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Oxaliplatin-Based Versus Alkylating Agent in Neuroendocrine Tumors According to the O⁶-Methylguanine-DNA Methyltransferase Status: A Randomized Phase II Study (MGMT-NET)

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ABSTRACT

PURPOSE Alkylating agents (ALKY) are the main chemotherapies used for advanced neuroendocrine tumors (NETs). O⁶-Methylguanine-DNA methyltransferase (MGMT) status, as proficient (p) or deficient (d), may predict the response to ALKY.

PATIENTS AND METHODS MGMT-NET (ClinicalTrials.gov identifier: NCT03217097) was a phase II trial randomly assigning 1:1 for pMGMT or 2:1 for dMGMT-NETs to either ALKY or oxaliplatin (Ox). Inclusion criteria were a confirmed advanced pancreatic, thoracic, or unknown primary NETs with an indication for chemotherapy and tissue available. The primary aim was to detect a difference of 35% between the 3-month objective response rate (ORR) in pMGMT-NETs versus in dMGMT-NETs when treated with ALKY. A biomarker-stratified design was performed to compare ALKY and Ox in the dMGMT and pMGMT strata for the secondary end points. dMGMT was defined using pyrosequencing (PSQ; methylated *MGMT* ≥9%) and using immunochemistry (*H*-score of MGMT <50) when PSQ was not interpretable.

RESULTS From October 2018 to October 2021, 105 patients (55 pancreas, 38 thorax, 12 unknown) started either ALKY (n = 62) or Ox (n = 43). The median age was 63 years (range, 30-84), and 59% were males. NETs were G1 (19%), G2 (69%), or G3 (10%). Among patients with interpretable MGMT status, 56.9% (58 of 102) had a dMGMT-NET. The primary end point was not reached; the 3-month ORR was 10 (29.4%) versus 2 (8%), and the odds ratio was 3.5 (0.58-21.16), *P* = .172. However, best ORR (18 [52.9%] *v* 3 [11.5%]) and median progression-free survival (14.6 [95% CI, 7.2 to 22.1] *v* 11.3 [9.4 to 13.2] months) were higher for dMGMT-NETs versus pMGMT-NETs. MGMT status does not seem to affect the Ox efficacy.

CONCLUSION Despite the fact that the primary end point was not reached, ALKY has clinical activity in patients with dMGMT-NETs.

INTRODUCTION

Most well-differentiated neuroendocrine tumors (NETs) occur in the digestive system and the bronchopulmonary system and are often diagnosed at advanced stages.[1,2] Chemotherapy is used against aggressive NETs (ie, high tumor burden, progressive tumor, and/or high Ki67 index) or when a tumor shrinkage is needed.[3,4] Alkylating agents (ALKY), such as temozolomide, dacarbazine, and streptozotocin, are the backbone of chemotherapy[5-8]; the objective response rate (ORR) is 30%-40%, and the median progression-free survival (PFS) is 4-18 months.[5-8] However, it is of note that

CONTEXT

Key Objective

Is O[6]-methylguanine-DNA methyltransferase (MGMT) relevant to predict the response to alkylating agents (ALKY) such as temozolomide in neuroendocrine tumors (NETs)?

Knowledge Generated

In 57% of patients enrolled in this randomized study (ALKY v oxaliplatin-based chemotherapy), MGMT was deficient (d) in their NET. Despite the fact that the primary end point (gain of at least 35% of objective response rate at 3 months of ALKY) was not reached, ALKY has clinical activity in patients with dMGMT-NETs.

Relevance (E.M. O'Reilly)

In this biomarker-focused trial, MGMT deficiency (immunohistochemistry, pyrosequencing) served as a biomarker of enrichment for response to alkylating therapy. The data are consistent with prior reports, and although there are limitations of this small trial, provide support for the validity of MGMT deficiency as a selection tool for further development.*

*Relevance section written by *JCO* Associate Editor Eileen M. O'Reilly, MD.

the level of evidence regarding the efficacy of these treatments for pulmonary NETs is lower than that for pancreatic NETs.[9]

One of the mechanisms of ALKY cytotoxicity is the induction of DNA alkylation/methylation at O[6]-guanine sites, resulting in DNA mismatch and cell death in the tumor tissue.[4,10] However, ALKY-induced DNA damages can be reversed by O[6]-methylguanine-DNA methyltransferase (MGMT). Thus, any reduction in the MGMT activity may therefore increase the effect of ALKY. In addition, many studies in glioma found that the loss of MGMT expression is associated with the methylation of CpG island on the *MGMT* promoter and not with gene deletion, mutation, rearrangement, or unstable RNA.[11] The MGMT status can be assessed at the protein level (by immunohistochemistry [IHC]) and at the gene level (through methylation analysis). The assessment of MGMT status to predict the response to ALKY is debated in the current literature, in part since it is performed using multiple techniques with various accuracies and because of the retrospective design of most reported studies.[4]

Furthermore, although ALKY are commonly recommended in NETs,[3] an interesting activity of oxaliplatin (Ox), either with 5-fluorouracil[12-14] or with gemcitabine,[15,16] was reported, with the ORR ranging from 17% to 30%. In a retrospective study, we reported that gemcitabine and oxaliplatin (GEMOX) was effective in NETs and that its activity was similar to that of ALKY, but irrespective of the MGMT status.[15] In this context, the purpose of this prospective study was to evaluate the predictive effect of MGMT on the ORR of patients treated using ALKY. A control arm (Ox) was used, as in a biomarker-stratified design,[17,18] to evaluate whether MGMT is a predictive factor of response to ALKY or a prognostic factor regardless of the chemotherapy given.

PATIENTS AND METHODS

Study Design and Patients

MGMT-NET was a national, multicenter, open-label, randomized phase II study assessing the safety and efficacy of ALKY-based and Ox-based chemotherapy arms, according to the MGMT status. Patients with proficient (p) MGMT NETs were randomly assigned 1:1, whereas patients with deficient (d) MGMT NETs were randomly assigned 2:1, to either the ALKY- or the Ox-based chemotherapy arm (see Fig 1 in the study by Lemelin et al[18]).

