 (0.8)	3 (1.2)	
Stage III surgery characteristics				
Days from stage III diagnosis to surgery, mean \pm SD [median]	30.7 \pm 89.7 [8]	28.4 \pm 56.2 [10]	31.9 \pm 102.8 [7]	0.856
Year of surgery, N (%)				$< 0.001^\dagger$
– 2011	73 (19.2)	19 (14.7)	54 (21.5)	
– 2012	65 (17.1)	31 (24.0)	34 (13.5)	
– 2013	72 (18.9)	39 (30.2)	33 (13.1)	
– 2014	101 (26.6)	25 (19.4)	76 (30.3)	
– 2015	64 (16.8)	15 (11.6)	49 (19.5)	
– 2016	5 (1.3)	0 (0.0)	5 (2.0)	
BRAF mutation test				
Tested for BRAF mutation, N (%)				0.492
– Yes	245 (64.5)	80 (62.0)	165 (65.7)	
– No	125 (32.9)	44 (34.1)	81 (32.3)	
– Unknown	10 (2.6)	5 (3.9)	5 (2.0)	
Timing of first BRAF test, N (% tested)				
– Before relapse	182 (74.3)	67 (83.8)	115 (69.7)	0.028 [†]
– At/after relapse ^{††}	63 (25.7)	13 (16.3)	50 (30.3)	

[†] Statistical significance at the 5% level.

[‡] The adjuvant therapy cohort was defined as patients who received systemic therapy following initial surgery for stage III (but prior to relapse).

[§] The watch-and-wait cohort was defined as patients who did not receive any systemic therapy following initial surgery for stage III (i.e., watch-and-wait/observation) (prior to relapse).

[¶] Statistical comparisons between the adjuvant therapy and watch-and-wait cohorts were performed using Wilcoxon rank-sum tests for continuous variables and Chi-square tests for categorical variables.

[#] Other type of plan and no insurance plan categories for insurance coverage at the time of stage III melanoma are not shown, as no patient in the study sample was included in either of these categories.

^{††} During the follow up period, a relapse (loco-regional, unresectable/metastatic, or secondary primary melanoma) was observed for 168 patients (43 in adjuvant therapy cohort and 125 in watch-and-wait cohort).

CCI: Charlson Comorbidity Index; N: Sample size; SD: Standard deviation.

Table 1. Patient baseline characteristics (cont.).

Baseline characteristics	All patients N = 380	Adjuvant therapy [‡] N = 129	Watch-and-wait [§] N = 251	p-value [¶]
– Mutation identified, N (% tested)	136 (55.5)	47 (58.8)	89 (53.9)	0.566
Type of mutation, N (% with <i>BRAF</i>)				0.302
– V600E only	108 (79.4)	34 (72.3)	74 (83.1)	
– V600K only	9 (6.6)	3 (6.4)	6 (6.7)	
– V600R only	1 (0.7)	0 (0.0)	1 (1.1)	
– V600K and V600E	7 (5.1)	5 (10.6)	2 (2.2)	
– V600, not specified	3 (2.2)	1 (2.1)	2 (2.2)	
– Unknown	8 (5.9)	4 (8.5)	4 (4.5)	

[†]Statistical significance at the 5% level.

[‡]The adjuvant therapy cohort was defined as patients who received systemic therapy following initial surgery for stage III (but prior to relapse).

[§]The watch-and-wait cohort was defined as patients who did not receive any systemic therapy following initial surgery for stage III (i.e., watch-and-wait/observation) (prior to relapse).

[¶]Statistical comparisons between the adjuvant therapy and watch-and-wait cohorts were performed using Wilcoxon rank-sum tests for continuous variables and Chi-square tests for categorical variables.

[#]Other type of plan and no insurance plan categories for insurance coverage at the time of stage III melanoma are not shown, as no patient in the study sample was included in either of these categories.

^{††}During the follow up period, a relapse (loco-regional, unresectable/metastatic, or secondary primary melanoma) was observed for 168 patients (43 in adjuvant therapy cohort and 125 in watch-and-wait cohort).

CCI: Charlson Comorbidity Index; N: Sample size; SD: Standard deviation.

assessed using Kaplan–Meier analyses. RFS was measured from the date of initial surgery for stage III melanoma to the earliest among the date of first relapse (event), date of death (event), or end of follow up (i.e., end of care for the patient or date of data collection; censoring) among patients with known information on time of relapse/death. Similarly, OS was measured from the date of initial surgery for stage III melanoma to the earliest among date of death (event), or end of follow up (i.e., end of care for the patient or date of data collection; censoring) for patients with known information on time of death.

RFS and OS were also compared between cohorts using unadjusted and adjusted Cox proportional hazards models. Hazard ratios (HRs) and 95% CI were reported for each outcome evaluated. Adjusted Cox proportional hazard models were used to control for the following baseline covariates: age at index date, sex, insurance coverage, employment status, tumor substage and Charlson Comorbidity Index (CCI).

Analyses were conducted using SAS Enterprise Guide version 7.1 and R version 3.4.2.

Results

In this study, information was abstracted for 380 patients who met the inclusion criteria. The countries with the greatest geographical representation in the study sample were Germany (32%), Spain (21%), France (18%), the USA (16%) and Argentina (5%). Of the 380 patients, 129 (34%) were included in the adjuvant therapy cohort and 251 (66%) in the watch-and-wait cohort (Table 1; see Supplementary Table 1 for patients treated with IFN-based adjuvant therapy). Patients were followed, on average, for 3.5 years postindex date (median follow up: adjuvant therapy = 4.1 years; watch-and-wait = 3.1 years; Figure 1).

Baseline characteristics

Use of adjuvant therapy varied significantly across countries ($p < 0.001$; Table 1). For example, no patients were initiated on adjuvant therapy in Argentina as compared with >80% in Brazil (7/8 patients) and Canada (12/15 patients). Patients in the adjuvant therapy cohort were significantly younger than patients in the watch-and-wait cohort (median age [years]: adjuvant therapy = 52; watch-and-wait = 61; $p < 0.001$). Among these patients, 145 (38.2%) had primary stage III melanoma and 210 (55.3%) had recurrent stage III at the initial melanoma diagnosis (i.e., lymph node recurrence after resection of stage I or II melanoma); tumor stage at the initial diagnosis was unknown for 25 (6.6%) patients.

The proportion of patients working full time in the adjuvant therapy cohort was significantly greater than that in the watch-and-wait cohort (adjuvant therapy = 52%; watch-and-wait = 37%; $p < 0.01$). Patients in the adjuvant therapy cohort had a significantly lower CCI compared with those in the watch-and-wait cohort (CCI ≤ 2 :

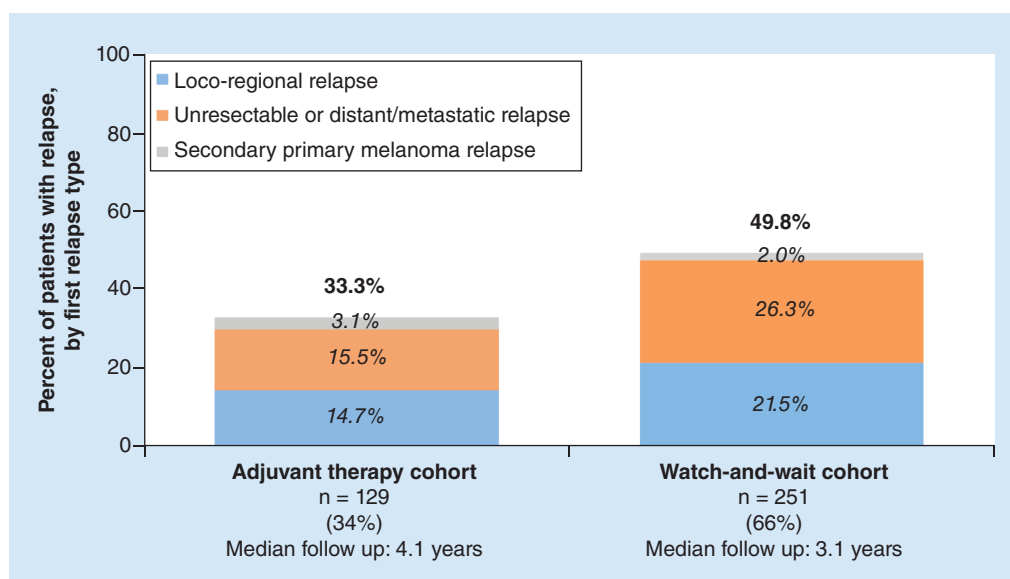


Figure 1. First relapse postindex date in adjuvant therapy and watch-and-wait cohorts, by type of first relapse.

adjuvant therapy = 87%; watch-and-wait = 72%; $p < 0.01$); however, melanoma clinical characteristics (e.g., stage, ulceration) were generally similar between cohorts.

