Should the treatment of advanced lepidic adenocarcinoma be adapted to the pathological subtype?

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Increased sensitivity to chemotherapy/TKI of mucinous variant in advanced L-ADC should be tested in a phase III trial http://ow.ly/TkWXi

In 2011, the pathological classification of lung adenocarcinoma was jointly revised by the International Association for the Study of Lung Cancer, the American Thoracic Society and the European Respiratory Society [1]. The former terminology adenocarcinoma with bronchiololalveolar features was recategorised as nonmucinous lepidic predominant adenocarcinoma (NM L-ADC) or mucinous variant (M L-ADC). The reason for this subclasssification was the identification of multiple differences: clinical, radiological, pathological and genetic. In particular, although bronchioloalveolar (BAC) features are overall an independent predictive factor for *EGFR* (epidermal growth factor receptor) mutation in a non-Asian population with an odds ratio of 2.84 (95% CI: 1.98–4.06) [2] compared with other types of lung adenocarcinoma, it was shown that NM tumours more frequently exhibit *KRAS* (Kirsten Ras) mutations and lack of *EGFR* mutations while M tumours are more likely to be *EGFR* mutated [3]. The creation of these two subcategories gives a rationale to investigate further whether the M or NM characteristic might be a new target for tailoring treatment of those patients with advanced lepidic adenocarcinoma.

For more than 10 years, lung cancer has been recognised as a heterogeneous disease and the management of lung cancer has changed with the identification of predictive biomarkers [4] that has led to change standard therapy and to improvement in outcome. Those include tumour histology with nonsquamous histology as a marker of sensitivity to pemetrexed in advanced tumours, *EGFR* mutations predicting response to tyrosine kinase inhibitors (TKI), anaplastic lymphoma kinase rearrangements and the subsequent development of a targeted treatment which is crizotinib. These markers are now of clinical utility in routine therapeutic decisions. More recently, *MET* oncogene amplification was shown to drive resistance to TKI and ROS-1 rearrangements are subject of ongoing research as well as *KRAS* mutations [4]. Finding a target for each individual tumour is a dream for the clinicians and obviously, this way appears the one having allowed improvement in the management of advanced nonsmall cell lung carcinoma, and research in this field appears the most attractive for lung tumours as well as for other tumours.

In this issue of the *European Respiratory Journal*, Cadranel *et al.* [5] report on a trial conducted, by the *Intergroupe Francophone de Cancérologie Thoracique* (IFCT-0504), in advanced lepidic carcinoma. The possible prognostic and predictive value of pathological subtype was investigated together with a panel of exploratory other markers (*EGFR*, *KRAS*, *TUBB3* and *MSH2* expression in tumour specimens). The same *Intergroupe* had previously shown an interest in the analysis of the impact of the M/NM status on treatment outcomes. Indeed, these authors had conducted another phase II trial (IFCT-0401) that primarily looked at

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the efficacy of gefitinib given at a 250 mg daily dose in a comparable patient population. Pathological subtype was not available in all patients but, in a subgroup of 88 patients, Cadranel *et al.* [6] analysed, as exploratory analysis, the impact on progression-free survival of the M/NM status. They showed improved progression-free survival for 21 patients with NM tumours (median 11.3 months, 95% CI 3.2–14.7) compared with 38 patients with M tumours (median 2.6 months, 95% CI 2.1–3.0). This difference was accompanied by a difference in overall survival: patients with NM tumour having longer survival (median 32.7 months, 95% CI: 18.2–not calculable) than patients with an M tumour (median 10.1 months, 95% CI 8.4–13.4). This interesting result is however not sufficient, in the absence of a control arm, to suggest any predictive value of NM/M status.

In the IFCT 0504 randomised trial, patients with advanced lepidic carcinoma, histologically or cytologically diagnosed, received, as first line treatment, either erlotinib or carboplatin–paclitaxel chemotherapy. Likely, due to the nonavailability of M/NM pathological subtype, randomisation was not stratified for this feature. The planned analysis included looking at the interaction between treatment effect and M/NM subtype but no formal research hypothesis was formulated. The trial was designed as a randomised phase II trial without formal comparison between arms. The statistical considerations were the same in both arms and the primary objective was to investigate whether the disease control rate (defined as the absence of disease progression) at 16 weeks was higher than 30% or not, and sample size was sufficient to reach 95% power, in case of a true disease control rate of 50%, using a two-stage design and a relaxed one-sided type I error rate of 10%. The number of patients enrolled in the trial was 133, and 130 patients were eligible. 67 patients (33 with NM tumour and 25 with M tumour) were randomised to the erlotinib arm and 66 to the chemotherapy arm (34 with NM tumour and 28 with M tumour). Consistently with the design and the relaxed one-sided type I error, the authors concluded that the efficacy of both treatments was demonstrated with disease control rates statistically significantly above the minimal acceptable pre-planned efficacy level of 30%. However, looking at the confidence intervals for disease control rates with a more usual 95% confidence level, they are, respectively, in the overall population (no stratification on the pathological subtype) for the TKI arm (27.1%–51.0%) and for the carboplatin-paclitaxel arm (42.0%–65.0%). Without going into formal comparison between arms, with a 5% two-sided type I error, the data, in the TKI arm, are compatible with a disease control rate lower than 30%. This is not the case for the chemotherapy arm (see table 1).

