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Triplet combination of durvalumab, tremelimumab, and paclitaxel in biliary tract carcinomas: safety run-in results of the randomized IMMUNOBIL PRODIGE 57 phase II trial

Running title: safety of durvalumab, tremelimumab, paclitaxel triplet

Alice Boilève^{1,2}, Marc Hilmi^{2,3}, Paul Gougis^{4*}, Romain Cohen^{2,5*}, Benoît Rousseau^{2,6*}, Jean-Frédéric Blanc⁷, Meher Ben Abdelghani⁸, Hélène Castanié⁹, Laëtitia Dahan¹⁰, David Tougeron¹¹, Jean-Philippe Metges¹², Christophe Tournigand¹³, Marie-Line Garcia-Larnicol², Dewi Vernerey^{2,14}, Anthony Turpin^{2,15}, Cindy Neuzillet^{2,3}

1. Department of Medical Oncology, Gustave Roussy Cancer Campus, Villejuif, France
2. GERCOR, Paris, France
3. Department of Medical Oncology, Institut Curie – site Saint Cloud, Saint-Cloud, France
4. Department of Pharmacology Sorbonne Université, INSERM, CIC-1901 Paris-Est, CLIP² Galilée, Assistance Publique - Hôpitaux de Paris, Pitié-Salpêtrière Hospital, Paris, France
5. Department of Medical Oncology, Sorbonne Université, Saint-Antoine Hospital, Assistance publique-Hôpitaux de Paris, Paris, France
6. Department of Medicine, Solid Tumor Division, Mortimer B. Zuckerman Research Center, Memorial Sloan Kettering Cancer Center, New York, USA
7. Department of Hepato-Gastro-Enterology and Digestive Oncology, Hôpital Haut-Lévêque, CHU de Bordeaux, Bordeaux, France
8. Department of Medical Oncology, Centre Paul Strauss, Strasbourg, France
9. Institut de Cancérologie Catherine de Sienne, L'Hôpital privé du Confluent, Nantes, France
10. Department of Digestive Oncology, Centre Hospitalo-Universitaire la Timone, Marseille, France
11. Department of Hepato-Gastro-Enterology, Centre Hospitalo-Universitaire de Poitiers, Poitiers, France
12. Centre Hospitalo-Universitaire Brest-Institut de Cancerologie et d'Hematologie, Brest, France
13. Department of Medical Oncology, Assistance publique-Hôpitaux de Paris, Hôpital Henri-Mondor; University Paris Est Créteil, Créteil, France
14. Unité de Méthodologie et de Qualité de Vie en Cancérologie (INSERM UMR 1098), CHU Besançon, Besançon, France
15. Department of Medical Oncology, Centre Hospitalo-Universitaire Lille, Lille, France

*= contribue equally

Correspondence to:

Dr Cindy Neuzillet, Ph.D., Département d'Oncologie Médicale, Institut Curie – site Saint Cloud, 35, rue Dailly, 92210 Saint Cloud, France; Email: cindy.neuzillet@curie.fr

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Highlights

- IMMUNOBIL phase II trial enrolls patients with advanced biliary tract cancers (BTC)
- Patients receive durvalumab and tremelimumab with or without paclitaxel
- With six dose-limiting toxicities in Arm B, a stopping rule was met
- An unexpected increase in anaphylactic adverse events was observed
- It raised concerns for durvalumab/tremelimumab combined with paclitaxel in BTC

1 **Abstract**

2 **Background:** The IMMUNOBIL PRODIGE 57 trial is a non-comparative randomized phase II
3 study assessing the efficacy and safety of the durvalumab (an anti-PD-L1) and tremelimumab
4 (an anti-CTLA4) combination with or without weekly paclitaxel in patients with advanced
5 biliary tract cancers (BTC) after failure of platinum-based chemotherapy. Taxanes have
6 already been safely combined with immune checkpoint inhibitors in other tumors. We
7 report results of the 20-patient safety run-in.

8 **Methods:** Patients received durvalumab (1,500 mg at day 1 [D1] of each
9 cycle)/tremelimumab (75 mg at D1 for 4 cycles; Arm A) or durvalumab/tremelimumab with
10 paclitaxel (80 mg/m² at D1, D8, D15; Arm B) every 28 days.

11 **Results:** Twenty patients were enrolled (Arm A/B: 10/10). There were no dose-limiting
12 toxicities (DLTs) in Arm A. Six DLTs were observed in five patients (50%) in Arm B, meeting a
13 stopping rule for the trial inclusions. DLTs included: three serious anaphylactic reactions
14 (with one cardiac arrest), two enterocolitis, and one infectious pneumopathy with septic
15 shock. There were no patients with history of personal or familial autoimmune disease.