This study included patients age at least 18 years, with a histologically proven well-differentiated NET from the pancreas, the lung, or an unknown primary site, grades 1-3, metastatic or locally advanced, unresectable, and with available tumor tissue. A systemic chemotherapy had to be indicated and validated by an NET-dedicated multidisciplinary tumor board within the French ENDOCAN-RENATEN network. Previous local or systemic treatments other than ALKY or Ox were allowed.

Study Procedures

MGMT methylation test (using pyrosequencing [PSQ])[18-20] and IHC[21] were performed in parallel (see the Data Supplement, online only for the details), but only the result of the methylation test was considered for the random assignment, unless the result was not interpretable. In such a case, the IHC result was used, considering that a loss of MGMT expression in IHC would correspond to a methylated *MGMT*. We defined an NET with a methylated *MGMT* or, when the *MGMT* methylation analysis was not interpretable, without expression of MGMT using IHC as dMGMT. Patients who are not dMGMT were randomly assigned as

pMGMT; patients with no interpretable MGMT status by methylation nor IHC were also randomly assigned in this group, but they were therefore not included in the analysis of outcomes according to MGMT status. Random assignment was also stratified on the origin of the NET. The random assignment lists were built by block and automatically generated by a computerized system using SAS statistical software (V9.3).

A pragmatic approach was performed by the physician to choose the ALKY or Ox regimens, with one recommended regimen for each arm. In the ALKY arm, the recommended regimen was capecitabine (750 mg/m² twice daily for 14 days, days 1-14) and temozolomide (temozolomide, 200 mg/m² once daily for 5 days, days 10-14), every 28 days,[8] and alternative intravenous leucovorin plus 5-fluorouracil (LV5FU2)-dacarbazine or 5-fluorouracil-streptozotocin was allowed.[22] In the Ox arm, the recommended regimen was GEMOX (gemcitabine 1,000 mg/m² followed by Ox 100 mg/m² both drugs once every 2 weeks),[15] and alternative LV5FU2 and oxaliplatin (FOLFOX) or capecitabine and oxaliplatin (CAPOX) regimens were allowed.[22] The chemotherapy doses and monitoring were in line with French recommendations on NET management.[22] The recommended duration of the chemotherapy was at least 3 months (assessment of the primary end point).

End Points

The primary end point was the 3-month ORR in the ALKY arm (compared between dMGMT and pMGMT). It was assessed according to the RECIST v1.1 criteria by the central review of an expert radiologist who was blinded to the result of the MGMT status and treatment assignment; this review was performed when the 3-month radiologic assessment of the last included patient was available. Patients and treating providers were also blinded to the MGMT status.

The secondary end points were (1) best ORR, PFS (both according to RECIST v1.1 criteria), and overall survival (OS) assessed according to the MGMT status in patients treated with ALKY; (2) the 3-month ORR, best ORR, PFS, and OS according to MGMT status in patients treated with Ox; (3) and the MGMT status as the predictive factor (3-month ORR, best ORR, PFS, and OS) evaluated using either methylation or IHC.

Radiologic assessment was performed at baseline (within a maximum of 4 weeks before inclusion) using a computed tomography (CT) scan and/or magnetic resonance imaging (MRI), and the same procedure (CT or MRI) was repeated every 3 months.

All adverse events (AEs) were assessed at each cycle of chemotherapy, therefore at least once a month during the chemotherapy administration, and for all patients at 3 and 4 months after the first administration of the chemotherapy, according to the Common Terminology criteria for Adverse Events version v4.03. In addition, all deaths (grade 5) were recorded until the end of study participation.

Statistical Analysis

Although the primary end point was scheduled in the ALKY arm, a biomarker-stratified design was used instead of an enrichment design to also compare ALKY and Ox in the dMGMT and pMGMT strata for the secondary end points.[17] The analysis of the primary end point compared the 3-month ORR between dMGMT and pMGMT using a logistic regression model adjusted on the tumor origin and the MGMT status. Sample size calculation was calibrated to detect a 35% absolute difference in the 3-month ORR according to the MGMT status among patients treated with ALKY. The assumption of the difference was hypothesized as an improvement in ORR from 15% in patients with pMGMT NETs to 50% in patients with dMGMT NETs, according to our previous study (ORR of 15% for unmethylated MGMT-NET and 53% for methylated MGMT-NET when assessed by PSQ).[23] This calculation was based on an expected number of 55 patients treated with ALKY (ie, 22 patients with dMGMT NETs and 33 patients with pMGMT NETs) to obtain a 75% power to find a statistically significant ORR difference with a one-sided risk of 5%. Considering the hypothesis that one third of patients might have a dMGMT NET,[23] 99 patients had to be randomly assigned in the study. However, assuming that MGMT would not be interpretable in 5% of the patients, we planned to include at least 104 patients for MGMT analysis.

For the analysis of the secondary end points, a post hoc analysis was performed to compare the ORR not only using a Fisher's exact test (one-sided) between the two groups (dMGMT v pMGMT) in each chemotherapy arm but also according to the biomarker-stratified design between ALKY and Ox in the dMGMT and pMGMT strata. Best ORR and PFS were also evaluated using a logistic regression model adjusted on the tumor origin, in addition to the MGMT status. A Kaplan-Meier analysis was used to estimate median PFS and OS according to MGMT status and treatment received and the associated 95% CI for each treatment group. Comparisons were performed using the log-rank test. A Cox proportional model was used to calculate hazard ratios (HRs) and the associated 95% CI. Survival curves were drawn using the survminer package on R Core Team (2021, R Foundation for Statistical Computing, Vienna, Austria).

Ethical Considerations

All patients provided their written informed consent to participate in this study. This study was approved by the National Agency for the Safety of Medicines and Health Products on June 27, 2018. It was submitted and approved (August 1, 2018) by the institutional review board. The study

complied with the Declaration of Helsinki and the principles of Good Clinical Practice guidelines.

