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ORIGINAL RESEARCH

Efficacy and safety of nivolumab for patients with pre-treated type B3 thymoma and thymic carcinoma: results from the EORTC-ETOP NIVOTHYM phase II trial

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Background: Thymic malignancies are rare intrathoracic tumors, which may be aggressive and difficult to treat. They represent a therapeutic challenge in the advanced/metastatic setting, with limited treatment options after the failure of first-line platinum-based chemotherapy. They are frequently associated with autoimmune disorders that also impact oncological management.

Materials and methods: NIVOTHYM is an international, multicenter, phase II, two-cohort, single-arm trial evaluating the activity and safety of nivolumab [240 mg intravenously (i.v.) q2 weeks] alone or with ipilimumab (1 mg /kg i.v. q6 weeks) in patients with advanced/relapsed type B3 thymoma or thymic carcinoma, after exposure to platinum-based chemotherapy. The primary endpoint is progression-free survival rate at 6 months (PFSR-6) based on RECIST 1.1 as per independent radiological review.

Results: From April 2018 to February 2020, 55 patients were enrolled in 15 centers from 5 countries. Ten patients (18%) had type B3 thymoma and 43 (78%) had thymic carcinoma. The majority were male (64%), and the median age was 58 years. Among the 49 eligible patients who started treatment, PFSR-6 by central review was 35% [95% confidence interval (CI) 22% to 50%]. The overall response rate and disease control rate were 12% (95% CI 5% to 25%) and 63% (95% CI 48% to 77%), respectively. Using the Kaplan—Meier method, median progression-free survival and overall survival by local assessment were 6.0 (95% CI 3.1-10.4) months and 21.3 (95% CI 11.6-not estimable) months, respectively. In the safety population of 54 patients, adverse events (AEs) of grade 1/2 were observed in 22 (41%) patients and grade 3/4 in 31 (57%) patients. Treatment-related AEs of grade 4 included one case of neutropenia, one case of immune-mediated transaminitis, and two cases of myocarditis.

Conclusions: Nivolumab monotherapy demonstrated an acceptable safety profile and objective activity, although it has been insufficient to meet its primary objective. The second cohort of NIVOTHYM is currently ongoing to assess the combination of nivolumab plus ipilimumab.

Key words: thymoma, immunotherapy, thymic carcinoma

INTRODUCTION

Thymic epithelial tumors are rare thoracic malignancies that may be aggressive and difficult to treat.[1,2] There are ∼1500 patients diagnosed every year in Europe.[3] Thymic tumors are classified according to the World Health Organization (WHO) histopathologic classification that distinguishes

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thymomas from thymic carcinomas.[4] Thymomas reproduce the architecture of the normal thymus, combining epithelial tumor cells with non-tumoral lymphocytes, and are further subdivided into different types (A, AB, B1, B2, and B3) based on the degree of cell atypia, the relative proportion of the lymphocytic component, and the resemblance to normal thymic architecture.[4] Thymic carcinomas are similar to their extra-thymic counterpart, and the most frequent morphological subtype is squamous cell carcinoma.[4]

Surgery has been the mainstay of the curative-intent treatment in limited-stage thymic epithelial tumors, as complete resection represents the most significantly favorable prognostic factor for overall survival (OS), both in thymomas and thymic carcinomas.[1,2] Systemic agents based on platinum-based combination regimens have been historically used for the treatment of unresectable, metastatic, and recurrent tumors, which are more frequently type B3 thymomas and carcinomas.[1,5] Several consecutive lines of chemotherapy, antiangiogenic agents, or targeted therapies may be administered during tumor progression.[5] However, efficacy has been highly variable and infrequently sustained over time. Currently, no standard of care exists beyond the first-line setting, while virtually all patients require second-line and beyond therapies.[1,2,5,6]

Immune checkpoint inhibitors (ICIs) have been an attractive option for the treatment of thymic malignancies. However, this has been a major challenge, as at the time of diagnosis, up to one-third of patients present with autoimmune disorders, especially myasthenia gravis,[7] that may be exacerbated by immunotherapeutic agents.[8,9] Nevertheless, thymic carcinoma may be considered a good candidate to assess the efficacy of such strategies, given (i) the histologic subtype, mostly consisting of squamous cells that are usually sensitive to immunotherapies; (ii) the frequent expression of programmed death-ligand 1 (PD-L1), even if viewed as constitutive of thymic epithelial cell phenotype;[9,10] and (iii) the high rate of genomic aberration, a criterion previously reported to predict durable benefit of immunotherapy in some patients.[11,12]

Based on this hypothesis, we conducted the NIVOTHYM trial evaluating the use of nivolumab alone (cohort 1) or—subsequently after completion of this cohort—in combination with ipilimumab (cohort 2) in patients with advanced/relapsed type B3 thymoma or thymic carcinoma, after exposure to platinum-based chemotherapy. Here, we report the results of the single-agent nivolumab cohort.

