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Francesco Gelsomino[1], Marcello Tiseo[2], Fausto Barbieri[3], Ferdinando Riccardi[4], Luigi Cavanna[5], Antonio Frassoldati[6], Angelo Delmonte[7], Lucia Longo[8], Claudio Dazzi[9], Saverio Cinieri[10], Ida Colantonio[11], Francesca Sperandi[1], Giuseppe Lamberti[1], Stefano Brocchi[12], Lorenzo Tofani[13], Luca Boni[13], Andrea Ardizzoni[1]

[1] Medical Oncology Unit, Policlinico Sant'Orsola-Malpighi, Bologna, Italy
[2] Medical Oncology Unit, Azienda Ospedaliero-Universitaria of Parma, Parma, Italy
[3] Medical Oncology Unit, Policlinico of Modena, Modena, Italy
[4] Medical Oncology Unit, Azienda Ospedaliera Cardarelli, Napoli, Italy
[5] Medical Oncology Unit, AUSL of Piacenza, Piacenza, Italy
[6] Medical Oncology Unit, Azienda Ospedaliero-Universitaria of Ferrara, Ferrara, Italy
[7] Medical Oncology Unit, IRST of Meldola, Meldola, Italy
[8] Medical Oncology Unit, AUSL of Modena, Hospital of Carpi, Carpi, Italy
[9] Medical Oncology Unit, AUSL of Romagna, Hospital of Ravenna, Ravenna, Italy
[10] Medical Oncology Unit, Hospital of Brindisi, Brindisi, Italy
[11] Medical Oncology Unit, Hospital of Cuneo, Cuneo, Italy
[12] Radiology Unit, Policlinico Sant'Orsola-Malpighi, Bologna, Italy
[13] Clinical Trial Center, Istituto Toscano Tumori, Azienda Ospedaliero-Universitaria Careggi, Firenze, Italy

Corresponding author:
Marcello Tiseo, M.D., PhD, Associate Professor
Medical Oncology Unit
Azienda Ospedaliero-Universitaria of Parma
Via Gramsci 14
43126 Parma, Italy
phone: +39 0521 70 2316
fax: +39 0521 99 5448
mail: mtiseo@ao.pr.it

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ABSTRACT

Background: Despite sensitivity to first-line chemotherapy, most small-cell lung cancer (SCLC) patients relapse. In this setting, topotecan demonstrated modest activity, but significant toxicity. Paclitaxel was also active. This study was designed to evaluate activity and safety of nab-paclitaxel in relapsed SCLC.

Methods: In this multicentre prospective phase II trial, patients with *refractory* or *sensitive* SCLC progressed to first-line platinum-based chemotherapy received nab-paclitaxel 100 mg/smq on days 1,8,15 every 4 weeks up to 6 cycles, progressive disease or intolerable toxicity. Primary endpoint was tumor response. Secondary endpoints were toxicity, progression-free survival (PFS) and overall survival (OS).

Results: Of the 68 patients treated, partial response was 8% in the *refractory* cohort and 14% in the *sensitive* cohort. Most common toxicities of any grade were fatigue (54%), anemia (38%), neutropenia (29%), leukopenia (26%) and diarrhoea (21%). Median PFS was similar in both *refractory* (1.8 months) and *sensitive* cohorts (1.9 months), while median OS was longer in *sensitive* one (6.6 versus 3.6 months).

Conclusions: Although the primary end-point of the study has not been reached, nab-paclitaxel showed a potential activity in refractory cohort, and favourable toxicity profile. Further studies comparing nab-paclitaxel to the standard-of-care, in refractory patients, would be worthwhile. (ClinicalTrials.gov Identifier: NCT03219762).

