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**Is chemotherapy rechallenge feasible in advanced-stage
non-small-cell lung cancer?**

**La ré-introduction de chimiothérapie est-elle faisable au
cours du traitement du cancer pulmonaire non à petites
cellules de stade avancé?**

Short title: Chemotherapy rechallenge in advanced NSCLC

Titre court: La ré-introduction de chimiothérapie dans le CBNPC de stade avancé

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27 **Abstract**

28 **Background:**

29 Despite recent progress, non-small cell lung cancer (NSCLC) first-line treatment remains a
30 platinum-based doublet in most cases. No guidelines exist beyond third line. Chemotherapy
31 rechallenge is an option, but little data is available in NSCLC. Our study aims to describe patients
32 who underwent chemotherapy rechallenge while assessing its efficacy and safety.

33 **Methods:**

34 Consecutive patients with advanced-stage NSCLC receiving first-line treatment in Tenon hospital
35 in 2011 were included, with a 5-year follow-up. Patients were analyzed according to chemotherapy
36 rechallenge or not. Chemotherapy rechallenge was defined as re-initiation of a previously
37 administered chemotherapy agent at any point in the treatment sequence, with at least one treatment
38 regimen between first use and rechallenge.

39 **Results:**

40 Of 149 patients, 18 underwent chemotherapy rechallenge (12%). They were younger (56 vs. 61
41 years, $p=0.04$), mostly women (61% vs. 30%, $p=0.02$), with lepidic adenocarcinoma (23% vs. 3.5%,
42 $p=0.03$), a better general state of health (100% performance status 0–1 vs. 74%, $p=0.04$), and fewer
43 cardiovascular comorbidities (16% vs. 42%, $p=0.04$). They were more likely to have received a
44 receptor tyrosine kinase inhibitor treatment (89% vs. 43%, $p=0.0003$). Progression-free survival was
45 longer at first use than at rechallenge (median 9.2 vs. 2.7 months, $p=0.002$). No increased toxicity
46 was observed at rechallenge compared to first use. Finally, a subsequent line of treatment was given
47 after rechallenge in 61% of the patients.

48 **Conclusion:**

49 Patients eligible for chemotherapy rechallenge were those with good prognostic factors.
50 Chemotherapy rechallenge may provide a well-tolerated additional line of treatment, with decreased
51 efficacy compared to its first application.

52

53

54 **Keywords**

55 NSCLC, chemotherapy, rechallenge

56

57 **Résumé**

58 **Introduction:**

59 Malgré des progrès récents, le traitement de première ligne des cancers broncho-pulmonaires non à
60 petites cellules (CBNPC) reste majoritairement un doublet à base de platine. Il n'existe pas de
61 recommandations après la troisième ligne. La ré-introduction de chimiothérapie est une option, mais
62 peu de données sont disponibles. Notre étude vise à décrire les patients ayant eu une ré-introduction
63 de chimiothérapie, ainsi que sa faisabilité et sa tolérance.

64 **Méthodes:**

65 Les patients consécutifs avec un CBNPC de stade avancé ayant reçu un traitement de première ligne
66 à l'hôpital Tenon en 2011 ont été inclus. Ceux ayant eu une ré-introduction de chimiothérapie ont
67 été comparés aux autres. Celle-ci était définie par la ré-utilisation d'un agent de chimiothérapie
68 utilisé antérieurement, avec au moins une ligne entre la primo-utilisation et la ré-utilisation.

69 **Résultats:**

70 Parmi 149 patients, 18 ont eu une ré-introduction de chimiothérapie (12%). Il étaient plus jeunes
71 (56 ans *vs.* 61, $p=0.04$), de sexe féminin (61% *vs.* 30%, $p=0.02$), avec un adénocarcinome lépidique
72 (23% *vs.* 3.5%, $p=0.03$), un meilleur état général (PS 0–1: 100% *vs.* 74%, $p=0.04$) et moins de
73 comorbidités cardiovasculaires (16% *vs.* 42%, $p=0.04$). La survie sans progression était plus longue
74 à la primo-utilisation qu'à la ré-introduction (médiane 9.2 mois *vs.* 2.7, $p=0.002$). Il n'y avait pas de
75 surcroît de toxicité à la ré-introduction. Enfin, une ligne supplémentaire était possible après ré-
76 introduction chez 61% des patients.