MATERIALS AND METHODS

Patients

Patients were eligible to enter the trial if they were at least 18 years old; had a WHO performance status of 0-2; a histologically confirmed thymoma B3 or thymic carcinoma not amenable to curative-intent radical treatment; a documented radiological progression as per RECIST version 1.1;[13] a failure after at least one previous line of platinum-based chemotherapy for advanced disease; an adequate hematological, liver, and renal function; and had provided a tumor sample for PD-L1 status assessment. Patients were excluded if they had an active autoimmune disease that required any systemic treatment in the past 2 years (i.e. use of disease-modifying agents, corticosteroids, or immunosuppressive drugs); evidence of active central nervous system metastases and/or carcinomatous meningitis; prior treatment with ICIs; known active hepatitis or current evidence of human immunodeficiency virus (HIV) (HIV-1/2 antibodies); chronic use of immunosuppressive agents and/or systemic corticosteroids or any use in the last 15 days before enrolment; or history of any other hematologic or primary solid tumor malignancy, unless in remission for at least 5 years. Because of an increased risk of myasthenia gravis, patients with the presence of acetylcholine receptor antibodies at baseline were also excluded.

Trial design

NIVOTHYM is an international, multicenter, phase II, two-cohort, single-arm study designed by the European Organisation for Research and Treatment of Cancer (EORTC) in collaboration with the European Thoracic Oncology Platform (ETOP) and sponsored by the EORTC (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2023.101576).

Procedures

Nivolumab, a human immunoglobulin G4 monoclonal antibody binding to the programmed cell death protein 1 (PD-1) receptor and blocking its interaction with PD-L1 and PD-L2, was administered at a dose of 240 mg intravenously every 2 weeks and continued until progression of disease (PD), unacceptable toxicity, patient refusal, or death. Patients who received nivolumab without progression after 1 year of treatment were allowed to interrupt it. If they, then, experienced a PD $>$3 months after completing 1 year of treatment and met all criteria for its administration, they had the opportunity to resume until PD as per investigator's decision. In case a patient continued to derive clinical benefit despite an initial documentation of PD (defined as investigator assessment of clinical benefit; stable PS; tolerance of study drug; absence of threatening or rapid progression), (s)he could continue nivolumab, with a new tumor assessment after $\sim$4 weeks to determine response, disease stabilization, or alternatively to confirm PD, which would ultimately terminate the trial treatment. Further progression was defined as an additional $>$10% increase in tumor dimension or presence of new lesions as per RECIST 1.1 criteria from the time of initial PD. An interim analysis for futility and efficacy was planned after a third of the information (17/50 patients) was available for cohort 1. Based on the results of the single-agent cohort reported here, a second, subsequent cohort of combination

nivolumab (240 mg every 2 weeks) plus ipilimumab (1 mg/kg every 6 weeks) therapy has been ongoing.

Assessments

Physical examination with an emphasis on monitoring signs and symptoms associated with a paraneoplastic syndrome and assessment of adverse events (AEs) were carried out at baseline and every 2 weeks. Acetylcholine receptor and antinuclear antibodies were assessed every 6 weeks. Disease assessment by a contrast-enhanced computed tomography (CT) scan/a magnetic resonance imaging (MRI) of the chest and upper abdomen was organized after 8 weeks of treatment and every 6 weeks thereafter until PD. Brain MRI or contrast-enhanced CT was carried out only if clinically indicated (new evidence of neurological symptoms/signs) or systematically, in case of history of brain metastasis.

Outcomes

The primary endpoint of NIVOTHYM was progression-free survival rate at 6 months (PFSR-6) in patients treated with nivolumab (this cohort) or—subsequently—nivolumab in combination with ipilimumab (cohort 2) as assessed by blinded independent central review committee retrospectively. The PFSR-6 was defined as the proportion of patients who were alive and non-progressing at 6 months, corresponding to 26 weeks $\pm$ 7 days after registration. Patients without adequate disease assessment at 26 weeks were initially considered as failures for the primary endpoint. However, a more relaxed approach was later implemented, accepting patients with a missing assessment at week 26 $\pm$ 7 days, to be still considered assessable provided the next assessment was available.