Keywords: small cell lung cancer; nab-paclitaxel; SCLC; relapsed; sensitive; refractory

Background

Small cell lung cancer (SCLC) is one of the most aggressive tumors and accounts for approximately 13-15% of all lung cancers.[1] Most patients with SCLC have extensive-disease (ED-SCLC) at the time of diagnosis, with a median overall survival (OS) of 8-12 months.[2]
In the last 30 years, platinum-based chemotherapy has been the standard of care in first-line setting, providing an objective response rate (ORR) of 70-80%. Unfortunately, despite high sensitivity to first-line chemotherapy, most SCLC patients eventually develop disease progression.[3] At relapse, efficacy of second-line treatment is modest and highly influenced by the type and duration of response to prior chemotherapy.[4] Topotecan, the only approved and marketed drug in Europe specifically for the treatment of relapsed SCLC, showed antitumor activity (7% and 21.7%)[5,6] and a significant improvement in overall survival (OS) over best supportive care (25.9 weeks versus 13.9 weeks, $p = 0.0104$)[5,6] and to have similar activity (24.3% versus 18.3%) and efficacy (median OS: 25.0 weeks versus 24.7 weeks) to CAV combination chemotherapy.[7]
However, the antitumor activity of topotecan is modest and transient and its use is outweighed by its poor compliance and inconvenient schedule.[8] Therefore, there is the need for more effective and better tolerated treatments.
Paclitaxel has also shown activity in the treatment of SCLC, both alone and in combination with carboplatin, even in *refractory* relapsed disease.[9-11] Notably, the use of paclitaxel is encumbered with a significant risk of severe hypersensitivity reactions and cumulative peripheral neurotoxicity that can limit its use.
Nanoparticles Albumin-Bound (Nab)-paclitaxel (Abraxane®; Celgene, Summit, New Jersey) is a new solvent-free formulation of paclitaxel made through high-pressure homogenization of paclitaxel in presence of serum albumin. In comparison to solvent-based paclitaxel, this formulation, demonstrating a better tumor penetration in preclinical studies, allows reductions in reconstitution volume, infusion time, risk of hypersensitivity reactions, incidence of neutropenia and time needed to recover from peripheral neuropathy.[12-14]
Nab-paclitaxel is currently approved both as single-agent, for the treatment of metastatic breast cancer,[15] and as combined therapy with gemcitabine or carboplatin in first-line setting, for the treatment of advanced pancreatic adenocarcinoma[16] or advanced non-small cell lung cancer (NSCLC),[17] respectively. Three Asian retrospective analyses conducted in relapsed SCLC patients showed some anticancer activity of nab-paclitaxel, although definitive conclusions could not be warranted.[18-20] Since nab-paclitaxel has not been prospectively studied in relapsed SCLC yet, we designed this open-label, prospective phase II trial with the aim to assess its activity and safety in patients with both *refractory* and *sensitive* disease.

Methods

Study design and participants

Nabster was a prospective, open-label, multicentre, phase II trial evaluating the activity and safety of nab-paclitaxel in SCLC patients who relapsed during or after first-line platinum-based chemotherapy. Patients were prospectively classified according to treatment free interval (TFI), i.e. the interval from the last chemotherapy administration during first-line chemotherapy and the occurrence of progressive disease, as *refractory* (TFI < 60 days) or *sensitive* (TFI ≥ 60 days).[4]
Patients aged 18 years or older were eligible for study participation if they had a histological or cytological confirmed diagnosis of SCLC, large cell neuroendocrine carcinoma (LCNEC) or undifferentiated neuroendocrine carcinoma of the lung, according to World Health Organization (WHO) classification 2015,[21] adequate liver, renal and bone marrow functions, measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1,[22] documented radiological evidence of disease progression during or after platinum/etoposide chemotherapy, Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 to 1. In addition, patients with treated, asymptomatic and stable brain metastases were allowed to be enrolled into the study.

The study protocol was approved by each local institutional ethics committee and conducted in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice and the Declaration of Helsinki. Written informed consent was obtained from all participants.
The study was sponsored by Gruppo Oncologico Italiano di Ricerca Clinica (GOIRC) and partially supported by Celgene that provided investigational medicinal product and a restricted grant for the management of study procedures. The trial was registered at ClinicalTrials.gov (number NCT03219762) and assigned its Eudract number (2016-000408-27).

