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Real-world management practices and characteristics of patients with advanced melanoma initiated on immuno-oncology or targeted therapy in the first-line setting during the period 2015–2018 in Greece. The 'SUMMER' study: a retrospective multicenter chart review project

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This study primarily aimed to generate real-world evidence (RWE) on the profile and first-line treatment (1LT) patterns of patients with advanced (unresectable Stage III/metastatic) cutaneous melanoma initiated on immuno-oncology (IO)- or targeted therapy (TT)-based 1LT between 1 January 2015 and 1 January 2018 (index period), in routine settings of Greece. This was a multicenter, retrospective chart review study. Eligible consented (unless deceased, for whom consent was waived by the hospital) patients were consecutively included by six oncology clinics. The look-back period extended from informed consent or death to initial melanoma diagnosis. Between 9 January 2021 and 9 February 2022, 225 eligible patients (all Caucasians; 60.4% male; 35.6% diagnosed with *de novo* advanced melanoma) were included. At 1LT initiation, median age was 62.6 years; 2.7/6.7/90.7% of the patients had Stage IIIB/IIIC/IV disease and 9.3% were unresected. Most frequent metastatic sites were the lung (46.7%), non-regional nodes (33.8%), and liver (20.9%). Among patients, 98.2% had single primary melanoma, 45.6% had disease localized on the trunk, and 63.6% were BRAF-mutant. Of the patients, 45.3% initiated 1LT with an IO-based, 53.3% with a TT-based regimen, and three patients (1.3%) received TT-based followed by IO-based or vice versa. Most common 1LT patterns (frequency ≥10%) were BRAFi/MEKi combination (31.6%), anti-PD-1 monotherapy (25.3%), BRAFi monotherapy (21.8%), and anti-CTLA-4 monotherapy (17.8%). Most frequent regimens were Dabrafenib+Trametinib in 25.3%, and monotherapies with Pembrolizumab/Ipilimumab/Vemurafenib/Dabrafenib in 23.6/17.8/11.1/10.7% of patients, respectively. SUMMER provides RWE on 1LT strategies and profile of patients initiated 1L IO- or TT-based therapy in Greece during the 3-year index period. *Melanoma Res* **34: 152–165**

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Introduction

Melanoma, the fastest-growing and most life-threatening form of skin cancer, accounts for 1.7% of global cancer diagnoses [1] with its incidence constantly increasing over the last decades [1–4]. In Europe, the age-standardized incidence and mortality rates of melanoma for 2020 were estimated at 11.4 cases and 1.6 deaths per 100 000 persons, respectively, while in Greece the age-standardized incidence rate was 7.2 cases/100 000 persons [1,5].

Before 2011, metastatic melanoma was considered incurable with limited treatment options comprising chemotherapy and interleukin-2, mostly prescribed with palliative intent and resulting in suboptimal response and no survival improvement [6]. The cumulative knowledge over time of the highly immunogenic nature of melanoma [6,7], led to the development of immuno-oncology (IO) therapies. Moreover, identification of mutations

frequently encountered in melanomas gave rise to several targeted therapies (TT). The most frequently mutated gene in melanoma is *BRAF* [8] with almost half of melanoma cases carrying *BRAF* mutations (with V600E *BRAF* mutation being present in >85% of BRAF-positive tumors). The second and third most common mutations are those of *NRAS*, and *NF1* identified in about 15–20% [8], and 10–15% of all melanoma cases [9], respectively.

Targeting the mitogen-activated protein kinase (MAPK) signaling pathway has opened new therapeutic prospectives in melanoma, with the inhibition of BRAF and MEK representing the most promising TT options. Multiple first- and second-generation selective BRAF inhibitors (BRAFi), including vemurafenib/dabrafenib/encorafenib, were approved based on their survival benefit in BRAF-mutant melanoma [8,10]. Although initial response rates to these agents and tumor control are encouraging, clinical benefit durability is limited due to resistance development [11]. Aiming to delay acquired resistance to BRAFi and further enhance MAPK pathway inhibition, combination TTs consisting of BRAFi plus MEKi (dabrafenib/trametinib, vemurafenib/cobimetinib, and encorafenib/binimetinib), were trialed and approved for the management of unresectable or metastatic melanoma [hereinafter referred to as advanced melanoma (AM)] [10,12–14].

IO agents approved for AM include the inhibitors of programmed cell death protein-1 (PD-1), pembrolizumab and nivolumab, and the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor, ipilimumab [15]. Ipilimumab was the first IO therapy to receive approval, based on its pivotal trials' results [16,17]. The clinical program of the PD-1 antibodies, pembrolizumab and nivolumab, demonstrated improved response rates, PFS and OS, compared to ipilimumab and chemotherapy [18–22]. The efficacy gains of ipilimumab/nivolumab combination compared to ipilimumab monotherapy, in terms of higher response rates, response durations, time to subsequent therapies, PFS and OS were also demonstrated [22,23]. Nonetheless, as OS gains with combination therapy were limited, search for biomarkers to pinpoint patients that would benefit from the combination was initiated. Examination of PD-L1, revealed its limited predictive value for response to combination therapy, while among clinical parameters, asymptomatic brain metastases and elevated lactate dehydrogenase (LDH) were suggested to favor the use of nivolumab/ipilimumab over nivolumab alone in the first-line (1L) setting [22,24].

The above along with the lack of direct comparisons between the recommended treatment approaches underline the complexity in first-line treatment (1LT) decision-making of AM, and emphasize the need to better understand the impact of different patient profiles on treatment choice. Several meta-analyses which attempted to bridge this gap, suggested better outcomes with TT during the first year but greater long-term survival benefits with anti-PD1 therapies [4,25–29].

Considering the aforementioned evidence, the 2019 European Society for Medical Oncology (ESMO) guidelines for cutaneous melanoma, recommend pembrolizumab or nivolumab monotherapy, or nivolumab/ipilimumab combination, as the standard of care 1LT for AM regardless of *BRAF* mutation status. For *BRAF* V600-mutated AM, BRAFi combined with MEKi are also recommended, while for unresectable stage IIIB/C, IVM1a, oncolytic viral treatment is also an option. In the case of *BRAF*-mutated AM, single-agent BRAFi should be used only when MEKi is absolutely contraindicated. Furthermore, 1L IO options for *NRAS*-mutated melanoma are identical to those of wild-type (WT) melanoma. In 2L setting, the choice between IO therapy and TT is guided by the type of 1LT and disease mutational status. It is recommended that patients for whom IO therapy can be administered safely for the first few months (i.e. with tumors not rapidly progressing and not immediately threatening an important organ/function), should be considered for IO therapy first, preserving TT for the subsequent lines [4]. Furthermore, the 2020 ESMO consensus conference attended by a multidisciplinary panel of 32 melanoma experts although recommended individualization of 1LT decisions based on patients' clinical status, comorbidities, treatment goals, and personal preferences, emphasized that IO treatment should still be preferred as 1LT as it may provide durable disease control even after stopping treatment [30]. This sequencing strategy is also supported by published results of two randomized trials [31,32] in BRAF-mutant patients.

In conclusion, the advent of IO therapies and TT in the past decade, particularly anti-PD-1 agents, have revolutionized AM management with dramatic improvements in outcomes; nevertheless, despite these advances, until the release of ESMO 2019 guidelines, evidence was limited and/or conflicting in some areas and the optimal 1L strategy remained controversial, with the ESMO 2015 guidelines being in effect until that time not providing clear recommendations for 1LT, nor for the treatment choice drivers [33]. A Delphi study conducted by 12 European Experts in 2018, concluded that tumor burden (encompassing factors such as brain metastases and location of metastases near critical organs) was among the most important factors guiding 1LT choice for BRAF-mutated AM [34].

