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ORIGINAL ARTICLE

A phase II randomized trial of cobimetinib plus chemotherapy, with or without atezolizumab, as first-line treatment for patients with locally advanced or metastatic triple-negative breast cancer (COLET): primary analysis

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Background: Resistance to standard chemotherapy in metastatic triple-negative breast cancer (mTNBC) is associated with upregulation of the mitogen-activated protein kinase (MAPK) pathway. Cobimetinib, an MAPK/extracellular signal-regulated kinase (MEK) inhibitor, may increase sensitivity to taxanes and programmed death-ligand 1 inhibitors. COLET is a three-cohort phase II study evaluating first-line cobimetinib plus chemotherapy, with or without atezolizumab, in patients with locally advanced or mTNBC.

Patients and methods: Patients were ≥18 years with locally advanced or mTNBC. Following a safety run-in, patients in cohort I were randomized 1:1 to cobimetinib (60 mg, D3-D23 of each 28-day cycle) or placebo, plus paclitaxel (80 mg/m^2, D1, 8, and 15). Additional patients were randomized (1:1) to cohort II or III to receive cobimetinib plus atezolizumab (840 mg, D1 and D15) and either paclitaxel (cohort II) or nab-paclitaxel [cohort III (100 mg/m^2, D1, D8, and D15)]. Primary endpoints were investigator-assessed progression-free survival (PFS) (cohort I) and confirmed objective response rate (ORR) (cohorts II/III). Safety and tolerability were also assessed.

Results: In the expansion stages, median PFS was 5.5 months for cobimetinib/paclitaxel versus 3.8 months for placebo/paclitaxel in cohort I [hazard ratio 0.73; 95% confidence interval (CI) 0.43-1.24; $P = 0.25$]. In cohort I, ORR was 38.3% (95% CI 24.40-52.20) for cobimetinib/paclitaxel and 20.9% (95% CI 8.77-33.09) for placebo/paclitaxel; ORRs in cohorts II and III were 34.4% (95% CI 18.57-53.19) and 29.0% (95% CI 14.22-48.04), respectively. Diarrhea was the most common grade ≥3 adverse events across all cohorts.

Conclusions: Cobimetinib added to paclitaxel did not lead to a statistically significant increase in PFS or ORR, although a nonsignificant trend toward a numerical increase was observed. Cobimetinib plus atezolizumab and a taxane did not appear to increase ORR. This demonstrates the potential activity of a combinatorial MEK inhibitor, chemotherapy, and immunotherapy in this difficult-to-treat population.

Key words: cobimetinib, triple-negative breast cancer, MEK inhibitor, atezolizumab, programmed death-ligand 1 inhibitor

INTRODUCTION

Chemotherapy remains standard of care for metastatic triple-negative breast cancer (mTNBC).[1,2] Resistance to taxanes is common,[1-3] and upregulation of the mitogen-activated protein kinase (MAPK) pathway may contribute.[4] In preclinical models, MAPK/extracellular signal-regulated kinase (MEK) inhibitors increase taxane sensitivity.[5,6] Cobimetinib (COTELLIC; F. Hoffmann-La Roche Ltd, Basel, Switzerland), a potent, selective MEK1/2 inhibitor,[7] may also modulate intrinsic taxane resistance in these models.[5,6]

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Use of MEK inhibitors may also increase major histocompatibility complex classes I and II, programmed death-ligand 1 (PD-L1) expression, and cluster of differentiation 8-positive T-cell accumulation, sensitizing tumors to PD-L1 inhibitors.[8,9] Atezolizumab targets PD-L1 in the tumor microenvironment, reactivating T cells by inhibiting binding of PD-L1 to programmed cell death protein 1 and B7.[10-12] In the IMpassion130 study (NCT02425891), atezolizumab plus nab-paclitaxel demonstrated prolonged progression-free survival (PFS) in patients with PD-L1-positive mTNBC (PD-L1-stained tumor-infiltrating immune cells covering ≥1% of the tumor area).[13] This led to approval of the regimen in this patient subset and its approval in first-line TNBC.[14,15]

COLET (NCT02322814; 2014-002230-32) is a three-cohort phase II study designed to evaluate efficacy/safety of cobimetinib plus chemotherapy, with or without atezolizumab, in patients with locally advanced TNBC or mTNBC. We present results from the primary analysis of all three cohorts.

METHODS

Study design and patients

COLET is a phase II, randomized, multicenter, three-cohort study (45 sites; 12 countries), investigating cobimetinib or placebo plus paclitaxel (cohort I), cobimetinib plus atezolizumab and paclitaxel (cohort II), and cobimetinib plus atezolizumab and nab-paclitaxel (cohort III), in patients ≥18 years old with histologically confirmed estrogen receptor-negative, progesterone receptor-negative, and HER2-negative mTNBC, or locally advanced TNBC not amenable to resection with curative intent (Figure 1). Inclusion criteria are in the Supplementary Material, available at https://doi.org/10.1016/j.annonc.2021.01.065.