16 **Conclusion:** The safety run-in part of IMMUNOBIL PRODIGE 57 raised concerns regarding co-
17 administration of paclitaxel with durvalumab and tremelimumab in BTC, with an unexpected
18 increase in anaphylactic adverse events. Phase II of the study will only evaluate the
19 durvalumab and tremelimumab combination arm.

20 ClinicalTrials registration: NCT03704480.

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22 **Keywords:** dose limiting toxicity – paclitaxel – durvalumab – tremelimumab – biliary tract
23 tumors

24 **Introduction**

25 Biliary tract carcinoma (BTC) is the second most common primary liver tumor [1].
26 BTCs are classified into intrahepatic cholangiocarcinoma (CCA), extrahepatic CCA, and
27 gallbladder carcinoma, with distinct biological/molecular features [2]. Sixty-five percent of
28 BTC patients are diagnosed at an advanced stage [1]. Moreover, those with a resectable
29 disease at diagnosis who undergo surgical resection often relapse (more than half of the
30 cases) [1].

31 Standard first-line treatment in advanced BTC is gemcitabine plus cisplatin (GEMCIS)
32 chemotherapy doublet [3]. After GEMCIS chemotherapy, second-line chemotherapy is based
33 on 5-fluorouracil/folinic acid and oxaliplatin (FOLFOX), with limited overall survival (OS)
34 improvement as compared with best supportive care (BSC) alone (6.2 vs. 5.3 months) [4],
35 warranting exploration of innovative treatments. Small-size phase II clinical studies reported
36 the efficacy of taxanes in patients with advanced BTC [5,6].

37 Immune checkpoint inhibitors (ICI) have opened new opportunities in cancer therapy
38 [7–9]. Recent data showed encouraging results with anti-programmed death-1 (PD-1)
39 monoclonal antibodies (mAb) monotherapy in pre-treated advanced BTC [10–14]. Phase III
40 studies combining ICI with first-line GEMCIS chemotherapy in advanced BTC are ongoing
41 (NCT04003636, NCT03875235, NCT04066491). The effects of ICI in combination with second-
42 line chemotherapy in patients with advanced BTC have not yet been explored.

43 Some chemotherapeutic agents stimulate both innate and adaptive immunity
44 providing the rationale for combining ICI with chemotherapy [15]. Among cytotoxic agents,
45 taxanes (*i.e.*, paclitaxel, nab-paclitaxel, docetaxel) have been shown to display different
46 immunostimulating effects by: (1) attenuating activity of specific immune cell populations
47 (such as T-reg) that restrain cytotoxic T-cells, (2) increasing tumor antigen presentation by

48 dendritic cells, (3) enhancing priming and activation of specific anti-tumoral cytotoxic T-cells,
49 and (4) sensitizing tumor cells to immune-mediated destruction [15,16]. Taxanes may also
50 play a role as an inducer of PD-1 ligand (PD-L1) expression by tumor cells [17]. Taxanes are
51 currently undergoing clinical evaluation as single agents or validation in combination with ICI
52 in breast [18], non-small-cell lung carcinoma (NSCLC) [19] (NCT03573947), and urothelial
53 carcinoma (NCT03575013). There have been no reported safety concerns with the use of the
54 gemcitabine and nab-paclitaxel in combination with durvalumab (anti-PD-L1 IgG1, fully-
55 human mAb) and tremelimumab (anti-CTLA4 IgG2, fully-human mAb) in the CCTG PA.7 trial
56 [20] of patients with metastatic pancreatic ductal adenocarcinoma.

57 The IMMUNOBIL PRODIGE 57 study was designed to assess the efficacy and safety of
58 the combination of durvalumab plus tremelimumab with or without weekly paclitaxel in
59 patients with advanced BTC after failure of platinum-based chemotherapy. A safety run-in
60 was planned to detect early and acute toxicity given that there are no safety data available
61 on the combination of taxane and ICI in BTCs. Here, we present the safety run-in results of
62 phase II IMMUNOBIL PRODIGE 57 trial.

63

64 **Patients and methods**

65 **Study design**

66 The IMMUNOBIL PRODIGE-57 (NCT03704480) is a two-arm, two-stage, open-label,
67 randomized, multicenter, and non-comparative phase II study with a safety run-in phase.
68 Patients with advanced unresectable BTC after failure of platinum-based first-line
69 chemotherapy were randomized in a 1:1 ratio to two experimental arms, Arm A
70 (durvalumab and tremelimumab) and Arm B (durvalumab and tremelimumab plus
71 paclitaxel).