Exploratory analyses were conducted stratifying patients for pathological subtype on a subset of 119 evaluable patients with pathological subtype available. Other exploratory analyses were conducted for pathological subtype and the other molecular markers (with a central review) on a subset of 96 patients. In these exploratory analyses, pathological subtype was not prognostic for disease control rate at 16 weeks and no interaction between treatment effect and pathological subtype was found. For progression-free survival, no difference between arms was observed (respective estimated medians of 3.4 months for the erlotinib arm and 5.7 months for the carboplatin–paclitaxel arm) while a nonmucinous subtype was found

TABLE 1 Outcomes stratified by treatment arm, NM/M subtype and both covariates

	Patients n	DCR % (95% CI)	PFS months median (95% CI)	OS months median (95% CI)
Arm				
E	64	39.1 (27.1–51.0)	3.4 (1.3–3.7)	21.2 (15.4–32.2)
CP	66	53.0 (42.0–65.0)	5.7 (2.6–8.7)	17.6 (11.3–28.8)
p-value		0.11	0.27	0.99
Pathological subtypes				
NM	67	50.7#	5.8 (1.9–8.7)	28.0 (13.0–32.9)
M	52	42.3#	3.5 (1.1–5.5)	18.9 (10.3–28.9)
p-value		0.36	0.01	0.09
Both covariates				
E arm – NM subtype	33	NR	3.6 (1.3–11.7)	NR
E arm – M subtype	24	NR	1.4 (0.9–3.6)	NR
CP arm – NM subtype	34	NR	4.8 (1.3–8.7)	NR
CP arm – M subtype	28	NR	6.0 (2.2–11.3)	NR
p-value for interaction		NS	0.009	NS

NM: nonmucinous; M: mucinous; DCR: disease control rate; PFS: progression-free survival; OS: overall survival; E: erlotinib; CP: carboplatin-paclitaxel; NR: not reported; NS: nonsignificant. #: 95% CI not reported. Data from [5].

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prognostic for improved progression-free survival (5.8 months *versus* 3.5 months; p=0.01). Finally, the mucinous subtype was predictive for increased sensitivity to chemotherapy (median of 6.0 months in the chemotherapy arm *versus* 1.4 months). A significant interaction was found between treatment effect and pathological subtype (p=0.009). For overall survival however, no difference between arms was found and no prognostic value of pathological subtype was identified. Treatment effect was not impacted by the pathological subtype (nonstatistically significant interaction term). The analysis on the subset of 96 patients with the molecular markers did not allow identification of any other significant impact, which is not too surprising as it likely suffers from lack of power. This is especially true for the *EGFR* mutation status as only five patients had a tumour with mutated *EGFR* (all of them being NM tumours).

The only formal conclusion that can be drawn, by trial design, is that carboplatin–paclitaxel showed activity warranting further testing and that TKI activity already identified in previous trials was confirmed. Indeed, we should keep in mind that the trial was a phase II trial with a much higher type I error level than generally accepted in a phase III and with a primary objective being not a definite one. Results should be confirmed in a phase III trial with overall survival as endpoint, disease control rate and progression-free survival having not been demonstrated, to our knowledge, as surrogate endpoints for survival.

Based on these results, should we then go for a phase III trial? And how should the findings about the role of pathological subtype be integrated? Can we consider that patients with M tumours should not be given erlotinib as first-line treatment? The answer is no in our opinion. Indeed, we should remember that all comparative analyses were exploratory and should therefore be confirmed. The findings about the impact of pathological subtype are coming from a subgroup analysis on a subset of patients not properly balanced by randomisation and showing an advantage of chemotherapy on progression-free survival overall but not on early progression (at 16 weeks) and not on overall survival. It should be noticed that cross-over was allowed in the trial but if the cross-over is responsible for the lack of difference in survival, it means that chemotherapy can be used as salvage treatment in the second line. Although documentation was centrally reviewed, progression-free survival is a less robust and convincing endpoint than survival and no impact on early progression assessed at a fixed timepoint was identified. There is also no biological hypothesis underlying the predictive value of pathological subtype. Therefore, the question of an improvement in survival in patients with M tumours for carboplatin-paclitaxel chemotherapy compared to the administration of a TKI remains open and might be the purpose of a phase III trial. For the patients with NM tumours, taking into account that carboplatin–paclitaxel met the primary objective in the overall patients population and, according to a comparison done by Hoering *et al.* [7] concluding that an all comers design is recommended when there is uncertainty about the predictive value of the marker and when the marker prevalence is large enough, both conditions met here. A design allowing formal testing of the hypothesis of improved survival with carboplatin–paclitaxel in the overall population and in the subset of patients with M tumours might therefore be considered.

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