RESULTS

Patient Characteristics

From October 2018 to October 2021, a total of 116 patients were enrolled and 109 patients were randomly allocated. Four patients did not start chemotherapy (one in ALKY and three in the Ox arm), and therefore, 105 patients were included in the modified intention-to-treat (mITT)/safety population, 62 in the ALKY arm and 43 in the Ox arm (CONSORT diagram in Fig 1).

Patient characteristics were balanced between chemotherapy arms. The main primary origins were the pancreas (n = 55, 52.4%) and the thorax (n = 38, 36.2%), including three thymic NETs. All patients except three had an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1. Seven patients had a secretory syndrome. The NET grade was atypical/G2 in more than two thirds of patients; 11.3% (n = 7 of 62) and 9.3% (n = 4 of 43) had an NET-G3 in ALKY and Ox arms, respectively. The median (IQR) Ki67 was 10% (5-20) in the ALKY arm and 10% (8-18) in the Ox arm (Data Supplement, Table S1).

Administration and Safety of Chemotherapies

Among the 62 patients in the ALKY arm, 31 (50.0%) received capecitabine-temozolomide (CAPTEM), whereas 28 (45.2%) received LV5FU2-dacarbazine and three (4.8%) received 5-fluorouracil-streptozotocine. Among the 43 patients in the Ox arm, 35 (81.4%) received GEMOX and eight (18.6%)
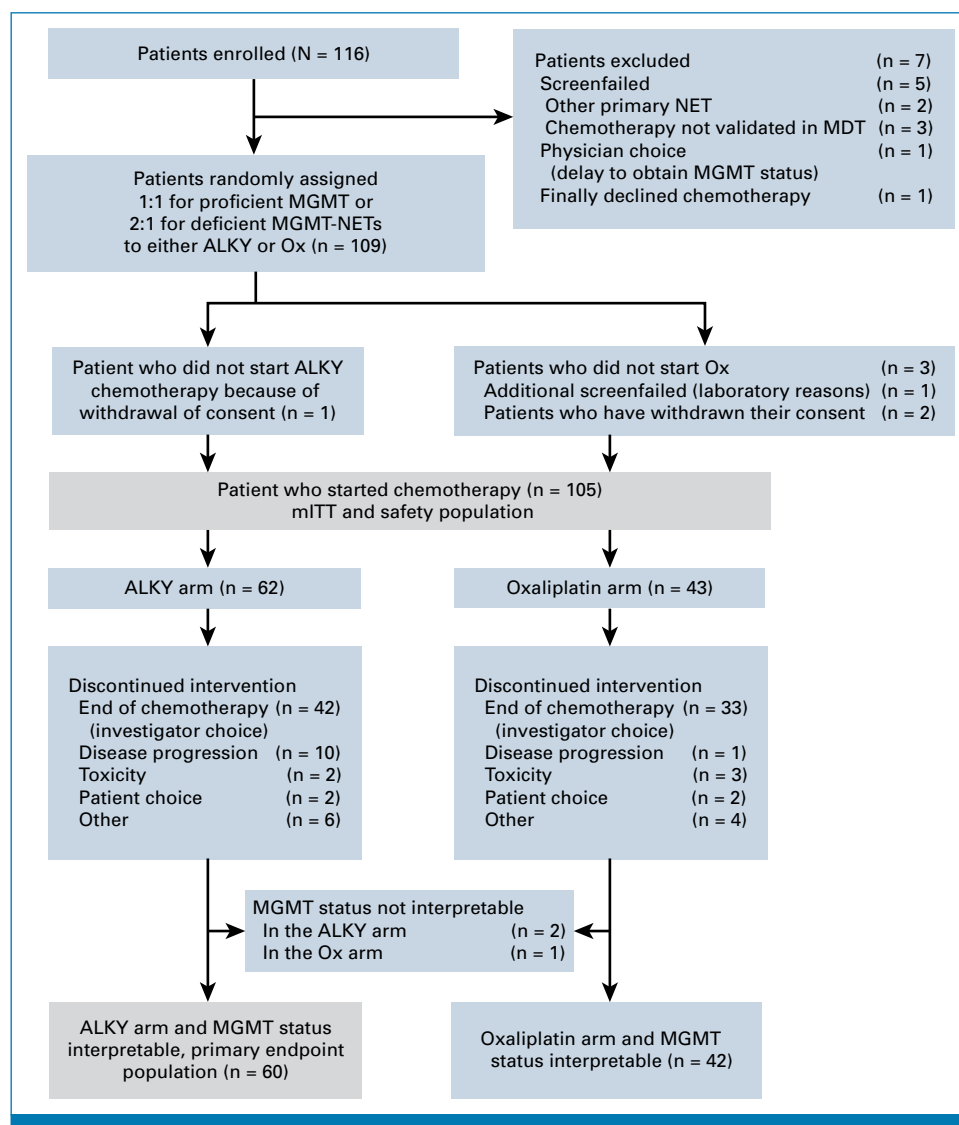
FIG 1. CONSORT diagram of the study population. ALKY, alkylating agent; MDT, multidisciplinary tumor board; MGMT, O⁶-methylguanine-DNA methyltransferase; mITT, modified intention-to-treat population; NET, neuroendocrine tumor; Ox, oxaliplatin-based chemotherapy.

received FOLFOX/CAPOX. The median (IQR) chemotherapy duration was 5.2 (3.7-6.0) months for the ALKY arm and 3.8 (3.2-5.1) months for the Ox arm. A total of 29 (46.8%) and 32 (74.4%) patients had at least one dose reduction within the first 3 months of chemotherapy, and granulocyte–colony stimulating factor was administered in 15 (24.2%) and seven (16.3%) in ALKY and Ox arms, respectively (Table 1). The AEs are described in the Data Supplement.