The study was conducted according to the International Council for Harmonisation E6 Guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research was conducted. The protocol and amendments were approved by independent review boards/ethics committees. All patients provided written, informed consent.

Procedures

Cohort I comprised a safety run-in (SRI), followed by a double-blind, placebo-controlled expansion stage, where patients were randomized 1:1 to receive cobimetinib (60 mg, oral, on D3-D23 of each 28-day cycle) or placebo, plus paclitaxel [80 mg/m^2, intravenous (IV), D1, D8, and D15 of each 28-day cycle]. SRI patients received the same dose/schedule for cobimetinib plus paclitaxel. Following completion of cohort I, additional patients were enrolled and randomized (1:1) to either cohort II [cobimetinib plus atezolizumab (840 mg, IV, D1 and D15 of each 28-day cycle) and paclitaxel] or III [cobimetinib plus atezolizumab and nab-paclitaxel (100 mg/m^2, IV, D1, D8, and D15 of each 28-day cycle)], with the two cohorts comprising an open-label SRI and expansion stage. Treatment continued until disease progression (per RECIST version 1.1) or unacceptable

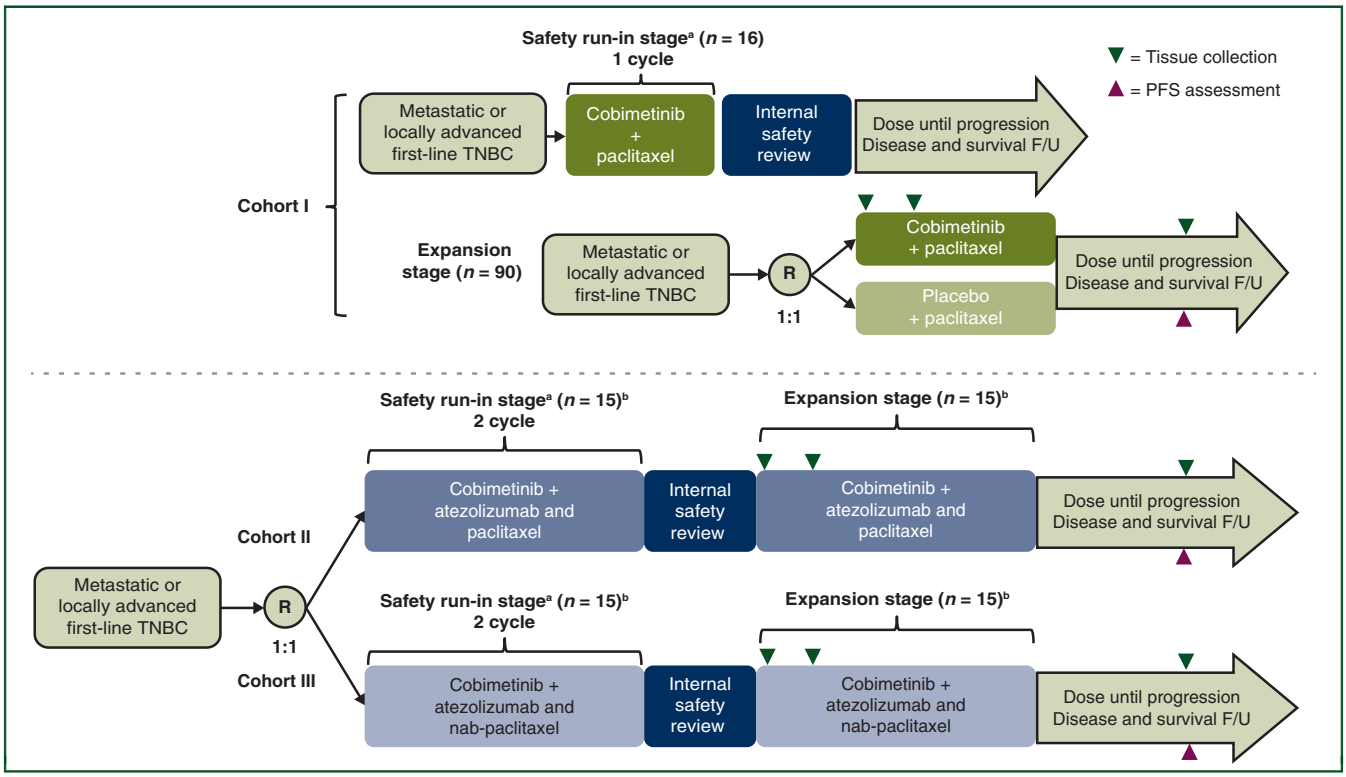

Figure 1. COLET study design.
F/U, follow-up; PFS, progression-free survival; TNBC, triple-negative breast cancer.
[a] Safety run-in population presented previously.[36]
[b] Numbers indicate planned patient enrollment.

toxicity. Stratification was by prior neoadjuvant/adjuvant taxane therapy (yes versus no) and disease-free interval from last chemotherapy dose (≤12 versus >12 months/no prior chemotherapy). Additional procedures are described in the Supplementary Material, available at https://doi.org/10.1016/j.annonc.2021.01.065.