Overall, 65% of the study samples were tested for *BRAF*V600 mutation at some time over their course of melanoma. Of the patients tested, the majority (74% overall) were tested before experiencing a relapse (Table 1; see Supplementary Table 1 for patients treated with IFN-based adjuvant therapy). Among the patients who were tested, 56% had a mutation identified, with V600E being the most common type of mutation (79% of those with mutation identified). Baseline characteristics of patients with stage IIIA–IIIC melanoma can be found in Table 2 (see Supplementary Table 2 for patients treated with IFN-based adjuvant therapy).

Treatment patterns

Adjuvant therapy

Treatment patterns for patients who received adjuvant therapy following surgery for stage III melanoma are summarized in Table 3. In 88% of this patient cohort, the primary reason cited by physicians' for initiating adjuvant therapy was it being an 'approved adjuvant therapy' (Table 3). Most patients in the adjuvant therapy cohort were treated with IFN α 2b (85%) followed by pegIFN α 2b (9%); the remaining patients received other systemic therapies (Table 3). Of the 110 patients treated with IFN α 2b, 74 (67%) received high-dose IFN α 2b, 15 (14%) received intermediate-dose IFN α 2b and 21 (19%) received low-dose IFN α 2b; the definition of high-, intermediate- and low-dose IFN α 2b was based on the information available in the patients' chart. There was considerable variation in the treatment doses and schedules for induction and maintenance therapy. The median duration of therapy, among patients who had stopped therapy by the time of data collection with known treatment duration, was 9.4 months.

Among patients whose IFN α 2b starting dose was known, almost half did not receive the recommended dose (33/72; 46%), and more than half did not receive the recommended schedule (57/103; 55%). Deviations from the recommended induction IFN α 2b dose/schedule among patients who did not receive the recommended dose included higher doses and/or less frequent induction schedules. A large proportion of IFN α 2b users (39%) did not go on to receive the maintenance phase.

Among patients who were treated with adjuvant therapy (IFN α 2b or other), 37% had a treatment modification during treatment (most commonly dose reduction), and 56% discontinued adjuvant treatment (as reported by the physician). Adverse events were the most common reason for both treatment modifications (81%) and treatment discontinuation (60%; Table 3). Ten (8%) patients received radiation therapy post surgery. Treatment patterns for patients with stage IIIA, IIIB and IIIC tumors are presented in Supplementary Tables 3–5.

Table 2. Patient baseline characteristics stratified by stage.

Baseline characteristics	Stage IIIA			Stage IIIB			Stage IIIC		
	All patients	Adjuvant therapy [‡]	Watch-and-wait [§]	All patients	Adjuvant therapy [‡]	Watch-and-wait [§]	All patients	Adjuvant therapy [‡]	Watch-and-wait [§]
	N = 146	N = 55	N = 91	N = 168	N = 58	N = 110	N = 66	N = 16	N = 50
Demographics									
Country of residence (%)									
– Argentina	10 (6.8) [†]	0 (0.0) [†]	10 (11.0) [†]	6 (3.6) [†]	0 (0.0) [†]	6 (5.5) [†]	4 (6.1)	0 (0.0)	4 (8.0)
– Brazil	7 (4.8) [†]	6 (10.9) [†]	1 (1.1) [†]	1 (0.6) [†]	1 (1.7) [†]	0 (0.0) [†]	0 (0.0)	0 (0.0)	0 (0.0)
– Canada	7 (4.8) [†]	5 (9.1) [†]	2 (2.2) [†]	5 (3.0) [†]	5 (8.6) [†]	0 (0.0) [†]	3 (4.5)	2 (12.5)	1 (2.0)
– France	14 (9.6) [†]	8 (14.5)	6 (6.6)	40 (23.8) [†]	7 (12.1) [†]	33 (30.0) [†]	13 (19.7)	2 (12.5)	11 (22.0)
– Germany	51 (34.9) [†]	15 (27.3) [†]	36 (39.6) [†]	49 (29.2) [†]	13 (22.4) [†]	36 (32.7) [†]	20 (30.3)	3 (18.8)	17 (34.0)
– Spain	31 (21.2) [†]	14 (25.5) [†]	17 (18.7) [†]	37 (22.0) [†]	26 (44.8) [†]	11 (10.0) [†]	12 (18.2)	6 (37.5)	6 (12.0)
– UK	1 (0.7) [†]	0 (0.0) [†]	1 (1.1) [†]	6 (3.6) [†]	0 (0.0) [†]	6 (5.5) [†]	3 (4.5)	1 (6.3)	2 (4.0)
– USA	25 (17.1) [†]	7 (12.7) [†]	18 (19.8) [†]	24 (14.3) [†]	6 (10.3) [†]	18 (16.4) [†]	11 (16.7)	2 (12.5)	9 (18.0)
Age at index date (years)									
Mean ± SD [median]	56.2 ± 14.2 [†] [55]	52.1 ± 10.6 [†] [50]	58.7 ± 15.5 [†] [60]	56.2 ± 14.1 [†] [56]	52.3 ± 11.5 [†] [55]	58.3 ± 14.9 [†] [59]	61.6 ± 13.8 [65]	58.2 ± 14.4 [61]	62.7 ± 13.5 [66]
>65 years, N(%)	44 (30.1) [†]	8 (14.5) [†]	36 (39.6) [†]	49 (29.2) [†]	7 (12.1) [†]	42 (38.2) [†]	34 (51.5)	7 (43.8)	27 (54.0)
Males, N (%)	90 (61.6)	36 (65.5)	54 (59.3)	87 (51.8)	29 (50.0)	58 (52.7)	34 (51.5)	8 (50.0)	26 (52.0)
Insurance coverage at the time of stage III melanoma[¶], N (%)									
Public insurance plan only	93 (63.7)	37 (67.3)	56 (61.5)	125 (74.4)	45 (77.6)	80 (72.7)	47 (71.2)	13 (81.3)	34 (68.0)
Private insurance plan only	22 (15.1)	8 (14.5)	14 (15.4)	14 (8.3)	3 (5.2)	11 (10.0)	6 (9.1)	1 (6.3)	5 (10.0)
Mix of public/private insurance plan	3 (2.1)	1 (1.8)	2 (2.2)	4 (2.4) [†]	4 (6.9) [†]	0 (0.0) [†]	2 (3.0)	0 (0.0)	2 (4.0)
Unknown	28 (19.2)	9 (16.4)	19 (20.9)	25 (14.9)	6 (10.3)	19 (17.3)	11 (16.7)	2 (12.5)	9 (18.0)
Employment status at the time of stage III melanoma, N (%)									
Full time	64 (43.8)	27 (49.1)	37 (40.7)	76 (45.2)	32 (55.2)	44 (40.0)	20 (30.3)	8 (50.0)	12 (24.0)
Part time	6 (4.1)	1 (1.8)	5 (5.5)	9 (5.4)	4 (6.9)	5 (4.5)	2 (3.0)	1 (6.3)	1 (2.0)
Voluntary work	1 (0.7)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	1 (2.0)
Sick leave	2 (1.4)	2 (3.6)	0 (0.0)	3 (1.8)	1 (1.7)	2 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Unemployed	7 (4.8)	4 (7.3)	3 (3.3)	13 (7.7)	6 (10.3)	7 (6.4)	3 (4.5)	0 (0.0)	3 (6.0)
Early retirement	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.2)	1 (1.7)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
Normal retirement	36 (24.7) [†]	4 (7.3) [†]	32 (35.2) [†]	34 (20.2) [†]	6 (10.3) [†]	28 (25.5) [†]	29 (43.9)	6 (37.5)	23 (46.0)
Other (e.g., military)	2 (1.4)	1 (1.8)	1 (1.1)	5 (3.0)	1 (1.7)	4 (3.6)	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	28 (19.2)	15 (27.3)	13 (14.3)	26 (15.5)	7 (12.1)	19 (17.3)	11 (16.7)	1 (6.3)	10 (20.0)
Comorbidity									
CCI									
– Mean ± SD [median]	2.3 ± 0.9 [2] [†]	2.2 ± 0.6 [2] [†]	2.4 ± 1.0 [2] [†]	2.3 ± 0.7 [2]	2.3 ± 0.7 [2]	2.3 ± 0.7 [2]	2.5 ± 0.7 [2]	2.2 ± 0.4 [2]	2.6 ± 0.8 [2]
– CCI ≤2, N (%)	115 (78.8) [†]	50 (90.9) [†]	65 (71.4) [†]	136 (81.0)	49 (84.5)	87 (79.1)	41 (62.1)	13 (81.3)	28 (56.0)
Tumor stage at initial diagnosis, N (%)									
Stage I	36 (24.7)	9 (16.4)	27 (29.7)	21 (12.5) [†]	2 (3.4) [†]	19 (17.3) [†]	7 (10.6)	0 (0.0)	7 (14.0)
Stage II	41 (28.1)	17 (30.9)	24 (26.4)	73 (43.5) [†]	30 (51.7) [†]	43 (39.1) [†]	32 (48.5)	7 (43.8)	25 (50.0)
Stage III	65 (44.5)	28 (50.9)	37 (40.7)	58 (34.5) [†]	26 (44.8) [†]	32 (29.1) [†]	22 (33.3)	7 (43.8)	15 (30.0)
Unknown	4 (2.7)	1 (1.8)	3 (3.3)	16 (9.5) [†]	0 (0.0) [†]	16 (14.5) [†]	5 (7.6)	2 (12.5)	3 (6.0)