In view of the above and in lack of a Greek national melanoma registry, the SUMMER study sought to capture the 1L management strategies and depict the profile of patients with AM who started IO-or TT-based 1LT during a period when agents of interest of both therapeutic categories were licensed and reimbursed in Greece and

before the release of the ESMO 2019 guidelines, aiming to identify drivers of 1LT choice in Greece.

Patients and methods

Study design and patient selection criteria

SUMMER was a non-interventional, multicenter, retrospective chart review study, that planned to include 350 AM patients initiated on 1L IO- or TT-based treatment between January 2015 and January 2018 (hereinafter referred to as 'index period'). This period was chosen as (1) it represents a period during which agents from all treatment classes of interest (anti-PD-1/anti-CTLA-4/BRAFi/MEKi) were approved and reimbursable in Greece throughout the entire period (ipilimumab/dabrafenib/vemurafenib) or during part of this period (pembrolizumab and nivolumab were reimbursed in February 2016, and cobimetinib and trametinib in February 2017; MEK and PD-1 inhibitors were also available via early access programs (EAPs) prior to 2016); (ii) it preceded the preferential access to dabrafenib/trametinib for BRAF-mutant disease introduced by the national health authorities in mid-2018; and (iii) it preceded the release of the ESMO-2019 guidelines that recommend IO therapies over TT as 1LT of AM, regardless of BRAF status.

Study sites were among the largest melanoma treatment centers in Greece and also included the Greek Centre of Excellence in Melanoma that acted as national coordinating site.

Medical charts were assessed through consecutive sampling that followed reverse chronological order based on 1LT start date in the AM setting, that is, starting from patients most recently initiated on 1LT, beginning from 1 January 2018 and moving back until 1 January 2015. All eligible patients (except for the deceased) at chart abstraction onset were contacted by the site and offered the opportunity for study participation. If the patient could not be reached, site re-attempted three contacts before considering the patient as 'not interested'.

Data were abstracted from medical records, documented in electronic case report forms, and included patient/disease characteristics, medical/surgical history, information on initial melanoma and AM diagnosis, molecular profiling, and management strategies for AM.

The look-back period extended from the date of informed consent (IC) (for alive patients) or death (for deceased patients) to initial melanoma diagnosis date.

Eligible patients were adults with histologically- or cytologically-confirmed diagnosis of unresectable Stage III or metastatic cutaneous melanoma, not amenable to curative local therapy at the time of 1LT decision-making, who initiated 1LT with locally approved IO- or TT-based treatment during the index period, and who had sufficient medical records for the required data abstraction. Patients were excluded if they had received anticancer systemic therapy for non-melanoma reasons concurrently with the 1LT for AM, had a diagnosis of mucosal-only melanoma, or were currently participating (at the time of IC) or had participated in the 1L or 2L setting (as applicable) of their AM, in any investigational program/trial.

The study followed the Guidelines for Good Pharmacoepidemiology Practice of the International Society for Pharmacoepidemiology [35], the Strengthening the Reporting of Observational Studies in Epidemiology guidelines [36], the European Union General Data Protection Regulation, and the local rules/regulations. The study protocol and IC were approved by the institutional review boards (IRBs) of all participating sites. All alive patients provided written IC, and a consent waiver for deceased patients was granted by the sites' IRBs.

Study objectives and definitions

The study primarily aimed to capture the RW 1L management strategies of AM in patients who started 1LT with an IO- or TT-based treatment during the index period in Greece, as well as to describe the patient/disease characteristics of the study population, overall and by 1L management strategy.

The secondary objectives presented herein were to describe the baseline patient/disease characteristics and 1LT patterns by BRAF mutation status, as well as to investigate factors guiding the 1LT decision-making for AM.

'Index date' was the start date of 1LT for AM, whereas 'baseline' referred to the timepoint closest to (within 30 days before index date) or on the index date.

1LT was defined as the sequence of all systemic anticancer medications (monotherapies or combination therapies), including those administered in the maintenance setting, given between the AM diagnosis and the start of the first subsequent therapy following the first occurrence of disease progression after AM diagnosis (or until chart abstraction initiation if the patient had not progressed at that time).

Sample size and statistical analysis

Sample size determination and all analyses were performed using SAS v.9.4 (SAS Institute Inc., Cary, NC, USA).

Sample size calculation was based on precision estimates of the primary outcomes. A sample of 350 patients was considered sufficient for the estimation of any qualitative variable at a frequency of 50% where the margin of error is largest, with a half-width of the 95% confidence interval (CI) < 5% using normal approximation method.

All data were analyzed descriptively. The normality of distribution of continuous variables was examined using Shapiro-Wilk test. Summary statistics of continuous

variables are presented as mean (standard deviation; SD) in cases data follow a normal distribution; otherwise, the median [interquartile range (interquartile range; IQR)] is presented. Regarding binomial proportions of the primary outcomes, 95% Wald CIs were calculated.

The association of patient/disease characteristics with 1LT choice was evaluated by univariate and multivariate logistic models. The multivariate model was derived from a stepwise procedure based on the minimization of Akaike's information criterion, excluding variables with missing rate >20%. No data imputation was applied except for partial dates. All statistical tests were two-sided and performed at a 0.05 significance level.

Results

Patient disposition

Over an 8.0-month patient accrual period, from 9 January 2021 to 9 February 2022, 227 patients were consecutively included, of whom 225 patients were eligible and analyzed (Fig. 1).

Eligible patients were included by six public or private hospital clinics, across three geographic regions of Greece; specifically, 92.4% (208/225) of patients were included by three sites located in Attica, and 7.6% (17/225) by three sites outside Attica (Central Macedonia and Crete). The ratio of the patients included by academic to those included by non-academic sites was 3:2 (60.4 vs. 39.6%), whereas the ratio of BRAF-mutant to BRAF-WT patients was 1.7:1 (63.6 vs. 36.4%) (Fig. 1).

In regards to the index period, the earliest and latest date of 1LT initiation among all eligible patients was 2 January 2015 and 19 December 2017, respectively. The majority of patients (96.4%; 217/225) were receiving medical care by the study sites at the time of 1LT initiation for AM.

Among patients with available data (N = 155), the median (IQR) time elapsed from initial and from AM diagnosis until the end of look-back period was 45.1 (19.9–78.7) and 22.5 (11.9–55.1) months, respectively; the respective time periods after partial missing data imputation were 36.9 (15.6–72.0) and 18.9 (10.1–46.7) months.

Baseline patient and disease characteristics in the overall eligible population

Of the evaluable patients, all were Caucasians (223/223) and 97.9% (183/187) had public health insurance coverage. The male:female ratio was 3:2 (60.4 vs. 39.6%). The patients' median age at initial diagnosis, AM diagnosis, and 1LT initiation was 60.5, 62.3, and 62.6 years, respectively, with a median of 2.1 months having elapsed from AM diagnosis to 1LT initiation.

Of the patients, 35.6% were initially diagnosed with *de novo* advanced disease. At baseline, the majority of patients had stage IV disease (90.7%; 204/225) with 76.0% (155/204) having visceral metastases. All but four patients (98.2%) had a single primary melanoma with the most prevalent anatomical site being the trunk (45.6%). Slightly less than half of patients (47.1%; 106/225) had undergone sentinel lymph node biopsy, with 48.0% (49/102) of those with available data having a positive result.

Among patients tested for BRAF mutation, 63.6% (140/220) had BRAF-mutant tumors, with V600E being the most common variant accounting for 91.0% (120/132) of all identified BRAF mutations (Fig. 2).

The primary tumor had been resected in 90.7% (204/225) of patients (completely in 201 patients). Furthermore, 11.1% (25/225) had received radiotherapy in the AM setting before 1LT initiation.