In the expansion stage of cohort I, the primary efficacy endpoint was investigator-assessed PFS (planned $N = 90$; the time from randomization to the first occurrence of disease progression or relapse per RECIST version 1.1, or death from any cause, whichever occurred first). The primary efficacy endpoint for cohorts II/III was confirmed objective response rate (ORR; the rate of partial response [PR] or complete response [CR] occurring after randomization and confirmed ≥28 days later per RECIST version 1.1).

Assessments

Tumor imaging occurred at baseline and every 8 weeks using RECIST version 1.1 until documented investigator-determined progressive disease, death, or withdrawal of consent, whichever came first. Follow-up for survival occurred every 3 months after study drug discontinuation.

Formalin-fixed paraffin-embedded samples for biomarker analysis were collected from all patients at pretreatment (archival or baseline; mandatory), on-treatment (C1, D15; optional), and disease progression (if accessible). The Supplementary Material, available at https://doi.org/10.1016/j.annonc.2021.01.065 provides details of the biomarker analysis, including PD-L1 (PD-L1-positive disease: ≥1% PD-L1-positive immune cells measured by SP142).

Adverse events (AEs) and laboratory abnormalities were graded using the National Cancer Institute—Common Terminology Criteria for Adverse Events version 4.0.

Statistical methods

COLET was designed as a signal-seeking phase II study. The primary objective in the cohort I expansion stage was to estimate the PFS hazard ratio (HR) of cobimetinib or placebo plus paclitaxel. Patients were followed until ∼60 investigator-assessed PFS events had occurred across treatment arms, providing 80% power to detect an HR of 0.48, or 51% power to detect an HR of 0.60 at a two-sided significance level of 5%.

COLET was also designed to estimate the effect of cobimetinib plus atezolizumab and taxane therapy for hypothesis generation. The primary objective in cohorts II/III was to estimate ORR in each cohort after the last recruited patients had completed two postbaseline tumor assessments. No formal statistical hypothesis testing was planned. Based on the Clopper—Pearson method, 30 patients provided reasonably reliable estimates of ORR and its 95% confidence interval (CI) for hypothesis generation.

Kaplan—Meier methodology was used to estimate median PFS, overall survival (OS), and duration of response (DoR), with stratified log-rank tests used to compare treatment arms in cohort I. HR estimates and their 95% CIs were determined by the stratified Cox proportional hazards model. An estimate of ORR and 95% CIs were calculated for each treatment arm using the Clopper—Pearson method, as well as CIs for differences in ORR between treatment arms in cohort I. Stratification data were determined using the electronic case report form, or for missing data, the interactive voice or web response system at time of randomization. Analysis of endpoints in cohorts II and III were descriptive.

The intention-to-treat population comprised all randomized or enrolled patients regardless of study treatment administration; the safety-evaluable population was patients who received any study drug.

RESULTS

Patients

Between 12 March 2015 and 31 October 2016, 106 patients were enrolled into cohort I, 16 into the SRI, and 90 randomized into the expansion stage to either cobimetinib ($n = 47$) or placebo ($n = 43$) plus paclitaxel (clinical cut-off: 8 March 2017; OS clinical cut-off: 29 September 2017; Supplementary Figure S1A, available at https://doi.org/10.1016/j.annonc.2021.01.065). Median (range) duration of follow-up was 8.5 months (1.6-16.8 months) in the cobimetinib plus paclitaxel arm and 7.7 months (0.7-15.7 months) in the placebo plus paclitaxel arm.

Following completion of cohort I, 63 patients were randomized into cohorts II ($n = 32$) and III ($n = 31$; November 2016-April 2018; Supplementary Figure S1B, available at https://doi.org/10.1016/j.annonc.2021.01.065). Clinical cut-off was 10 August 2018. Median duration of follow-up was 6.3 months for cohort II and 6.6 months for cohort III.

Baseline characteristics were similar across cohorts (median ages: 51.0-55.0 years; Table 1). In cohort I, 8/47 (17.0%) and 8/43 (18.6%) patients in the cobimetinib plus paclitaxel and placebo plus paclitaxel arms, respectively, had disease-free intervals of ≤12 months. The proportion in cohort II was greater than that in cohort III [9/32 (28.1%) versus 6/31 (19.4%), respectively].