Evaluation of MGMT Status

Among the 105 patients included in the mITT/safety population, the MGMT status was not interpretable in three patients using both techniques. MGMT methylation was interpretable in 92 patients. To not delay the beginning of chemotherapy (results being given within 2 weeks), 22 of them were randomly assigned on IHC results or 1:1 if IHC was not interpretable. The specimens contained a median (IQR) of 60% of tumor cells (43-80). The median (IQR) MGMT methylation was 10 (7-15.8). dMGMT was found in 55.4% (n = 51 of 92) of NETs with an interpretable methylation test and in 47.6% (n = 39 of 82) of NETs with interpretable IHC. The MGMT status was interpretable by both techniques in 72

NETs. The concordance between techniques was 58.3% (21 dMGMT by both + 21 pMGMT by both)/72; 19 NETs had methylated MGMT but persistent expression, and 11 had unmethylated MGMT but loss of MGMT expression (Fig 2).

A total of 102 patients started chemotherapy and had interpretable MGMT status by at least one technique (92 with an interpretable methylation test and 10 more with interpretable IHC); therefore, dMGMT was found in 56.9% (n = 58 of 102) of NETs using the study definition. Except the primary NET origin, patient characteristics were clinically similar between dMGMT (n = 58) and pMGMT (n = 44) groups (Data Supplement, Table S3) and between dMGMT and pMGMT groups according to the chemotherapy arm (Table 2).

Efficacy of Chemotherapies

The 3-month ORR and best ORR were obtained in 12 (19.7%) and 22 (35.5%) in the ALKY arm. They were 12 (27.9%) and 13 (30.2%) in the Ox arm. The median (IQR) time to response in the 35 patients with ORR was 5.6 months (3.4-6.7) in ALKY and 3.4 months (3.0-3.7) in Ox. The median (IQR) follow-up

TABLE 1. Administration of Chemotherapy

Characteristic	ALKY Arm (n = 62)	Ox Arm (n = 43)
Type of chemotherapy, No. (%)		
Capecitabine-temozolomide	31 (50.0)	—
LV5FU2-dacarbazine	28 (45.2)	—
5-fluorouracil-streptozotocine	3 (4.8)	—
GEMOX	—	35 (81.4)
FOLFOX	—	6 (14.0)
CAPOX	—	2 (4.7)
No. of cycles, median (IQR)	6 (5-8)	8 (6-10)
Chemotherapy duration in months, median (IQR)	5.2 (3.7-6.0)	3.8 (3.2-5.1)
Dose reduction within 3 first months, No. (%)	29 (46.8)	32 (74.4)
GCSF administration, No. (%)	15 (24.2)	7 (16.3)
First subsequent antitumor treatment, No. (%)		
None	17 (27.4)	4 (9.3)
Chemotherapy		
ALKY-based	14 (22.6)	15 (34.9)
Ox-based	12 (19.4)	7 (16.3)
Other	0	1 (2.3)
Everolimus	3 (4.8)	5 (11.6)
Tyrosine kinase inhibitor (sunitinib, surufatinib[a])	6 (9.7)	1 (2.3)
Somatostatin analogs	3 (4.8)	6 (14.0)
Peptide receptor radionuclide therapy	4 (6.5)	3 (7.0)
Locoregional treatment (surgery, TAE/TACE)	1 (1.6)	1 (2.3)
Phase I clinical trial	2 (3.2)	0

Abbreviations: ALKY, alkylating agent; CAPOX, capecitabine and oxaliplatin; FOLFOX, infusional LV5FU2 and oxaliplatin; GCSF, granulocyte-colony stimulating factor; GEMOX, gemcitabine and oxaliplatin; LV5FU2, leucovorin plus 5-fluorouracil; Ox, oxaliplatin; TACE, transarterial chemoembolization; TAE, transarterial liver embolization.
[a]In clinical trial.
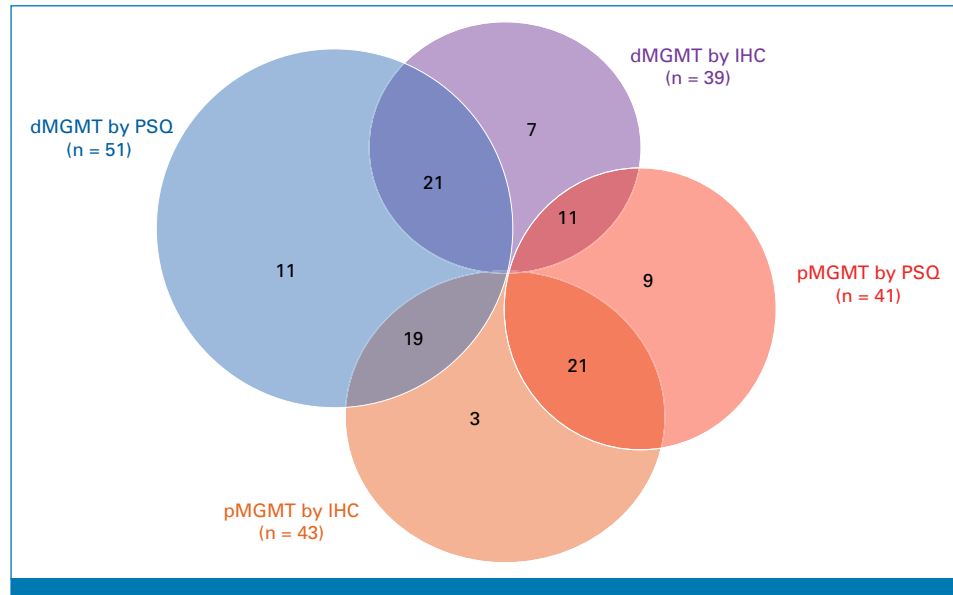
FIG 2. MGMT status assessed by PSQ and/or IHC. d, deficient; IHC, immunochemistry; MGMT, O⁶-methylguanine-DNA methyltransferase; p, proficient; PSQ, pyrosequencing.

duration was 29.3 months (21.9-35.8), and the median (95% CI) PFS was 12.1 (9.9 to 14.3) months in the ALKY arm and 12.6 (11.3 to 13.9) months in the Ox arm. At progression, 84 patients received a subsequent antitumoral treatment at a median of 8.3 months (21.9-35.8) after the end of ALKY/Ox chemotherapy, which was mainly another course of chemotherapy (ALKY or Ox), a targeted therapy, a somatostatin analog, or a peptide receptor radionuclide therapy (Table 1). The median (95% CI) OS was 50.2 (19.1 to 81.3) months in the ALKY arm and 48.8 (30.3 to 67.3) in the Ox arm (Data Supplement, Fig S1).

