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1 **Can intercalating chemotherapy with Epidermal Growth Factor Receptor inhibitors**
2 **delay development of treatment resistance in advanced Non-Small Cell Lung**
3 **Cancer?**

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25 Receptor; T790M; resistance.

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1. Introduction

Lung cancer is the leading cause of cancer-related mortality in the world. Non-small cell lung cancer (NSCLC) accounts for more than 80% of all lung cancers. By the time of diagnosis, the majority of patients are already at advanced stage of disease, and they can only benefit from a systemic palliative treatment. At present, the choice of pharmacological treatment for patients with metastatic disease is based on subject's characteristics, on tumor histology and on genetic alterations (namely, Epidermal Growth Factor Receptor (*EGFR*) activating mutations, Anaplastic Lymphoma Kinase (*ALK*) and Proto-Oncogene Tyrosine-Protein Kinase reactive oxygen species (*ROS-1*) translocations), that are present in only about 20% of Western patients. While platinum-based chemotherapy is the standard of care for patients who do not exhibit *EGFR* activating mutations or other oncogene addictions, the first-line option for NSCLC patients who have tumors that harbor activating *EGFR* mutations is treatment with *EGFR*-tyrosine kinase inhibitors (*EGFR*-TKIs), such as gefitinib, erlotinib or afatinib. [1] In these patients, *EGFR*-TKIs are better than chemotherapy as first-line treatment, in terms of progression-free survival (PFS), objective responses rates (ORR), safety profile and health-related quality of life.[2] Unfortunately, despite the initial efficacy of the treatments, drug resistance and disease progression almost always emerge. Although the combination of anti-angiogenic drugs and *EGFR*-TKIs (namely, the addition of the anti-VEGF bevacizumab to erlotinib) as first-line therapy has produced a significant improvement in PFS, the occurrence of resistance remains the clinical rule even in patients treated with this combination.[3]

Therefore, together with the identification of better treatments to use as first-line therapy of *EGFR* mutated NSCLC patients, another challenging open question regards the optimal management of those patients who develop resistance to first-line *EGFR*-TKIs. Different mechanisms can lead to acquired resistance to *EGFR*-TKIs: among the mechanisms described, the threonine to methionine point mutation in codon 790 of exon

53 20 (*T790M*), the human *HER2* amplification, and the activation of secondary signaling
54 such as *MET* amplification or *phosphatidylinositol 3-kinase* mutation. In addition, the
55 transformation from NSCLC to SCLC or the epithelial-to-mesenchymal transition have
56 been identified as further mechanisms of acquired resistance to EGFR-TKIs. Among these
57 mechanisms, the *T790M* missense mutation is responsible for the acquired resistance in
58 nearly 60% of patients.[4] Osimertinib, a third-generation EGFR-TKI, has shown high
59 activity in *EGFR T790M* positive cases.[5] However, although exciting data of PFS and
60 ORR have been reported in patients treated with osimertinib and other third-generation
61 EGFR-TKIs, unfortunately acquired resistance occurs in all patients. Furthermore, the
62 mechanisms of acquired resistance to third-generation EGFR-TKIs have not been
63 completely understood and seems to be extremely various and heterogeneous, probably
64 more complex than resistance to first- and second-generation EGFR-TKIs. [6] Thus
65 nowadays, for *T790M* positive disease progressing after treatment with osimertinib, there
66 are no other targeted agents approved. On the other hand, in *T790M* negative cases
67 progressing after first-line EGFR-TKIs, no active biological drugs are available in clinical
68 practice. [3] Therefore, chemotherapy remains the standard of care for patients with
69 *T790M* positive tumor progressing after first-line EGFR-TKIs and second-line osimertinib,
70 and for *T790M* negative patients progressing after first-line EGFR-TKIs. Immune
71 checkpoint inhibitors (such as nivolumab, pembrolizumab, atezolizumab) are potential
72 alternative salvage treatments in NSCLC, but subgroup analyses of randomized trials did
73 not show a significant improvement in OS over chemotherapy in EGFR-mutated advanced
74 NSCLC. [7]