Procedures
Eligible patients received weekly intravenous administration of nab-paclitaxel 100 mg/smq on days 1,8,15 of a 28-days cycle until a maximum of 6 cycles, progressive disease or unacceptable toxicity. Treatment could be continued beyond the 6th cycle in patients with confirmed and prolonged objective response, clinical benefit and good tolerance to study drug. Dose reductions and delays were permitted as per-protocol definitions (Study protocol is available in **S.1, Supplemental Data**).
At screening, disease assessment included a computed tomography (CT) scan of the thorax and upper and lower abdomen with contrast. A brain CT or magnetic resonance imaging (MRI) scan had to be performed only if previously abnormal or clinically indicated.
Tumor response was assessed with computed tomography (CT) scan every 8 weeks (± 7 days), according to RECIST criteria v.1.1, and at least 4 weeks after the first observation of a complete or partial response. Furthermore, brain CT scans had to be repeated if initially abnormal or to be performed if clinically indicated. Patients who discontinued nab-paclitaxel without evidence of progressive disease, continued to be evaluated for disease status every 8 weeks, unless they started new anticancer therapy. Complete response (CR) was defined as the complete disappearance of all target lesions and all non-target lesions, if present. Partial response (PR) was defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. Progressive disease (PD) was defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. The appearance of one or more new lesions and/or unequivocal progression of pre-existing non-target lesions were also considered criteria defining disease progression. Laboratory testing was performed before each study drug administration.

Outcomes
The primary endpoint was objective tumor response. Tumor response was evaluated according to standard RECIST v.1.1 and based on Investigator's assessment. Data were reported as percentage of CR, PR, stable disease (SD) and PD. Patients with no tumor assessment after baseline were classified as non-responders. Furthermore, to ensure consistency of tumor response measurements among Centres, CT scans performed for all evaluable patients at baseline and during study treatment could be reviewed by a blinded independent radiological committee (BIRC).
Secondary endpoints were toxicity, progression free survival (PFS) and overall survival (OS). The assessment of safety was based mainly on the frequency of adverse events; toxicity was measured according to NCI Common Toxicity Criteria Adverse Events (NCI-CTCAE), version 4.03.
PFS was defined as the time from the date of patient's registration to the date of the evidence of progressive disease, death due to any cause, or the last date the patient was known to be progression-free or alive. OS was calculated from the date of patient's registration to the date of death from any cause or the last date the patient was known to be alive.

Statistical design
The aim of this study was to evaluate if nab-paclitaxel objective tumor response rate in each of the two cohorts, *sensitive* and *refractory* relapsed SCLC, was sufficient to justify further investigation of the drug in these patients.

In *refractory* disease, an objective response rate (ORR) ≤ 5% would not have been considered of further interest. According to the Fleming's single stage design, based on our hypothesis that experimental treatment could guarantee an ORR ≥ 20% (for a 5% significance level and 80% power), 22 patients with *refractory* disease were to be enrolled into the study. An ORR > 5% was considered possible if at least 4 objective responses had been observed.
In *sensitive* disease, an ORR ≤ 15% would not have been considered of further interest. According to the Fleming's single stage design, based on our hypothesis that experimental treatment could guarantee an ORR ≥ 30% (for a 5% significance level and 80% power), 43 patients with *sensitive* disease were to be enrolled into the study. An ORR > 15% was considered possible if at least 11 objective responses had been observed.
The study was not designed to perform any comparison between the two cohorts.
Registered population included all patients who were enrolled into the trial. All enrolled patients who received at least one dose of nab-paclitaxel were included in the modified intention-to-treat (mITT) population and considered evaluable for activity and safety.
Descriptive tables were produced for the ORR and the best overall response. Exact binomial method was used to estimate the ORR and its 90% confidence interval.
The assessment of safety was based on the frequency of adverse events that were described as the number (and percentage) of patients reporting any adverse event, as adverse event in each body system and each individual adverse event.
Probabilities of PFS and OS were calculated according to the Kaplan-Meier product-limit method. The data cut-off for analysis was October 18, 2018.

Results

Patient and treatment characteristics

Between February 2017 and March 2018, 72 patients were enrolled into the trial from 18 Italian Centres (a list of all participating Centres is available in **S2, Supplemental Data**). Of them, 68 patients (25 *refractory* and 43 *sensitive*) were evaluable for safety and activity and included in the mITT population (**Fig. 1**). Baseline patients' characteristics are shown in **Table 1**. With a median age of 68.5 years (44-80), a male predominance (65%) and a high prevalence of extensive disease (84%), our study population was quite representative of clinical practice. Notably, among patients with extensive disease, 42% had liver involvement, 12% had central nervous system (CNS) disease and 16% had both liver and brain metastases at the time of study enrolment.
The mean number of courses per patient was 2.48 in *refractory* group and 3.00 in sensitive one. Only 12% of patients concluded the planned treatment courses. Dose reduction occurred 61 times (32%) in 39 patients, mainly due to haematological toxicity (26 cases). Dose delay was reported 49 times (25%) in 33 patients. Despite dose reductions and delays, the relative dose intensity remained good (76% in *refractory* cohort and 80% in *sensitive* cohort). All information on treatment distribution is available in **S.3 (Supplemental data)**.

