



Further defining the role of nanoliposomal irinotecan in pancreatic cancer

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Introduction

Pancreatic ductal adenocarcinoma (PDA) is a relatively uncommon but lethal malignancy; when diagnosed at an advanced stage, the 5-year survival rate is 2% (1). Unfortunately, the majority of PDA patients are diagnosed at an advanced stage, where the median overall survival (OS) is only 4.6 months (2). Gemcitabine-based chemotherapy regimens have been the longstanding, first-line treatment option for locally advanced or metastatic PDA (3-5). Both gemcitabine plus nab-paclitaxel and FOLFIRINOX [5-fluorouracil/leucovorin (5-FU/LV) + irinotecan + oxaliplatin] have shown clear survival benefit and gained acceptance as frontline therapy for otherwise fit patients (6,7). Until the recent past, we were without proven second-line treatment options for patients who progressed on first-line gemcitabine-based regimens. In 2015, based upon the results of the phase 3 NAPOLI-1 trial (NCT01494506) (8), the nanoliposomal irinotecan (nal-IRI) plus 5-FU/LV regimen was approved for advanced PDA patients after failure of gemcitabine-based chemotherapy. Recently, Mercadé *et al.* (9) reported subgroup analyses of the NAPOLI-1 trial that investigated the patient, tumor, and prior treatment characteristics and their effects on survival outcomes.

NAPOLI-1 was a global, phase 3, randomized, open-label trial at 76 sites in 14 countries. In this trial, 417 patients with metastatic PDA who were previously treated with gemcitabine-based chemotherapy were randomly assigned (1:1:1) to three treatment arms: nal-IRI (80 mg/m²

plus 5-FU/LV (400 mg/m² of LV and 2,400 mg/m² of 5-FU over 46 hours) every two weeks, nal-IRI monotherapy (120 mg/m²) every three weeks or 5-FU/LV monotherapy (200 mg/m² of LV followed by 2,000 mg/m² of 5-FU over 24 hours) in a four weeks on, two weeks off schedule. Patients receiving combination treatment with nal-IRI+5-FU/LV demonstrated a significantly longer median OS compared with the 5-FU/LV cohort [6.1 *vs.* 4.2 months (HR: 0.67, 95% CI: 0.49–0.92; P=0.012)] (8). Also, median progression-free survival (PFS) was significantly longer in the nal-IRI+5-FU/LV cohort compared to the 5-FU/LV cohort (3.1 *vs.* 1.5 months; HR 0.56; P=0.0001). Median OS (4.9 *vs.* 4.2 months; P=0.94) and PFS (2.7 *vs.* 1.6 months; P=0.1) were not significantly different between patients in the nal-IRI monotherapy group and those in the 5-FU/LV monotherapy group. Objective response rates (ORR) were superior in the nal-IRI+5-FU/LV cohort compared with those in the 5-FU/LV cohort (16% *vs.* 1%; P<0.0001). The grade 3 or 4 adverse events (AEs) that occurred most frequently in the nal-IRI+5-FU/LV cohort were neutropenia, diarrhea, vomiting, and fatigue. Although AEs observed were higher in patients receiving nal-IRI+5-FU/LV, the quality of life was not significantly different from patients in the 5-FU/LV cohort.

The NAPOLI-1 clinical trial showed a 45% increase in median OS in nal-IRI+5-FU/LV cohort as compared to patients who received 5-FU/LV in the post-gemcitabine metastatic PDA population. In January 2020, Mercadé *et al.* (9) published a post hoc subgroup analysis of the