72

73 **Study objectives and endpoints**

74 The trial was designed to assess progression-free survival (PFS) per iRECIST [21] of
75 durvalumab plus tremelimumab (Arm A) and durvalumab, tremelimumab plus paclitaxel
76 (Arm B) in advanced BTC patients previously treated with platinum-based first-line
77 chemotherapy. The primary endpoint was PFS rate at 4 months by centralized and blinded
78 review of computed tomography (CT)-scan imaging in evaluable patients according to
79 iRECIST criteria.

80 Secondary objectives were safety profile according to CTCAE v4.03, OS, objective
81 response rate (ORR), health-related quality of life (HRQoL), quality-adjusted time without
82 symptoms of disease or toxicity of treatment (Q-TWIST), predictive markers of response
83 (tumor, blood, imaging), and tumor response evaluation according to RECIST v1.1 and
84 iRECIST criteria.

85

86 **Study population**

87 Patients could be included if they had histologically or cytologically proven recurrent or
88 advanced BTC (extrahepatic CCA, intrahepatic CCA, or gallbladder carcinoma) not amenable
89 to surgery, radiation, or combined modality therapy with curative intent (previous resection
90 of primary tumor was allowed), and failed (documented progression or toxicity) a platinum-
91 based (cisplatin or oxaliplatin) therapy (*e.g.* GEMCIS, gemcitabine plus oxaliplatin [GEMOX],
92 or 5-fluorouracil/folonic acid, irinotecan and oxaliplatin [FOLFIRINOX]).

93 All inclusion and exclusion criteria can be found in the study protocol (supplementary
94 data Table S1).

95

96 **Treatment scheme and modalities**

97 Patients in Arm A received durvalumab 1,500 mg by intravenous (IV) infusion on day
98 (D) 1 of each cycle, with tremelimumab 75 mg by IV infusion on D1 for the first 4 cycles (1
99 cycle equals 4 weeks, D1-D28). Patients in Arm B received durvalumab 1,500 mg by IV
100 infusion on D1 of each cycle, with tremelimumab 75 mg by IV infusion on D1 for the first 4
101 cycles, and weekly paclitaxel 80 mg/m² by IV infusion on D1, D8, and D15 (for a maximum of
102 6 cycles; 1 cycle equals 4 weeks, D1-D28). Patients were treated until progression (iRECIST),
103 unacceptable toxicity, death, or withdrawal of consent. Regarding the sequence of drug
104 administration, tremelimumab was administered first (60 minutes), followed by durvalumab
105 (60 minutes), 1 hour (maximum 2 hours) after the end of the tremelimumab infusion (Figure
106 1). In Arm B on D1, tremelimumab and durvalumab were administered as in Arm A and were
107 followed by (i) paclitaxel premedication, which consisted of methylprednisolone 80 mg to
108 120 mg IV, diphenhydramine 50 mg IV, and either cimetidine 300 mg IV or ranitidine 50 mg
109 IV, administered 30 minutes after the end of the durvalumab infusion, and (ii) paclitaxel (60

110 minutes) starting 1 hour (maximum 2 hours) after the end of the durvalumab infusion
111 (Figure 1).

112

113 **Treatment evaluation**

114 Treatment visits were performed on D1 of each treatment cycle with a physical
115 examination, laboratory assessments, adverse events (AEs) collection, and concomitant
116 treatments description. In addition, weekly phone calls were performed to assess patients
117 symptoms. Treatment efficacy was evaluated by tumor markers change and CT scan every 8
118 weeks.

119

120 **Safety run-in analysis**

121 Given that the safety profile of the durvalumab and tremelimumab combination with
122 paclitaxel have not been evaluated in advanced BTC patients so far, a safety run-in phase
123 was requested by French regulatory authorities (Agence nationale de sécurité du
124 médicament [ANSM]). Accrual was suspended after the inclusion of 10 patients in both arms
125 and safety data were collected to be evaluated by the Data Safety Monitoring Board (DSMB)
126 after 2 months of follow-up. In addition, safety was monitored after 1 month for every
127 patient to early detect unexpected non-tolerable toxicities. The occurrence of a so-called
128 dose-limiting toxicity (DLT) led to study treatment withdrawal. Predefined DLT criteria are
129 summarized in Table S2.