75

2. Body of evidence

To date, combination regimens of EGFR-TKIs and chemotherapy have no role in clinical practice. Several randomized phase III trials testing continuous daily administration of erlotinib or gefitinib, in combination with platinum-based chemotherapy doublets, as first-line treatment of patients with advanced NSCLC, have failed to improve survival.**[8,9]** The phase III TRIBUTE trial randomly assigned patients with advanced NSCLC to erlotinib or placebo combined with up to six cycles of carboplatin and paclitaxel, followed by maintenance monotherapy with erlotinib. Median survival was 10.6 months for patients treated with erlotinib and 10.5 months for placebo (hazard ratio, HR 0.99; 95% CI, 0.86 to 1.16; P= .95).**[8]** The phase III INTACT 2 trial, randomized untreated patients with advanced NSCLC to receive chemotherapy with paclitaxel and carboplatin plus the EGFR-TKI gefitinib at the dose of 500 mg/day, or gefitinib 250 mg/day, or placebo. There was no difference in overall survival (OS) (median, 8.7, 9.8, and 9.9 months for gefitinib 500 mg/day, 250 mg/day, and placebo, respectively; P =0.64), TTP, or RR between arms.**[9]** Those negative clinical results were obtained in a population of patients unselected for *EGFR* mutational status, whereas exist evidences of PFS and OS improvement with first-line concurrent combination therapies of the EGFR-TKI gefitinib plus platinum-based doublet chemotherapy (carboplatin/pemetrexed) compared to the sequential alternating administration of gefitinib and chemotherapy. **[10]** A phase III study comparing gefitinib with gefitinib plus concomitant carboplatin/pemetrexed in EGFR mutated NSCLC has recently concluded enrollment, and results are still not available. **[11]** Recently, Cheng *et al* reported the results of a randomized phase II trial comparing gefitinib alone vs. pemetrexed + gefitinib (continuous administration) as first-line therapy in 195 East Asian patients with advanced nonsquamous NSCLC with activating *EGFR* mutations. **[12]** PFS, that was the primary endpoint, was significantly longer with pemetrexed plus gefitinib (median, 15.8 months) than with gefitinib (median, 10.9 months).

102 Although the latter promising results underline that combination of chemotherapy
103 and EGFR TKIs could perform better when tested in properly selected patients, it has been
104 speculated that the previous negative clinical results - that were obtained in a population of
105 patients unselected for *EGFR* mutational status - were possibly due not only to
106 inadequate selection of patients, but also to the cell-cycle timing interference. There is
107 growing laboratory evidence of a possible sequence-dependent antagonism as a result of
108 the well-known G₁-phase arrest of tumor cells by EGFR-TKIs, which protect tumor cells
109 from the cell cycle-specific cytotoxic agents.[13] Similarly, the attempt of combining
110 continuous administration of EGFR-TKIs with platinum-based doublets chemotherapy after
111 progression to EGFR-TKIs in patients affected by *EGFR* mutation positive NSCLC, did not
112 produce significant improvement in patients' outcome.[14] With this background, based on
113 several preclinical data, some interest has grown for a strategy of sequencing and
114 intercalating administration of chemotherapy and EGFR-TKIs. In particular, chemotherapy
115 should be given after EGFR-TKI (pharmacodynamic separation), in order to avoid cell
116 cycle-specific antagonism. Li *et al.* showed that interrupting erlotinib before the subsequent
117 administration of pemetrexed in NSCLC cells should be the most effective sequence for
118 combined treatment with these agents.[15] Interestingly, the synergism observed was
119 independent from the mutational status of the *EGFR* or the intrinsic sensitivity to erlotinib.

120 In another preclinical experience, La Monica *et al* demonstrated that simultaneous
121 treatment with pemetrexed and gefitinib in NSCLC cell lines harboring a deletion in exon
122 19 of *EGFR* gene enhanced cell growth inhibition and prevented the appearance of
123 gefitinib resistance of mediated by T790M mutation, only when pemetrexed was the initial
124 treatment. [16]

125 Cheng *et al.* proved that the sequence of paclitaxel followed by gefitinib may be superior to
126 other sequences in treating NSCLC cell lines; in fact, they demonstrated that exposure to
127 paclitaxel in these cell lines resulted in an increased level of phosphorylated *EGFR*, and