Treatment exposure

In the cohort I expansion stage, median (range) durations of cobimetinib and paclitaxel treatment in the cobimetinib plus paclitaxel arm were 19.0 weeks (1-51 weeks) and 18.3 weeks (1-43 weeks), respectively. In the placebo plus paclitaxel arm, median duration of paclitaxel exposure was 15.1 weeks (1-44 weeks).

Atezolizumab exposure was 14.1 weeks (4-79 weeks) for cohort II and 20.4 weeks (0-57 weeks) for cohort III; for cobimetinib, median durations for cohorts II and III were 15.1 weeks (3-79 weeks) and 17.2 weeks (6-58 weeks), respectively. Mean durations of exposure for paclitaxel/nab-paclitaxel were 15.1 weeks (5-79 weeks) for cohort II and 18.6 weeks (0-46 weeks) for cohort III.

Table 1. Patient demographics and disease characteristics at baseline (intention-to-treat population)

Characteristic, *n* (%)	Cohort I		Cohort II	Cohort III
	Cobimetinib + paclitaxel (*n* = 47)	Placebo + paclitaxel (*n* = 43)	Cobimetinib + atezolizumab + paclitaxel (*n* = 32)	Cobimetinib + atezolizumab + nab-paclitaxel (*n* = 31)
Median age (range), years	55.0 (34-73)	53.0 (31-80)	52.0 (26-79)	51.0 (20-75)
Disease stage				
Locally advanced	5 (10.6)	3 (7.0)	5 (15.6)	7 (22.6)
Metastatic	42 (89.4)	40 (93.0)	27 (84.4)	24 (77.4)
Race				
White	32 (68.1)	34 (79.1)	28 (87.5)	25 (80.6)
Asian	11 (23.4)	9 (20.9)	2 (6.3)	5 (16.1)
Other/unknown	4 (8.5)	0	2 (6.3)	1 (3.2)
Prior neoadjuvant/adjuvant taxane therapy	27 (57.4)	28 (65.1)	21 (65.6)	20 (64.5)
Disease-free interval from last dose of chemotherapy				
≤12 months	8 (17.0)	8 (18.6)	9 (28.1)	6 (19.4)
>12 months/no prior chemotherapy	39 (83.0)	35 (81.4)	23 (71.9)	25 (80.6)
PD-L1 status				
Negative	26 (55.3)	18 (41.9)	9 (28.1)	11 (35.5)
Positive	7 (14.9)	11 (25.6)	16 (50.0)	15 (48.4)
Missing	14 (29.8)	14 (32.6)	7 (21.9)	5 (16.1)

PD-L1, programmed death-ligand 1.

Efficacy

Cohort I. At data cut-off in the cohort I expansion stage, 31/47 (66.0%) patients in the cobimetinib plus paclitaxel arm and 31/43 (72.1%) in the placebo plus paclitaxel arm had a PFS event. Median (range) PFS was 5.5 months (4.2-7.4 months) for cobimetinib plus paclitaxel versus 3.8 months (1.9-7.2 months) for placebo plus paclitaxel (Figure 2A). The stratified log-rank HR comparing the treatment arms was 0.73 (95% CI 0.43-1.24; $P = 0.25$; not statistically significant). The difference was more pronounced in individuals with a disease-free interval of ≤12 months [$n = 16$; 5.4 versus 1.7 months (HR 0.29, 95% CI 0.09-0.95)]. There was a 17.4% increase in ORR [cobimetinib plus paclitaxel arm: 38.3% (18/47 patients; 95% CI 24.40-52.20); placebo plus paclitaxel arm: 20.9% (9/43 patients; 95% CI 8.77-33.09)] (Table 2).

No confirmed CR was observed in either arm (Table 2); seven patients in the cobimetinib plus paclitaxel arm continued on single-agent cobimetinib (range 2-9 further treatment cycles) following paclitaxel discontinuation, and response (PR or stable disease) was maintained (Supplementary Figure S2A/B, available at https://doi.org/10.1016/j.annonc.2021.01.065). At the 40-week assessment, in the cobimetinib plus paclitaxel arm, four patients maintained a PR, and two had stable disease; in the placebo plus paclitaxel arm one patient maintained a PR. Median DoR was comparable between arms [cobimetinib plus paclitaxel: 5.3 months (95% CI 3.71-6.11); placebo plus paclitaxel: 5.5 months {[3.94-not evaluable (NE)]} (Table 2). At OS data cut-off, 22/47 (46.8%) patients in the cobimetinib plus paclitaxel arm and 17/43 (39.5%) in the placebo plus paclitaxel arm had died. Median (range) OS was 16.0 months (1.6-21.1 months) for cobimetinib plus paclitaxel versus 19.6 months (0.7-24.1 months) for placebo plus paclitaxel (HR 1.05; 95% CI 0.55-2.01; Supplementary Figure S3A, available at https://doi.org/10.1016/j.annonc.2021.01.065).