Primary End Point

The primary end point was assessed in all patients treated with ALKY, except for one; 34 had a dMGMT-NET, and 26 a pMGMT-NET. The 3-month ORR was two (8.0%) in the pMGMT group and 10 (29.4%) in the dMGMT group. The odds ratio for patients with dMGMT-NETs compared with pMGMT-NETs, for identical tumor origin, was 3.5 (0.58-21.16), $P = .172$ (one-sided).

Secondary End Points

In the ALKY arm, the best ORR was three (11.5%) in the pMGMT group and 18 (52.9%) in the dMGMT group; the median (95% CI) PFS was 11.3 (9.4 to 13.2) in the pMGMT group and 14.6 (7.2 to 22.1) in the dMGMT group, whereas the OS was 50.2 months (95% CI not defined) in pMGMT and not reached in dMGMT. Conversely, the efficacy of Ox (ORR, PFS, and OS) was clinically similar between both groups (Table 3; Fig 3). In the dMGMT group, the best ORR was greater under ALKY compared with Ox (52.9% and 25.0%, respectively; $P = .031$) as well as the PFS (HR, 0.56 [95% CI, 0.31 to 1.01];

$P = .053$). In the pMGMT group, the best ORR was 11.5% under ALKY and 38.9% under Ox ($P = .040$), but the PFS was not significantly different between chemotherapy arms (HR, 1.12 [95% CI, 0.060 to 2.10]; $P = .716$).

The same trend was observed, with fewer patients, when MGMT was assessed by methylation only or by IHC (Table 3; Data Supplement, Figs S2 and S3). In patients treated with ALKY with concordant MGMT results between both techniques, the best ORR was 91.7% (n = 11 of 12) for dMGMT-NETs, whereas it was 13.3% (n = 2 of 15) for pMGMT-NETs (Fig 3A; Data Supplement, Table S4).

Subgroup analyses in pancreatic and thoracic NETs according to MGMT status are presented in the Data Supplement (Tables S5 and S6).

DISCUSSION

To our knowledge, the MGMT-NET study is the first randomly assigning ALKY and Ox to evaluate the predictive effect of MGMT on the outcome of patients with NETs treated with ALKY. The study did not reach its primary end point, but the 35% difference between dMGMT and pMGMT groups in patients treated with ALKY was obtained for the best ORR, which is in concordance with the literature.[8,23] In addition, ALKY provided a longer PFS and OS in dMGMT-NETs versus pMGMT-NETs. Conversely, the outcomes of patients treated with Ox seemed to be not affected by the MGMT status. Therefore, according to the guidelines, ALKY remains the chemotherapy of choice for patients with pancreatic NETs,[3,8] and even more for those with dMGMT-NETs,[8] whereas Ox has an interesting activity in pMGMT-NETs, which is the case for most thoracic NETs.[24]

TABLE 2. Patient Characteristics, According to MGMT Status Assessed by Methylation or Immunohistochemistry if Methylation Is Not Interpretable, and Chemotherapy Arm (n = 102)

	ALKY Arm		Ox Arm	
Characteristic	dMGMT (n = 34)	pMGMT (n = 26)	dMGMT (n = 24)	pMGMT (n = 18)
Male, No. (%)	23 (67.6)	15 (57.7)	12 (50.0)	10 (55.6)
Age, years, median (IQR)	64.0 (57.0-70.0)	64.5 (58.0-70.0)	60.0 (53.0-68.5)	58.0 (48.0-71.0)
Primary tumor location, No. (%)				
Pancreas	20 (58.8)	10 (38.5)	16 (66.7)	6 (33.3)
Thoracic	11 (32.4)	12 (46.2)	7 (29.2)	8 (44.4)
Unknown	3 (8.8)	3 (11.5)	0	1 (5.6)
Performance status 0-1, No. (%)	33 (97.1)	24 (92.3)	24 (100.0)	18 (100.0)
Secretory syndrome, No. (%)[a]	4 (14.8)	2 (6.1)	0	1 (4.3)
Presence of pain, No. (%)	8 (23.5)	9 (34.6)	8 (33.3)	8 (44.4)
Presence of other symptoms, No. (%)	6 (17.6)	7 (26.9)	2 (8.3)	6 (33.3)
Biologic examination in the two ULNs				
Chromogranin A, median (IQR)	6.5 (0.9-76.5)	4.2 (1.6-12.2)	5.2 (1.8-27.6)	6.9 (2.2-19.9)
NSE, median (IQR)	1.9 (1.2-4.2)	2.3 (1.4-5.0)	2.9 (1.9-5.7)	1.7 (1.1-3.2)
WHO classification, No. (%)				
NET/typical grade 1	7 (20.6)	6 (23.1)	2 (8.3)	5 (27.8)
NET/atypical grade 2	23 (67.6)	16 (61.6)	19 (79.2)	11 (61.1)
NET grade 3	3 (8.8)	4 (15.4)	2 (8.3)	2 (11.1)
Undetermined	1 (2.9)	0	1 (4.2)	0
Ki67 index, %, median (IQR)	10.0 (5.0-17.0)	15.0 (8.0-25.0)	12.0 (9.0-18.0)	9.0 (5.0-18.5)
Progressive disease at study inclusion, No. (%)	21 (61.8)	17 (65.4)	13 (54.2)	10 (55.6)
Median No. of metastatic sites >1, No. (%)	24 (70.6)	16 (61.5)	10 (41.7)	12 (66.7)
Location of metastasis, No. (%)				
Liver	31 (91.2)	23 (88.5)	20 (83.3)	17 (94.4)
Bone	16 (47.1)	8 (30.8)	7 (29.2)	9 (50.0)
Distant lymph nodes	14 (41.2)	8 (30.8)	7 (29.2)	9 (50.0)
Peritoneum	4 (11.8)	1 (3.8)	1 (4.2)	0
Lung	3 (8.8)	2 (7.7)	2 (8.3)	3 (16.7)
Brain	1 (2.9)	1 (3.8)	0	1 (5.6)
Adrenal	0	2 (7.7)	1 (4.2)	1 (5.6)
Other	4 (11.8)	6 (23.1)	2 (8.4)	4 (22.2)
Positive PET DOTATOC/octreoscan, No./N assessed (%)	19/21 (90.5)	13/14 (92.9)	11/11 (100.0)	8/10 (80.0)
Previous local intervention, No. (%)				
Resection of primary tumor and/or metastases	14 (41.2)	9 (34.6)	9 (37.5)	5 (27.8)
Liver (chemo)embolization	5 (14.7)	6 (23.1)	1 (4.2)	1 (5.6)
External radiotherapy	0	2 (7.7)	0	2 (11.1)
Previous lines of systemic treatment, No. (%)				
No prior systemic treatment	16 (47.1)	12 (46.2)	15 (62.5)	13 (72.2)
Somatostatin analogs	16 (47.1)	12 (46.2)	9 (37.5)	4 (22.2)
Peptide receptor radionuclide treatment	1 (2.9)	1 (3.8)	3 (12.5)	0
Targeted therapies	2 (5.9)	4 (15.4)	2 (8.3)	2 (11.1)
Current administration of somatostatin analogs, No. (%)	4 (11.8)	3 (11.5)	1 (4.2)	1 (5.6)