[†]Statistical significance at the 5% level.
[‡]The adjuvant therapy cohort was defined as patients who received systemic therapy following initial surgery for stage III (but prior to relapse).
[§]The watch-and-wait cohort was defined as patients who did not receive any systemic therapy following initial surgery for stage III (i.e., watch-and-wait/observation) (prior to relapse).
[¶]Other type of plan and no insurance plan categories for insurance coverage at the time of stage III melanoma are not shown, as no patient in the study sample was included in either of these categories.
[#]During the follow up, a relapse (loco-regional, unresectable/metastatic, or secondary primary melanoma) was observed for 168 patients (43 in adjuvant therapy cohort and 125 in watch-and-wait cohort).
^{††}Statistical comparisons between the adjuvant therapy and watch-and-wait cohorts were performed using Wilcoxon rank-sum tests for continuous variables and Chi-square tests for categorical variables.
CCI: Charlson Comorbidity Index; N: Sample size; SD: Standard deviation.

Table 2. Patient baseline characteristics stratified by stage (cont.).

Baseline characteristics	Stage IIIA			Stage IIIB			Stage IIIC		
	All patients	Adjuvant therapy [‡]	Watch-and-wait [§]	All patients	Adjuvant therapy [‡]	Watch-and-wait [§]	All patients	Adjuvant therapy [‡]	Watch-and-wait [§]
Stage III characteristics									
Lymph node involvement, N (%)									
– Yes	145 (99.3)	54 (98.2)	91 (100.0)	167 (99.4)	57 (98.3)	110 (100.0)	65 (98.5)	15 (93.8)	50 (100.0)
– No	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
– Unknown	1 (0.7)	1 (1.8)	0 (0.0)	1 (0.6)	1 (1.7)	0 (0.0)	1 (1.5)	1 (6.3)	0 (0.0)
Tumor ulceration or mitoses $\geq 1/\text{mm}^2$, N (%)									
– Absent	126 (86.3)	47 (85.5)	79 (86.8)	55 (32.7) [†]	10 (17.2) [†]	45 (40.9) [†]	26 (39.4)	6 (37.5)	20 (40.0)
– Present	14 (9.6)	4 (7.3)	10 (11.0)	94 (56.0) [†]	42 (72.4) [†]	52 (47.3) [†]	37 (56.1)	10 (62.5)	27 (54.0)
– Unknown	6 (4.1)	4 (7.3)	2 (2.2)	19 (11.3) [†]	6 (10.3) [†]	13 (11.8) [†]	3 (4.5)	0 (0.0)	3 (6.0)
Tumor thickness, N (%)									
– ≤ 1.0 mm	16 (11.0)	5 (9.1)	11 (12.1)	16 (9.5)	4 (6.9)	12 (10.9)	7 (10.6)	1 (6.3)	6 (12.0)
– 1.01–2.0 mm	14 (9.6)	6 (10.9)	8 (8.8)	50 (29.8)	25 (43.1)	25 (22.7)	31 (47.0)	8 (50.0)	23 (46.0)
– 2.01–4.0 mm	58 (39.7)	17 (30.9)	41 (45.1)	38 (22.6)	8 (13.8)	30 (27.3)	10 (15.2)	3 (18.8)	7 (14.0)
– >4.0 mm	52 (35.6)	23 (41.8)	29 (31.9)	45 (26.8)	15 (25.9)	30 (27.3)	15 (22.7)	4 (25.0)	11 (22.0)
– Unknown	6 (4.1)	4 (7.3)	2 (2.2)	19 (11.3)	6 (10.3)	13 (11.8)	3 (4.5)	0 (0.0)	3 (6.0)
Primary location of melanoma, N (%)									
– Legs	45 (30.8)	18 (32.7)	27 (29.7)	62 (36.9)	21 (36.2)	41 (37.3)	25 (37.9)	6 (37.5)	19 (38.0)
– Back	35 (24.0)	19 (34.5)	16 (17.6)	30 (17.9)	13 (22.4)	17 (15.5)	16 (24.2)	5 (31.3)	11 (22.0)
– Trunk	35 (24.0)	11 (20.0)	24 (26.4)	23 (13.7)	9 (15.5)	14 (12.7)	11 (16.7)	2 (12.5)	9 (18.0)
– Arms	19 (13.0)	4 (7.3)	15 (16.5)	28 (16.7)	11 (19.0)	17 (15.5)	7 (10.6)	1 (6.3)	6 (12.0)
– Head	6 (4.1)	1 (1.8)	5 (5.5)	18 (10.7)	3 (5.2)	15 (13.6)	4 (6.1)	1 (6.3)	3 (6.0)
– Other	5 (3.4)	1 (1.8)	4 (4.4)	5 (3.0)	1 (1.7)	4 (3.6)	2 (3.0)	1 (6.3)	1 (2.0)
– Unknown	1 (0.7)	1 (1.8)	0 (0.0)	2 (1.2)	0 (0.0)	2 (1.8)	1 (1.5)	0 (0.0)	1 (2.0)
Stage III surgery characteristics									
Days from stage III diagnosis to surgery, mean \pm SD [median]	39.0 \pm 126.8 [11.5]	23.4 \pm 41.1 [10]	48.5 \pm 157.0 [13]	24.8 \pm 49.6 [6.5]	32.5 \pm 66.9 [6.5]	20.8 \pm 37.2 [6.5]	27.4 \pm 66.8 [12.5]	31.1 \pm 61.0 [17.5]	26.2 \pm 69.1 [9]
Year of surgery, N (%)									
– 2011	28 (19.2) [†]	7 (12.7) [†]	21 (23.1) [†]	28 (16.7) [†]	8 (13.8) [†]	20 (18.2) [†]	17 (25.8)	4 (25.0)	13 (26.0)
– 2012	20 (13.7) [†]	10 (18.2) [†]	10 (11.0) [†]	35 (20.8) [†]	19 (32.8) [†]	16 (14.5) [†]	10 (15.2)	2 (12.5)	8 (16.0)
– 2013	26 (17.8) [†]	17 (30.9) [†]	9 (9.9) [†]	35 (20.8) [†]	17 (29.3) [†]	18 (16.4) [†]	11 (16.7)	5 (31.3)	6 (12.0)
– 2014	41 (28.1) [†]	13 (23.6) [†]	28 (30.8) [†]	45 (26.8) [†]	8 (13.8) [†]	37 (33.6) [†]	15 (22.7)	4 (25.0)	11 (22.0)
– 2015	29 (19.9) [†]	8 (14.5) [†]	21 (23.1) [†]	24 (14.3) [†]	6 (10.3) [†]	18 (16.4) [†]	11 (16.7)	1 (6.3)	10 (20.0)
– 2016	2 (1.4) [†]	0 (0.0) [†]	2 (2.2) [†]	1 (0.6) [†]	0 (0.0) [†]	1 (0.9) [†]	2 (3.0)	0 (0.0)	2 (4.0)
BRAF mutation test									
– Tested for <i>BRAF</i> mutation, N (%)									
– Yes	75 (51.4)	30 (54.5)	45 (49.5)	117 (69.6)	39 (67.2)	78 (70.9)	53 (80.3)	11 (68.8)	42 (84.0)
– No	64 (43.8)	20 (36.4)	44 (48.4)	49 (29.2)	19 (32.8)	30 (27.3)	12 (18.2)	5 (31.3)	7 (14.0)
– Unknown	7 (4.8)	5 (9.1)	2 (2.2)	2 (1.2)	0 (0.0)	2 (1.8)	1 (1.5)	0 (0.0)	1 (2.0)