Cohort II. At data cut-off, ORR in cohort II (primary endpoint) was 34.4% (11/32 patients; 95% CI 18.57-53.19; Table 2). Two (6.3%) CRs were observed (Table 2); nine patients had a PR and 11 had stable disease (Supplementary Figure S2C, available at https://doi.org/10.1016/j.annonc.2021.01.065). Median DoR was 5.8 months (95% CI 4.44-NE; Table 2). As much as 22 of 32 (68.8%) patients had a PFS event; median (range) PFS was 3.8 months (1.6-18.1 months; 95% CI 3.02-7.36; Figure 2B). At OS data cut-off, 10/32 (31.3%) patients had died; median (range) OS was 11.0 months (1.8-18.2 months; 95% CI 9.53-NE; Supplementary Figure S3B, available at https://doi.org/10.1016/j.annonc.2021.01.065).

Cohort III. At data cut-off, ORR in cohort III was 29.0% (9/31 patients; 95% CI 14.22-48.04; Table 2). No CRs were observed (Table 2); nine patients had a PR and 16 had stable disease (Supplementary Figure S2D, available at https://doi.org/10.1016/j.annonc.2021.01.065). Median DoR was 11.0 months (95% CI 7.26-NE; Table 2). As much as 17 of 31 (54.8%) patients had a PFS event; median (range) PFS was 7.0 months (0.0-13.3 months; 95% CI 3.65-12.81; Figure 2C). At OS data cut-off, 6/31 (19.4%) patients had died. Median (range) OS was NE (0.3-16.4 months; 95% CI 10.15-NE; Supplementary Figure S3C, available at https://doi.org/10.1016/j.annonc.2021.01.065).