Data about medical/surgical history, patients' performance status, and signs/symptoms at baseline were missing in more than half of patients and thus are not reported.

The baseline patient/disease characteristics of interest for the overall study population (with a missing data rate ≤30%) are presented in Table 1.

Management strategies employed in the 1L setting of AM

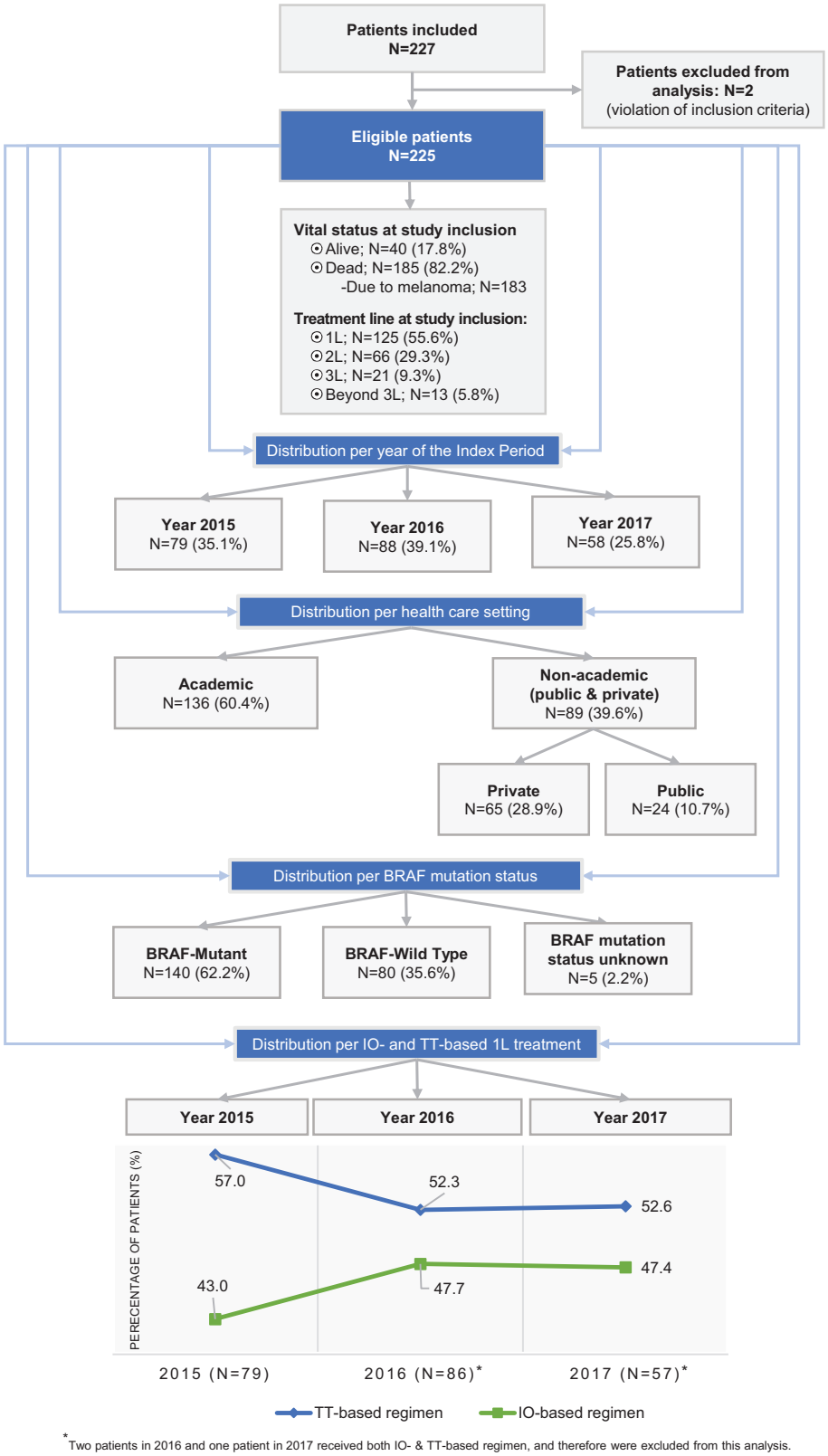
Overall eligible study population

The prescription ratio of TT- over IO-based 1LT throughout the index period was approximately 1.2:1. In particular, 53.3% (120/225; 95% CI: 46.81–59.85) of patients initiated 1LT with a TT-based regimen, 45.3% [102/225; 95% CI: 38.83–51.84] with an IO-based regimen, and three patients [3/225 (1.3%), 95% CI: 0.00–2.83)] received either TT-based followed by IO-based therapy (N = 2) or vice versa (N = 1) (Fig. 3a). The respective prescription ratio among academic and non-academic sites was 1.5:1 and 0.8:1, respectively (Fig. 3a). The respective patient distribution for each year of the index period is presented in Fig. 1.

At a drug class level, the most prevalent 1LT regimens (frequency ≥10%) were BRAFi/MEKi combination in 31.6% (71/225; 95% CI: 25.48–37.63), followed by monotherapy with anti-PD-1 in 25.3% (57/225; 95% CI: 19.65–31.02), BRAFi in 21.8% (49/225; 95% CI: 16.38–27.17), and anti-CTLA-4 agent in 17.8% (40/225; 95% CI: 12.78–22.77) of patients (Fig. 3b). The respective treatment frequencies among patients included by academic and non-academic sites are presented in Fig. 3b.

At a modality level, the most prevalent 1LT regimens (frequency ≥10%) were dabrafenib plus trametinib in 25.3% (57/225; 95% CI: 19.65–31.02), followed by monotherapy with pembrolizumab in 23.6% (53/225; 95% CI: 18.01–29.10), ipilimumab in 17.8% (40/225; 95% CI: 12.78–22.77), vemurafenib in 11.1% (25/225; 95% CI: 7.00–15.22), and dabrafenib in 10.7% (24/225; 95% CI: 6.63–14.70) (Fig. 3c).

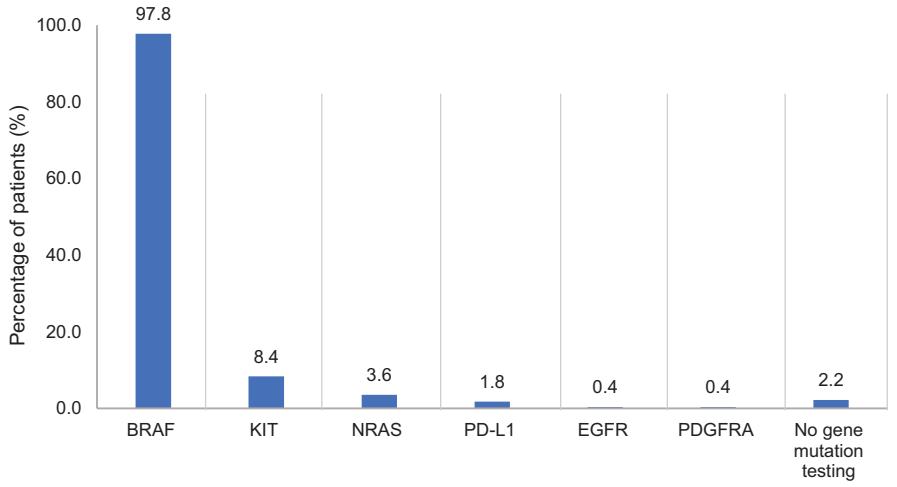
Fig. 1



Patient disposition. 1L/2L/3L/4L+, first-/second-/third-/beyond third-line; IO, immuno-oncology; N, number of patients with available data; TT, targeted therapy.