Tumor response

According to Investigator's assessment, PR was observed in 2 (8%; IC 90%, 1.7-24.0) patients in *refractory* cohort and in 6 (13.9%; IC 90%, 6.6-26.1) patients in *sensitive* one. Thirteen (19.1%) patients had SD, 5 patients (20.0%) of them in *refractory* cohort, while 36 (52.9%) patients had PD as best response, of whom 14 (56.0%) in *refractory* group (**Table 2**).
Investigator-assessed responses were reviewed by a BIRC. According to central review assessment (**Table 2**), PR was observed in 4 (16.0%; IC 90%, 6.1-33.5) patients in *refractory* cohort and in 8 (18.6%; IC 90%, 9.9-31.4) patients in *sensitive* one. Eleven (16.2%) had SD, 4 patients (16.0%) of them in refractory cohort, while 34 (50.0%) patients had PD as best response, of whom 13 (52.0%) in *refractory* group. Finally, 11 (16.2%) patients was not evaluated for response, 4 in *refractory* group and 7 in *sensitive* one. Waterfall plot (**Fig. 2**) shows the distribution and depth of response in patients evaluated for target lesions.

Notably, among 16 (28%) patients with CNS involvement at baseline, 5 (31.2%) patients obtained a brain disease control, including also 2 (22.2%) patients with concomitant CNS and liver disease.

Safety

All 68 patients included in the mITT population were evaluable for safety. Adverse events of any grade occurred in 53 patients (77.9%) (**Table 3**). Haematological and non-haematological toxicities of any grade were reported in 36 (52.9%) and in 49 (72.0%) patients, respectively, whereas the same toxicities of grade 3-4 were observed in 9 (13.2%) and 6 (8.8%) patients, respectively. The most frequent adverse event of any grade was fatigue (54.4%), the only toxicity which led to permanent discontinuation of study drug in 2 (4.6%) patients. Only one treatment-related adverse event of grade 4 (leuko-neutropenia) was reported throughout the study period. There was no treatment-related death.

Survival

The median duration of follow-up was 8.4 months (IQR, interquartile range: 5.8-12.4). Median PFS (mPFS) was 1.84 months (IC 95%, 1.02-3.16) in *refractory* cohort, and 4.2% (IC 95%, 0.3-17.7) of these patients were free from disease progression at 6 months (**Fig. 3A**). Similar results were observed in *sensitive* group, for which mPFS was 1.88 months (IC 95%, 1.81-2.37), with a 6-month PFS rate of 10.1% (IC 95%, 3.2-21.5) (**Fig. 3A**).

Median OS (mOS) was 3.65 months (IC 95%, 2.07-4.57) in *refractory* cohort and 20.9% (IC 95%, 7.6-38.6) of these patients were alive at 6 months (**Fig. 3B**), whereas in *sensitive* cohort mOS was 6.64 months (IC 95%, 3.16-9.70), with a 6-month OS rate of 60.8% (IC 95%, 44.1-73.9) (**Fig. 3B**).

At the time of data cut-off, no patient was still being treated, although 4 (5.9%) patients (1 in *refractory* cohort and 3 patients in *sensitive* one) had no event, and 58 (85.3%) patients progressed, of whom 22 (88.0%) were refractory. Twenty-one (30.9%) patients were alive (3 *refractory* and 18 *sensitive*), while 47 (69.1%) patients were dead, 40 (58.8%) of them due to disease progression (19 and 21 patients in *refractory* and *sensitive* cohorts, respectively).