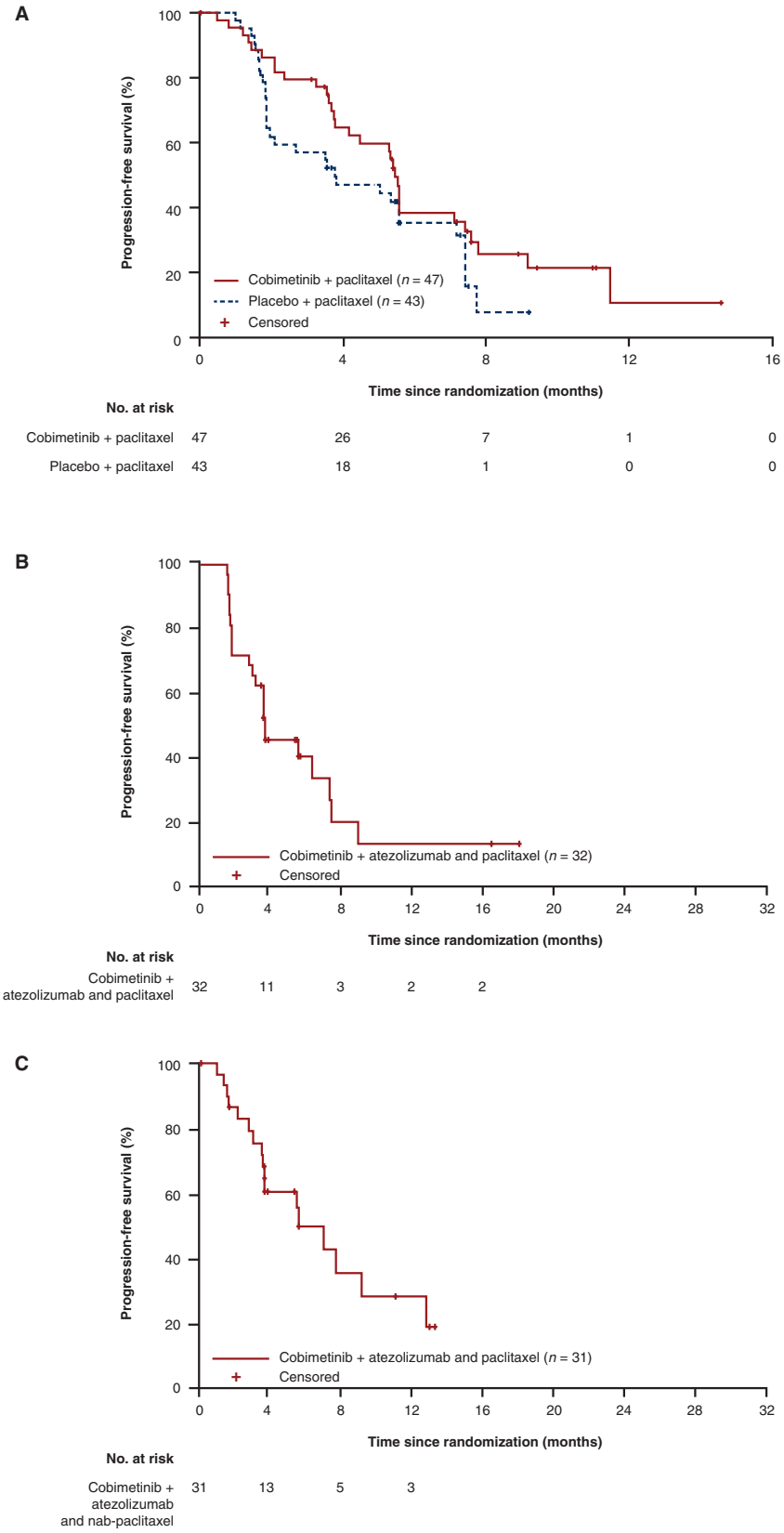

Figure 2. Investigator-assessed progression-free survival (PFS).[a]
(A) Cohort I: cobimetinib or placebo + paclitaxel treatment arm. (B) Cohort II: cobimetinib + atezolizumab + paclitaxel arm. (C) Cohort III: cobimetinib + atezolizumab + nab-paclitaxel arm.
[a] Investigator-assessed PFS was defined as the time from randomization to the first occurrence of disease progression or relapse per RECIST version 1.1, or death from any cause, whichever occurred first.

Table 2. Best overall response rate, confirmed (intention-to-treat population)

Response	Cohort I		Cohort II	Cohort III
	Cobimetinib + paclitaxel ($N = 47$), n (%) (95% CI)	Placebo + paclitaxel ($N = 43$), n (%) (95% CI)	Cobimetinib + atezolizumab + paclitaxel ($N = 32$), n (%) (95% CI)	Cobimetinib + atezolizumab + nab-paclitaxel ($N = 31$), n (%) (95% CI)
Confirmed overall response rate	18 (38.3) (24.40-52.20)	9 (20.9) (8.77-33.09)	11 (34.4) (18.57-53.19)	9 (29.0) (14.22-48.04)
Prior taxane therapy	9 (33.3) (15.50-51.11)	3 (14.3) (1.32-27.25)	7 (21.9) (9.28-39.97)	7 (22.6) (9.59-41.10)
No prior taxane therapy	9 (45.0) (23.20-66.80)	5 (33.3) (9.48-57.19)	4 (12.5) (3.51-29.00)	2 (6.5) (0.79-21.42)
Complete response	0	0	2 (6.3) (0.77-20.81)	0 (0.00-11.22)
Partial response	18 (38.3) (24.40-52.20)	9 (20.9) (8.77-33.09)	9 (28.1) (13.75-46.75)	9 (29.0) (14.22-48.04)
Stable disease	18 (38.3) (24.40-52.20)	16 (37.2) (22.76-51.66)	11 (34.4) (18.57-53.19)	16 (51.6) (33.06-69.85)
Progressive disease	8 (17.0) (6.28-27.77)	17 (39.5) (24.92-54.15)	10 (31.3) (16.12-50.01)	3 (9.7) (2.04-25.75)
Not done[a]	3 (6.4)[b]	1 (2.3)[b]	0	3 (9.7) (0.00-20.08)

CI, confidence interval.
[a] Patients were classified as 'Not done' if no postbaseline response assessments were available.
[b] Data presented as n (%).

Safety

Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2021.01.065 provides a summary of the safety-evaluable population (cohorts I-III). Most patients [46/47 (97.9%)] had ≥1 AE in the cobimetinib plus paclitaxel arm; all patients in the placebo plus paclitaxel arm of cohort I, and cohorts II and III had ≥1 AE. Most common AEs in the cobimetinib plus paclitaxel arm of cohort I and in cohorts II and III were diarrhea [cobimetinib plus paclitaxel arm: 36/47 (76.6%) versus placebo plus paclitaxel arm: n = 12/43 (27.9%); cohort II: 21/32 (65.6%); cohort III: 27/30 (90.0%)], nausea [cobimetinib plus paclitaxel arm: 21/47 (44.7%) versus placebo plus paclitaxel arm: n = 16/43 (37.2%); cohort II: 13/32 (40.6%); cohort III: 15/30 (50.0%)], and rash [cobimetinib plus paclitaxel arm: 20/47 (42.6%) versus placebo plus paclitaxel arm: n = 5/43 (11.6%); cohort II: 12/32 (37.5%); cohort III: 16/30 (53.3%); Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2021.01.065].

Most events of diarrhea across all cohorts were grade 1/2, except in the cobimetinib plus paclitaxel arm of cohort I, where 11/36 events were grade 3 (23.4%), including one serious AE resulting in treatment discontinuation. Median duration of diarrhea varied by cohort [I (cobimetinib plus paclitaxel, n = 36): 2.07 weeks; I (placebo plus paclitaxel, n = 12): 1.93 weeks; II (n = 21): 4.57 weeks; III (n = 27): 3.43 weeks]. At data cut-off, most diarrhea events had resolved/were resolving.