[†]Statistical significance at the 5% level.
[‡]The adjuvant therapy cohort was defined as patients who received systemic therapy following initial surgery for stage III (but prior to relapse).
[§]The watch-and-wait cohort was defined as patients who did not receive any systemic therapy following initial surgery for stage III (i.e., watch-and-wait/observation) (prior to relapse).
[¶]Other type of plan and no insurance plan categories for insurance coverage at the time of stage III melanoma are not shown, as no patient in the study sample was included in either of these categories.
[#]During the follow up, a relapse (loco-regional, unresectable/metastatic, or secondary primary melanoma) was observed for 168 patients (43 in adjuvant therapy cohort and 125 in watch-and-wait cohort).
^{††}Statistical comparisons between the adjuvant therapy and watch-and-wait cohorts were performed using Wilcoxon rank-sum tests for continuous variables and Chi-square tests for categorical variables.
 CCI: Charlson Comorbidity Index; N: Sample size; SD: Standard deviation.

Table 2. Patient baseline characteristics stratified by stage (cont.).

Baseline characteristics	Stage IIIA			Stage IIIB			Stage IIIC		
	All patients	Adjuvant therapy [‡]	Watch-and-wait [§]	All patients	Adjuvant therapy [‡]	Watch-and-wait [§]	All patients	Adjuvant therapy [‡]	Watch-and-wait [§]
– Timing of first <i>BRAF</i> mutation test, N (%)									
– Before relapse	50 (66.7)	22 (73.3)	28 (62.2)	96 (82.1)	34 (87.2)	62 (79.5)	36 (67.9) [†]	11 (100.0) [†]	25 (59.5) [†]
– At/after relapse [#]	25 (33.3)	8 (26.7)	17 (37.8)	21 (17.9)	5 (12.8)	16 (20.5)	17 (32.1) [†]	0 (0.0) [†]	17 (40.5) [†]
Mutation identified, N (tested)	43 (57.3)	16 (53.3)	27 (60.0)	68 (58.1)	27 (69.2)	41 (52.6)	25 (47.2)	4 (36.4)	21 (50.0)
Type of mutation, N (% with <i>BRAF</i>)									
– V600E only	36 (83.7)	13 (81.3)	23 (85.2)	50 (73.5)	18 (66.7)	32 (78.0)	22 (88.0)	3 (75.0)	19 (90.5)
– V600K only	1 (2.3)	0 (0.0)	1 (3.7)	7 (10.3)	3 (11.1)	4 (9.8)	1 (4.0)	0 (0.0)	1 (4.8)
– V600K and V600E	2 (4.7)	1 (6.3)	1 (3.7)	1 (1.5)	0 (0.0)	1 (2.4)	2 (8.0)	1 (25.0)	1 (4.8)
– Unknown	4 (9.3)	2 (12.5)	2 (7.4)	3 (4.4)	3 (11.1)	0 (0.0)	–	–	–

[†]Statistical significance at the 5% level.
[‡]The adjuvant therapy cohort was defined as patients who received systemic therapy following initial surgery for stage III (but prior to relapse).
[§]The watch-and-wait cohort was defined as patients who did not receive any systemic therapy following initial surgery for stage III (i.e., watch-and-wait/observation) (prior to relapse).
[#]Other type of plan and no insurance plan categories for insurance coverage at the time of stage III melanoma are not shown, as no patient in the study sample was included in either of these categories.
[#]During the follow up, a relapse (loco-regional, unresectable/metastatic, or secondary primary melanoma) was observed for 168 patients (43 in adjuvant therapy cohort and 125 in watch-and-wait cohort).
^{††}Statistical comparisons between the adjuvant therapy and watch-and-wait cohorts were performed using Wilcoxon rank-sum tests for continuous variables and Chi-square tests for categorical variables.
 CCI: Charlson Comorbidity Index; N: Sample size; SD: Standard deviation.

Watch-and-wait approach

Treatment patterns for patients in the watch-and-wait cohort are summarized in Table 4. The primary reasons for choosing a watch-and-wait approach over adjuvant therapy were heterogeneous. Two of the most common reasons were ‘currently approved therapies have poor tolerability profile’ (44/251 patients; 18%) and ‘patient decision’ (48/251 patients; 19%). Nineteen (8%) patients received radiation therapy post surgery (Table 4). Treatment patterns for patients with different substages are presented separately for each tumor substage in Supplementary Table 6.

Time-to-event analyses

Overall, 44% (168/380) of patients in the study sample experienced a relapse over a median follow up of 3.3 years post index (adjuvant therapy = 33% [43/129] over 4.1 years, watch-and-wait = 50% [125/251] over 3.1 years; Figure 1). The risk of relapse was highest for patients with stage IIIC melanoma (70%); patients with stage IIIA or IIIB had a similar risk of relapse (stage IIIA: 39%, stage IIIB: 39%; Supplementary Figure 1). The first relapse was characterized as unresectable or distant/metastatic for 47% (20/43) of patients with a relapse in the adjuvant therapy cohort and 53% (66/125) of patients with a relapse in the watch-and-wait cohort. Among patients who relapsed, 74% (32/43) and 74% (93/125) of those in the adjuvant therapy cohort and watch-and-wait cohort, respectively, experienced an unresectable or distant/metastatic relapse by the end of follow up.