130 Grading was made according to the Common Terminology Criteria for Adverse Events
131 version 4.03 (CTCAE 4.03). At any time of the study, if excessive numbers ($\geq 20\%$) of DLTs
132 were to be seen according to Pocock-type boundary (Table S3) [22], the accrual was to be
133 halted and the DSMB to be convened to decide on the study continuation.

134

135 **Ethical considerations**

136 A written informed consent was obtained from all patients. The protocol was
137 submitted for formal approval to the French the Health Authorities (i.e. the ANSM) and an
138 independent Ethics Committee.

139

140 **Statistical analysis**

141 Sample size calculation for phase II considered the following hypothesis : H0 (null)
142 with a PFS rate at 4 months of 27% (uninteresting to pursue any further investigation), H1
143 (alternative) with a PFS rate at 4 months of 50%. According to Fleming two-stage design with
144 a one-sided 2.5% type I error and power of 90%, 46 patients in both experimental arms
145 needed to be randomized in order to test the hypotheses. Considering that the two arms are
146 experimental, the overall one-sided type I error of 5% was applied.

147 The final sample size in the safety run-in of the study was 20 patients (10 patients per
148 arm). In parallel, a semi-continuous monitoring for toxicity using Pocock-type boundary
149 (Table S3) was performed. Briefly, in each arm, the accrual had to be halted and the DSMB to
150 be convened if the number of DLTs was equal to or exceeded a boundary out of n patients
151 with completed follow-up (probability of early stopping: 0.05, targeted DLT rate: 0.20). This

152 boundary was equivalent to testing the null hypothesis with the event rate of 0.2 and a one-
153 sided level of 0.012327 [22].

154 All variables were expressed as median and range or number and percentages.

155 **Results**

156 **Patient characteristics**

157 Twenty patients, 10 in Arm A and 10 in Arm B, were enrolled in the safety run-in part
158 of the study between 22 November 2018 and 3 March 2019. The median age was 67 (range
159 63-76) and eight patients (40%) were female. Eight patients (40%) had Eastern Cooperative
160 Oncology Group (ECOG) performance status (ECOG PS) 0 and most of them (70%) had
161 intrahepatic CCA. Regarding prior chemotherapy regimen, 13 patients (65%) received
162 GEMCIS, five (25%) GEMOX, and two (10%) FOLFIRINOX. Patient characteristics and baseline
163 demographics are summarized in Table 1.

164

165 **Adverse events in overall population**

166 Adverse events are summarized in Table 2. Overall, 10 out of 20 patients (50%)
167 experienced grade 3 or 4 toxicities (including DLTs); four in Arm A and six in Arm B. In the
168 Arm B, most of AEs were immune-related AEs (irAE): colitis (30%, one grade 2, and two
169 grade 3-4), diarrhea (10%, grade 2), anaphylaxis (30%, two grade 3 and one grade 4). Three
170 patients (30%) exhibited grade 2 skin rash. None of the patients from Arm A presented 3-4
171 irAE.

172

173 **Characteristics of patients experiencing DLTs**

174 Overall, 25% of patients exhibited DLTs (5 out of 20); all were treated in Arm B (50%
175 of patients enrolled in Arm B). One patient experienced two DLTs. Clinical and biological
176 characteristics of these patients are presented in Table 3. Overall, these were similar except
177 that patients with DLTs were older (median age 73 versus 53 years).

178 Five patients presented six different DLTs and one exhibited two successive DLTs
179 (grade 4 infectious pneumopathy with septic shock) despite treatment interruption. Among
180 irAE, there were three anaphylactic reactions including one cardiac arrest, and two
181 enterocolitis (grade 3). Regarding anaphylactic reactions, they occurred at cycle 2 (n=2) and
182 4 (n=1) and always after at least one ICI, less than 4 hours after injection in every cases.
183 Overall, five DLTs out of six led to an admission of patients to an intensive care unit. No
184 medical history of allergy or auto-immune disease were found and no paclitaxel dose
185 reduction was needed for these patients. The characteristics of these patients are
186 summarized in Table 4.

187

188 **Outcomes and response rates of Arm B**

189 Overall, five patients discontinued treatment for toxicity (DLTs) in Arm B. After a
190 median follow-up of 9.8 months, two out of 10 patients in Arm B were still alive and one
191 patient in Arm B remained on experimental treatment. Five patients (50%) experienced
192 stable disease as best RECIST response, three (30%) had progressive disease, one complete
193 remission, and one was not evaluable.

194 **Discussion**

195 Here, we report the safety run-in results from the IMMUNOBIL PRODIGE 57 trial, with
196 six DLTs in the triplet B arm; three anaphylactic reactions, two grade 3 enterocolitis, and one
197 grade 4 infectious pneumopathy.