Abbreviations: ALKY, alkylating agent; d, deficient; MGMT, O[6]-methylguanine-DNA methyltransferase; NET, neuroendocrine tumor; NSE, neuron-specific enolase; p, proficient; PET, positron emission tomography; ULNs, upper limits of normal.

[a]Type of secretory syndrome: four carcinoid syndromes, two Cushing syndromes, and one glucagonoma.

TABLE 3. Efficacy of Chemotherapy According to the Chemotherapy Arm and MGMT Status

| Efficacy | MGMT Status Assessed by PSQ and/or by Immunochemistry if Methylation Is Not Available (n = 102) | | | | | |
| | ALKY Arm | | | Ox Arm | | |
	dMGMT (n = 34)	pMGMT (n = 26)	P	dMGMT (n = 24)	pMGMT (n = 18)	P
Three-month objective response, No. (%)	10 (29.4)	2 (8.0)	.042	7 (29.2)	5 (27.8)	.600
Best objective response, No. (%)	18 (52.9)	3 (11.5)	.001[a]	6 (25.0)	7 (38.9)	.265
PFS, months, median (95% CI)	14.6 (7.2 to 22.1)	11.3 (9.4 to 13.2)		12.9 (11.8 to 14.0)	12.2 (11.7 to 12.7)	
	HR = 0.53 (95% CI, 0.30 to 0.94)		.029[a]	HR = 0.84 (95% CI, 0.45 to 1.59)		.600
OS, months, median (95% CI)	Not reached	50.2 (not defined)		48.8 (22.8 to 74.8)	39.8 (16.8 to 62.8)	
	HR = 0.39 (95% CI, 0.15 to 0.99)		.048	HR = 0.78 (95% CI, 0.29 to 2.11)		.625

| Efficacy | MGMT Status Assessed by PSQ (n = 92) | | | | | |
| | ALKY Arm | | | Ox Arm | | |
	dMGMT (n = 31)	pMGMT (n = 23)	P	dMGMT (n = 20)	pMGMT (n = 18)	P
Three-month objective response, No. (%)	10 (32.3)	2 (9.1)	.046	5 (25.0)	5 (27.8)	.568
Best objective response, No. (%)	16 (51.6)	3 (13.0)	.003	6 (30.0)	7 (38.9)	.407
PFS, months, median (95% CI)	14.6 (8.8 to 20.4)	11.2 (9.6 to 12.8)		13.2 (10.1 to 16.3)	12.2 (11.8 to 12.6)	
	HR = 0.52 (95% CI, 0.25 to 0.96)		.036	HR = 0.75 (95% CI, 0.38 to 1.47)		.399
OS, months, median (95% CI)	Not reached	50.2 (not defined)		48.8 (28.1 to 69.5)	39.8 (16.8 to 62.8)	
	HR = 0.37 (95% CI, 0.14 to 1.03)		.057	HR = 0.86 (95% CI, 0.31 to 2.38)		.771

| Efficacy | MGMT Status Assessed by Immunochemistry (n = 82) | | | | | |
| | ALKY Arm | | | Ox Arm | | |
	dMGMT (n = 19)	pMGMT (n = 32)	P	dMGMT (n = 20)	pMGMT (n = 11)	P
Three-month objective response, No. (%)	9 (47.4)	1 (3.1)	<.001	7 (35.0)	3 (27.3)	.490
Best objective response, No. (%)	14 (73.7)	4 (12.5)	<.001	9 (45.0)	2 (18.2)	.135
PFS, months, median (95% CI)	18.3 (9.5 to 27.1)	9.2 (5.6 to 12.8)		12.2 (11.6 to 12.9)	12.4 (9.0 to 16.8)	
	HR = 0.63 (95% CI, 0.33 to 1.19)		.151	HR = 0.88 (95% CI, 0.40 to 1.89)		.739
OS, months, median (95% CI)	Not reached	50.2 (not defined)		48.8 (35.4 to 62.2)	20.6 (15.0 to 26.3)	
	HR = 0.79 (95% CI, 0.29 to 2.17)		.657	HR = 0.17 (95% CI, 0.05 to 0.58)		.005

Abbreviations: ALKY, alkylating agent; d, deficient; HR, hazard ratio; MGMT, O^6-methylguanine-DNA methyltransferase; NETs, neuroendocrine tumors; OS, overall survival; Ox, oxaliplatin; p, proficient; PFS, progression-free survival; PSQ, pyrosequencing.