Patients who received adjuvant therapy had a significantly longer RFS compared with those in the watch-and-wait cohort, even after adjusting for differences in baseline characteristics between the cohorts (adjusted HR [95% CI] = 0.63 [0.44–0.90]; $p < 0.05$; Figure 2A). After 3 years of follow up, 68.7% of patients in the adjuvant therapy cohort were alive and free of relapse; this figure was 52.0% in the watch-and-wait cohort (Figure 2A). When evaluating RFS for patients with different melanoma substages, effect size numerically increased with tumor severity (i.e., stage IIIA: adjusted HR [95% CI] = 0.74 [0.40–1.37], stage IIIC: adjusted HR [95% CI] = 0.54 [0.26–1.15], all $p > 0.05$), but statistical significance was not reached for any of these comparisons between cohorts for each stage separately (Figure 2B–D). The results from the multivariate Cox model for RFS are summarized in Supplementary Tables 7–10. Results were largely similar when comparing RFS in a subset of patients treated with IFN-based adjuvant therapy and watch-and-wait (overall: HR [95% CI] = 0.57 [0.39–0.84]; $p < 0.01$; Supplementary Figure 2).

There was a trend toward worse OS in the watch-and-wait cohort, but the difference was not statistically significantly different between both cohorts (adjusted HR [95% CI] = 0.79 [0.47–1.31]; $p = 0.36$; Figure 3A).

Table 3. Treatment patterns of patients who received adjuvant therapy post surgery for stage III melanoma.

Treatment patterns	All patients N = 129	Interferon α -2b N = 110	Peginterferon α -2b N = 11	Other systemic therapy [†] N = 8
Primary reason for choosing therapy[‡], N (%)				
Approved adjuvant therapy	114 (88.4)	100 (90.9)	11 (100.0)	3 (37.5)
As per national treatment guidelines	3 (2.3)	2 (1.8)	0 (0.0)	1 (12.5)
As per institutional treatment guidelines	5 (3.9)	5 (4.5)	0 (0.0)	0 (0.0)
Potential improvement on health-related QOL	1 (0.8)	1 (0.9)	0 (0.0)	0 (0.0)
Potential prolongation of survival	2 (1.6)	0 (0.0)	0 (0.0)	2 (25.0)
Unknown	4 (3.1)	2 (1.8)	0 (0.0)	2 (25.0)
Starting dose, N (%)				
Starting dose: MU/m ²	NA			NA
Lower dose than recommended		5 (4.6)	0 (0.0)	
20 MU/m² (recommended)		39 (35.5)	0 (0.0)	
Higher dose than recommended		28 (25.5)	0 (0.0)	
Unknown		38 (34.5)	11 (100.0)	
Schedule, N (%)				
Induction	NA			NA
Less frequent than recommended		56 (50.9)	9 (81.8)	
Five-times a week for 4 weeks (recommended)		46 (41.8)	0 (0.0)	
More frequent than recommended		1 (0.9)	0 (0.0)	
Unknown		7 (6.4)	2 (18.2)	
Maintenance	NA			NA
Less frequent than recommended		35 (31.8)	5 (45.5)	
Three-times a week for 48 weeks (recommended)		17 (15.5)	0 (0.0)	
More frequent than recommended		13 (11.8)	1 (9.1)	
No maintenance		43 (39.1)	5 (45.5)	
Unknown		2 (1.8)	0 (0.0)	
Overall treatment duration				
Patients who stopped therapy with known treatment duration information	110 (85.3)	98 (89.1)	8 (72.7)	4 (50.0)
Months of adjuvant therapy (among patients who stopped therapy), mean \pm SD [median]	9.5 \pm 6.5 [9.4]	9.2 \pm 6.1 [9.6]	13.7 \pm 10.6 [8.9]	7.4 \pm 6.6 [7.0]
Modification of adjuvant treatment, N (%)				
Any modification [§]	48 (37.2)	40 (36.4)	7 (63.6)	1 (12.5)
Dose interruption	22 (17.1)	17 (15.5)	4 (36.4)	1 (12.5)
Dose decrease	34 (26.4)	28 (25.5)	6 (54.5)	0 (0.0)
Dose increase	2 (1.6)	2 (1.8)	0 (0.0)	0 (0.0)
Reason(s) for first modification[§]				
Adverse events	39 (81.3)	32 (80.0)	7 (100.0)	0 (0.0)
Disease relapse	2 (4.2)	1 (2.5)	0 (0.0)	1 (100.0)
Decrease in QOL	4 (8.3)	4 (10.0)	0 (0.0)	0 (0.0)
Other	6 (12.5)	5 (12.5)	1 (14.3)	0 (0.0)
Discontinuation of adjuvant treatment, N (%)				
Yes	72 (55.8)	57 (51.8)	10 (90.9)	5 (62.5)
Discontinuation decision				
– Physician decision	56 (77.8)	48 (84.2)	5 (50.0)	3 (60.0)
– Patient decision	15 (20.8)	8 (14.0)	5 (50.0)	2 (40.0)
– Unknown	1 (1.4)	1 (1.8)	0 (0.0)	0 (0.0)

[†] Other systemic therapies include melphalan + TNF α , pembrolizumab, dabrafenib + trametinib, dabrafenib, dacarbazine, sargramostim.
[‡] Response options not selected are not shown (i.e., patient's request; patient age or co-morbidities; intolerance to previous treatment regimen; other).
[§] Multiple response options may be selected for one patient.
[¶] Response options not selected are not shown (i.e., resource/budget constraint; death).
[#] A severe adverse event was defined as an event that led to a hospitalization or urgent intervention, limited the patient's ability to care for him/herself, was life threatening or resulted in death.
 MU: Million unit; QOL: Quality of life; N: Sample size; SD: Standard deviation.

Table 3. Treatment patterns of patients who received adjuvant therapy post surgery for stage III melanoma (cont.).

Treatment patterns	All patients N = 129	Interferon α -2b N = 110	Peginterferon α -2b N = 11	Other systemic therapy [†] N = 8
Reason(s) ^{§, ¶} , N (%)				
– Severe adverse events [#]	16 (22.2)	15 (26.3)	1 (10.0)	0 (0.0)
– Nonsevere adverse events	27 (37.5)	23 (40.4)	2 (20.0)	2 (40.0)
– Disease relapse	12 (16.7)	8 (14.0)	1 (10.0)	3 (60.0)
– Decrease in QOL	5 (6.9)	2 (3.5)	3 (30.0)	0 (0.0)
– Completion of planned therapy	8 (11.1)	5 (8.8)	3 (30.0)	0 (0.0)
– Other	4 (5.6)	3 (5.3)	1 (10.0)	0 (0.0)
No	50 (38.8)	47 (42.7)	0 (0.0)	3 (37.5)
– Unknown	7 (5.4)	6 (5.5)	1 (9.1)	0 (0.0)

[†]Other systemic therapies include melphalan + TNF α , pembrolizumab, dabrafenib + trametinib, dabrafenib, dacarbazine, sargramostim.
[‡]Response options not selected are not shown (i.e., patient's request; patient age or co-morbidities; intolerance to previous treatment regimen; other).
[§]Multiple response options may be selected for one patient.
[¶]Response options not selected are not shown (i.e., resource/budget constraint; death).
[#]A severe adverse event was defined as an event that led to a hospitalization or urgent intervention, limited the patient's ability to care for him/herself, was life threatening or resulted in death.
 MU: Million unit; QOL: Quality of life; N: Sample size; SD: Standard deviation.