198 While enterocolitis have been previously described with ICIs, our results showed an
199 unexpected high rate of anaphylactic reactions and several admissions of patients to an
200 intensive care unit, raising safety concerns regarding co-administration of paclitaxel with
201 durvalumab and tremelimumab in BTCs. These findings led to the discontinuation of Arm B
202 with paclitaxel, as decided by the sponsor and DSMB.

203 Several clinical trials using combination of taxanes with ICIs have been published. The
204 KEYNOTE-407 [19] phase III trial randomized 559 patients with untreated stage IV squamous
205 NSCLC to carboplatin and paclitaxel/nab-paclitaxel plus pembrolizumab (anti-PD1 mAb) or
206 the same chemotherapy combination plus placebo. Safety concerns were identified. Grade
207 3/4 AEs occurred in 69.8% of patients in the pembrolizumab-combination group vs. 68.2%
208 patients in the placebo-combination group. IrAEs were observed in 28.8% of patients in the
209 pembrolizumab-combination group (2.5% colitis and 6.5% pneumonitis) and in 8.6% of
210 patients in the placebo-combination group; only eight patients (2.6%) experienced infusion
211 reactions. Similarly, no safety signal regarding anaphylactic reactions was detected in the
212 IMpower131 phase III trial of carboplatin and nab-paclitaxel +/- atezolizumab as first-line
213 therapy in stage IV squamous NSCLC [23]. The combination of atezolizumab with taxane-
214 based chemotherapy also seemed safe in the IMpower150 phase III study [24], where NSCLC
215 patients were randomized to receive atezolizumab plus carboplatin and paclitaxel,
216 atezolizumab plus bevacizumab plus carboplatin and paclitaxel, or bevacizumab plus
217 carboplatin plus paclitaxel. Only 0.3% of infusion-related reactions were observed. The

218 nivolumab and ipilimumab plus paclitaxel combination in NSCLC patients is currently being
219 evaluated in TOP 1705 trial (NCT03573947). The recruitment in the study started in October
220 2018 and no safety issue has been raised so far.

221 Different mechanisms can be involved in the immune-related toxicity, but they
222 mostly remain unclear. No clinical or biological variables were identified to be related to the
223 occurrence of these DLTs, except for the age factor. Moreover, it should be noted that four
224 out of five patients who exhibited DLTs had intrahepatic cholangiocarcinoma. Although the
225 sample size is too limited, one could hypothesize that patients with extrahepatic CCA
226 tolerates triplet therapy better than intrahepatic CCA even if there is currently no biological
227 rationale to explain this difference. Our patients exhibited mostly hypersensitivity type
228 1/anaphylactic reactions and colitis and there might be a synergy between paclitaxel and ICI
229 that enhanced ICI-related toxicity, especially anaphylaxis. Paclitaxel is known to enhance
230 both Th1 and Th2 responses [25] and is allergenic, which itself requires premedication. It
231 might overstimulate immunity in combination with ICIs. Nevertheless, few hypotheses can
232 be raised. First, there was no signal of toxicity for the association of paclitaxel with anti PD-1
233 or anti-PDL1 in large studies [23] and the toxicity we observed could be more specific of the
234 combination with an anti-CTLA4. Secondly, the combination of durvalumab and
235 tremelimumab with a taxane has been previously tested [20], but in the contrary to our
236 study it was nab-paclitaxel, which might explain the different safety profile we observed
237 here. Indeed, nab-paclitaxel is an albumin-bound form of paclitaxel with a different toxicity
238 profile from solvent-based paclitaxel and with a lower rate of hypersensitivity reactions [26].
239 Thirdly, the sequence of administration might be also important. ICIs were administered
240 before paclitaxel in our study while it could be infused, together with its premedications,
241 before ICIs. Fourthly, this combination was never tested in BTC and one cannot exclude that

242 this tumor type might have favoured these toxicities [27]. Fifthly, patients in Arm B tended
243 do be older (even if not statistically significant). Since age has been associated with the
244 immune balance disfunction and therefore with dysimmunity [28], this might partly account
245 for the irAEs observed in Arm B. Evaluation of the durvalumab, tremelimumab, and
246 paclitaxel combination may be of interest and safer in younger patients with BTC. Finally,
247 very small sample size might have led to an overestimation of the incidence if DLTs.