[a]The odds ratio for best objective response of patients with dMGMT-NETs compared with pMGMT-NETs in ALKY after adjustment on tumor location (pancreas v nonpancreas) was 11.5 (2.1-58.0), P = .005. After Cox regression with adjustment on tumor location for the PFS, the HR was 0.62 (95% CI, 0.35 to 1.12), P = .112.

The efficacy of ALKY was better for dMGMT-NETs (v pMGMT-NETs), and the MGMT status seemed to have no impact under Ox. However, the choice of the technique to assess MGMT remains a debate, between methylation (MS-PCR or PSQ) and IHC (type of antibody, method for MGMT expression scoring).[4] The present results are concordant with the randomized ECOG-ACRIN-E2211 study, in which the MGMT status of pancreatic NETs was assessed either by MS-PCR for the methylation (n = 57) or IHC (n = 97); using MS-PCR, the ORR was 6 of 7 (85%) for dMGMT and 19 of 50 (38%) for pMGMT, whereas using IHC, the ORR was 33 of 63 (52%) for dMGMT and 5 of 34 (15%) for pMGMT.[8] In this study, all the seven patients with methylated *MGMT* had low IHC expression; however, the concordance between methylation and IHC was lower (20 of

55, 36.4% using MS-PCR) than herein (58.3% using PSQ). This low concordance was poorly evaluated in NETs[23] but is well-known in glioblastoma and partly related to various regulatory mechanisms of MGMT expression.[19] The present study was not designed to compare the superiority of a technique over another nor to explore the value of this biomarker when an NET is classified dMGMT by PSQ but not by IHC or the opposite; further studies are warranted not only to do so but also to investigate the best cutoff for the H-score by IHC and the best cutoff of methylation by PSQ and/or to find a better epigenetic signature of response to ALKY since pMGMT is probably only one of the resistance mechanisms to ALKY. In addition, the results were also affected by the proportion of dMGMT in the study population, which is directly related to the population (more
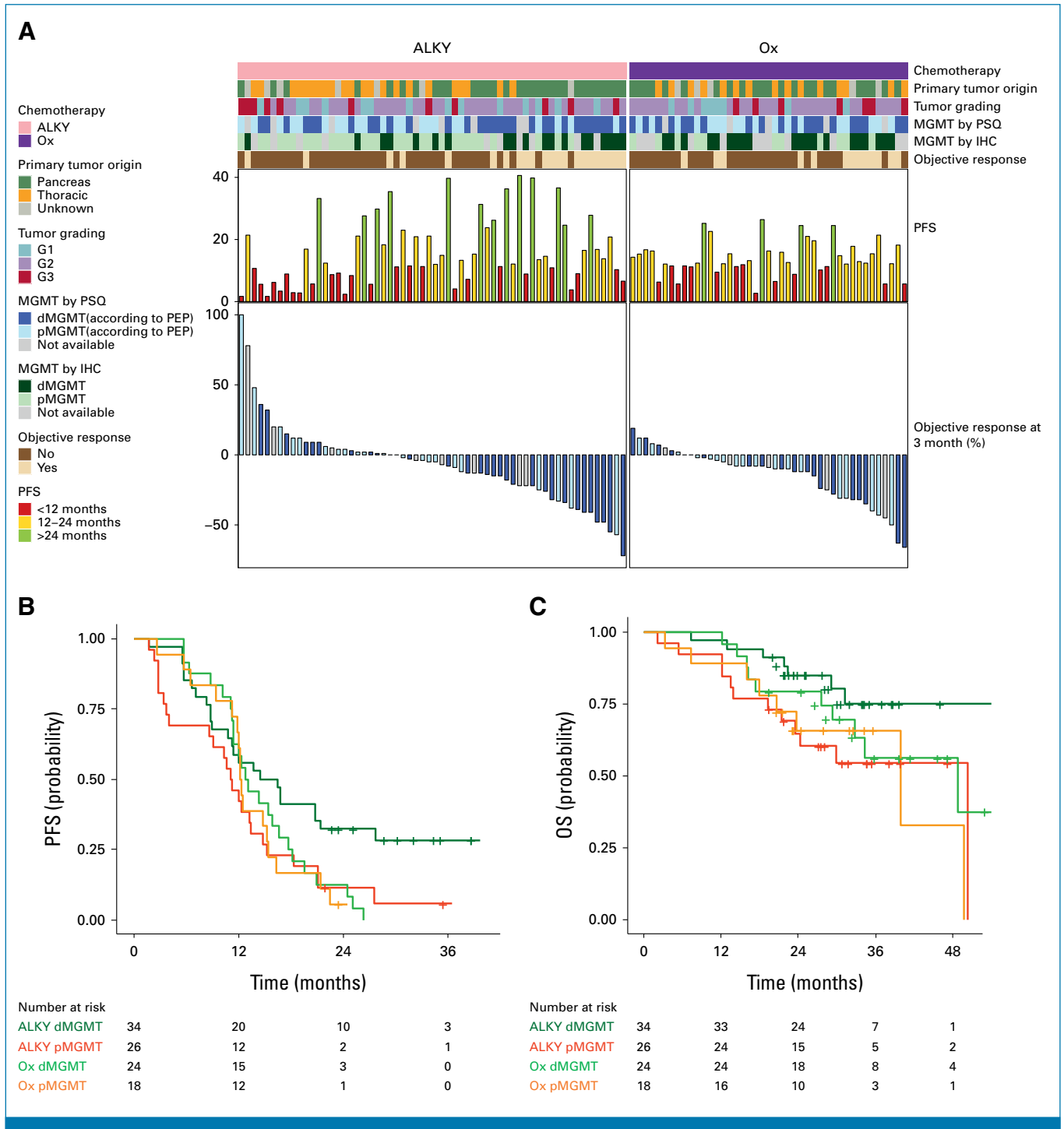
FIG 3. (A) Heatmap of main tumor characteristics and efficacy according to MGMT status and chemotherapy arm. (B) PFS in months and (C) OS in months in patients treated with alkylating-based chemotherapy (ALKY) or oxaliplatin-based chemotherapy (Ox), according to MGMT status by pyrosequencing and/or IHC when methylation is not interpretable (n = 102). ALKY, alkylating agent; d, deficient; G, tumor grading; IHC, immunochemistry; MGMT, O^6-methylguanine-DNA methyltransferase; ORR, objective response rate; OS, overall survival; Ox, oxaliplatin; p, proficient; PEP, primary end point; PFS, progression-free survival; PSQ, pyrosequencing.