pivotal NAPOLI-1 trial investigating the prognostic effects of tumor characteristics and disease stage, prior treatment characteristics, baseline patient characteristics on survival outcomes. Four variables across tumor characteristics and disease stage, six variables across prior treatment characteristics, and four variables across patient baseline characteristics were assessed. Tumor characteristics investigated were initial disease stage, primary tumor location, the number, and the location of baseline metastatic lesions. As expected, locally advanced disease stage at initial diagnosis was associated with better median OS as compared to metastatic disease both in the entire NAPOLI-1 ITT (intention-to-treat) population and the nal-IRI+5-FU/LV subgroup. Interestingly, treatment with Nal-IRI+5-FU/LV demonstrated improved median OS and median PFS in patients without a tumor in the head of the pancreas, whereas primary tumor location wasn't related to survival outcomes in the entire ITT population. A greater number of measurable metastatic lesions were associated with worse survival outcomes in the NAPOLI-1 trial; however, this impact was not seen in the nal-IRI+5-FU/LV treatment group. In terms of baseline metastatic lesions location, any liver metastases were associated with lower median OS and PFS both in ITT and nal-IRI+5-FU/LV treatment arm. The same survival effect wasn't seen in patients with baseline lung metastases versus no lung metastases. Prior treatment characteristics were analyzed, first by dividing patients into subgroups based on prior irinotecan or gemcitabine-based therapy, prior surgery, prior biliary stent placement, prior Whipple procedure, and prior lines of anti-neoplastic treatments in the metastatic setting. The survival benefit was seen in irinotecan naïve patients in the nal-IRI+5-FU/LV treatment group *vs.* 5-FU/LV alone. On the other hand, no significant treatment benefit was seen in those who previously received irinotecan. In terms of prior surgical history, patients who previously underwent Whipple resection experienced a survival benefit in the ITT population versus no Whipple procedure; however, this survival benefit was not seen in the nal-IRI+5-FU/LV cohort *vs.* 5-FU/LV. The line of therapy was also important. While receiving nal-IRI+5-FU/LV in the first or second line of therapy demonstrated significantly improved survival compared with 5-FU/LV, this difference was smaller in later lines of therapy. Several baseline patient characteristics were investigated, specifically the impact of baseline pain intensity and analgesic use, baseline weight parameters, presence of metabolism, and nutrition disorders. Interestingly, decreased appetite, higher baseline

pain intensity, and analgesic use were associated with poor survival outcomes; however, metabolism and nutrition disorders did not seem to have a survival impact in the NAPOLI-1 population. Survival outcomes in nal-IRI+5-FU/LV treatment arm were consistently improved in most of the NAPOLI-1 subgroups.

The NAPOLI-1 subgroup analysis performed by Mercadé and colleagues provides added detail to the topline results showing the efficacy of nal-IRI+5-FU/LV treatment in patients with advanced PDA. This study adds to a limited but growing number of studies providing guidance for how best to integrate nal-IRI+5-FU/LV into our treatment algorithms. Analyzing the impact of variables on the entire ITT population compared with treatment groups helps to differentiate whether the variable is merely prognostic versus predictive. Most variables are prognostic and do not help practitioners choose the most effective therapy. As examples, stage, liver metastases, and tumor burden predict survival, regardless of the therapy administered in NAPOLI-1, and are long-established prognostic variables. The identification of baseline pain, analgesic use, and anorexia are interesting prognostic symptoms that were prognostic in this study, and consistent with prior studies. One of the key predictive variables studied was prior lines of therapy. Patients who previously received irinotecan did not benefit from nal-IRI+5-FU/LV treatment, compared with 5-FU/LV alone. This may only tell part of the story. Only 29 patients in NAPOLI-1 received irinotecan in a prior line of treatment, making the sample size too small to draw definitive conclusions. Furthermore, in our single-institution, retrospective analysis, we found that patients who received irinotecan, but had not progressed in an earlier line of therapy, experienced a survival benefit, whereas patients who had previously progressed on irinotecan did not, when treated with nal-IRI+5-FU/LV (10). This is a question that is worth investigating further in larger patient cohorts as increasing numbers of patients will have been exposed to irinotecan as part of FOLFIRINOX perioperative therapy (11). Our study also suggested that specific deleterious mutations, for example, in TP53, SMAD4 and CDKN2A, may also be predictive of response to nal-IRI/5-FU/LV; as comprehensive genomic profiling becomes more commonplace, identification of genomic factors predictive of specific drug responses is a promising research avenue for further study.