248

249 **Conclusion**

250 The safety run-in results of the IMMUNOBIL PRODIGE 57 raise concerns regarding the
251 co-administration of paclitaxel with anti-PDL1 and anti-CTLA4, which appears much more
252 toxic than the combination of taxane without anti-CTLA4, with an unexpectedly high
253 anaphylaxis rate. The study will continue only with arm A. Data on the primary and
254 secondary endpoints will be fully presented in the final analysis.

255 More data is needed to better characterize toxicity of paclitaxel combined with anti-
256 PDL1 and anti-CTLA4. Overall, these results should encourage clinicians to direct efforts
257 towards phase I trials exploring cautiously the combination of anti-PD1/PDL1, anti-CTLA4,
258 and paclitaxel. Nab-palcitaxel or another less allergenic chemotherapy agent with known
259 toxicity profile when combined with ICIs should be considered, which might exclude high-risk
260 patients (e.g. older adults).

261 **Declarations**

262 **Conflict of interests**

263 Benoît Rousseau served in a consulting/advisory role for Bayer, Roche, Novartis, Gilead,
264 Servier and has received travel, accommodations, and expenses from Bayer, Servier,
265 Astellas.

266 Romain Cohen received honoraria from Servier, Amgen and Sanofi.

267 Jean-Frédéric Blanc is a member of the advisory board for Bayer, IPSEN, ESAI.

268 Meher Ben Abdelghani has COI with Amgen, Sanofi, Bayer, Roche, Servier

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272 Jean-Philippe Metges has COI with Amgen, Merck.

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277 Dewy Vernerey served in a consulting/advisory role for GERCOR HalioDX Cellprothera Incyte
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279 Anthony Turpin has served in a consulting/advisory role and or received honoraria for
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281 Astra-Zeneca, Pfizer, Sanofi.

282 Cindy Neuzillet has served in a consulting/advisory role and or received honoraria for
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286 Other authors declare no conflict of interests.

287

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392

393 **Table legends**

394 **Table 1**

395 Characteristics of patients.

396 **Table 2**

397 Adverse events in the whole population.

398 **Table 3**

399 Characteristics of patients in Arm B (Triplet arm), DLT vs. no DLT, at baseline.

400 **Table 4**

401 Description of dose limiting toxicities.

402

403

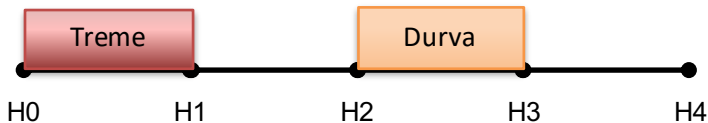
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405 **Figures legends**

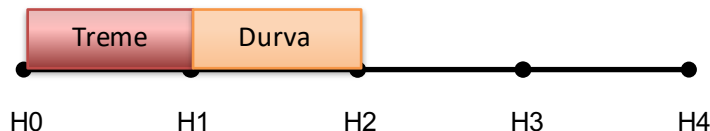
406 **Figure 1**

407 Durvalumab plus tremelimumab combination therapy with or without paclitaxel
408 administration schedule.

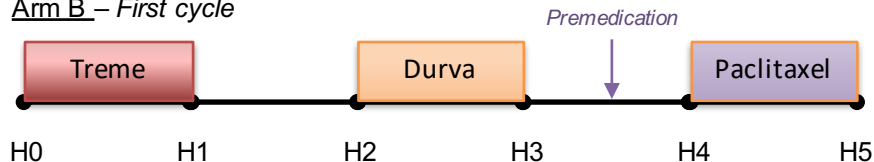
Arm A – First cycle



Following cycles if there are no clinically significant concerns after the first cycle



Arm B – First cycle



Following cycles if there are no clinically significant concerns after the first cycle

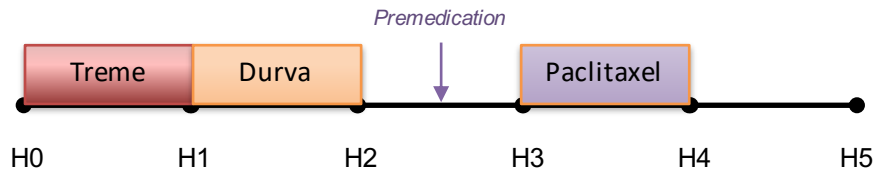


Table 1. Characteristics of patients (n=20)