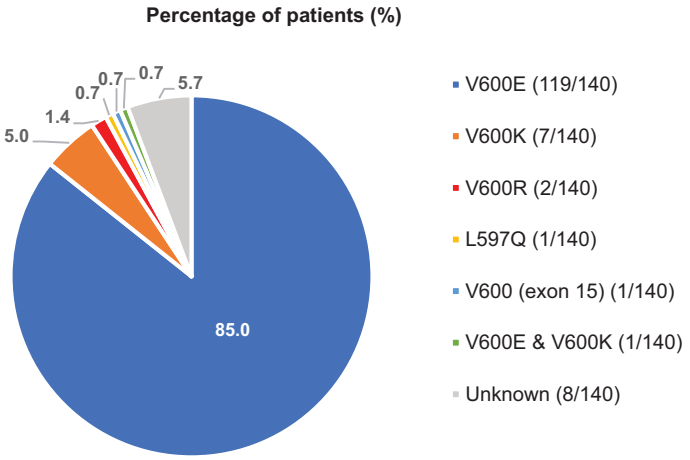
Fig. 2

(a) **Gene mutation testing at baseline in the overall population (N=225)**



n_{tested}	220/225	19/225	8/225	4/225	1/225	1/225	5/225
$n_{positive}$	140/220	1/19	1/8	3/4	0/1	0/1	-

(b) **BRAF mutation types in the BRAF-mutant subpopulation (N=140)**



Molecular characterization. (a) Frequency of gene mutation/biomarker testing in the overall study population. (b) Frequency of BRAF mutation types in the BRAF-mutant subpopulation. N, number of patients with available data.

Subgroups by BRAF mutation status

Of the BRAF-mutant patients, 85.7% (120/140) initiated 1LT with a TT-based regimen, 12.1% (17/140) with an IO-based regimen, and three patients (2.1%) received either TT-based followed by IO-based therapy (N = 2) or vice versa (N = 1) (Fig. 3a). The most frequent (≥10%) treatment option was BRAFi/MEKi combination therapy in 50.7% (71/140; dabrafenib plus trametinib in 40.7% and vemurafenib plus cobimetinib in 10.0%), followed by BRAFi monotherapy in 35.0% (49/140; vemurafenib in 17.9% and dabrafenib in 17.1%) (Fig. 3b and d).

All (80/80) BRAF-WT patients initiated 1LT with an IO-based regimen, comprising anti-PD-1 monotherapy in 58.8% [47/80; pembrolizumab in all but two patients], anti-CTLA-4 monotherapy (ipilimumab) in 37.5% of patients, and nivolumab plus ipilimumab in three patients (Fig. 3b and d).

Baseline patient/disease characteristics by 1LT option and BRAF mutation status

BRAF-WT patients compared to BRAF-mutant were older in age at both initial diagnosis (median age 67.7 vs.

Table 1 Patient and disease characteristics at baseline, overall and by 1LT regimen

	Overall	IO-based therapy				TT-based therapy			Both IO- & TT-based regimen
	(N = 225)	IO-based Total (N = 102)	Anti-PD-1 MONO (N = 57)	Anti-CTLA-4 MONO (N = 40)	Anti-PD-1/anti-CTLA-4 COMBI (N = 5)	TT-based Total (N = 120)	BRAFi MONO (N = 49)	BRAFi/MEKi COMBI (N = 71)	Total (N = 3)
Disease characteristics at initial diagnosis									
Age at initial melanoma diagnosis, median (IQR), years	60.5 (48.3–70.9)	63.0 (48.3–74.7)	67.8 (54.3–75.2)	60.7 (47.5–71.3)	56.4 (44.8–59.2)	58.5 (48.1–68.7)	59.0 (49.0–69.6)	57.2 (46.2–68.2)	68.5 (40.7–72.7)
Age at AM diagnosis, median (IQR), years	62.3 (50.1–71.7)	66.6 (50.4–75.2)	69.2 (54.3–75.2)	63.3 (47.6–74.5)	61.9 (44.8–62.3)	61.3 (49.9–69.5)	61.3 (52.5–69.8)	61.2 (49.6–68.8)	68.5 (40.7–74.7)
Previously diagnosed at an earlier stage (IA-IIIA), % (n/N)	64.4 (145/225)	61.8 (63/102)	57.9 (33/57)	67.5 (27/40)	60.0 (3/5)	67.5 (81/120)	67.3 (33/49)	67.6 (48/71)	33.3 (1/3)
Time from initial to AM diagnosis, median (IQR) months	14.9 (1.9–42.1)	11.3 (2.0–35.2)	6.5 (2.0–23.8)	16.1 (1.6–42.5)	37.4 (8.8–65.8)	21.3 (1.8–45.4)	10.9 (1.6–45.4)	25.1 (2.7–45.6)	24.3 (24.3–24.3)
Time from AM diagnosis to 1LT initiation, median (IQR) months	2.1 (1.2–5.6)	2.4 (1.3–6.3)	2.1 (1.2–7.3)	3.1 (1.8–5.6)	1.9 (0.7–2.1)	1.8 (1.0–5.2)	2.3 (1.2–5.1)	1.5 (0.9–5.3)	0.6 (0.3–21.1)
Baseline sociodemographic characteristics									
Age, median (IQR) years	62.6 (51.2–72.0)	67.0 (51.7–75.7)	69.4 (56.3–75.8)	63.6 (48.1–75.6)	62.1 (44.9–62.5)	61.5 (51.0–70.1)	62.4 (52.9–71.0)	61.4 (50.9–69.4)	68.6 (40.7–76.4)
Age <65 years, % (n/N)	54.7 (123/225)	49.0 (50/102)	43.9 (25/57)	52.5 (21/40)	80.0 (4/5)	60.0 (72/120)	53.1 (26/49)	64.8 (46/71)	33.3 (1/3)
Male, % (n/N)	60.4 (136/225)	62.7 (64/102)	59.6 (34/57)	67.5 (27/40)	60.0 (3/5)	59.2 (71/120)	59.2 (29/49)	59.2 (42/71)	33.3 (1/3)
Urban residence, n (%)	86.2 (181/210)	86.9 (86/99)	85.5 (47/55)	87.2 (34/39)	100.0 (5/5)	85.2 (92/108)	86.4 (38/44)	84.4 (54/64)	100.0 (3/3)
Treated by academic institution, % (n/N)	60.4 (136/225)	52.9 (54/102)	45.6 (26/57)	70.0 (28/40)	-	67.5 (81/120)	71.4 (35/49)	64.8 (46/71)	33.3 (1/3)
Baseline disease and primary tumor characteristics									
Disease stage									
IIIB, % (n/N)	2.7 (6/225)	3.9 (4/102)	7.0 (4/57)	.	.	1.7 (2/120)	2.0 (1/49)	1.4 (1/71)	.
IIIC, % (n/N)	6.7 (15/225)	6.9 (7/102)	3.5 (2/57)	10.0 (4/40)	20.0 (1/5)	5.8 (7/120)	2.0 (1/49)	8.5 (6/71)	33.3 (1/3)
IV, % (n/N)	90.7 (204/225)	89.2 (91/102)	89.5 (51/57)	90.0 (36/40)	80.0 (4/5)	92.5 (111/120)	95.9 (47/49)	90.1 (64/71)	66.7 (2/3)
Multiple primary melanomas, % (n/N)	1.8 (4/225)	3.9 (4/102)	5.3 (3/57)	2.5 (1/40)	.	.	.	.	.
Nodular histologic subtype, % (n/N)	49.4 (82/166)	51.3 (41/80)	55.6 (25/45)	45.2 (14/31)	50.0 (2/4)	47.0 (39/83)	44.8 (13/29)	48.1 (26/54)	66.7 (2/3)
Superficial spreading subtype, % (n/N)	44.0 (73/166)	41.3 (33/80)	35.6 (16/45)	48.4 (15/31)	50.0 (2/4)	48.2 (40/83)	68.4 (13/19)	50.0 (27/54)	-
Tumor thickness (Breslow's depth) > 4.0 mm, % (n/N)	33.8 (54/160)	38.2 (29/76)	33.3 (14/42)	50.0 (15/30)	.	29.3 (24/82)	38.7 (12/31)	23.5 (12/51)	50.0 (1/2)
Tumor ulceration, % (n/N)	70.6 (115/163)	70.5 (55/78)	70.5 (31/44)	70.0 (21/30)	75.0 (3/4)	71.1 (59/83)	77.4 (24/31)	67.3 (35/52)	50.0 (1/2)
Anatomical sites of the primary tumor in ≥10.0%									
Trunk, % (n/N)	45.6 (94/206)	40.9 (38/93)	44.2 (23/52)	38.9 (14/36)	20.0 (1/5)	50.0 (55/110)	53.5 (23/43)	46.4 (32/69)	33.3 (1/3)
Extremities, % (n/N)	31.1 (64/206)	35.5 (33/93)	28.8 (15/52)	44.4 (16/36)	40.0 (2/5)	26.4 (29/110)	27.9 (12/43)	24.6 (17/69)	66.7 (2/3)
Head, % (n/N)	18.9 (39/206)	18.3 (17/93)	21.2 (11/52)	13.9 (5/36)	20.0 (1/5)	20.0 (22/110)	16.3 (7/43)	21.7 (15/69)	.
Unresected primary tumor, % (n/N)	9.3 (21/225)	10.8 (11/102)	10.5 (6/57)	12.5 (5/40)	.	8.3 (10/120)	10.2 (5/49)	7.0 (5/71)	.
Regional lymph node metastasis, % (n/N)	38.4 (81/211)	43.9 (43/98)	38.2 (21/55)	48.7 (19/39)	75.0 (3/4)	33.6 (37/110)	39.5 (17/43)	29.0 (20/69)	33.3 (1/3)
Non-nodal locoregional metastasis, % (n/N)	14.8 (31/209)	17.7 (17/96)	14.8 (8/54)	21.1 (8/38)	25.0 (1/4)	10.9 (12/110)	4.7 (2/43)	14.5 (10/69)	66.7 (2/3)
Sites of distant metastasis in ≥10.0%									
Lung, % (n/N)	46.7 (105/225)	52.9 (54/102)	63.2 (36/57)	40.0 (16/40)	40.0 (2/5)	41.7 (50/120)	38.8 (19/49)	43.7 (31/71)	33.3 (1/3)
Non-regional node, % (n/N)	33.8 (76/225)	32.4 (33/102)	28.1 (16/57)	42.5 (17/40)	.	35.8 (43/120)	24.5 (12/49)	43.7 (31/71)	.
Liver, % (n/N)	20.9 (47/225)	18.6 (19/102)	19.3 (11/57)	15.0 (6/40)	40.0 (2/5)	23.3 (28/120)	24.5 (12/49)	22.5 (16/71)	.
Brain, % (n/N)	16.0 (36/225)	11.8 (12/102)	12.3 (7/57)	12.5 (5/40)	.	20.0 (24/120)	20.4 (10/49)	19.7 (14/71)	.
Soft tissue (including muscle), % (n/N)	11.6 (26/225)	8.8 (9/102)	8.8 (5/57)	10.0 (4/40)	.	14.2 (17/120)	14.3 (7/49)	14.1 (10/71)	.

