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Nadunolimab (CAN04), a first-in-class monoclonal antibody against IL1RAP, in combination with chemotherapy in subjects with pancreatic cancer (PDAC) and non-small cell lung cancer (NSCLC)

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Background

The Interleukin-1 Receptor Accessory Protein (IL1RAP) is expressed by cancer and stromal cells of many tumors. The interleukin-1 (IL-1) pathway is upregulated in response to cytotoxic agents as a survival signal and both IL-1α and IL-1β bind the IL-1 receptor 1 (IL-1R1). This induces dimerization of IL-1R1 with IL1RAP, which is a requirement for IL-1 signal transduction.

Nadunolimab (CAN04) is a first-in-class IgG1 antibody that targets IL1RAP and blocks IL-1α and IL-1β signaling. The antibody is non-fucosylated for a more potent antibody-dependent cellular cytotoxicity. CAN04 has been assessed as monotherapy in solid tumors without reaching maximum tolerated dose (Awada et al, 2019).

Here we report the interim efficacy and safety results of CAN04 in combination with gemcitabine/nab-paclitaxel in pancreatic ductal adenocarcinoma (PDAC) and with gemcitabine/cisplatin in non-small cell lung cancer (NSCLC) from the CANFOUR Phase 1/2a study (NCT03267316).

Methods

The primary objective of the CANFOUR study was to determine the safety of CAN04 in combination with standard of care chemotherapy. Efficacy by RECIST1.1/iRECIST is a secondary endpoint.

Initial CAN04 dose was 5 mg/kg weekly. A priming dose of 0.5 mg/kg was given on day -7 to mitigate the risk of infusion related reaction (IRR).

CANFOUR study design and patient disposition

CANFOUR is a Phase 1/2a multi-center open label study. Here we present interim results of two Phase 2 expansions of CAN04 in combination with standard of care chemotherapy:

- CAN04 combined with gemcitabine/nab-paclitaxel as first line treatment of PDAC (n=36):
  - Safety population: n=36
  - Efficacy population, modified intention to treat (mITT): n=33 (3 did not receive chemotherapy due to IRR with priming dose; two Grade 2 and one Grade 3)
  - Enrollment is completed
- CAN04 combined with gemcitabine/cisplatin as first line treatment or progression after pembrolizumab in NSCLC (n=31):
  - Safety population: n=31
  - Efficacy population, mITT: n=27 (2 did not receive chemotherapy (1 consent withdrawn, 1 spinal cord compression); 2 have not reached first evaluation and are ongoing)
  - Enrollment is ongoing

Results

Patient Characteristics

Key characteristics of the patient populations are summarized in Table 1.

Table 1. Baseline characteristics

A

PDAC (n=36)	
Age	
Median	64
Range	46-87
Sex	
Female	53%
Male	47%
PS	
0	64%
1	36%
Stage	
IV	94%
III	6%
CA19-9	
Median	4483
Range	1-47929
Previous therapy	
Adjuvant chemotherapy	15%
Biliary stent	13%
Radiation	8%
Surgery	36%

B

NSCLC (n=31)	
Age	
Median	64
Range	39-77
Sex	
Female	34%
Male	66%
PS	
0	48%
1	52%
Histology	
Non-squamous	58%
Squamous	35%
Unknown	6%
Stage	
IV	90%
III	10%
Previous pembrolizumab	
Yes	45%
No	55%
Previous therapy	
Radiation	19%
Surgery	6%

Safety

Table 2. Safety summary

A

PDAC (n=36)	All Grade n (%)	Grade ≥3 n (%)
Number of patients with at least 1 TEAE	36 (100%)	33 (92%)
Hematological TEAEs		
Neutropenia	27 (75%)	24 (67%)
Thrombocytopenia	14 (39%)	7 (19%)
Anemia	14 (39%)	5 (14%)
Febrile neutropenia	6 (17%)	6 (17%)
Lymphopenia	3 (6%)	2 (6%)
Non-hematological TEAEs		
Cholangitis	4 (11%)	4 (11%)
Hypokalemia	9 (25%)	3 (8%)
Hypertension	5 (14%)	3 (8%)
GGT increased	4 (11%)	3 (8%)
General physical deterioration	4 (11%)	3 (8%)
Cholestasis	3 (8%)	3 (8%)
Nausea	24 (67%)	2 (6%)
Fatigue	21 (58%)	2 (6%)
Vomiting	14 (39%)	2 (6%)
Ascites	3 (8%)	2 (6%)
Pulmonary embolism	2 (6%)	2 (6%)
Hyponatremia	2 (6%)	2 (6%)