Secondary endpoints included: PFSR-6 as per local assessment, overall response rate (ORR), disease control rate (DCR), duration of response (DoR), OS, progression-free survival (PFS), and safety. OS was defined as the time interval from the date of registration till the date of death from any cause and PFS as the time between registration and PD or death, whichever occurred first. All AEs were recorded starting from patient registration and followed until resolution or stabilization.

Statistical analysis

The single-agent study cohort was designed according to a two-stage single-arm design, with a one-sided α of 10% and 90% power ($\beta = 10\%$), taking into account one interim analysis for both futility (non-binding) and efficacy when ~33% information was available. We hypothesized that, if the result was compatible with a PFSR-6 of 60% in the studied population, the drug should be further investigated. However, if we were unable to demonstrate a PFSR-6 of at least 40%, nivolumab should have been rejected from further testing. Based on this assumption, 50 eligible patients starting treatment were required. Considering patients who might be ineligible or have not started treatment, an additional 10% (five patients) were needed to be accrued.

The primary analysis of the efficacy endpoints was carried out on the per-protocol population, including all eligible patients having at least one dose of the study drug. The primary endpoint was analyzed using a *Z*-test. The study drug will be considered worthwhile of further investigation if $Z \geq 1.29$ (corresponding to 49% or more patients alive and progression free at 6 months). The 95% confidence intervals (CIs) for PFSR-6 and DCR have been calculated using the exact method. Time-to-event endpoint (PFS, OS) curves were estimated using the Kaplan—Meier technique and CIs for the medians were calculated using the reflected CI method. For the analysis of PFS, patients who missed two or more consecutive assessments have been censored at the last assessment regardless of events occurring past the missing assessments. Safety analysis was carried out according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 on the safety population, including all patients having at least one dose of the study drug. The clinical cut-off date for this analysis was 25 September 2020. The statistical analysis was conducted using SAS 9.4 (SAS Institute, Cary, NC).

Table 1. Baseline characteristics

Baseline characteristics	Patients ($n = 55$)
Median age (range), years	58 (32-82)
Gender, *n* (%)	
Male	35 (64)
Female	20 (36)
Performance status (ECOG), *n* (%)	
0-1	53 (96)
2	2 (4)
Presence of acetylcholine receptor antibodies, *n* (%)	
No	53 (96)
Yes (ineligible)	2 (4)
Histological type, *n* (%)	
Thymoma	10 (18)
Thymic carcinoma	43 (78)
Other (ineligible)	2 (4)
Prior radical treatment, *n* (%)	
Previous primary resection	16 (29)
Prior (neo)adjuvant platinum-based chemotherapy combined with radical surgery or radical chemoradiotherapy	7 (13)

ECOG, Eastern Cooperative Oncology Group.

RESULTS

Patient disposition and characteristics

In total, 55 patients were recruited in the nivolumab monotherapy cohort, in 15 institutions from 5 countries, from April 2018 to February 2020. At the time of interim analysis, accrual was almost completed due to faster than anticipated accrual rate and no futility or safety concerns were identified. Demographics, disease characteristics, and previous treatment are presented in Table 1. The majority of patients were male (64%), and the median age at registration was 58 years (range 32-82 years). There were 43 cases (78%) diagnosed with thymic carcinoma, 10 cases