128 this increase in phosphorylation was inhibited by subsequent exposure to gefitinib.[17] In
129 addition, Bello *et al.*, with the aim of identifying the optimal schedule for translation into the
130 clinical setting, demonstrated the efficacy of different treatment schedules involving
131 vinorelbine and gefitinib in NSCLC cell lines (either with the L858R/T790M *EGFR* mutation
132 or wild-type).[18] Tsai *et al.*, using a panel of 12 NSCLC cell lines that had no sensitizing
133 *EGFR* mutations (SEM), demonstrated synergism in combining gefitinib with
134 antimicrotubule agents.[19] The same authors tested six different gefitinib–drug
135 combinations in 15 NSCLC cell lines with and without SEMs. They showed that in the
136 *EGFR* wild-type NSCLC cells, gefitinib created synergism when treated in combination
137 with pemetrexed or other cytotoxic agents (antagonism with cisplatin). Instead, NSCLC
138 cells with SEMs seemed to be more chemo-refractory and showed a tendency toward
139 consistent antagonism when gefitinib was used concurrently with chemotherapy. They
140 concluded that concomitant administration of EGFR-TKI and chemotherapeutic agents is
141 not a good treatment strategy for NSCLC patients harboring SEMs, and suggested a
142 strategy of intercalated administration of same agents.[20]

143 Based on those encouraging preclinical evidence, the intercalated administration of
144 EGFR-TKIs (in particular gefitinib or erlotinib), and chemotherapy in patients with
145 advanced NSCLC has been investigated in phase II and phase III, randomized and non-
146 randomized, clinical trials.[21, 22, 23, 24] For instance, a phase II study evaluated the
147 administration of cisplatin and docetaxel based chemotherapy plus intercalated gefitinib for
148 advanced NSCLC EGFR mutated patients. [24] The primary endpoint of the study was the
149 two–year PFS rate. The 1–, 2–, and 3–year estimated PFS rates were 59.4%, 37.5%, and
150 33.8%, respectively, and the median PFS time was 19.2 months. The 1–, 2–, and 3–year
151 estimated survival rates were 90.0%, 82.9%, and 62.4%, respectively, and the median
152 survival time had not been reached at the time of analysis. A recent meta-analysis of
153 randomized trials (RCTs) [21] showed that this therapeutic strategy might be effective in

154 the treatment of advanced NSCLC patients, not selected by *EGFR* mutational status.
155 According to the results of this meta-analysis, the intercalated schedule is associated with
156 a significant improvement in OS (hazard ratio [HR], 0.82; 95% confidence interval [CI],
157 0.71-0.95; P = .01), PFS (HR, 0.60; 95% CI, 0.53-0.68; P < .00001), and objective
158 response rate (ORR; odds ratio [OR], 2.70; 95% CI, 2.08-3.49; P < .00001), compared to
159 chemotherapy alone. Notably, the RCTs considered in this meta-analysis were
160 heterogeneous for the EGFR-TKI used, for the type of chemotherapy (platinum-based or
161 single-agent), for the line of treatment (first-line versus pretreated patients), for the *EGFR*
162 mutational status (which was known only in 43% of the patients included) and for the
163 clinical characteristics of eligible patients (in terms of ethnicity, age, PS, smoking history
164 and tumor histology). Subgroup analyses suggested that in patients with tumors harboring
165 *EGFR*-activating *mutations*, there was a significant benefit in PFS (HR, 0.24; 95% CI,
166 0.16-0.37; P < .00001) and ORR (OR, 11.59; 95% CI, 5.54-24.25; P < .00001) with the
167 addition of intercalated EGFR-TKI to chemotherapy.