| Variables | All patients (n=20) | Arm A (no paclitaxel) (n=10) | Arm B (paclitaxel) (n=10) |
|--------------------------------------|--------------------------------|---|--------------------------------------|
| Clinical characteristics | | | |
| Age (years) | 67 [63-73] | 67 [60-75] | 70 [61-75] |
| Female (n,%) | 8 40% | 5 50% | 3 30% |
| Height (cm) | 169 [164-177] | 169 [162-178] | 169 [166-175] |
| Weight (kg) | 70 [61-86] | 69 [60-82] | 71 [63-88] |
| Body mass index (kg/m ²) | 24 [22-28] | 23 [22-28] | 25 [21-30] |
| Performans status | | | |
| PS= 0 (n,%) | 8 40% | 5 50% | 3 30% |
| PS= 1 (n,%) | 12 60% | 5 50% | 7 70% |
| Tumor characteristics | | | |
| Primary tumor site | | | |
| Intrahepatic CCA (n,%) | 14 70% | 7 70% | 7 70% |
| Extrahepatic CCA (n,%) | 5 25% | 2 20% | 3 30% |
| Gallbladder carcinoma (n,%) | 1 5% | 1 10% | 0 0% |
| Tumor stage at diagnosis | | | |
| Localized (n,%) | 4 20% | 2 20% | 2 20% |
| Locally advanced (n,%) | 4 20% | 1 10% | 3 30% |
| Metastatic (n,%) | 12 60% | 7 70% | 5 50% |
| Prior treatments | | | |
| Radioembolisation (n,%) | 0 0% | 0 0% | 0 0% |
| External radiotherapy (n,%) | 6 30% | 3 30% | 3 30% |
| Prior chemotherapy | | | |
| GEMCIS (n,%) | 13 65% | 7 70% | 6 60% |
| GEMOX (n,%) | 5 25% | 2 20% | 3 30% |
| Other (n,%) | 2 10% | 1 10% | 1 10% |
| Surgery (n,%) | 9 45% | 4 40% | 5 50% |

Data are summarized as median [interquartile range] or number (percentages). *p<0.05 Paclitaxel vs. no-Paclitaxel patients.

CCA : cholangiocarcinoma

GEMCIS : Gemcitabine-Cisplatine

GEMOX : Gemcitabine-Oxaliplatine

PS : Performans status

Table 2. Adverse events in the whole population (n=20)

| | Arm A Grade 1/2 (n=10) | Arm A Grade 3/4 (n=10) | Arm B Grade 1/2 (n=10) | Arm B Grade 3/4 (n=10) |
|--|---|---|---|---|
| Patients exhibiting at least one toxicity | 4 40% | 4 40% | 5 50% | 6 60% |
| Skin rash | 0 0% | 0 0% | 3 30% | 0 0% |
| Lung infection | 0 0% | 0 0% | 0 0% | 1 10% |
| Colitis | 1 10% | 0 0% | 1 10% | 2 20% |
| Diarrhea | 0 0% | 0 0% | 1 10% | 0 0% |
| Pneumonitis | 0 0% | 0 0% | 0 0% | 1 10% |
| Fever | 2 20% | 0 0% | 0 0% | 0 0% |
| Infusion-related reaction, anaphylaxy | 0 0% | 0 0% | 0 0% | 3 30% |
| Abdominal pain | 1 10% | 0 0% | 0 0% | 1 10% |
| General physical health deterioration | 0 0% | 2 20% | 0 0% | 0 0% |
| Subocclusive syndrome | 0 0% | 1 10% | 0 0% | 0 0% |
| Biliary tract occlusion | 0 0% | 0 0% | 0 0% | 1 10% |
| Breaking of oesophagian varices* | 0 0% | 0 0% | 0 0% | 1 10% |
| Brain tumour operation [†] | 0 0% | 0 0% | 0 0% | 1 10% |
| Spinal cord compression | 0 0% | 0 0% | 0 0% | 1 10% |
| Thromboembolic event | 0 0% | 1 10% | 0 0% | 0 0% |
| Hematoma | 0 0% | 0 0% | 1 10% | 0 0% |

Data are summarized as number (percentages).