After 3 years of follow up, 87.5% of patients in the adjuvant therapy cohort were still alive; this figure was 81.2% among those in the watch-and-wait cohort (Figure 3A). Similar results were observed when assessing patient subgroups defined by melanoma substages, except in patients with stage IIIA melanoma for whom OS was numerically – albeit nonsignificantly – lower in the adjuvant therapy cohort relative to the watch-and-wait cohort (Figure 3B–D). The results from the multivariate Cox model for OS are summarized in Supplementary Tables 11–14. Results were largely similar when comparing OS in a subset of patients treated with IFN-based adjuvant therapy and watch-and-wait (overall: HR [95% CI] = 0.75 [0.43–1.31]; $p = 0.31$; Supplementary Figure 3).

Discussion

In this multicountry, center-based chart review study, real-world treatment patterns and outcomes were evaluated for patients diagnosed with stage III melanoma who underwent complete resection in years 2011–2016 (IFN era) and were treated in a melanoma center. Results demonstrated that only a third of patients with stage III melanoma received adjuvant therapy following surgical resection and that the vast majority of patients were treated with high-dose IFN α 2b. Overall, use of adjuvant therapies versus watch-and-wait varied considerably by country. While a lot of heterogeneity was observed in physicians' reasons for selecting the watch-and-wait approach, the tolerability of approved adjuvant therapies available during the study period (i.e., mainly IFN α 2b and pegIFN α 2b) was one of the most commonly cited reasons. Approximately half of patients did not receive the recommended treatment schedule of IFN-based adjuvant therapy, and about a quarter were initiated on higher-than-recommended IFN doses. Among patients who received adjuvant therapy, most discontinued treatment prematurely due to unacceptable adverse events. The results of the time-to-event analyses support a clear benefit of adjuvant therapy use with respect to RFS, although the OS benefit was less clear.

The use of high-dose IFN α 2b as an adjuvant therapy was a topic of intense debate prior to the advent of new therapies [35,36]. An earlier study from the initial Eastern Cooperative Oncology Group 1684 trial reported a significant, albeit relatively modest, improvement in RFS and OS among patients with melanoma stage IIB or III treated with high-dose IFN α 2b versus observation only (median: 1.7 vs 1 year; 3.8 vs 2.8 years, respectively) [17]. These observations may not, however, be comparable to those of the present study due to the inclusion of stage IIB patients, the exclusion of patients with resectable lymph node recurrence and the many updates of the AJCC staging system since this trial was conducted. However, in a subsequent study, the improvement in OS vanished over a longer follow up period [19], and a second trial conducted by the same group of investigators failed to reproduce the OS benefit initially observed [18]. It is nonetheless important to acknowledge that the patient populations enrolled across these trials differed with respect to clinical characteristics due to the different time periods of enrollment [19]. In addition to inconsistencies in survival benefits, high-dose IFN α 2b is associated with substantial toxicities [17]. Common adverse events include hepatotoxicity, chronic fatigue and neurological abnormalities [37].

Table 4. Treatment patterns of patients who received watch-and-wait post surgery for stage III melanoma.

Treatment patterns	All patients N = 251
Reason for selecting watch-and-wait, N (%)	
Clinical symptoms/co-morbidity making patient ineligible	15 (6.0%)
–Atherosclerotic disease	1 (0.4%)
– Autoimmune disease	1 (0.4%)
– Bipolar disorder, schizophrenia	1 (0.4%)
– COPD, chronic anemia	1 (0.4%)
– Coronary artery disease	1 (0.4%)
– Depressive syndrome	1 (0.4%)
– Diabetes, heart valve	1 (0.4%)
– Hypertrophic cardiomyopathy, cardiac arrhythmia	1 (0.4%)
– Myocardial infarction	2 (0.8%)
– Pregnancy	1 (0.4%)
– Primary biliary cirrhosis	1 (0.4%)
– Rheumatic arthritis	1 (0.4%)
– Rhizomelic arthritis	1 (0.4%)
– Stroke	1 (0.4%)
Patient not eligible for clinical trial	20 (8.0%)
No clinical trial available	7 (2.8%)
Per treatment guidelines, adjuvant therapy is not recommended if disease-free post surgery	11 (4.4%)
Uncertainty about impact of therapy on future treatment	2 (0.8%)
Currently approved therapies have limited efficacy	28 (11.2%)
Currently approved therapies have poor tolerability profile	44 (17.5%)
Currently approved therapies have negative impact on health-related quality of life	3 (1.2%)
Currently approved therapies are burdensome and inconvenient for patient's daily life	11 (4.4%)
Other reasons	82 (32.7%)
–Considered radiotherapy	3 (1.2%)
–Disease progression	3 (1.2%)
– Disease surveillance and monitoring	9 (3.6%)
– Inconvenient systemic therapies with limited efficacy	1 (0.4%)
– Patient's age	9 (3.6%)
–Patient decision	48 (19.1%)
–Patient did not return to center	2 (0.8%)
–Physician decision	1 (0.4%)
–Systemic therapies with limited efficacy and binding treatment	1 (0.4%)
– Unknown	5 (2.0%)
Unknown	28 (11.2%)
Observed duration of 'watch-and-wait' period post stage III surgery	
Months to relapse/end of follow up (all patients), mean ± SD [median]	28.0 ± 19.8 [27.5]
Months to relapse (126 patients with relapse), mean ± SD [median]	14.7 ± 13.8 [11.7]
Radiation therapy post stage III surgery and prior to first relapse	
Patients with radiation therapy, N (%)	19 (7.6%)
Months with radiation therapy, mean ± SD [median]	0.9 ± 0.8 [0.9]
Primary reason for radiation therapy, N (%)	
–As per institutional guidelines	3 (15.8%)
– As per national treatment guidelines in Argentina	1 (5.3%)
– As per national treatment guidelines in Germany	9 (47.4%)
– Benefits shown in delaying time to relapse	5 (26.3%)
– Unknown	1 (5.3%)
COPD: Chronic obstructive pulmonary disease; N: Sample size; SD: Standard deviation.	