168

169 **3. Expert opinion**

170 Unfortunately, the results of the meta-analysis[21] document the efficacy of the
171 combination compared to chemotherapy, while there is no robust evidence to define the
172 relative efficacy of the intercalated combination compared to single-agent EGFR-TKIs.
173 However, the addition of an EGFR-TKI to chemotherapy could be of interest in the
174 treatment of patients with unknown *EGFR* mutational status: this strategy should be tested
175 in dedicated prospective trials to better define its role, although the lack of information
176 about *EGFR* mutational status should be no longer acceptable in modern clinical practice.
177 As for patients with *EGFR* mutation, who are candidates to receive chemotherapy as
178 second-line (if *T790M* negative) or further line of therapy (if *T790M* positive), the results of
179 the meta-analysis are not directly applicable, because most patients included in the trials
180 considered were treatment-naïve and were not pre-treated with an EGFR-TKI. However,
181 despite the occurrence of molecular changes associated with resistance, the original
182 *EGFR* mutation remains detectable at the onset of resistance, and this finding suggests
183 that *EGFR* should be considered a principal driver for progressing neoplastic clones even
184 after disease progression. [19] As a consequence, on the basis of the preclinical data
185 reported and considering the positive results obtained in response rate and survival
186 endpoints with the intercalated combination of EGFR-TKI and chemotherapy in NSCLC,
187 we suggest that intercalated schedule could represent not only a promising way to delay
188 the development of treatment resistance, but also a potentially active strategy after EGFR-
189 TKI resistance development.[23] Of course, only well designed randomized trials may help
190 in verifying this hypothesis.

191 In conclusion, dedicated prospective studies are needed to assess the impact of the
192 intercalated regimen as a weapon to delay or revert the onset of EGFR-TKI resistance in
193 NSCLC patients. Currently, several different clinical trials regarding intercalated EGFR-TKI
194 and chemotherapy in advanced NSCLC are ongoing: both single-arm and randomized

195 studies, regarding first- or subsequent lines setting, with heterogeneous treatment
196 administered **[Table 1]**. Some of these trials will help to better define the role of
197 intercalated administration of EGFR-TKIs and chemotherapy.

Table 1. Ongoing trials with intercalated EGFR-TKI and chemotherapy in patients with advanced NSCLC

Clinicaltrials.gov Identifier	Phase	Patients	Control arm	Experimental arm	Primary endpoint	Accrual*
NCT02031601	III	EGFR mutated, first-line treatment	Single-agent TKI (erlotinib or gefitinib or icotinib)	Chemotherapy (docetaxel or pemetrexed plus platinum), day 1, plus TKI (erlotinib or gefitinib or icotinib), days 2-15, every 3 weeks	PFS	Recruiting
NCT02064491	II	EGFR mutated, progressed after first-line EGFR-TKI	Chemotherapy (cisplatin or carboplatin plus docetaxel or paclitaxel or pemetrexed), day 1 every 3 weeks	Chemotherapy (same as in control arm), day 1, plus intercalated erlotinib, every 3 weeks	PFS	Completed
NCT02775006	III	EGFR wild type, progressed after one platinum- containing regimen	Chemotherapy (docetaxel), day 1 every 3 weeks	Chemotherapy (docetaxel), day 1, plus intercalated erlotinib, days 2-16 every 3 weeks	PFS	Recruiting
NCT03151161	II	EGFR mutated, first-line treatment	Chemotherapy (carboplatin plus pemetrexed), day 1 every 3 weeks	Chemotherapy (carboplatin plus pemetrexed), day 1, plus intercalated icotinib, days 2-15, every 3 weeks	Response rate	Recruiting
UMIN000020242	III	EGFR mutated, first-line treatment	Single-agent TKI Gefitinib	Gefitinib on days 1-56 ,cisplatin and pemetrexed on days 71, 92, 113 and again Gefitinib on day 134	OS	Recruiting

EGFR: Epidermal Growth Factor Receptor; TKI: tyrosine kinase inhibitor; NSCLC: non-small cell lung cancer; PFS: progression-free survival;

*as reported in *ClinicalTrials.gov* and *UMIN-CTR Clinical Trial* on July 2, 2017,

Declaration of interest

In accordance with Taylor & Francis policy and our ethical obligation as researchers, we are reporting that Massimo Di Maio has received honoraria for lectures from Novartis, Amgen, Bristol Myers Squibb, and acted as consultant for AstraZeneca, Boehringer Ingelheim, Merck Sharp & Dohme. Antonio Rossi has received honoraria for lectures from Eli-Lilly, Roche, AstraZeneca, Boehringer Ingelheim, and acted as consultant for Eli-Lilly, AstraZeneca, Roche. Anna La Salvia and Emmanuele De Luca have no conflicts of interest to declare. We have disclosed those interests fully to Taylor & Francis.

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