77 **Conclusion:**

78 La ré-introduction de chimiothérapie fournit une ligne supplémentaire de traitement bien tolérée,
79 avec une efficacité moindre par rapport à la primo-utilisation.

80

81

82 **Mots-clés**

83 CBNPC, chimiothérapie, ré-introduction

84

85

86 Introduction

87 Despite recent progress, mortality from non-small-cell lung cancer (NSCLC) remains high.
88 During the last decade, therapeutic advances have included targeted therapies, mainly small-
89 molecule tyrosine kinase receptor inhibitors (TKIs) [1]. However, these advances involve non-
90 squamous NSCLC only, and targetable anomalies are harbored by a minority of NSCLC patients,
91 for instance by 10 to 15% for *EGFR* [2], by around 5% for *ALK* [3], and by less than 2% for *ROS1*.
92 More recently, immunotherapy in the form of checkpoint inhibitors, such as anti-PD-1
93 (Programmed Death 1) and anti-PD-L1 (Programmed Death Ligand 1) antibodies, have resulted in
94 improved overall survival in second-line [4,5] for all comers and in first-line therapy, but only in
95 patients with strong PD-L1 expression (>50%) [6].

96 In patients who are ineligible for TKIs or immunotherapy, which remains the majority of
97 patients, standard first-line treatment consists of a platinum-based chemotherapy doublet combined
98 with pemetrexed, paclitaxel, gemcitabine, or vinorelbine [7]. This standard is also recommended for
99 progressive patients after first-line immunotherapy (more than 40% at six months of treatment). The
100 use of either cisplatin or carboplatin depends on age, performance status, and comorbidities like
101 chronic kidney or heart failure [8]. The benefit of a second-line treatment has been proven for
102 pemetrexed [9], docetaxel [10], erlotinib [11], and immunotherapy [4]. Third-line treatment proves
103 also effective for eligible patients [12,13], without any guidelines for treatment beyond this point.

104 Rechallenge with a conventional cytotoxic chemotherapy may be attempted if the disease
105 has initially responded. Chemotherapy rechallenge is recommended in other cancer treatments.
106 Pemetrexed rechallenge is indicated in malignant pleural mesothelioma when initial progression-
107 free survival exceeds 12 months [14]. In disseminated relapsing small-cell lung cancer, rechallenge
108 with a platinum doublet plus etoposide is considered an option in platinum-sensitive disease [15]. In
109 the same manner, carboplatin rechallenge is common practice in platinum-sensitive relapsing
110 ovarian cancer [16]. In metastatic castration-resistant prostate cancer, taxanes like docetaxel or
111 cabazitaxel can likewise be reintroduced [17]. Following its introduction, immunotherapy became
112 an additional treatment option; prior to its advent, chemotherapy rechallenge was practiced
113 whenever other alternatives proved scarce. Chemotherapy rechallenge may still be worth
114 considering, especially after progression on immunotherapy. Rechallenge with the various
115 immunotherapy agents is presently being discussed. Little data currently exists on chemotherapy
116 rechallenge in NSCLC. This work sought to better describe the characteristics of patients who

117 underwent chemotherapy rechallenge in a retrospective study, while assessing the efficacy and
118 safety of this practice.

119

120 Patients and Methods

121 Inclusion criteria

122 All consecutive adult patients with advanced-stage NSCLC receiving first-line treatment from
123 January 1, 2011, to December 30, 2011, in a French university hospital were included. Advanced-
124 stage NSCLC was defined as Stage IIIB (ineligible for curative therapy) and Stage IV NSCLC
125 according to the 7th edition of the International Association for the Study of Lung Cancer (IASLC)
126 classification. First-line treatment consisted of either chemotherapy or TKI for patients with
127 oncogenic addiction. Patients with metastatic relapse after previous curative surgery could be
128 included. Neo-adjuvant or adjuvant chemotherapy as well as radiotherapy were accepted and were
129 not considered as a first-line treatment. Patients list was generated from the chemotherapy
130 prescription software.