In cohort I, the most common grade ≥3 AEs occurring in ≥2 patients in any treatment arm included diarrhea, neutropenia, and stomatitis; diarrhea and stomatitis occurred more frequently in the cobimetinib plus paclitaxel arm versus the placebo plus paclitaxel arm (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2021.01.065). Serious AEs were reported in 17/47 (36.2%) patients in the cobimetinib plus paclitaxel arm and 9/43 (20.9%) in the placebo plus paclitaxel arm. There were no grade 5 (fatal) AEs (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2021.01.065).

Grade ≥3 AEs occurring in ≥2 patients in either cohort II or III were diarrhea, anemia, neutropenia, and decreased neutrophil count (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2021.01.065). Serious AEs were reported in 15/32 (46.9%) patients in cohort II and 13/30 (43.3%) in cohort III (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2021.01.065). There were two (6.3%) fatal AEs in cohort II (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2021.01.065), namely, pulmonary embolism (occurred after treatment discontinuation due to disease progression) and lung infiltration; neither were suspected to be treatment-related.

Exploratory biomarker analysis

Gene expression profiling was performed for 72/106 (67.9%) patients in cohort I, including 13 patients from SRI. As much as 56 of 72 (78%) patients had basal-like subtypes at baseline, per intrinsic subtyping.[16] Cobimetinib plus paclitaxel demonstrated a more favorable HR for PFS for patients with basal subtype tumors [n = 56 (cobimetinib plus paclitaxel: n = 34; placebo plus paclitaxel: n = 22); HR 0.49, 95% CI 0.26-0.92], but not for those with nonbasal subtype tumors [n = 16 (cobimetinib plus paclitaxel: n = 12; placebo plus paclitaxel: n = 4); HR 0.85, 95% CI 0.15-4.72], compared with the intention-to-treat population. Patients with basal subtype tumors displayed a greater ORR than their nonbasal subtype counterparts [ORR 51% (n = 19/37) versus 27% (n = 4/15)]; however, the latter

displayed overall better prognosis [median PFS: 6.9 (95% CI 2.33-not reached) versus 5.4 months (95% CI 3.52-7.10); HR 0.45, 95% CI 0.19-1.05]. PD-L1-positive samples were enriched in tumors of basal versus nonbasal subtype [n = 21/56 (37.5%) versus 3/14 (21.4%); Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2021.01.065]. All immune-enriched tumor subtypes were basal-like (n = 26/26; 100%).

In cohorts II and III, patients with PD-L1-positive disease had numerically higher ORRs than those with PD-L1-negative disease [39% (12/31 patients) versus 19% (4/21)] and median PFS [7.0 (95% CI 3.65-9.10) versus 3.7 months (95% CI 2.14-6.41); Supplementary Figure S4, available at https://doi.org/10.1016/j.annonc.2021.01.065]. Patients with basal tumors showed higher ORRs than those with nonbasal disease [35.6% (16/45 patients) versus 12.5% (1/8)], but no clear difference in median PFS [5.59 (95% CI 3.65-7.49) versus 3.68 months (95% CI 1.71-not reached); Supplementary Figure S5, available at https://doi.org/10.1016/j.annonc.2021.01.065]. ORR and median PFS were similar between patients with low or high MAPK activity [ORR 33.3% (8/24 patients) versus 31.0% (9/29); PFS 5.49 (95% CI 2.14-7.49) versus 6.41 months (95% CI 3.02-12.81); Supplementary Figure S6, available at https://doi.org/10.1016/j.annonc.2021.01.065].

DISCUSSION

COLET is the first study evaluating first-line PD-L1 inhibitor, MEK inhibitor, and taxane combination (cobimetinib plus atezolizumab and paclitaxel/nab-paclitaxel) for locally advanced or mTNBC.

Consistent with cobimetinib modulating intrinsic taxane resistance, its addition to paclitaxel did not lead to a statistically significant increase in median PFS or ORR, but resulted in a nonsignificant trend toward a numerical increase, with ORR more pronounced in individuals with a disease-free interval of $\leq$12 months. The ORR and reductions in tumor volume suggest a biologic effect, and the HR for cohort I PFS suggests there may be activity of cobimetinib versus placebo when combined with paclitaxel. Cobimetinib is approved in combination with the B-Raf proto-oncogene serine/threonine kinase (BRAF) inhibitor vemurafenib for patients with $BRAF^{V600}$-mutated advanced melanoma and resistance to single-agent BRAF inhibitor therapy,[7,17] in which reactivation of MAPK through MEK is the most common mechanism.[18,19] Given that upregulation of the MAPK pathway may also contribute to taxane resistance in mTNBC,[4] it is not unexpected that cobimetinib plus paclitaxel led to modest clinical improvement. Small patient numbers, the statistical design of COLET, the heterogeneity of TNBC,[20] and the many potential mechanisms simultaneously contributing to taxane resistance[21-23] may also have contributed to the lack of significant improvement.