(*Continued*)

Table 1
(*Continued*)

	Overall	IO-based therapy				TT-based therapy			Both IO- & TT-based regimen
		IO-based Total	Anti-PD-1 MONO	Anti-CTLA-4 MONO	Anti-PD-1/anti-CTLA-4 COMBI	TT-based Total	BRAFi MONO	BRAFi/MEKi COMBI	
	(N = 225)	(N = 102)	(N = 57)	(N = 40)	(N = 5)	(N = 120)	(N = 49)	(N = 71)	Total (N = 3)
Bone, % (n/N)	10.7 (24/225)	10.8 (11/102)	8.8 (5/57)	10.0 (4/40)	40.0 (2/5)	10.8 (13/120)	6.1 (3/49)	14.1 (10/71)	.
Skin, % (n/N)	8.9 (20/225)	10.8 (11/102)	12.3 (7/57)	10.0 (4/40)	.	6.7 (8/120)	8.2 (4/49)	5.6 (4/71)	33.3 (1/3)
BRAF-mutant, % (n/N)	63.6 (140/220)	17.5 (17/97)	13.0 (7/54)	23.1 (9/39)	25.0 (1/4)	100.0 (120/120)	100.0 (49/49)	100.0 (71/71)	100.0 (3/3)
Baseline LDH ≤ 1xULN, % (n/N)	51.1 (93/182)	53.6 (45/84)	51.1 (24/47)	55.9 (19/34)	66.7 (2/3)	47.9 (46/96)	53.8 (21/39)	43.9 (25/57)	100.0 (2/2)

1LT, first-line treatment; AM, advanced melanoma; COMBI, combination therapy; IQR, interquartile range; LDH, lactate dehydrogenase; MONO, monotherapy; n, number of patients; N, number of patients with available data (excluding missing data); ULN, upper limit of normal.

57.9 years) and baseline (median age 69.4 vs. 61.4 years); had shorter time from initial to AM diagnosis among those initially diagnosed at earlier stages (7.8 vs. 21.1 months); had higher rate of extremity primary lesions (34.2 vs. 28.7%), tumor Breslow thickness of >4 mm (43.3 vs. 27.8%), elevated LDH level (54.4 vs. 46.0%), and lung metastasis (57.5 vs. 41.4%); and had lower rate of brain (11.3 vs. 19.3%), and soft tissue (7.5 vs. 14.3%) metastases.

Differences in baseline patient/disease characteristics by 1LT option are relatively consistent, in line with the differences in BRAF-mutant and WT composition of each 1LT subgroup. Specifically, IO-treated patients compared to TT-treated patients were older in age at both initial diagnosis (median age 63.0 vs. 58.5) and baseline (median age 67.0 vs. 61.5); had shorter time from initial to AM diagnosis among those initial diagnosed at earlier stages (11.3 vs. 21.3); had higher rate of extremity primary lesions (35.5 vs. 26.4%), tumor Breslow thickness of >4 mm (38.2 vs. 29.3%), and lung metastasis (52.9 vs. 41.7%); and had lower rate of brain (11.8 vs. 20.0%), and soft tissue (8.8 vs. 14.2%) metastases. Furthermore, IO-treated patients had considerably lower incidence of BRAF-mutant tumors (17.5 vs. 100%), had started 1LT after a longer time period since AM diagnosis (median of 2.4 vs. 1.8 months) and had higher rate of multiple primary melanomas (3.9 vs. 0.0%) compared to TT-treated patients.

The aforementioned between-group differences were not assessed for statistical significance due to the descriptive study nature.