131

132 Data collection

133 The following data were collected: age at diagnosis; gender; smoking history, namely number of
134 pack-years, years of smoking, and current smoking status defined as never-smoker (<100 cigarettes
135 in life), former smoker (>100 cigarettes in life but stopped >1 year) or current smoker (>100
136 cigarettes in life and either still smoking or stopped <1 year); performance status at diagnosis
137 according to the ECOG scale; disease stage according to the 7th edition of the IASLC clinical TNM
138 classification; occurrence of central nervous system (CNS) or sub-diaphragmatic metastases.
139 Comorbidities like cardiovascular diseases (high blood pressure, stroke, myocardial ischemia, or
140 arteriosclerosis obliterans), diabetes, neoplasms of other organs, chronic respiratory failure (CRF)
141 or chronic obstructive pulmonary disease (COPD), chronic renal failure, HIV infection, psychiatric
142 disorder, or alcoholism were recorded. Histological types were defined according to the 2004 WHO
143 classification [18] as adenocarcinoma, squamous-cell carcinoma, large cell carcinoma, and
144 sarcomatoid carcinoma. Adenocarcinoma subtypes were defined as acinar, mucinous, lepidic,
145 papillary or undifferentiated. Oncogenic addiction was defined as *EGFR* mutation or *ALK* or *ROS1*
146 rearrangement. *ALK* or *ROS1* rearrangements were detected by immunohistochemistry and
147 confirmed by fluorescence *in situ* hybridization. *EGFR*, *KRAS*, *BRAF*, *HER2*, and *PI3KCA*
148 mutations were screened by previously described techniques [19]. The number of treatment lines
149 received by each patient, including targeted therapies, and for each line of treatment were recorded,

150 as well as its duration, how many cycles were administered (including maintenance if relevant), and
151 whether the dose was reduced. Patients were treated in accordance with routine clinical care.

152 Chemotherapy rechallenge was defined as the re-use of a drug that had been administered earlier in
153 the course of treatment and stopped due to disease progression or toxicity. At least one line of
154 treatment had to have been received between first use and re-use. Resuming treatment after a break
155 was not considered rechallenge, even if treatment was halted for a long period. The same agent had
156 to be used, except for platinum-derived products like cisplatin or carboplatin. Re-using an agent as
157 monotherapy when it was first used in a platinum-based doublet was considered as a rechallenge
158 (Fig. 1). Rechallenge with targeted therapy was not taken into account for this study.

159

160 The following data were collected for each chemotherapy rechallenge: treatment duration,
161 performance status at rechallenge, number of previous lines, use as maintenance or not,
162 progression-free survival at first-use and at rechallenge, line of treatment after rechallenge, and
163 toxicity (hematological, gastrointestinal, or other) graded according to the WHO classification.
164 Rechallenged patients were divided into five groups: platinum-based doublet or triplet
165 (cisplatin/carboplatin + other agent \pm bevacizumab), or pemetrexed, gemcitabine, paclitaxel and
166 vinorelbine monotherapy.

167

168 **Statistical analyses**

169 Patients were analyzed according to whether they received chemotherapy rechallenge or not.
170 Continuous variables were expressed as median and associated range [min–max]. Categorical
171 variables were expressed as percentages. Comparisons between non-parametric continuous
172 variables were conducted using the Mann-Whitney test. Comparisons between categorical variables
173 were conducted by means of the Chi-squared test or Fisher's exact test when the number of
174 observations was less than 5. Progression-free survival rates at first use and at rechallenge were
175 compared with the Wilcoxon test. Toxicity at first use and at rechallenge were compared using
176 McNemar's Chi-squared test. Results were considered statistically significant when $p < 0.05$.
177 Analyses were performed with SPSS 20.0 (IBM France) software. Data were reviewed by a
178 statistician.

179

180 **Ethics and regulations**

181 The local database was declared, and it obtained authorization from the bodies that monitor the
182 application of data privacy laws according to French guidelines.