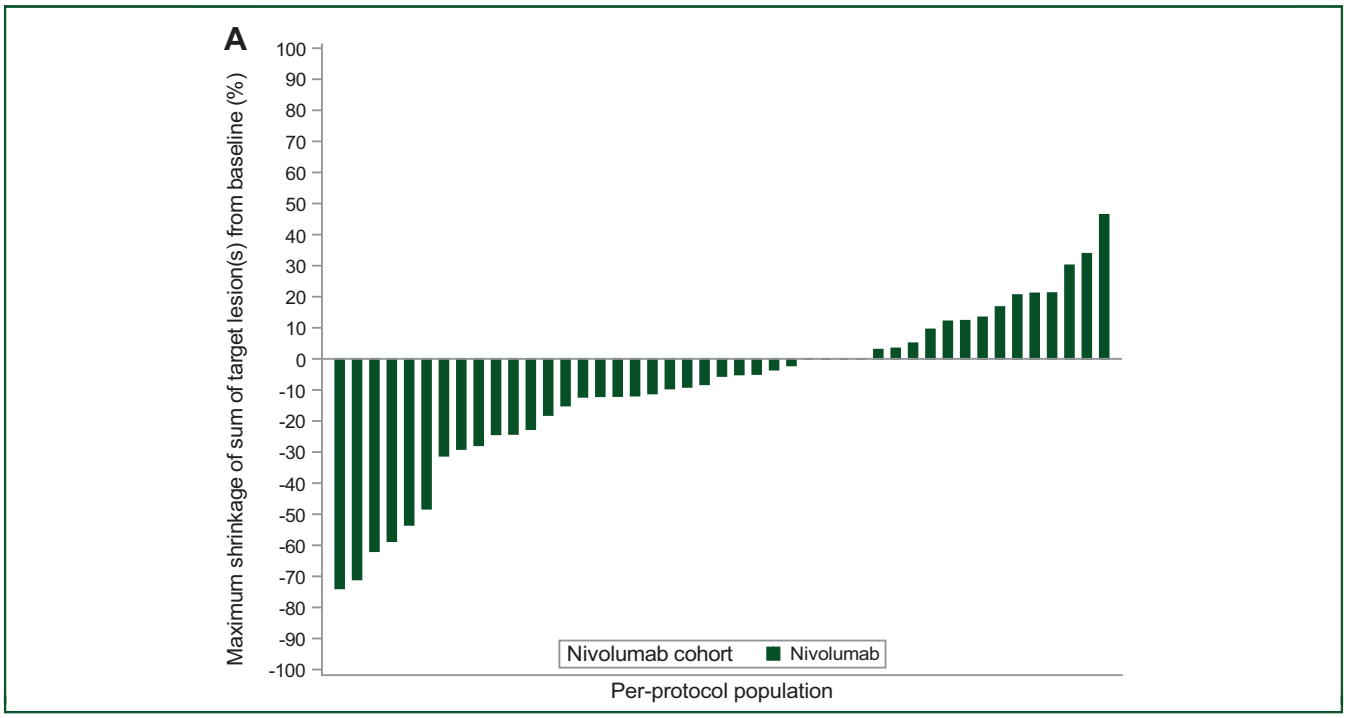


Figure 1. Objective response (A), progression-free (B), and overall survival (C) of patients enrolled in NIVOTHYM who received nivolumab.
CI, confidence interval; NE, not estimable.

(16%) with type B3 thymoma, and 2 cases (4%) with other histologies not fulfilling the eligibility criteria for histology. A total of 16 patients (29%) had a previous surgery of the primary tumor and another 7 (13%) had treatment in the (neo)adjuvant setting.

From the 55 patients registered, 54 had at least one dose of nivolumab (safety population), whereas 6 were declared ineligible and were not included in the efficacy analysis (2 based on histology, 2 had positive acetylcholine receptor antibodies at baseline, 1 based on previous treatment, and 1 after investigator's decision) (Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2023.101576). There was one patient with a history of psoriasis at baseline, not requiring systemic treatment, registered and received treatment.

Efficacy of nivolumab

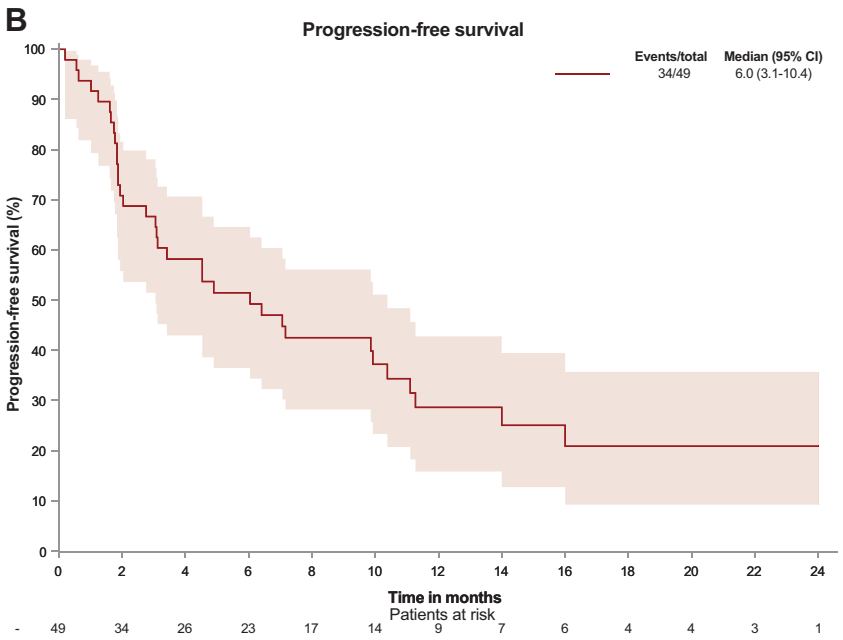
The PFSR-6 by central review was 35% (95% CI 22% to 50%), corresponding to 17/49 patients being successful with respect to the primary endpoint. Reasons for failure were: 24 due to PD (49%), 4 due to unknown disease status (8%), 1 due to start of another anticancer treatment without a documented PD (2%), and 3 due to death without PD (6%). The Z value for the test is −0.758 and the corresponding P value is 0.776, meaning that the primary objective of the study was not met. PFSR-6 based on local investigator assessment was 39% (95% CI 25% to 54%) corresponding to 19/49 patients being progression free after 6 months of nivolumab. Discrepancies between central review and local assessment of PFSR-6 were observed for six patients: four considered as failures due to PD by central review but successes by local assessment, and vice versa for the remaining two.