frequent in pancreatic NET) and the type of techniques used to assess MGMT. In the ECOG–ACRIN–E2211 study[8] that only included pancreatic NETs, MGMT was deficient in 12% (7 of 57) using MS–PCR and in 65% (63 of 97) using IHC; in the present study, when focusing on pancreatic NET, dMGMT was found in 68% (30 of 44) using PSQ and 70% (28 of 40) using IHC. The proportion of dMGMT in the overall population was greater than initially expected, which is in part also explained by greater dMGMT in thoracic NETs (23%) than initially reported by Kulke et al.[24] This might have

favorably affected the rate of ORR found in pancreatic NETs under ALKY (62.5%), which was, for instance, 39.7% in the ECOG-ACRIN-E2211 under CAPTEM.[8]

The primary end point was not reached. However, the 3-month ORR as the primary end point was retrospectively not optimal as the hypothesis was made from data on best ORR, without data regarding the ORR at 3 months. However, the present study and another recently published study found that ORs often occur later than 3 months of ALKY.[25] In addition, PFS under ALKY was shorter herein compared with other studies, such as in the randomized study by Kunz et al[8] (median PFS of 14.4 months for temozolomide and 22.7 months for CAPTEM). This could be explained not only (1) by different baseline characteristics (more aggressive disease herein according to the presence of NET-G3 and higher proliferative index/Ki67) but also (2) by a short chemotherapy duration herein as most French physicians stop the chemotherapy after 6 months of disease control.[4,8,15] The optimal duration of chemotherapy remains a debate. A too short course may impair the outcome, especially in patients without OR. In contrast, in patients with OR, it seems not necessary to treat patients until progression because some patients can remain stable for more than 6 months without any treatment[26]; therefore a stop-and-go strategy may be an option, as performed in colorectal cancer.[27]

The present study using a biomarker-stratified design, which randomly assigns all patients between ALKY and Ox with a valid MGMT result as a stratification factor, allowed us to evaluate the distinction between the prognostic factor and the predictive factor of response to ALKY of this biomarker.[17,28] We found interesting efficacy (ORR and PFS) of Ox, close to that obtained with ALKY, but not significantly affected by the MGMT status.[15] This is clinically relevant for patients with pMGMT-NETs, which is the case in the majority of thoracic NETs, as shown herein and by Kulke et al.[24] GEMOX could be preferred to a CAPTEM regimen, for instance, in thoracic NETs when a chemotherapy is required (no 3-month ORR under ALKY). Interestingly, herein, OS was also better in dMGMT-NETs in the Ox arm, which could be explained by the further use of ALKY performed in that arm. The random assignment used herein with the Ox regimen as a control arm gives us some data on the predictive effect of MGMT status under ALKY. However, this raises the question of the prognostic impact of MGMT status in NETs apart from ALKY efficacy. The present data, against a prognostic impact of MGMT, are in accordance with the study by Schmitt et al[29] that included 141 patients with pancreatic NETs and found in univariate analysis that the loss of MGMT protein expression correlates with an adverse outcome; this prognostic value was not retained in a multivariate analysis that included widely accepted prognostic markers, such as grade and stage. Similarly, Walter et al[23] reported that although patients with a hypermethylated NET phenotype (containing more than three methylated genes) had a worse survival, MGMT only was not prognostic in this group of hypermethylator phenotype.

The MGMT-NET study has limitations. The results by subgroups must be interpreted with caution because of the small number of patients. In addition, the included population was heterogeneous and had different primary NET origin and different types of regimens per chemotherapy arm. According to the present study including a majority of pancreatic NETs and the study reported by Kunz et al[8] focusing on pancreatic NETs, much stronger evidence is available for pancreatic NETs rather than for thoracic NETs. In thoracic NETs, further studies are warranted to implement the use of MGMT for the chemotherapy choice in the guidelines. In addition, although there was an interesting activity of Ox for pMGMT-NETs, the study does not report the superiority of Ox over ALKY in pMGMT-NETs or the opposite in dMGMT-NETs. We considered that a phase III study to evaluate the best chemotherapy (Ox v ALKY) according to the MGMT status would have been impossible to perform, given the high number of patients needed and the rarity of the disease.[18] Finally, while the 3-month ORR was centrally reviewed, all the CT/MRI images were not for the secondary end points (best ORR and PFS); this explains the discordance in the dMGMT-Ox group, with best ORR being worse than the 3-month ORR.

In conclusion, despite the fact that the primary end point was not reached, ALKY has clinical activity in patients with dMGMT-NETs.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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DATA SHARING STATEMENT

Qualified researchers with appropriate proposals can request deidentified individual participant data. Full details of the protocol are available online. The data that support the findings of this study are available upon reasonable request (equivalent purposes to those for which the patients grant their consent to use the data). The data will be shared after approval of a proposal, with a signed data access agreement. Requests should be sent to the corresponding author.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Oxaliplatin-Based Versus Alkylating Agent in Neuroendocrine Tumors According to the O⁶-Methylguanine-DNA Methyltransferase Status: A Randomized Phase II Study (MGMT-NET)

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