183

184 Results

185 Patients characteristics

186 In 2011, 149 patients underwent first-line treatment for advanced-stage NSCLC, in our French
187 university hospital. Median age was 60 years [36–87]. Overall, 66% of the patients were men,
188 47.5% were smokers, 39% were former smokers, and 8.5% were never-smokers. Histology showed
189 66.5% had adenocarcinoma, 21% squamous-cell carcinoma, 10.5% large cell carcinoma, and 2%
190 sarcomatoid carcinoma. Among non-squamous NSCLCs, 6.5% were *EGFR* mutated, 16% *KRAS*
191 mutated, 0.5% *BRAF* mutated, and 5% harbored *ALK* rearrangement. No *ROS1* rearrangement was
192 observed. The mutation status of 11 patients (7.5%) was unknown. Regarding comorbidities, 39%
193 of the patients had at least one cardiovascular comorbidity, 11.5% had diabetes, 14.5% had a
194 current neoplasm or had had a prior neoplasm in another organ, and 11.5% had either CRF or
195 COPD. Most patients were in good general condition (77% had a performance status of 0–1) at
196 first-line treatment. Patients received a mean of 2.8, or a median of 2.0 [1–11], treatment lines, and
197 almost half of them received TKI (regardless of mutation status) in accordance with current
198 guidelines.

200 Characteristics of chemotherapy rechallenge

201 Altogether, 18 of 149 patients (12%) underwent chemotherapy rechallenge: 13 had a single
202 rechallenge and five two rechallenges with different agents. Hence, 23 distinct rechallenges were
203 noted across our five groups, namely eight rechallenges with a platinum-based doublet (carboplatin,
204 $n=5$; cisplatin, $n=3$), seven with pemetrexed, four with gemcitabine, three with paclitaxel and one
205 with vinorelbine. No rechallenge with docetaxel was observed.

206 The median number of cycles was 4 [1–16] at both first use and rechallenge. For platinum-based
207 doublets, the median cycle number at rechallenge was 4 [2–5] *versus* 4 [4–5] at first use. The
208 median cycle number was lower at rechallenge than at first use for pemetrexed (3 [2–8] *vs.* 7 [1–
209 16]) and for gemcitabine (2 [1–16] *vs.* 5.5 [4–8]). At rechallenge, patients were mostly at their
210 fourth line of treatment (4 [3–6]) and mostly (78%) with a favorable PS (0-1). A subsequent line of
211 treatment was feasible in 61% of patients. Pemetrexed and gemcitabine were initially used as
212 maintenance therapy in respectively 43 and 50% of the patients (Table 1).

213

214 **Characteristics of patients according to chemotherapy rechallenge**

215 In univariate analyses, rechallenged patients were younger (median age 56 *vs.* 61 years, $p = 0.04$),
216 were more often women (61% *vs.* 30.5%, $p = 0.021$), had fewer cardiovascular comorbidities
217 (16.5% *vs.* 42%, $p = 0.039$), and had a better PS (100% 0–1 performance status at diagnosis *vs.*
218 74%, $p = 0.043$). Rechallenged patients tended to smoke less (median smoking duration of 30.5 *vs.*
219 40 years, $p = 0.086$). They received a higher number of treatment lines (median 5.0 *vs.* 2.0, p
220 <0.0001) and received a targeted therapy (TKI) more often (89% *vs.* 43.5%, $p = 0.0003$), regardless
221 of the presence or absence of oncogenic addiction. A higher proportion of adenocarcinomas was
222 noted in rechallenged patients (72% *vs.* 65% other histology, $p = 0.57$) particularly of the lepidic
223 subtype (23% *vs.* 3.5%, $p = 0.037$). No difference was found according to *EGFR* or *ALK* status.
224 *KRAS*-mutated patients tended to be less rechallenged than others (1/24 rechallenged *vs.* 23/24 not
225 rechallenged, $p = 0.18$) (tables 2 and 3). Regarding overall survival, patients with chemotherapy
226 rechallenge had a longer overall survival (median 32.7 months *vs.* 13.4 months, $p = 0.0002$).

227

228 **Progression-free survival at first use and rechallenge**

229 Progression-free survival was shorter at rechallenge than at first use, namely 2.7 months [0.2–22.5]
230 *versus* 9.2 months [2.7–31.6] ($p = 0.0021$). Progression-free survival by drug is given in Table 4.