The median PFS was 6.2 months (95% CI 3.1-10.4 months; Figure 1B) and OS 21.3 months (95% CI 11.6 months-not estimable; Figure 1C), based on local assessment. The Kaplan—Meier estimate of PFS was 29% (95% CI 16.8% to 42.8%) at 12 months and 14.8% (95% CI 5% to 29.5%) at 18 months, whereas OS was 67.8% (95% CI 50% to 80.4%) at 12 months and remained the same at 18 months. The main cause of death amongst the 16 patients (33%) censored as dead was PD (12 patients), whereas the remaining 2 had other causes of death than toxicity and 2 had unknown reason of death.

Among the 49 eligible patients who were evaluated for response, 7 (14%) achieved partial response, 26 (53%) had stable disease (SD), and 13 (27%) had a PD during the trial period (treatment and follow-up period), as per local investigator review (Figure 1A). There were no patients with complete response. Thus, disease control occurred in 67% (95% CI 53% to 80%). From the seven patients with a document response, six achieved a response during treatment and one during the follow-up, and there were two thymomas and five thymic carcinomas. The median DoR was 162 days (range 121-378 days).

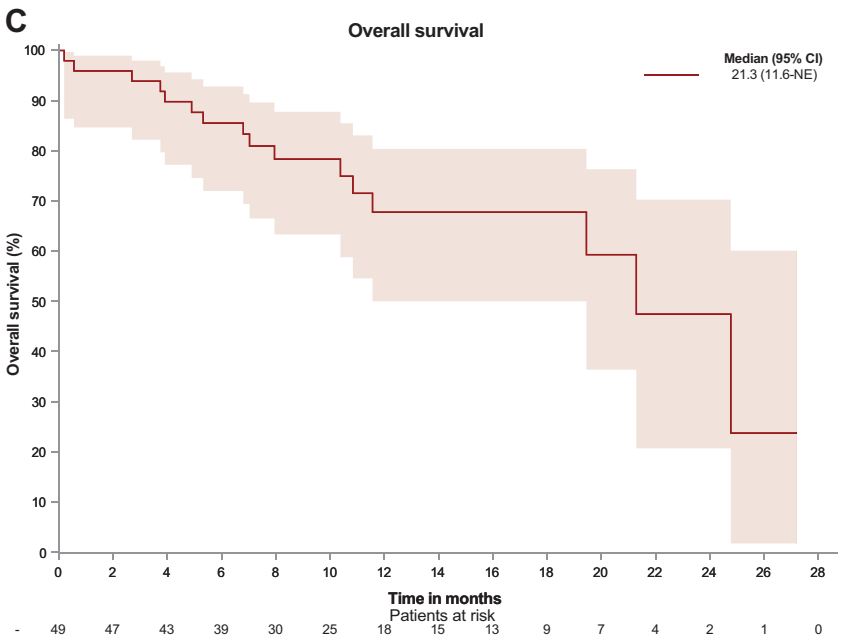
Treatment with nivolumab

At the time of database lock, from the 54 patients who had at least one treatment, 45 patients (83%) had stopped and 9 (17%) were still on treatment. The median follow-up was 13.3 months (95% CI 10.2-16.8 months). The median treatment duration was 21 weeks (range 2-120 weeks) and



	Event/total	Median (95% CI)[1]	Survival Estimates (95% CI)[1]
Progression-free survival	34/49	6.0 (3.1-10.4)	6 Month: 51.5 (36.5-64.6%) 12 Month: 28.6 (15.8-42.8%) 18 Month: 20.9 (9.2-35.7%) 24 Month: 20.9 (9.2-35.7%)

[1]Kaplan-Meier method;



	Event/total	Median (95% CI)[1]	Survival Estimates (95% CI)[1]
Overall survival	16/49	21.3 (11.6-NE)	6 Month: 85.5 (72.0-92.8%) 12 Month: 67.8 (50.0-80.4%) 18 Month: 67.8 (50.0-80.4%) 24 Month: 47.4 (20.7-70.3%)

[1]Kaplan-Meier method;

Figure 1. Continued.

