

## Comment on: 'Nab-paclitaxel plus gemcitabine for metastatic pancreatic adenocarcinoma after Folfirinox failure: an AGEO prospective multicentre cohort'

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Sir,

We have read with great interest the recent paper by Portal *et al* (2015), who reported the results of a prospective multicentre cohort study evaluating the efficacy and safety of nab-paclitaxel plus gemcitabine after FOLFIRINOX failure in patients with metastatic pancreatic cancer (mPC). The authors collected the data of 110 patients from 12 French centres who progressed to FOLFIRINOX: 77 (70%) were eligible to receive nab-paclitaxel and gemcitabine, and 57 (51.8%) actually underwent treatment. Results in terms of survival are encouraging, with a median overall survival (OS) of 8.8 months and a median progression-free survival (PFS) of 5.1 months. Even with regard to treatment activity, objective responses were observed in up to 17.5% of the patients (with disease stabilisation in another 40.5%).

We thank the authors, as this experience suggests that a subgroup of mPC may benefit from second-line chemotherapy after an intensive first-line regimen. Some patients retain adequate general conditions and organ function after the first progression and are able to receive combination chemotherapy in the second line. These data suggest that more active treatments might improve survival compared with monotherapy. In the phase III ACCORD/PRODIGE study, second-line chemotherapy was administered in 46.7% of the patients after FOLFIRINOX and the majority (82.5%) received gemcitabine monotherapy: indeed, post-progression survival after first-line FOLFIRINOX or gemcitabine did not diverge (median: 4.4 months in each group) (Conroy *et al*, 2011).

On such basis, the results reported with second-line nab-paclitaxel plus gemcitabine by Portal *et al* are particularly impressive, as they resemble those achieved with the same combination administered upfront in the MPACT study (Von Hoff *et al*, 2013). Indeed, in that trial, median OS and PFS in the combination arm were 8.5 and 5.5 months, respectively. Regarding antitumour activity, response rates (RRs) for gemcitabine plus nab-paclitaxel appear similar in the first- and second-line settings, with the global disease control rate (DCR) being slightly higher in the MPACT trial.

The authors explain their encouraging results by stating that this is a highly selected population. However, we notice that 21% of the patients had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2. This percentage is somewhat higher than that reported in the MPACT trial, in which patients with PS <60% according to the Karnofsky scale were <1%. We would have anticipated a greater impact of PS deterioration on patient survival in the second line.

We have recently conducted a prospective evaluation of mPC patients who underwent second-line chemotherapy after modified FOLFIRINOX (Caparelli *et al*, 2016). Similar to the report by the French colleagues, 66% of the progressed patients were able to start a second-line treatment, with a combination regimen in 52% of the cases. Disappointingly, in our experience, second-line treatment did not provide such encouraging results, achieving a median PFS of only 2.5 months, a median OS of 6.2 months and even a lower DCR compared with the report published by Portal *et al* (34% vs 58%). Of note, baseline patient characteristics in the two series were similar, with the sole exception of PS, as we included only 2.8% of patients with ECOG PS 2. We identified 13 patients (18%) treated with gemcitabine plus nab-paclitaxel after FOLFIRINOX, but even in this small subgroup we obtained disappointing results in terms of both activity (RR: 7%; DCR: 23%) and survival (median PFS: 1.95 months; median OS: 5.4 months). With the limitations of a retrospective

evaluation in a small patient cohort, it is difficult to explain this poor second-line outcome: results with first-line FOLFIRINOX confirm that we did not select patients with a chemo-refractory disease, as median first-line PFS was 5.7 months and first-line DCR was 69% (similar to the 71% reported by Portal *et al*).

For these reasons, we are interested in knowing the criteria the authors applied to select patients for second-line nab-paclitaxel plus gemcitabine. As the role of second-line chemotherapy is emerging and different regimens demonstrated efficacy in patients pretreated with gemcitabine-based therapy (Oettle *et al*, 2014; Wang-Gillam *et al*, 2016), it is of particular interest to identify some clinical parameters that can be useful for patient stratification after FOLFIRINOX. As the goal of treatment in mPC is optimal palliation, it is crucial to identify and select the right patient who could benefit for a more intensive treatment. Which is, in the authors' opinion, the best strategy to maximise the impact of available treatment options in mPC?

### CONFLICT OF INTEREST

The authors declare no conflict of interest.

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