231

232 **Toxicity at first use and rechallenge**

233 During the 23 rechallenges, at least one Grade-3 or -4 toxicity was observed in seven cases (30%) at
234 first use and in five cases (24%) at rechallenge ($p = 0.62$). No toxicity gain was found at rechallenge
235 compared to first use, except one case of Grade-4 neutropenia during paclitaxel rechallenge.
236 Toxicity was mostly hematological. There was no Grade-3 or -4 neurological or renal toxicity (data
237 not shown) nor iatrogenic death.

238

239 Discussion

240 Of 149 patients with advanced NSCLC, 18 underwent at least one chemotherapy rechallenge
241 during treatment, with five being rechallenged twice. Hence, we recorded a total of 23 distinct
242 rechallenges. The most commonly used drugs for rechallenge were pemetrexed and platinum-based
243 doublets, which were given in, respectively, 7 and 8 cases. Rechallenge was carried out with
244 gemcitabine in four cases, with paclitaxel in three cases, and with vinorelbine in one case.

245 Those who received chemotherapy rechallenge were characterized as patients exhibiting
246 favorable prognostic factors. Younger age, female gender, better general condition, fewer
247 comorbidities, and lepidic histological subtype have previously been shown to be associated with
248 longer overall survival [20],[21],[22]. Our results are consistent with the study of Girard *et al.*, in
249 which patients who benefited the most from third-line therapy were those with good prognostic
250 factors [13].

251 *KRAS*-mutated patients received chemotherapy rechallenge less than others (1 patient
252 rechallenged vs. 23 non-rechallenged, $p = 0.18$). *KRAS* mutation seems to be associated with worse
253 survival for patients with advanced NSCLC [23], but its involvement in chemotherapy resistance is
254 still debatable [24].

255 Progression-free survival at rechallenge was 2.7 months for all treatments, which was
256 significantly shorter than progression-free survival at first use (9.2 months). For platinum-based
257 doublets, progression-free survival at rechallenge was non-significantly shorter (3.0 months) than at
258 first use (7.4 months), which might be due to lack of statistical power. For pemetrexed, progression-
259 free survival was significantly shorter at rechallenge (2.5 months) than at first use (7.7 months). The
260 longest progression-free survival at rechallenge was obtained with paclitaxel (5.4 months) and the
261 shortest with gemcitabine (1.8 months).

262 Petrelli *et al.* reported a progression-free survival of 3.9 months with platinum/pemetrexed
263 rechallenge in a pooled analysis of 11 studies [25]. In a retrospective study, when pemetrexed
264 rechallenge was given as monotherapy or as combination therapy with a platinum salt, it showed a
265 progression-free survival of 3.8 months in a second-line setting only [26]. Median age was similar
266 and patients were in good general condition (97% had a performance status of 1). In both studies,
267 patients were rechallenged earlier than in ours (second line vs. fourth), which may explain why they
268 observed longer progression-free survival. In another retrospective study, 25 patients had
269 pemetrexed rechallenge [27]. Progression-free survival was shorter (1.5 month). The patients were

270 mostly men (64%) and mostly had a performance status of 2 (60%). The discrepancies between all
271 these studies may be due to their retrospective design and small sample sizes.

272 In our study, Grade-3 or -4 toxicities did not increase at rechallenge except for one patient
273 with paclitaxel (Grade-4 neutropenia). A rise in toxicity could have been expected, since
274 chemotherapy rechallenge is practiced on heavily pre-treated patients. For example, docetaxel
275 rechallenge in metastatic castration-resistant prostate cancer is risky, owing to cumulative
276 neurotoxicity [17]. No cumulative toxicity was found in our study, especially no renal toxicity.

277 A further line of treatment was administered after rechallenge in 61% of our patients.
278 The rechallenge was not, therefore, their last line of treatment, which suggests that their general
279 condition permitted them to receive the additional treatment line. PFS was shorter at rechallenge
280 than at first-use in our study. These results are coherent with other studies describing a decreased
281 disease control between first-line and subsequent lines [28]. This retrospective study does not
282 answer the question of whether rechallenge proves cost-effective or of benefit in terms of quality of
283 life. Our study reflects the realities of routine practice in this patient population. Immune checkpoint
284 inhibitors are considered a new option and may delay the need for chemotherapy rechallenge in the
285 course of the disease. Our study's limitations were its retrospective design, single-center data, small
286 sample size, and heterogeneity of administered treatments (including those administered twice).
287 However, our findings may further improve our understanding of chemotherapy rechallenge.