Discussion

Based on its poor prognosis and survival plateau achieved in the last decades, SCLC has been defined one of the *recalcitrant* cancers. Till now, several treatment strategies and clinical trial designs have been developed with daunting results. Therefore, there is an urgent need for additional and effective therapeutic innovations. The impressive results of the use of immune checkpoint inhibitors, such as the monoclonal antibodies directed against programmed cell death-1 (PD-1) and its ligand (PD-L1), for the treatment of different solid tumors, has led to evaluate them also in SCLC. In the last year, two randomised, controlled phase III trials showed that adding atezolizumab (IMpower-133 study) or durvalumab (CASPIAN study), two antibodies directed against PD-L1, to standard first-line chemotherapy significantly improved the OS in patients with ED-SCLC.[23,24] These results have defined a new paradigm shift for the treatment of ED-SCLC, leading to a new standard of care in first-line setting.

In second-line setting, different clinical studies are investigating the efficacy of several new agents, either alone, combined or compared to standard chemotherapy.

Our study is the first prospective trial of nab-paclitaxel for relapsed SCLC. Overall, this trial showed a modest anticancer activity, so that it did not meet its primary endpoint (ORR), in both *refractory* and *sensitive* cohorts. Based on investigator's assessment and study design, there were 2 tumor responses (ORR, 8%) out of 4 or more required in *refractory* group and 6 tumor responses (ORR, 13.9%) out of 11 or more required in *sensitive* one needed to reach the primary objective of the study. However, after central independent radiological review, 2 additional cases of objective response were identified in the *refractory* group which would qualify the study as positive, at least in this cohort. Secondary endpoints of the study included PFS, OS and toxicity. Data on survival outcomes confirmed the dismal prognosis of these patients, with a mPFS less than 2 months in both

refractory and *sensitive* cohorts and a mOS that was almost double in sensitive group (6.64 months) compared to refractory one (3.65 months). Furthermore, although nearly 30% of patients with CNS involvement at baseline had a brain disease control, 11 (68.7%) out of 16 patients experienced a rapid progressive disease (within 1-2 courses), including 2 patients with early death. These data confirmed the unfavourable prognostic role of CNS involvement, especially in relapsed SCLC.

Our results were similar to those reported from a retrospective study[18] in which 9 of the 14 enrolled patients were treated with nab-paclitaxel, as third-line or later. In this subgroup, ORR, mPFS and mOS were 11%, 2.0 months and 4.0 months, respectively. Almost all patients were refractory to first-line chemotherapy regimen, but the authors did not report any information on the prevalence of brain and liver metastases in this population.

Similarly, a retrospective analysis reported outcome of 31 heavily pre-treated Japanese SCLC patients of whom only 4 received nab-paclitaxel, preventing any meaningful consideration.[20]

In our study, the discordance in terms of ORR between local and central assessment has been mainly due, at least in some cases, to an improper application of RECIST criteria v1.1 by local radiologists. For example, two refractory patients considered stable were reclassified as responders after central radiological review because of a misleading interpretation of two target liver lesions in one case and two pathological mediastinal lymph nodes in the other one. These results in refractory cohort are quite similar to those reported from different phase II trials that showed how paclitaxel had a promising antitumor activity, reaching a response rate of 20-29%. [9,25] A higher response rate (41%) was reported from a phase II trial of irinotecan administered in 30 Japanese patients with relapsed SCLC. However, it is reasonable to believe that patient population included into this study was "positively" selected. In fact, all patients had ECOG PS 0 or 1, one third of them had LD-stage, 60% had sensitive recurrent disease, with only 10% and 13% of patients having brain and liver involvement, respectively. [26] Similar results was reported from a multicentre, single-arm phase II basket study of lurbinectedin, a RNA polymerase II inhibitor, in patients across advanced solid tumors. Thirty-seven (35.2%) out of 105 enrolled SCLC patients had a partial response. Overall, median PFS and OS times were 3.9 months (95% CI, 2.6-4.6) and 9.3 months (95% CI, 6.3-11.8). According to TFI (< or ≥ 90 days), these clinical outcomes have more than doubled in sensitive patients (45%, 4.6 months and 11.9 months) compared to refractory ones (22.2%, 2.6 months and 5.0 months). Lurbinectedin showed a favourable and manageable toxicity profile. The most common grade 1-2 adverse events were fatigue (51.4%), nausea (32.4%), decreased appetite (21%), vomiting (18.1%) and diarrhea (12.4%). Grade 3-4 adverse events included neutropenia (22.9%), anemia and fatigue (6.7% each), febrile neutropenia and thrombocytopenia (4.8% each).[27]