Table 2. Adverse events

All patients ($n = 54$), *n* (%)

Event	Any grade	Grade 1-2	Grade 3	Grade 4	Fatal
Adverse event		22 (40.7)	18 (33.3)	5 (9.3)	1 (1.9)
Treatment-related AE	44 (81.5)	30 (55.6)	10 (18.5)	4 (7.4)	—
Treatment-related AE leading to discontinuation	9 (20)				
Treatment-related AE of any grade occurring in >5% or that was grade ≥3					
Anemia	4 (7.4)	3 (5.6)	1 (1.9)		
Hypothyroidism	3 (5.6)	3 (5.6)			
Colitis	2 (3.7)		2 (3.7)		
Diarrhea	6 (11.1)	6 (11.1)			
Nausea	6 (11.1)	6 (11.1)			
Fatigue	19 (35.2)	18 (33.4)	1 (1.9)		
Non-cardiac chest pain	2 (3.7)	1 (1.9)	1 (1.9)		
Lung infection	2 (3.7)	1 (1.9)	1 (1.9)		
Alanine aminotransferase increased	6 (11.2)	5 (9.3)	1 (1.9)		
Aspartate aminotransferase increased	7 (13)	6 (11.2)			
Lipase increased		2 (3.7)	1 (1.9)		
Lymphocyte count decreased	3 (5.6)	2 (3.7)	1 (1.9)		
Platelet count decreased	1 (1.9)		1 (1.9)		
Hypercalcemia	1 (1.9)		1 (1.9)		
Arthritis	2 (3.7)	1 (1.9)	1 (1.9)		
Proteinuria	1 (1.9)		1 (1.9)		
Dyspnea	4 (7.4)	3 (5.6)	1 (1.9)		
Pneumonitis	4 (7.4)	3 (5.6)	1 (1.9)		
Pruritus	6 (11.1)	6 (11.1)			
Rash	4 (7.4)	4 (7.4)			

For patients who had an AE of multiple grades, the worst grade is reported. AEs were graded with the use of the Common Terminology Criteria for Adverse Events, version 5.0, which incorporates certain elements of Medical Dictionary for Regulatory Activities (MedDRA) terminology.
AE, adverse event.

46 (85%) patients received at least 70% of treatment dose. About 60% of the patients (32 cases) required a treatment modification defined as at least one cycle on hold (24 cases, 44%) or delayed (22 cases, 41%) or anticipated (2 cases, 4%). Median relative dose intensity was 96%.

In the subset of patients stopped from protocol treatment (45 cases), there was a case completing 1 year of treatment without a PD; 9 cases (20%) discontinued due to treatment-related toxicity, 4 cases after patient's or investigator's decision (9%), and 1 case after the diagnosis of other malignancy. Nonetheless, the majority (30 cases, 67%) had stopped due to PD.

Safety of nivolumab

All 54 treated patients experienced at least one AE of any grade, regardless of attribution. The most common AEs occurring in >20% of the cases were fatigue (24 patients, 44%), dyspnea (14 patients, 26%), nausea, and diarrhea [11 patients (20%) each] (Table 2). More than half of them (32 cases, 59%) experienced at least a grade 3 AE, and 5 cases (9%) had a grade 4 AE and there was a case of respiratory failure not related to nivolumab leading to death (grade 5).

A total of 44 patients (81%) reported an AE of any grade that was considered by the investigator as related to treatment. The worst of the treatment-related AE was grade 3 in 14 cases (26%) and grade 4 in 4 cases (1 case of neutropenia, 2 cases of myocarditis, and 1 case of transaminitis). There were no lethal treatment-related AEs (grade 5). The most frequent treatment-related AEs occurring in >10% of patients were fatigue (35%), diarrhea (11%), nausea (11%), alanine aminotransferase increase (11%), and pruritus (11%).

Treatment-related AEs led to dose discontinuation in nine cases and the most common causes were transaminitis or hepatitis (one patient with grade 2, three patients with grade 3, and one patient with grade 4), recurring colitis (one patient with grade 3), pneumonitis (one patient with grade 2), neutropenia (one patient with grade 4), and myocarditis (one patient with grade 4).

Subsequent therapies

Among the 32 patients who had PD, 13 received at least one subsequent line of systemic therapy. One patient without a progression was diagnosed with breast cancer and underwent surgery and adjuvant treatment. From those who had a subsequent line, eight patients received chemotherapy (one case had pemetrexed, three cases platinum/doxorubicin/cyclophosphamide, one case pemetrexed/carboplatin, one case platinum/paclitaxel, one case carboplatin/paclitaxel/etoposide), two patients had targeted therapy (one case had erdafitinib and one case sunitinib), and six patients had palliative radiotherapy. The median time from progression to start of subsequent line was 9.7 weeks (range 1.3-22.9 weeks). There were no patients receiving immunotherapy after PD.