288

289 **Conclusion**

290 Of 149 patients with advanced NSCLC, 18 (12%) underwent chemotherapy rechallenge. These
291 patients had good prognostic factors. Progression-free survival was shorter at rechallenge than at
292 first use. No toxicity gain was noted at rechallenge. Thus chemotherapy rechallenge should be
293 considered a treatment option in suitable patients.

294

295 **Acknowledgments**

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298 histological data, and Ms. N. Mathiot and Ms. G. Pontdeme for their overall contribution to this
299 work.

300

301 **Figure 1: Illustration of chemotherapy rechallenge in the course of treatment**

302 Figure 1: The x-axis represents treatment course. Re-use of a platinum salt was considered as
303 platinum salt rechallenge, regardless of the drug it was combined with. Re-use of an agent as
304 monotherapy when it was first used in a platinum-based doublet was considered as a rechallenge.

305

306

307

Table 1: Description of chemotherapy rechallenge

308

Characteristics of rechallenge according to drug						
Variable	All <i>n</i> =23	Platinum + X <i>n</i> =8	Pemetrexed <i>n</i> =7	Gemcitabine <i>n</i> =4	Paclitaxel <i>n</i> =3	Vinorelbine <i>n</i> =1
Number of cycles at first use						
Median	4	4	7	5.5	4	5
[range]	[1–16]	[4–5]	[1–16]	[4–8]	[4–4]	[5–5]
Initially used as maintenance	NA*	NA	3 (43)	2 (50)	NA	NA
Performance status at rechallenge						
0 - 1	18 (78)	7 (87.5)	5 (71)	3 (75)	100 (0)	0 (0)
2	5 (22)	1 (12.5)	2 (29)	1 (25)	0 (0)	1 (100)
Histology						
Adenocarcinoma	17 (74)	6 (75)	6 (86)	2 (50)	3 (100)	0 (0)
Squamous cell carcinoma	4 (17)	2 (25)	0 (0)	1 (25)	0 (0)	1 (100)
Large cell carcinoma	1 (4.5)	0 (0)	0 (0)	1 (25)	0 (0)	0 (0)
Sarcomatoid carcinoma	1 (4.5)	0 (0)	1 (14)	0 (0)	0 (0)	0 (0)
Number of lines at rechallenge						
Median	4	4	5	4.5	3	5
[range]	[2–6]	[2–6]	[2–6]	[3–5]	[2–4]	[5–5]
Number of cycles at rechallenge						
Median	4	4	3	2	6	2
[range]	[1–16]	[2–5]	[2–8]	[1–16]	[5–7]	[2–2]
Subsequent line of treatment after rechallenge	14 (61)	6 (75)	4 (57)	2 (50)	2 (67)	0 (0)

309

310 *NA= not applicable

311

312

313

Table 2: Histological subtypes according to rechallenge of treatment

314

Variable	Overall <i>n</i>=99 n (%)	Rechallenged <i>n</i>=13 n (%)	Not rechallenged <i>n</i>=86 n (%)	Univariate analysis (p)
Adenocarcinoma histologic subtype				
Acinar	26 (26.5)	3 (23)	23 (26.5)	p = 0.74
Mucinous	14 (14)	3 (23)	11 (13)	p = 0.42
Lepidic	6 (6)	3 (23)	3 (3.5)	p = 0.037
Papillary	3 (3)	0 (0)	3 (3.5)	p = 1.0
Undifferentiated	34 (34.5)	3 (23)	31 (36)	NC*
Unknown	16 (16)	1 (8)	15 (17.5)	NC

315

316 *NC = not calculated

317 Comparisons between categorical variables were conducted with the Chi-squared test or Fisher's exact test when $n < 5$.