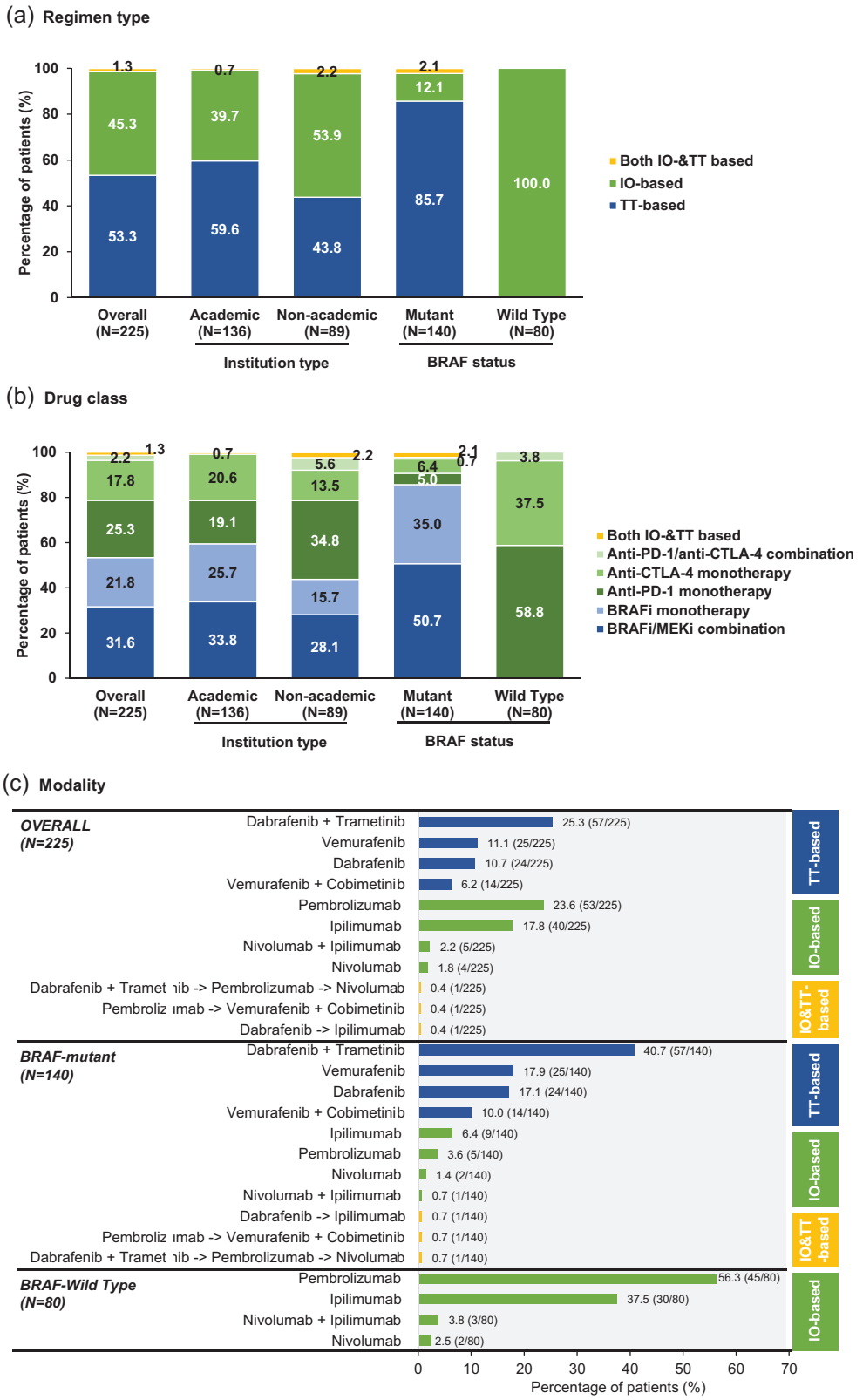
Baseline patient/disease characteristics per 1LT strategy and BRAF status are presented in Tables 1 and 2, respectively.

Associations of baseline patient and disease characteristics with the choice of 1LT for AM

The baseline factors examined with univariate logistic models as per their association with the choice of IO-based vs. TT-based regimens included 'age', 'sex', 'place of residence', 'disease stage', 'presence of *de novo* advanced disease', 'LDH level', 'primary tumor site', 'presence of brain metastases', and 'presence of visceral metastases'. Furthermore, 'the index period year during which 1LT was initiated' and 'institution type' were also considered as potential confounders. Of the aforementioned factors, only 'institution type' was significantly associated with administration of IO-based vs. TT-based 1LT (Fig. 4a).

The final multivariable model, which retained the variables 'disease stage', 'and 'type of institution', demonstrated that patients cared for by non-academic institutions had significantly higher odds of receiving IO- vs. TT-based regimens than those treated by academic institutions when adjusted for baseline disease stage ($P = 0.027$) (Fig. 4b).

Fig. 3



1L treatment patterns, overall, per type of healthcare institution and per BRAF status. (a) Frequency of regimen types. (b) Frequency of drug classes. (c) Frequency of modalities. 1L, first-line; BRAFi, BRAF inhibitor; CTLA-4, Cytotoxic T-Lymphocyte Antigen 4; IO, immuno-oncology; MEKi, MAPK/ERK kinase inhibitor; PD-1, Programmed Cell Death-1; TT, targeted therapy.

Table 2 Patient and disease characteristics at baseline in the subgroups of patients per BRAF mutation status

	BRAF-mutant (N = 140)	BRAF WT (N = 80)	BRAF status unknown (N = 5)
Disease characteristics at initial diagnosis			
Age at initial melanoma diagnosis, median (IQR), years	57.9 (46.2–68.6)	67.7 (53.8–76.0)	58.5 (57.1–59.1)
Age at advanced melanoma diagnosis, median (IQR), years	60.7 (49.3–69.2)	69.2 (54.3–77.0	60.0 (58.5–62.3)
Previously diagnosed at an earlier stage (IA-IIIA), % (n/N)	66.4 (93/140)	62.5 (50/80)	40.0 (2/5)
Time from initial to AM diagnosis, median (IQR) months	21.1 (2.0–44.1)	7.8 (1.6–26.2)	36.3 (35.2–37.4)
Time from AM diagnosis to 1LT initiation, median (IQR) months	1.8 (1.0–5.2)	2.6 (1.4–6.9)	2.4 (0.4–3.6)
Baseline sociodemographic characteristics			
Age, median (IQR) years	61.4 (49.8–69.8)	69.4 (54.5–78.1)	60.1 (58.8–62.5)
Age <65 years, % (n/N)	61.4 (86/140)	41.3 (33/80)	80.0 (4/5)
Male, % (n/N)	60.7 (86/140)	61.3 (49/80)	40.0 (2/5)
Urban residence, n (%)	78.3 (108/138)	90.9 (70/77)	60.0 (3/5)
Baseline disease and primary tumor characteristics			
Disease stage			
IIIB, % (n/N)	1.4 (2/140)	5.0 (4/80)	-
IIIC, % (n/N)	7.9 (11/140)	3.8 (3/80)	20.0 (1/5)
IV, % (n/N)	90.7 (127/140)	91.3 (73/80)	80.0 (4/5)
Multiple primary melanomas, % (n/N)	1.4 (2/140)	2.5 (2/80)	-
Nodular histologic subtype, % (n/N)	47.5 (48/101)	51.6 (32/62)	66.7 (2/3)
Superficial spreading subtype, % (n/N)	46.5 (47/101)	40.3 (25/62)	33.3 (1/3)
Tumor thickness (Breslow's depth) > 4.0 mm, % (n/N)	27.8 (27/97)	43.3 (26/60)	33.3 (1/3)
Tumor ulceration, % (n/N)	70.0 (70/100)	71.7 (43/60)	66.7 (2/3)
Anatomical sites of the primary tumor in ≥10.0%			
Trunk, % (n/N)	48.1 (62/129)	43.8 (32/73)	-
Extremities, % (n/N)	28.7 (37/129)	34.2 (25/73)	50.0 (2/4)
Head, % (n/N)	19.4 (25/129)	17.8 (13/73)	25.0 (1/4)
Unresected primary tumor, % (n/N)	7.9 (11/140)	11.3 (9/80)	20.0 (1/5)
Regional lymph node metastasis, % (n/N)	38.5 (50/130)	37.7 (29/77)	50.0 (2/4)
Non-nodal locoregional metastasis, % (n/N)	13.2 (17/129)	15.8 (12/76)	50.0 (2/4)
Sites of distant metastasis in ≥10.0%			
Lung, % (n/N)	41.4 (58/140)	57.5 (46/80)	20.0 (1/5)
Non-regional node, % (n/N)	34.3 (48/140)	33.8 (27/80)	20.0 (1/5)
Liver, % (n/N)	20.0 (28/140)	21.3 (17/80)	40.0 (2/5)
Brain, % (n/N)	19.3 (27/140)	11.3 (9/80)	-
Soft tissue (including muscle), % (n/N)	14.3 (20/140)	7.5 (6/80)	-
Bone, % (n/N)	9.3 (13/140)	12.5 (10/80)	20.0 (1/5)
Skin, % (n/N)	6.4 (9/140)	13.8 (11/80)	-
Baseline LDH ≤ 1xULN, % (n/N)	54.0 (61/113)	45.6 (31/68)	100.0 (1/1)

1LT, first-line treatment; AM, advanced melanoma; IQR, interquartile range; LDH, lactate dehydrogenase; MONO, monotherapy; n, number of patients; N, number of patients with available data (excluding missing data); ULN, upper limit of normal.