DISCUSSION

Nivolumab, a PD-1 ICI antibody, showed a potential clinical activity with an acceptable safety profile as a second-line monotherapy in patients with type B3 thymomas and

thymic carcinomas. PFSR-6 was 35% (95% CI 22% to 50%, $P > 0.05$), by central review, and median PFS was 6.2 months (95% CI 3.1-10.4 months) based on local assessment. DCR occurred in 67% (95% CI 53% to 80%). Treatment-related toxic effects were mainly of grade 1/2 (41%). Although we have been unable to reach our primary endpoint, NIVOTHYM adds evidence on the value and safety of ICIs targeting PD-1 in type B3 thymomas and thymic carcinomas, while demonstrating that accrual feasibility is not only realistic but fast across Europe.

At the time NIVOTHYM was designed, a hypothesis of a 60% PFSR-6 was set up to be considered as a success for the trial, based on existing data from phase II studies in the second-line setting of advanced, refractory thymic malignancies. Sunitinib,[14] everolimus,[15] chemotherapy as single agent (pemetrexed,[16] amrubicin[17]), or combination (carboplatin—paclitaxel,[18] gemcitabine—capecitabine[19]) reported a median PFS ranging from 8.5 to 12.5 months in thymomas and 1.1 to 8.7 months in thymic carcinomas. The most recent phase II study with palbociclib reported a PFSR-6 of 66% in thymomas and 52% in thymic carcinomas.[20] Lenvatinib showed a PFSR-6 >65%.[21] Additionally, real-world data, such as the RYTHMIC network study, reported a PFSR-6 of 50% and 55% for second- and subsequent-line therapies, in thymomas and thymic carcinomas, respectively.[5,22] In a survey about thymic malignancies conducted through the EORTC network at major European centers, the reported response rate (RR) in the second-line setting was 20% and the median PFS 4 months.[23]

Most studies investigating the activity of systemic therapy in thymic cancers chose response as their primary endpoint.[14-20] In the majority of these trials, RR ranged from 5% to 41% in thymomas and 8% to 38% in thymic carcinomas based on investigator assessment.[14-20] Nonetheless, response may not be the optimal endpoint in thymic malignancies: the 'challenging' location of lesions in the mediastinum or the pleura precludes reproducible assessment, while the slow growth of many thymomas exhibiting an SD as best response is something 'hardly' considered as an objective efficacy by systemic therapy. In NIVOTHYM, response was assessed based on central radiological review, with ORR achieved in 12% (95% CI 5% to 25%) of patients, and disease control in 63% (95% CI 48% to 77%). Given the advanced disease setting and the expected enrolment of a majority of patients with thymic carcinoma, we assessed response based on RECIST 1.1, without taking into account modified criteria.[24] Similarly, in phase II trials of pembrolizumab in thymic carcinomas[25] and in type B3 thymomas and thymic carcinomas,[26] or nivolumab in thymic carcinomas,[27] response rates ranged from 0% to 23%.

The efficacy of nivolumab is in line with other trials assessing anti-PD-1 ICIs in advanced, refractory thymic malignancies, although the PFSR-6 appears to be lower. In phase II trials with pembrolizumab and nivolumab, median PFS was 3.8-6.1 months and PFSR-6 50%-55%, while in this study they were 6.2 months and 35%, respectively.[25-27] The discrepancy between the endpoint of PFSR-6 and the Kaplan—Meier estimate at 6 months can be explained by the endpoint definitions and the underlying statistical analysis methodology. Based on the definition of PFSR-6, for patients having no adequate disease assessment at 6 months, the next scan was used to evaluate the disease status. As a result, for patients who lost primary disease assessment at 6 months, if a progression was declared on the next scan, this was considered as an event for the endpoint of PFSR-6. In the Kaplan—Meier analysis, however, time was taken into account and as a result, the 6-month PFS estimate did not include events occurring past 6 months.