318

319

320

Table 3: Characteristics of rechallenged and non-rechallenged patients

Variable	Rechallenged <i>n</i> = 18 n (%) or median [range]	Not rechallenged <i>n</i> = 131 n (%) or median [range]	Univariate analysis (<i>p</i>)
Age (years)	56 [42–72]	61 [36–87]	<i>p</i> = 0.04
Gender			<i>p</i> = 0.021
Male	7 (39)	91 (69.5)	
Female	11 (61)	40 (30.5)	
Smoking history			<i>p</i> = 0.87
Non-smoker	2 (11)	11 (8.5)	
Former smoker	8 (44.5)	50 (38)	
Current smoker	8 (44.5)	63 (48)	
Pack-years	39 [0–92]	40 [0–150]	<i>p</i> = 0.21
Smoking duration (years)	30.5 [0–53]	40 [0–64]	<i>p</i> = 0.086
Histology			
Adenocarcinoma	13 (72.5)	86 (65)	<i>p</i> = 0.57
Squamous cell carcinoma	3 (16.5)	28 (21.5)	<i>p</i> = 0.77
Large cell carcinoma	1 (5.5)	15 (12)	<i>p</i> = 0.69
Sarcomatoid carcinoma	1 (5.5)	2 (1.5)	NC
Mutations (*)			
<i>EGFR</i> mutation	2 (11)	8 (6)	<i>p</i> = 0.61
<i>ALK</i> rearrangement	1 (5.5)	6 (4.5)	<i>p</i> = 1.0
<i>KRAS</i> mutation	1 (5.5)	23 (17.5)	<i>p</i> = 0.18
<i>BRAF</i> mutation	0 (0)	1 (1)	NC
No mutation	10 (55.5)	55 (42)	NC
Initial stage			<i>p</i> = 1.0
IA–IIIA	2 (11)	18 (14)	
IIIB/IV	16 (89)	112 (86)	
Metastases at diagnosis			
CNS	3 (16.5)	32 (24.5)	<i>p</i> = 0.56
Subdiaphragmatic	6 (33.5)	47 (36)	<i>p</i> = 0.84
Comorbidities			
Yes/No	9 (50)/9 (50)	85 (65)/46 (35)	<i>p</i> = 0.22
Cardiovascular comorbidities	3 (16.5)	55 (42)	<i>p</i> = 0.039
Diabetes	1 (5.5)	16 (12)	<i>p</i> = 0.7
Other neoplasm	2 (11)	20 (15.5)	<i>p</i> = 1.0
CRF/COPD	2 (11)	15 (11.5)	<i>p</i> = 1.0
Chronic renal failure	0 (0)	3 (2.5)	<i>p</i> = 1.0
HIV	1 (5.5)	1 (1)	<i>p</i> = 0.23
Psychiatric comorbidity	4 (22)	8 (6)	<i>p</i> = 0.04
Alcoholism	0 (0)	5 (4)	<i>p</i> = 1.0
Performance status at diagnosis			<i>p</i> = 0.043
0–1	18 (100)	97 (74)	
2–4	0 (0)	23 (17.5)	
Number of treatment lines			<i>p</i> < 0.0001
Mean	5.5	2.4	
1–3 lines	2 (11)	99 (76)	
> 3 lines	16 (89)	32 (24)	
Targeted therapy (TKI) received	16 (89)	57 (43.5)	<i>p</i> = 0.0003
No oncogenic addiction	13 (72)	44 (34)	<i>p</i> = 0.044

322 Comparisons between non-parametric continuous variables were conducted with the Mann-Whitney test. Comparisons between categorical variables
323 were conducted with the Chi-squared test or Fisher' exact test when $n < 5$. (*) Mutational status research doesn't include patients with squamous
324 histology ($n=131$). Among patients with non-squamous histology, 11 have unknown mutational status.a

325

Table 4: Progression-free survival according to first use and rechallenge for each drug