The NAPOLI-1 trial has been analyzed by other groups. Chen *et al.* (12) investigated the impact of nal-IRI dose and schedule on efficacy. A per-protocol (PP) population

was separated out from the ITT population, defined as having received at least 80% of planned treatment in the first six weeks without more than one dose reduction. The PP cohort treated with nal-IRI+5-FU/LV experienced an 8.9-month median OS *vs.* 5.1 months in the 5-FU/LV treatment arm (median OS difference: 3.8 months, $P=0.011$), numerically greater than the survival benefit found in the ITT population (median OS difference: 1.9 months, $P=0.012$). Real-world studies are necessary to study the impact of dose and schedule. In our retrospective study, the median starting dose of Nal-IRI was only 55 mg/m^2 ; however, outcomes were similar to what was seen in the NAPOLI-1 ITT cohort. In a retrospective single-center analysis, Kieler *et al.* (13) investigated the safety and efficacy of nal-IRI+5-FU/LV as compared to another commonly used second-line treatment option, oxaliplatin plus fluoropyrimidines in advanced PDA patients in the second-line setting after the failure of the first-line gemcitabine-based regimen. Median PFS was 4.49 months in nal-IRI+5-FU/LV treatment arm, whereas in those who received oxaliplatin plus fluoropyrimidines, median PFS was 3.44 months ($P=0.07$). The median OS was 6.79 months in the nal-IRI+5-FU/LV cohort; however, an OS benefit compared to the oxaliplatin plus fluoropyrimidines cohort was not seen. This real-world retrospective analysis has importance being the first analysis that compared nal-IRI+5-FU/LV regimen with another commonly used second-line regimen. Macarulla *et al.* (14) designed a subgroup analysis to examine the impact of age on outcomes in NAPOLI-1 patients. They stratified patients by age cut-offs at 65, 70, and 75 years of age. The survival benefit of the nal-IRI+5-FU/LV regimen was preserved in their older patient population without additional toxicities.

Conclusion and future expectations

PDA has a poor prognosis because of its aggressive tumor characteristics and the fact that most patients present at late stages. Although PDA remains a challenging disease, new effective treatment options have been introduced within the last few years. Nal-IRI is the latest addition to our clinical practice with highly promising results in pancreatic cancer. The results of the phase 3 NAPOLI-1 trial showed that the nal-IRI+5-FU/LV combination regimen is relatively well tolerated with a demonstrated survival advantage in metastatic PDA patients who progressed after first-line gemcitabine-based regimens. Subsequently, several post hoc subgroup analyses assessed the impact of a number of

baseline patient and tumor characteristics and therapeutic backgrounds. Many of these factors appear more prognostic than predictive of nal-IRI+5-FU/LV response. Overall, these analyses improve our understanding of the effectiveness and safety profile of the nal-IRI+5-FU/LV regimen in the gemcitabine refractory setting. Safety data from all subgroup analyses were generally consistent with those reported for the whole ITT population (9,12,14). The survival benefit was observed across all nal-IRI+5-FU/LV treatment subgroups except for the patients who underwent prior Whipple procedure and those who received an irinotecan-based regimen in prior setting (9). These types of analyses and ongoing real-world analyses will help guide practitioners with regards to patient selection and treatment sequencing. This is especially important as use of nal-IRI continues to be actively investigated in the frontline setting for the treatment of PDA (in combination with 5-FU/LV and oxaliplatin, ClinicalTrials.gov Identifier: NCT04083235), and for the treatment of a wide variety of other malignancies, such as cholangiocarcinoma (ClinicalTrials.gov Identifier: NCT03043547) and esophageal cancer (ClinicalTrials.gov Identifier: NCT03719924).

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