To date, topotecan remains the only drug approved for relapsed SCLC patients, based on the results of different phase II-III trials that showed a response rate of 7-38% among sensitive patients and of 2-7% among refractory ones.[5-7,28,29] A recent meta-analysis described clinical outcomes of 1347 SCLC patients treated with topotecan from 14 prospective trials.[30] Objective tumor response and 6-month OS rates were 5% and 37% in refractory patients and 17% and 57% in sensitive ones, respectively. Notably, these data are aligned with the results reported from our study, although survival outcome in our refractory patients was worse. Results from clinical studies investigating the role of anti-PD-1/PD-L1 drugs in second- or further-line setting were conflicting so far, particularly when used as single agent.[31-36] In the recently reported phase III CheckMate-331 trial of nivolumab, a human IgG4 monoclonal antibody against PD-1, 569 SCLC patients relapsed on or following platinum-based chemotherapy were randomized (1:1) to receive either nivolumab (N=284) or standard second-line chemotherapy (topotecan or amrubicin, N=285).[37] Results of this study showed that, after 7.0-7.6 months of median follow-up, nivolumab did not yield a significant survival improvement (primary endpoint) compared to the standard chemotherapy arm (7.5 months [95% CI 5.6 – 9.2] vs 8.4 months [95% CI 7.0 – 10.0], p = 0.11). This confirms that, at least in a subset of relapsed SCLC patients, chemotherapy is the option of choice.

Based on safety, nab-paclitaxel has shown a favourable toxicity profile, particularly considering historical data on topotecan. Nab-paclitaxel was well tolerated and proposed schedule was feasible.

The most common adverse events of grade 3-4 were neutropenia (10%), leukopenia and fatigue (4% each) and anaemia (1%). Conversely, topotecan was encumbered with a high incidence of severe (grade 3-4) haematological toxicity, including neutropenia (69%), thrombocytopenia (41%) and anemia (24%).[30]

Although the primary end-point of the study did not meet, nab-paclitaxel demonstrated a potential antitumor activity in refractory patients, and a favourable toxicity profile. Nevertheless, and based on the lack of evidence of a higher efficacy of immune checkpoint inhibitors over second-line chemotherapy, we believe that further studies comparing nab-paclitaxel to the standard-of-care in refractory SCLC, would be worthwhile.

Additional information

Competing interest: Prof. Ardizzoni has received research grant support from BMS and Celgene; personal fees for serving in a consultant and/or advisory role for BMS, MSD and Boehringer; honoraria from Eli-Lilly and Pfizer. Prof. Frassoldati has received personal fees for serving in a consultant and/or advisory role for Novartis, Roche and Astrazeneca; honoraria from Novartis, Astrazeneca, Pfizer, Lilly, Eisai, Roche, Novartis and Celgene. Dr. Cavanna has received personal fees for serving in a consultant and/or advisory role for Astrazeneca and Merck; honoraria from Celgene, Pfizer and Ipsen. The remaining authors declare no conflict of interest.

Ethics approval and consent to participate: The study protocol was approved by each local institutional ethics committee and conducted in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice and the Declaration of Helsinki. Written informed consent was obtained from all participants.

Consent for publication: No individually identifiable data is presented.

Data availability: Anonymised dataset may be available from the corresponding author on reasonable request.

Funding: The study was sponsored by Gruppo Oncologico Italiano di Ricerca Clinica (GOIRC) and partially supported by Celgene that provided investigational medicinal product and a restricted grant for the management of study procedures.

Author contributions: FG, MT, GL, LB and AA wrote full protocol and defined study design. AA obtained funding for the study. FG, MT, FB, FR, LC, AF, AD, LL, CD, SC, IC, FS, and AA enrolled patients onto the study. SB reviewed in blinded all available imaging scans. FG, LT, LB and AA collected and prepared data for the analysis. LT and LB conducted the analyses. FG, MT, LB and AA wrote full paper. All authors read and approved the final manuscript.

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Figure 1. CONSORT flow diagram

Figure 2. Waterfall plot on depth and type of response in patients with evaluable target lesions.

Figure 3. PFS and OS in modified ITT population

Table 1. Patients' demographic characteristics and tumor features

Table 2. Best overall response based on both Investigator and BIRC assessment

Table 3. Toxicity profile

Supplementary information
S1. Nabster full protocol
S2. List of all participating Centres
S3. Treatment distribution