326

Variable	Rechallenge according to drug					
	All <i>n</i> =23	Platinum+X <i>n</i> =8	Pemetrexed <i>n</i> =7	Gemcitabine <i>n</i> =4	Paclitaxel <i>n</i> =3	Vinorelbine <i>n</i> =1
PFS at first use (months)						
Median	9.2	7.4	7.7	9.2	7.1	15.7
[min–max]	[2.7–31.7]	[4.3–15.7]	[2.7–12.8]	[8.7–11.5]	[4.3–31.7]	[NA]
PFS at rechallenge (months)						
Median	2.7	3.0	2.5	1.8	5.4	4.5
[min–max]	[0.25–22.5]	[1.0–22.5]	[1.0–6.6]	[0.25–12.1]	[4.5–6.3]	[NA]
Wilcoxon test	p = 0.002	p = 0.16	p = 0.027	NA*	NA	NA

327

328 *NA = not applicable; PFS = progression-free survival

329 Progression-free survival at first use and at rechallenge were compared with the Wilcoxon test.

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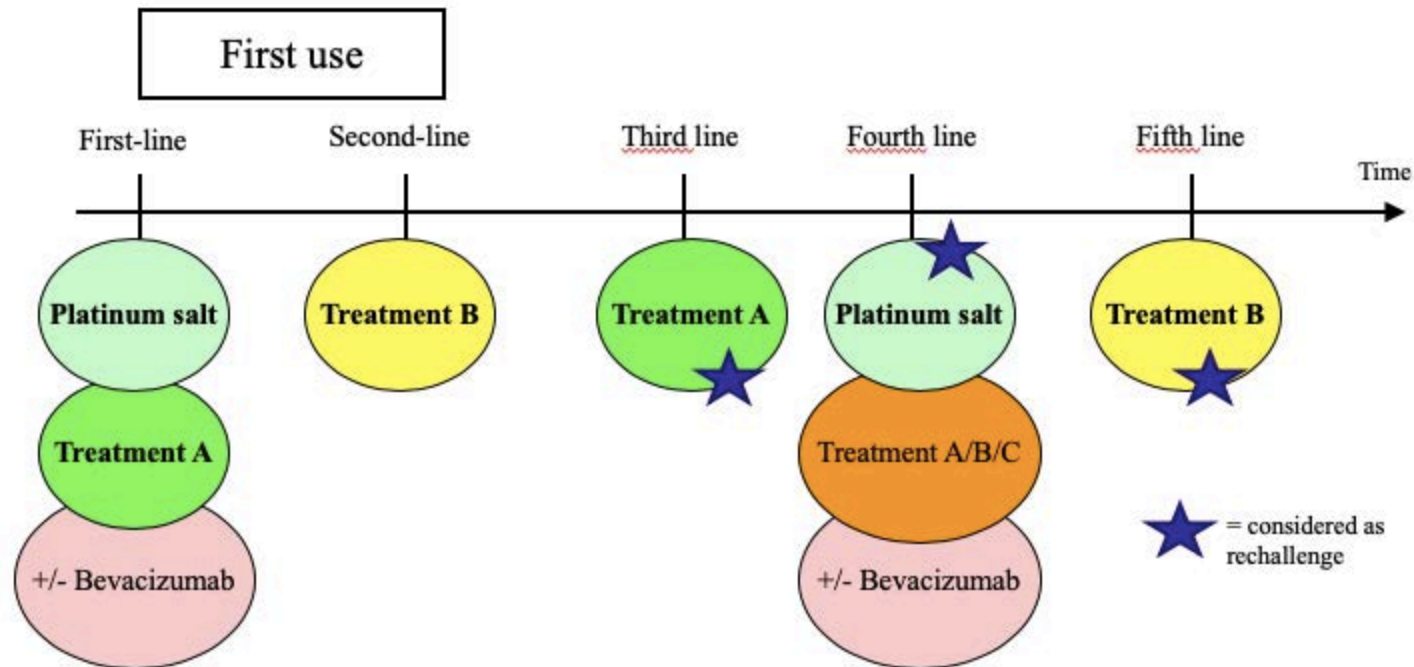


Figure 1: Representation of chemotherapy rechallenge in the course of treatment

The x-axis represents treatment course. Re-use of a platinum salt was considered as platinum salt rechallenge, regardless of the drug it was combined with. Re-use of an agent as monotherapy when it was first used in a platinum-based doublet was considered as a rechallenge.