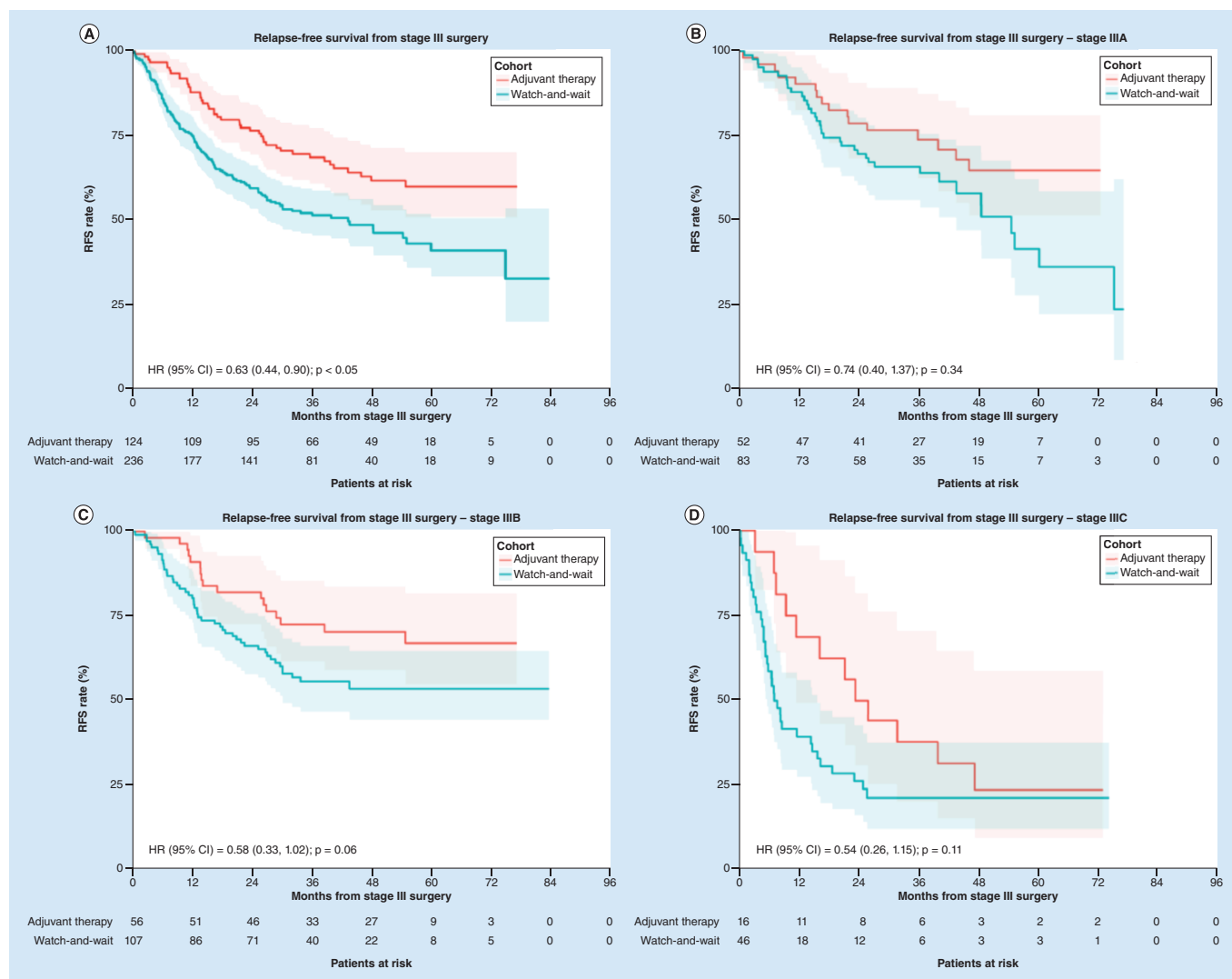


Figure 2. Relapse-free survival following surgery for stage III melanoma among patients who received adjuvant therapy versus watch-and-wait. (A) Overall, (B) among patients with stage IIIA, (C) stage IIIB, (D) and stage IIIC melanoma. The adjusted hazard ratio was estimated from a model controlling for baseline characteristics including age at surgery date for stage III, sex, insurance coverage, employment status, subclass of stage III and Charlson Comorbidity Index. HR: Hazard ratio; RFS: Relapse-free survival.

Although toxicities associated with high-dose IFN α 2b have been reported to be reversible or mitigated following dose reduction, it remains a common reason for premature treatment discontinuation [38,39].

In the present study, only a minority (~a third) of the patients used adjuvant therapy. This finding is consistent with the results from two previously published retrospective cohort studies by Zhang *et al.* [40] and Hackshaw *et al.* [41], although the proportions of patients on adjuvant therapy were much lower in the two latter studies (Zhang *et al.*: 9%; Hackshaw *et al.*: 8.4%). This apparent discrepancy can be attributed to the fact that these studies included many patients with earlier stage disease who did not require adjuvant therapy based on guidelines [9,10] rather than focusing on patients with stage III melanoma. It is possible that the limited use of IFN α 2b in the real-world practice of included melanoma centers reflects the inconclusive impact of high-dose IFN α 2b on OS as well as its poor tolerability profile reported in trials and meta-analyses [17,18,19,24,42]. This possibility could also account for the variability in the dosing regimens at treatment initiation and during treatment observed in the present study. For example, the recommended induction and maintenance schedules were adhered to in 42 and 16% of patients, respectively. More specifically, a quarter received a higher starting dose than recommended, and less frequent induction and maintenance dosing schedules than recommended were used by 58 and 32%

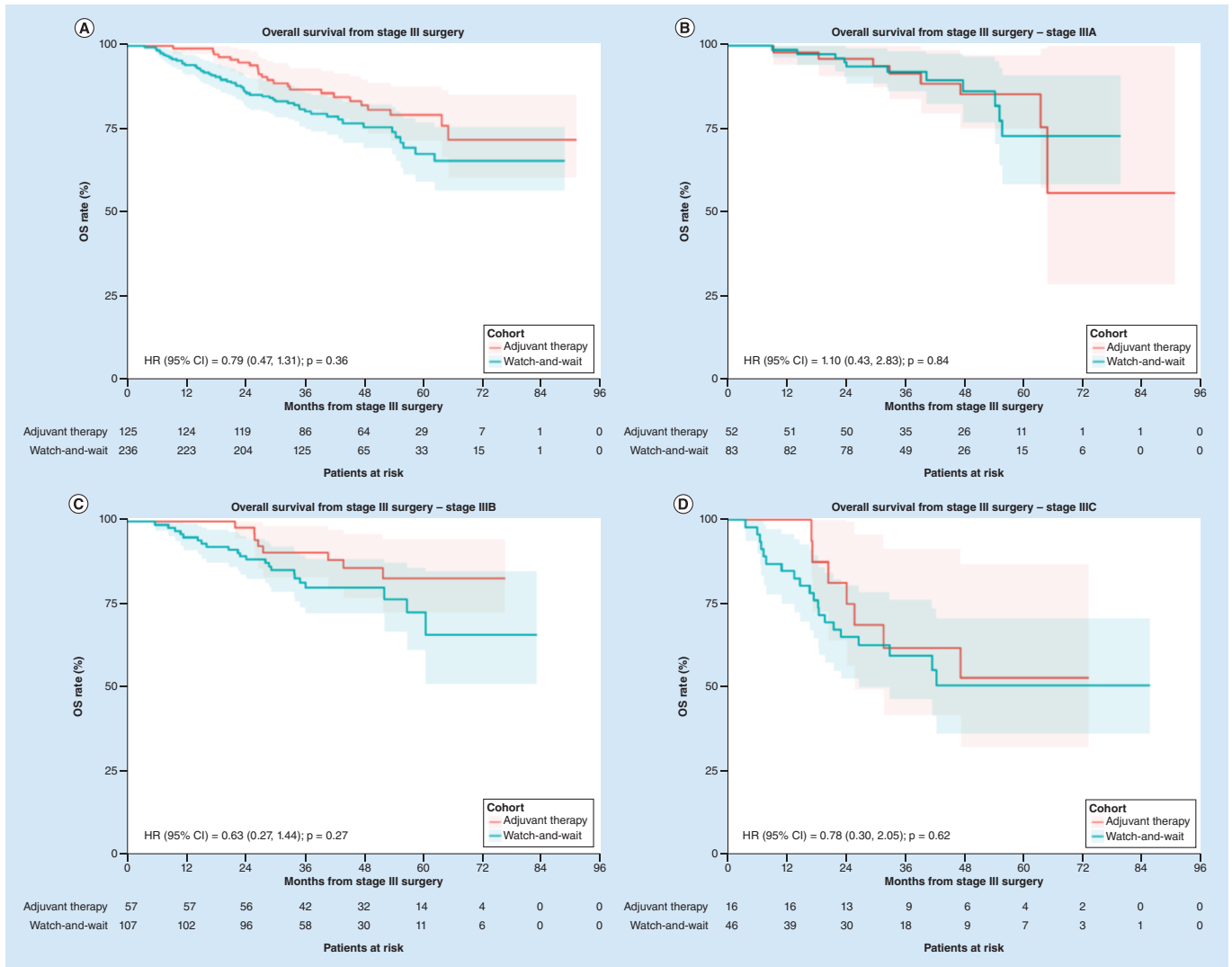


Figure 3. Overall survival following surgery for stage III melanoma among patients who received adjuvant therapy versus watch-and-wait. (A) Overall, (B) among patients with stage IIIA, (C) stage IIIB and (D) stage IIIC melanoma. The adjusted hazard ratio was estimated from a model controlling for baseline characteristics including age at surgery date for stage III, sex, insurance coverage, employment status, subclass of stage III and Charlson Comorbidity Index. HR: Hazard ratio; OS: Overall survival.