We also hypothesized that cobimetinib may increase major histocompatibility complex classes I and II, PD-L1 expression, and cluster of differentiation 8-positive T-cell accumulation, sensitizing tumors to atezolizumab; however, the combination of atezolizumab, cobimetinib, and a taxane in cohorts II and III demonstrated a modest ORR. This contrasts with IMpassion130, where adding atezolizumab versus placebo to nab-paclitaxel resulted in a ~10% improvement in ORR [ORR 56.0% (51.3-60.6) versus 45.9% (41.2-50.6)], statistically significant increase in PFS (7.2 versus 5.5 months; HR 0.80, 95% CI 0.69-0.92; P = 0.002), and numerical increase in OS (21.0 versus 18.7 months; HR 0.86, 95% CI 0.72-1.02; P = 0.08).[13,24] This apparent disparity may be due to the 23.8% of patients in cohorts II/III of COLET who had a disease-free interval of $\leq$12 months, which is associated with worse prognosis. Furthermore, ORR has been shown to be only modestly correlated with OS benefit following checkpoint inhibitor therapy.[25] Nonetheless, although the short median follow-ups limit interpretation of OS benefit or trends, the observed median PFS in cohort III of COLET was similar to that in IMpassion130[13]; the lower PFS in cohort II may be due to the small sample size, therapeutic superiority of nab-paclitaxel compared with paclitaxel,[26] and increased proportion of early relapse patients. Additionally, preclinical evidence suggests that MEK inhibition may be detrimental on early T-cell proliferation and function, which is particularly relevant in the 'cold' tumor microenvironment of mTNBC and may explain the lack of a clinically relevant therapeutic benefit here.[27,28] However, due to our small study sample size and retrospective comparisons between studies of differing demographics, no definitive conclusions can be drawn.

Of interest, a retrospective, exploratory analysis of pooled biomarker data in COLET demonstrated a trend toward improved ORR and PFS in patients with PD-L1-positive disease in cohorts II and III. This aligns with IMpassion130, which demonstrated a significantly improved PFS and ORR of atezolizumab plus nab-paclitaxel in the PD-L1-positive population, as well as an OS benefit of ~10 months.[13] However, lack of OS-PD-L1-status association analysis in COLET, as well as small patient numbers and absence of a placebo arm in cohorts II/III, means that all comparisons are descriptive and should be interpreted with caution. Ongoing phase II/III randomized immunotherapy trials in TNBC should shed further light on the current findings.[29] Interestingly, there was no association between MAPK activity and patient outcome; this contrasts with previous studies demonstrating shorter OS in patients with MAPK-activated TNBC.[30,31] This may be explained by the small patient numbers in COLET; further studies are required to elucidate the prognostic significance of MAPK activity in patients with TNBC.

The safety profiles of the COLET study drug combinations were consistent with those for the individual drugs, and AEs were generally manageable.[7,15,32,33] In all cohorts, diarrhea was the most common any-grade AE; most events were grade 1-2 and managed with loperamide. More grade 3 diarrhea events were observed in the cobimetinib plus paclitaxel arm of cohort I (versus cohorts II/III), which can mainly be attributed to earlier intervention with antidiarrheal treatment and/or dose interruption.

Although no further trials assessing first-line cobimetinib for mTNBC are planned, other MEK inhibitors, for example, selumetinib, are currently being investigated as combination therapies. Selumetinib plus the PI3K inhibitor buparlisib has demonstrated efficacy in preclinical mouse models of intracranial mTNBC, significantly improving survival and reducing tumor burden.[34] Selumetinib plus the mTORC1/2 inhibitor vistusertib has also shown an acceptable safety profile in an ongoing phase Ib/IIa trial in TNBC, with stable responses for >16 weeks in seven patients.[35]

In conclusion, results from COLET showed that addition of cobimetinib to paclitaxel did not lead to a statistically significant increase in PFS or ORR, but resulted in a nonsignificant trend toward a numerical increase. Cobimetinib, atezolizumab, and a taxane also led to modest clinical response, although this was more pronounced in patients with PD-L1-positive disease. These results demonstrate the potential activity of combinatorial MEK inhibitor, chemotherapy, and immunotherapy in this difficult-to-treat patient population. No trials assessing first-line cobimetinib for mTNBC are planned, but future studies will improve understanding of the therapeutic value of other MEK inhibitors in TNBC.

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DATA SHARING STATEMENT

Qualified researchers may request access to individual patient-level data through the clinical study data request platform (https://vivli.org/). Further details on Roche's criteria for eligible studies are available here: https://vivli.org/members/ourmembers/. For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here: https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm.

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