Discussion

SUMMER study provides RW evidence on 1LT strategies and patient/disease characteristics of AM patients treated in routine care settings of Greece between January 2015 and January 2018, a period during which agents from all IO and TT drug classes of interest were licensed and reimbursable in Greece.

In the overall study population (60% males, 55% aged >65 years, 91% metastatic, and 64% BRAF-positive), 45% of patients initiated 1LT with an IO-based regimen, and 53% with a TT-based regimen, while three patients (1%) received both IO- and TT-based regimens. At a drug class level, within the TT-based subgroup, the most frequent regimen was BRAFi/MEKi combination therapy (59%) followed by BRAFi monotherapy (41%), while among IO-treated patients, the most prevalent regimen was anti-PD-1 monotherapy (56%), followed by anti-CTLA-4 monotherapy (39%). Among the BRAF-mutant patients, as low as 12% initiated 1LT with an IO regimen, whereas as expected, all BRAF-WT patients initiated IO-based 1LT.

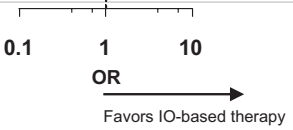
Several other RW studies have previously reported on 1LT patterns in AM at periods close to that of SUMMER in the USA and Europe [37–44]. In these studies, the percentage of patients receiving IO regimens, among those with known BRAF-mutation status and treated with IO and/or TT regimens, ranged from 55 to 76%, while the percentage of those receiving TT varied from 24 to 45%, with the combination of IO and TT treatments reported by Cowey *et al.* at a proportion <6.2% [37]. Across these studies, BRAF mutation frequency ranged from 39 to 61%, patients' median age from 57.1 to 69.0 years and the proportion of males from 48 to 68%, with the SUMMER cohort characteristics falling within the reported ranges except for BRAF positivity rate which was numerically higher in SUMMER; the latter may be justified by the fact that SUMMER represented a selected population of IO- and/or TT-treated patients excluding other treatment modalities, while is consistent with and presumably partly explains the predominance of TT over IO regimens in the SUMMER cohort contrary to the pattern seen in the other aforementioned studies.

Regarding RW studies conducted in the USA [37–40], their respective index periods spanned from 2014 to 2017. The observed 1LT strategies for AM were considerably different from the ones in SUMMER, clearly

Fig. 4

(a) **Univariate analysis**

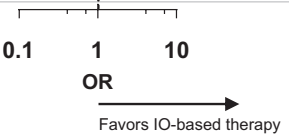
Variables	Reference versus category	N	$n_{IO\text{-}based\ therapy}$	Crude OR	95% CI	p-value
Age at baseline (N=222)	<65 vs ≥65 years	122 vs 100	50 vs 52	0.64	(0.38-1.09)	0.102
Sex (N=222)	Male vs Female	135 vs 87	64 vs 38	1.16	(0.68-2.00)	0.586
Place of residence (N=207)	Urban vs Other	178 vs 29	86 vs 13	1.15	(0.52-2.53)	0.728
Disease stage (N=222)	III vs IV	20 vs 202	11 vs 91	1.49	(0.59-3.75)	0.397
De novo advanced disease (N=222)	Yes vs No	78 vs 144	39 vs 63	1.29	(0.74-2.23)	0.373
LDH (N=180)	≤1 x ULN vs >1 x ULN	91 vs 89	45 vs 39	1.25	(0.70-2.26)	0.449
Anatomical site of the primary tumor (N=203)	Extremities vs Other	62 vs 141	33 vs 60	1.54	(0.84-2.80)	0.161
Presence of brain metastases (N=222)	Yes vs No	36 vs 186	12 vs 90	0.53	(0.25-1.13)	0.101
Presence of visceral metastases* (N=222)	Yes vs No	153 vs 69	72 vs 30	1.16	(0.65-2.05)	0.620
Year of 1L treatment initiation (N=222)	2015 vs 2016/2017	79 vs 143	34 vs 68	0.83	(0.48-1.45)	0.518
Type of healthcare institution (N=222)	Non-Academic vs Other	87 vs 135	48 vs 54	**1.85**	(1.07-3.18)	**0.027**



*Visceral metastases include lung, liver, brain, gastrointestinal tract, adrenal glands, pancreas, spleen, peritoneum, abdominal region (ascites)

(b) **Multivariate analysis**

Variables	Reference versus category	n_{pt}	$n_{IO\text{-}based\ therapy}$	Adjusted OR	95% CI	p-value
Disease stage (N=222)	III vs IV	20 vs 202	11 vs 91	1.19	(0.46-3.09)	0.725
Type of healthcare institution (N=222)	Non-academic vs Other	87 vs 135	48 vs 54	**1.80**	(1.03-3.16)	**0.039**



Forest plots showing associations between baseline patient/disease characteristics and 1L treatment choice, by (a) univariate and (b) multivariate analysis. 1L, first-line; CI, confidence interval; IO, immuno-oncology; LDH, lactate dehydrogenase; N, number of patients in each category; n, number of patients treated with IO 1L treatment; OR, odds ratio; ULN, upper limit of normal.

favoring IO over TT with treatment rates ranging from 70 to 76% and 24 to 30%, respectively; this may be partly explained by the lower proportion of patients with BRAF-mutant AM, which ranged from 39 to 47%. Nonetheless, among the BRAF-mutant subgroup, the percentage of IO-treated patients ranged from 37 to 50%, as opposed to 12% in SUMMER. Focusing on the RW studies performed in Europe, index periods overlapped with that of SUMMER, with the exception of one study with a patient identification period extending until the end of 2020 [42]. The 1L IO- and TT-based treatment rates ranged from 53 to 79% and 21 to 47%, respectively, also favoring IO therapy, whereas the frequency of BRAF positivity ranged from 54 to 61%. Among BRAF-mutant patients, the treatment rate of 1L IO regimens was 42% in the study of Van Breeschoten *et al.* [43] and 20% in the study of Cybulska-Stopa *et al.* [41], with the latter being closer to that observed in SUMMER (12%).

Concerning drug classes, despite numerical variations across studies, BRAFi/MEKi combination was reported at higher frequency than BRAFi monotherapy, and anti-PD-1 monotherapy at higher frequency than anti-CTLA-4 monotherapy, similar to SUMMER, with the exception of the studies by Whitman *et al.* [40] and Crispo *et al.* [44], where anti-CTLA-4 monotherapy was administered more frequently than anti-PD-1 monotherapy, and the latter study which also reported higher frequency of BRAFi monotherapy than BRAFi/MEKi combination [37–44].