of patients, respectively. The high proportion of patients initiated on higher than recommended starting doses may be explained by the fact that previous studies have shown RFS benefits following increasing IFN dose [17]. Furthermore, more than a quarter had a dose reduction during follow up. This finding may be related to a previous study, which showed that reducing the dose of the conventional regimen by 25% did not hinder efficacy [43]. Due to lack of alternative treatment options at the time of data collection, physicians may also try to find ways to improve tolerability without compromising efficacy. This variation in treatment schedules aligns with prior studies, for example, a multicountry retrospective and prospective observational study found that 33% of patients with stage IIIB/C melanoma who were treated with high-dose IFN experienced a dose delay and/or reduction, and 29% discontinued therapy [44]. Similarly, results from another retrospective study reported modifications in both induction and maintenance schedules in 38 and 28% of patients, respectively [45]. The variability in treatment dose, schedule and duration, has resulted in a lack of clear insight regarding the risk benefit to patients [46,47]. Although it is known that adverse events can affect patient adherence to therapy, the threshold of toxicity that some patients can tolerate varies widely resulting in a dramatic impact on treatment patterns and patient outcomes [46,47,48,49].

The most common reasons for adopting a watch-and-wait approach were the poor tolerability profile of approved adjuvant therapies and patient decision, which align with the possibility that the poor tolerability of IFN α 2b contributes to its low use in the real-world practice of included melanoma centers. In addition, patients initiated on adjuvant therapy were significantly younger and had less co-morbidities, suggesting physicians deemed them fitter to receive IFN α 2b and tolerate its side effects. However, despite their seemingly superior health status, most of these patients did not remain on therapy for the full duration of the original Kirkwood 52 week, which is consistent with results from several previous studies [38,40,41]. Adverse events were cited as the main reason for treatment discontinuation. Notably, the observed proportion of patients who did not initiate any maintenance phase reached nearly 40%. Given that a one-month induction phase alone (i.e., without any maintenance phase) is not better than observation [50], this result suggests that a large fraction of patients may not experience any benefits from IFN-based adjuvant therapy due to early discontinuation before the initiation of the maintenance phase.

With respect to the effectiveness of adjuvant therapy, the findings of the current study align with previous trials. For example, results pertaining to RFS were consistent with the effectiveness of adjuvant therapy to reduce the risk of relapse in stage III melanoma, which has been reported in virtually all pivotal trials and meta-analyses [17,18,19,24,42]. The marginal and nonsignificant impact on OS also aligns with most, though not all, trials and meta-analyses on IFN α 2b [18,19,42], which was, by far, the most common regimen in the current study.

However, the magnitude of the difference in RFS observed in the current study was higher than expected based on previous trials evaluating newer agents. Of note, all of these trials used a placebo control instead of an IFN-based adjuvant treatment, and regulatory bodies determined that this was a sufficient evidence to warrant drug approval. The HR in this study was seemingly better than that reported in the placebo-controlled trial of ipilimumab (HR = 0.76 vs placebo) [51] but worse than that from other trials that evaluated more recently approved therapies like dabrafenib plus trametinib (HR = 0.47 vs placebo) [52], nivolumab (HR = 0.65 vs ipilimumab) [53] and pembrolizumab (HR = 0.57 vs placebo) [54]. Two factors may explain this observation. First, the median RFS in the watch-and-wait cohort in the current study (43.1 months) appeared much longer than that observed in the placebo arms of previous randomized controlled trials (~15 months) [52,54]. This suggests that patients included in the watch-and-wait cohort in the current study had a more favorable prognosis than the patients enrolled in the clinical trials. The present study also included fewer patients with stage IIIC disease (17%) as compared with other randomized controlled trials (~40%) [51,52,53,54]. A recent Phase III placebo-controlled trial conducted by Maio *et al.* investigated the efficacy of the *BRAF* inhibitor vemurafenib as postsurgical adjuvant therapy for melanoma and enrolled patients with stage IIC, IIIA, or IIIB (cohort 1) and patients with stage IIIC melanoma (cohort 2) [55]. While the difference in RFS was significant in cohort 1 (HR = 0.54; $p = 0.0010$), a nonsignificant and substantially reduced impact was observed in cohort 2 (HR = 0.80; $p = 0.26$) [55]. Thus, it is conceivable that the inclusion of fewer patients with stage IIIC led to a more pronounced impact, although this possibility has not been formally tested.

Taken together, the results of this study highlight the lack of consensus regarding the use of adjuvant therapy for stage III melanoma following surgical resection, and the high rate of treatment discontinuation in the IFN era. Despite this, treated patients had significantly longer RFS than those in the watch-and-wait cohort. Nevertheless, there was no significant difference in OS. The benefits associated with adjuvant therapy are expected to improve with the recent introduction of novel therapies. Future research should aim to assess whether and how the benefits of these novel therapies translate into the real world.

Limitations

This study should be interpreted within the context of certain limitations. First, results pertaining to the overall study population may not apply to patients in each country assessed. For example, no patients were initiated on adjuvant therapy in Argentina as compared with >80% initiated on adjuvant therapy in Brazil and Canada. Furthermore, the melanoma centers included in this study may have heterogeneous practice patterns to treat melanoma such as different recommendations for initiating a patient on adjuvant therapy, different preferences for dosage and schedule of IFN therapy, or different recommendations for *BRAF*V600 testing. Second, approximately two-thirds of the patients in this study were covered by public insurance plans, which may limit generalizations of these results to patients insured under other types of plans. Third, most patients included in the present study were treated before the advent of new adjuvant therapies. The diagnostic workup, treatment patterns and outcomes of these patients may not reflect those of contemporary patients with stage III melanoma.

Conclusion

During the 2011–2016 study period, only about a third of patients were initiated on adjuvant therapy following surgical resection for stage III melanoma, with IFN α 2b and pegIFN α 2b being, by far, the most common adjuvant treatments. The majority of treated patients did not receive the recommended starting dosage of 20 million unit/m², did not receive the treatment on the recommended schedule, and also discontinued treatment before the end of the standard 52-week schedule; similar results were found when separately assessing patients with different tumor substage. Despite this, RFS was significantly higher among patients who received adjuvant therapy versus those who underwent a watch-and-wait approach in the main analysis. In light of the recent approval of new treatments in the adjuvant setting, these data contribute to documenting the reasons for using or withdrawing adjuvant therapy as well as the potential challenges, which new agents may help overcome.

Future perspective

The treatment landscape for stage III melanoma has evolved considerably since the recent approval of several novel immunotherapies (i.e., nivolumab, pembrolizumab and ipilimumab) and small molecule inhibitors (i.e., dabrafenib plus trametinib). Treatment with these recently approved agents is expected to improve treatment efficacy by extending RFS and OS while also reducing the intolerable adverse events commonly associated with IFN-based therapies. As more data on these new therapies become available, real-world analyses like those performed in the present study will be important to help choose between *BRAF/MEK* inhibitors and immunotherapies in patients with *BRAF*-mutated tumors.

Author contributions

P Mohr, F Kiecker, V Soriano, O Dereure, K Mujika, P Saiag, J Utikal, R Koneru, C Robert, F Cuadros, M Chacon, RU Villarroel, YG Najjar, L Kottschade, EM Couselo, R Koruth, A Guérin, R Burne, R Ionescu-Iltu and JS Zager contributed to the study design, data collection, analysis, interpretation and writing of the manuscript. M Perrinjaquet contributed to the study design, data collection and writing of the manuscript.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/full/10.2217/mmt-2019-0015

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Ethical conduct of research

The study underwent ethics committee review and obtained institutional review board approval for all participating sites. Upon regulatory or institutional review board requirements where applicable, informed consent forms were signed by patients included in the study.

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