*in a context of portal hypertension

[†]metachronous metastase

Table 3. Characteristics of patients in Arm B (Triplet arm), DLT vs. no DLT, at baseline

| Variables | DLT patients (n=5) | No DLT patients (n=5) |
|--|-------------------------------|----------------------------------|
| Clinical characteristics | | |
| Age (years) | 73 [67-79] | 53 [28-77] |
| Female (n,%) | 1 20% | 2 40% |
| Performans status (PS) | | |
| PS= 0 (n,%) | 4 80% | 1 20% |
| PS= 1 (n,%) | 1 20% | 4 80% |
| Prior treatments | | |
| Prior chemotherapy | | |
| GEMCIS (n,%) | 3 60% | 3 60% |
| GEMOX (n,%) | 2 40% | 1 20% |
| Other (n,%) | 0 0% | 1 20% |
| Surgery (n,%) | 3 60% | 2 40% |
| Biological variables | | |
| Neutrophils (/mm ³) | 5727 [2253-11956] | 5222 [3199-7860] |
| Lymphocytes (/mm ³) | 1548 [899-2394] | 1135 [800-1740] |
| C-Reactive Protein (mg/L) | 46 [3-139] | 12 [1-27] |
| Lactate deshydrogenase (UI/L) | 216 [147-308] | 212 [171-266] |
| Albumine (g/L) | 38 [29-45] | 36 [32-39] |
| Creatininemia (umol/L) | 94 [82-110] | 104 [56-157] |
| Tobacco status | | |
| Non-smoker | 0 0% | 1 20% |
| Former smoker (stopped >1year) | 5 100% | 4 80% |
| Active smoker | 0 0% | 0 0% |
| DLT : dose limiting toxicity PS : performans status | | |

Table 4: Description of dose limiting toxicities (triplet arm)

| Patient number | Sex | Age | Tumor site | Initial stage | Previous CT | PS | Medical history | Cycle | MedDRA | Grade | Causality | Outcome | Event description | Patient status |
|----------------|-----|-----|------------|---------------|-------------|----|--|-------|-------------------------------|-------|--|---------|--|--|
| FRA008-002 | F | 74 | iCCA | Localized | GEMOX | 1 | Atrial fibrillation | 4 | Colitis | 3 | Durva/treme interacting CMV suspecting | 1 | Diarrhea under colitis, coproculture cytomegalovirus-positive, treated with antibiotics (ceftriaxone and metronidazole) for 5 days and ganciclovir. | Died (11 months after inclusion) from PD |
| FRA106-001 | M | 64 | iCCA | Advanced | GEMCIS | 0 | Hypercholesterolemia Prostate adenoma | 2 | Immune-mediated enterocolitis | 3 | Durva/treme suspected | 2 | Colitis post-immunotherapy confirmed by rectosigmoidoscopy with grade III enterocolitis. Concomitant grade 2 hypokalemia and acute renal insufficiency. No infectious cause was found. | Complete remission |
| FRA025-003 | M | 76 | iCCA | Metastatic | GEMCIS | 1 | Pulmonary infection | 4 | Cardiac arrest | 4 | Durva/treme suspected Polaramine suspected Paclitaxel concomittant | 1 | Cardiac arrest during paclitaxel premedication's administration and after ICIs infusion (treated with cardiac massage - 4mg of adrenalin). Recovered from cardiac arrest after 9 min of low-flow. No argument for a cardiac-related etiology and the diagnosis retained was anaphylaxis. | Died (7 months after inclusion) from PD |
| FRA094-001 | M | 80 | iCCA | Metastatic | GEMCIS | 1 | Arterial hypertension | 2 | Infusion related reaction | 3 | Treme suspected Durva concomitant Paclitaxel concomittant | 1 | Laryngeal and lingual edema with bronchospasm (and desaturation) and maculo-papular exanthema at the end of tremelimumab infusion, without arterial hypotension. | Dead (9 months after inclusion) from PD |
| FRA008-004 | M | 74 | eCCA | Advanced | GEMOX | 0 | None | 2 | Anaphylactic reaction | 3 | Durva suspected Treme interacting Paclitaxel concomittant | 1 | Anaphylaxy with hypotension and bronchospasm during durvalumab infusion, for a total duration of 20min, resolved after medication (antihistaminic, corticosteroid and physiological serum) | Dead (13 months after inclusion) from PD |
| | | | | | | | | 2 | Lung infection | 4 | Paclitaxel suspected Durva/treme concomittant | 1 | 15 days after first DLT, bilateral interstitial pneumopathy complicated with a septic shock treated in ICU by large spectrum antibiotherapy (tazocillin and amikacin), catecholamines and mechanical ventilation without microbiological documentation. | |

CT : chemotherapy, PS : Performans Status, BMI : Body mass indec (kg/m²), Grade : according to CTCAE V5.0, Outcome : 1 Resolved, 2 : Resolved with sequelae, F : Female, M : Male, iCCA : intrahepatic cholangiocarcinoma, eCCA: extrahepatic cholangiocarcinoma, CMV : cytomegalovirus; Durva : durvalumab; Treme : tremelimumab; ICU : intensive care unit; PD: progressive disease; DLT : dose-limiting toxicity