Ultimately, a prolonged follow-up is required to fully assess the actual proportion of patients deriving a long-term benefit from immunotherapy, which may be higher compared to other available therapeutic systemic treatment options. This is especially plausible, if considering the indolent growth rate of thymomas even in the advanced, refractory setting. In NIVOTHYM, after a median follow-up of 13.3 months, median OS was 21.3 months, suggesting that the majority of patients were alive in a situation of disease control or receiving a subsequent line of treatment. At the last follow-up, 14 out of 33 (42%) alive patients received or were receiving further treatment. In one of the pembrolizumab trials, Giaccone and Kim reported a median OS of 25.4 months and a 5-year OS of 18%.[28] Interestingly, a plateau was observed on survival curves, suggesting that these patients may achieve a durable clinical benefit without any subsequent therapy or some may have also been rechallenged after discontinuation.

In NIVOTHYM, nivolumab monotherapy demonstrates a manageable toxicity profile for the majority of patients. About one to four patients (26%) experienced a grade 3 immune-related AE, with four cases having a grade 4 treatment-related AE (two cases of myocarditis and one case of transaminitis and neutropenia each). In line with this, trials with pembrolizumab reported AEs of grade 3-4 in ~35% of the population, the most common related to hepatitis/transaminitis and myocarditis.[25-27] They additionally reported cases of polymyositis, pancreatitis, diabetes mellitus type 1, bullous pemphigoid,[25] as well as thyroiditis, glomerulonephritis, colitis, and subacute myoclonus. Based on these data, a rigorous pre-treatment and on-treatment assessment was included, leading investigators to adopt a more proactive and close monitoring.

The role of immunotherapy in thymic epithelial tumors remains controversial. The National Comprehensive Cancer Network (NCCN) guidelines integrated pembrolizumab as a second-line treatment option for thymic carcinomas, but not in thymomas. The most recent Italian guidelines recommend patients to be enrolled in clinical trials, if available on sunitinib, while in thymomas, chemotherapy remains the mainstay.[29,30] The controversy stems from the challenging benefit—risk ratio and the inherent differences in biology between thymic carcinomas and thymomas. In

thymic carcinomas, the aggressiveness of the disease, the rapid resistance to chemotherapy, and the lower risk of immune-related AEs may lead to consideration of immunotherapy as the most appropriate second-line therapeutic option.[26] This is not the case for thymomas, which are frequently associated with autoimmune disorders independently from exposure to immunotherapy[7] and are exacerbated by other antitumor agents.[14] There are numerous reports of severe toxicities, frequently leading to death in type B1 or B2 tumors treated with immunotherapy.[8,31,32] These subtypes were therefore excluded in NIVOTHYM, which focused on type B3 thymoma and thymic carcinomas. An additional work remains crucial for identifying those patients most likely to develop serious immune-related AEs, alongside with those most likely to benefit.

Another challenge from a clinical standpoint is to ascertain a correct and accurate pathological diagnosis before considering immunotherapy as a treatment option for thymic malignancies. The high frequency of discrepant diagnoses between initial assessment and expert review,[33] as well as the high intra-observer variability, highlights the importance of a systematic pathological review and it is recommended by the European Society for Medical Oncology (ESMO) clinical practice guidelines.[1]

In line with this, the differential diagnosis between thymic and lung carcinomas is also critical given the different therapeutic strategies in regard to immunotherapy.

Despite previous data correlating response to pembrolizumab with PD-L1 expression in thymic carcinoma,[25,26] PD-L1 should probably not be considered as a predictor of efficacy for immunotherapy in thymic epithelial tumors. It is rather a hallmark of any epithelial cell originating from the thymus, thus not reflecting the presence of antitumor immune response.[34,35] Predictive and prognostic biomarkers related to immunotherapy are currently lacking in thymic malignancies, underscoring the important role of translational research. Translational material banked from our study will facilitate this important future work.

Ultimately, ICIs targeting PD-1/PD-L1 show promising efficacy in thymic carcinomas, thus adding an option for patients. NIVOTHYM showed that nivolumab could be a potential option more than routine standard of care in refractory type B3 thymoma or thymic carcinoma, although our results did not reach statistical significance ($P > 0.05$). Our efficacy figures are in line with other available treatments in advanced, refractory disease. Toxicity is a major concern, with a higher prevalence of severe autoimmune AEs compared to other solid tumors. Our results are consistent with the safety findings of other trials, with nivolumab producing primarily manageable low-grade toxicities, with a few high-grade toxicities affecting liver and myocardium. Therefore, nivolumab should not be routinely delivered without full discussion of expected benefit versus the potential risks. Future trials on ICIs for thymic malignancies [NIVOTHYM, cohort 2 of nivolumab plus ipilimumab, CAVEATT with avelumab plus axitinib (EUDRACT, 2017-004048-38),[36] PECATI with pembrolizumab plus lenvatinib (NCT04710628)[37]] will shed more light related to the role of immunotherapy in epithelial tumors.

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