In any case, when viewing the SUMMER results in the context of the published literature, it should be kept in

mind that besides differences in the timing of 1LT initiation among different cohorts (with variations in patient/disease characteristics particularly those affecting treatment choice), market authorization and pricing/reimbursement processes effective in each country may have also affected the observed treatment patterns. This is also illustrated by the increased uptake of IO treatments between 2015 and 2016 in the SUMMER cohort (43% vs. 48%), which may be attributed to the entrance of PD-1 inhibitors into the Greek market in 2016, 1 year after the start of the SUMMER index period. Notwithstanding, it is noteworthy that this increase was not continued in 2017 (47%). The availability of MEK and PD-1 inhibitors through EAPs is unlikely to have substantially influenced the treatment patterns, as the proportion of these patients among the overall population is anticipated to be low.

Considering the above, the divergence of SUMMER cohort from the other similar RW studies with respect to the ratio of patients treated with IO over TT regimens may be attributed to the earlier approval of immunotherapies in USA compared to Europe, as well as to the inter-country variation of access to new cancer drugs among the European countries. This was documented in a recently published work [45] that aimed to assess the access in Europe to newly registered cancer drugs, and involved 12 drugs including, among others, ipilimumab/vemurafenib/pembrolizumab/nivolumab for melanoma indication, and 28 European countries during the period 2011–2018. Based on the results, marketing approval for the newly registered cancer drugs occurred on average 8 months later in Europe than in the USA. At a European level, the actual time to market (i.e. from marketing authorization to market access) varied extensively across countries and amounted to an average of 398 days (range: 17–1187 days). Specifically, Greece ranked among countries with the longest delay in patient access, whereas patient access in the European countries where the RW studies discussed above were conducted, was faster than the European average.

Finally, it may be concluded that the SUMMER findings suggest a physician preference for TT-based therapy in BRAF-mutated patients. This was despite guideline-recommended PD-1 blockade alone or in combination with CTLA-4 blockade as 1LT, regardless of BRAF status [33]. Although the reasons for this choice are difficult to infer given the study's retrospective nature, it is possible that BRAF testing served as the key decision-making driver, considering also that none of the baseline factors examined in the regression analysis was significantly associated with treatment choice. Notably, there were no factors other than patient/disease characteristics (such as patient preference) that weighed on clinicians' decision, while chronic therapy with systemic steroids or other immunosuppressants that could preclude IO prescription was reported for a minority of patients. Other explanations for clinicians' preference over TT could be treatment goals focusing on rapid response with BRAF-TT, as well as tumor burden, patients' clinical status, symptoms and comorbidities which although collected are not reported due to high missingness rate. Future studies should address how recent evidence from the two trials [31,32] on BRAF-mutant patients and updated guidelines on the preferred sequencing strategies [4,30] are incorporated in clinical practice. The key patient/disease characteristics of BRAF-mutant and BRAF-WT patients at 1LT initiation in our cohort are consistent with other studies [46–49] however no reliable inferences can be drawn in lack of between-group statistical comparisons. Specifically, when contrasted against those with BRAF-WT disease, BRAF-positive patients were younger [46,49], had more frequent disease localization on the trunk [46,47] but less frequent on the extremities [46], were less likely to have tumor thickness (Breslow's depth) > 4 mm [46] and more likely to have superficial spreading subtype [46,47], while they presented more frequently with soft tissue metastases but less frequently with lung metastases [49].

Limitations in our study are mainly attributable to its retrospective design and involve selection bias, confounding and information/misclassification bias. Patient selection bias was minimized by consecutive sampling regardless of the candidate patient's vital status (alive/deceased) at the time of assessment for study inclusion, and through the implementation of a predefined selection process previously described. The major limitation pertains to the systematic error arising from missing data, which may have resulted in hidden or non-response bias. This bias is not a major concern in the context of the primary outcome addressing 1LT strategies due to the study's requirement for sufficient medical records. Nonetheless, regarding patient/disease characteristics, certain key variables were missing for a substantial number of participants and are not reported herein. For instance, information on medical history, patients' clinical/performance status, organ function parameters, and primary tumor features was not available for more than one-third of patients. With respect to baseline characteristics presented per 1LT option, caution is required when interpreting the data and any observed differences between the subgroups, considering the limited size of some subgroups and the absence of between-group statistical comparisons due to the descriptive nature of the study.

Lastly, the eligible population actually included 225 patients which is lower than the planned size of 350 patients. Nevertheless, the margin of error generated with the actual size still represents an acceptable level of precision (half-width of CI < 7.0%) for the qualitative outcomes pertaining to the overall study population as well as for those addressed in the IO- and TT-treated subgroups which comprised >100 patients each, thus ensuring a margin of error <10.0%.

The aforementioned limitations are outweighed by the fact that such studies follow less restrictive methodological standards than controlled trials in terms of patient selection, treatment and other design issues, thus their results are better generalizable especially for populations with diseases of complex/heterogeneous biology, such as melanoma. Moreover, the fact that the participating centers treat more than two-thirds of all melanoma cases in Greece reinforces the results' generalizability. Representativeness was also enhanced by including patients from both academic and non-academic (both public and private) institutions in Greece, accounting for variations in medical practice paradigms.

In conclusion, SUMMER results shed insight on the 1LT strategies and profile of AM patients initiated on IO- or TT-based 1LT from 2015 to 2018, in Greece. Although, 1LT options were evenly distributed between IO- and TT-based therapy in the overall study population, among BRAF-positive patients comprising almost two-thirds of the overall cohort, the frequency of IO-based 1LT was only 12%. Since these results may also corroborate the presence of therapeutic inertia, it would be interesting to see in the future how the contemporary European guidelines, that strongly recommend IO therapy as the 1L standard of care irrespective of BRAF status, are taken up in clinical practice in the rapidly evolving era of immunotherapeutics, also considering that since their introduction in the market clinicians have become increasingly familiar with the use of immunotherapies.

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H.G. contributed to the study conception and design and original draft preparation. All authors contributed to data acquisition and/or interpretation, revised critically the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work. Writing and editorial assistance was provided by Qualitis SA., funded by MSD Greece, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of patients included in the study.

Conflicts of interest

D.B. declared consulting/advisory role or received speakers' honoraria from Bristol Myers Squibb, Roche, MSD, Amgen, Pierre-Fabre, Novartis, and Sanofi. P.G. has received honoraria from MSD, Bristol Myers Squibb, Novartis, and Pierre Fabre. I.B. has received honoraria from Roche, MSD, Bristol Myers Squibb, Pfizer, Novartis, Merck, AstraZeneca, LEOpharma, Servier, personal fees for advisory/consultancy by Roche, Sanofi, AstraZeneca, Bristol Myers Squibb, LEOpharma MSD, Novartis, Ipsen, Genesis Pharma and research funding from Roche, Novartis, Bristol Myers Squibb, MSD, Regeneron, Boehringer Ingelheim, Lilly, Pfizer and travel/accommodation fees from MSD, Roche, Pfizer, Bristol Myers Squibb. S.B. has received Research and advisory fees from MSD, AstraZeneca, Bristol Myers Squibb, Eisai, Roche, Regeneron, GlaxoSmithKline, Dainchi, Lilly, and Amgen. F.S. and I.D. are full-time employees of MSD, Greece, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA and may own stocks and/or stock options in Merck & Co., Inc., Rahway, NJ, USA. H.G. has received honoraria from Bristol Myers Squibb, MSD, Pierre Fabre, Sanofi/Regeneron and personal fees for advisory/consultancy by Bristol Myers Squibb, MSD, Pierre Fabre and Sanofi/Regeneron, research funding from Bristol Myers Squibb, Roche, MSD, Amgen, Novartis, Iovance Biotherapeutics regeneron, Boehringer Ingelheim, Lilly and travel/accommodation fees from MSD, Amgen, Pfizer. For the remaining authors, there are no conflicts of interest.

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