B

NSCLC (n=31)	All Grade n (%)	Grade ≥3 n (%)
Number of patients with at least 1 TEAE	27 (87%)	23 (74%)
Hematological TEAEs		
Neutropenia	20 (65%)	15 (48%)
Thrombocytopenia	20 (65%)	11 (36%)
Anemia	15 (48%)	5 (16%)
Febrile neutropenia	4 (13%)	4 (13%)
Non-hematological TEAEs		
Fatigue	7 (23%)	1 (3%)
Pneumonia	5 (16%)	3 (10%)
Hypokalemia	4 (13%)	1 (3%)
Infusion related reaction	4 (13%)	1 (3%)
Vomiting	3 (10%)	1 (3%)
Septic shock	2 (7%)	2 (7%)
GGT increased	2 (7%)	1 (3%)
Weight increased	2 (7%)	1 (3%)
Chronic kidney disease	2 (7%)	1 (3%)
Renal failure	2 (7%)	1 (3%)

Table 2 displays treatment emergent adverse events (TEAE) of All Grades and Grade ≥3 (n ≥2 for PDAC and n ≥1 for NSCLC). IRRs were reported in 44% of PDAC patients (Grade 3 in one patient), and in 13% of NSCLC patients (Grade 3 in one patient). Of these, 70% occurred with the priming dose. No Grade ≥3 neuropathy has been reported in this trial. Although occurrence of neutropenia is higher than historical control for chemotherapy only, this can be managed by dose modifications and/or G-CSF.

Efficacy PDAC

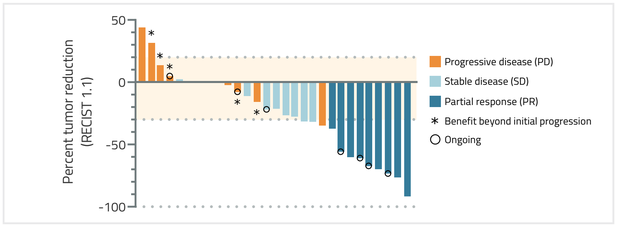

Figure 1. Waterfall plot for tumor reduction in PDAC

The plot in Figure 1 is based on largest percent tumor reduction (target lesions) and best overall response during study assessed as per RECIST1.1. Five patients with initial PD at first evaluation showed benefit beyond initial progression per iRECIST, with concomitant CA19-9 reduction, and thus continued therapy.

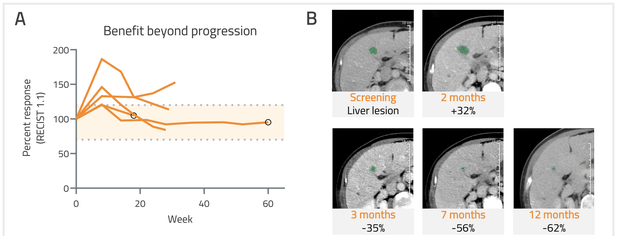

Figure 2. Benefit beyond initial progression observed in five PDAC patients

The plot in Figure 2a shows individual growth curves for target lesions of the five (15%) PDAC patients demonstrating signs of benefit beyond initial PD, predicting long iPFS (lines ending with a circle symbol indicate patients still on treatment). Figure 2b shows CT scans from one of the five patients.

A summary of the PDAC patient response parameters is disclosed in Table 3.

Table 3. Response parameters in PDAC

Response parameter	PDAC (n=33)
ORR per investigator	27 % (9 PR)
Benefit beyond initial PD (iRECIST)	15%
Disease control rate (PR+SD+iRECIST iUPD/iSD*)	72%
Median duration of response	6.8 months (range 1.9 to 13.8)
iPFS	7.8 months

* Includes patients with initial RECIST 1.1 PD that continued treatment after the confirmatory scan showing repeated iUPD or better.

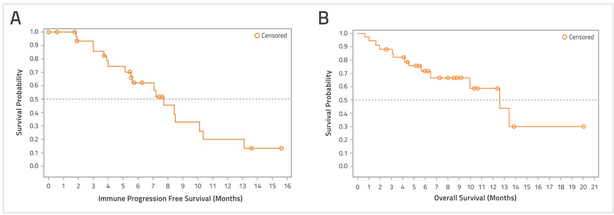

Figure 3. iPFS and OS for PDAC

Median iPFS is 7.8 months (95% CI 5.2 to 10.2) with 55% of events (Figure 3a). iPFS ranges from 0 to 15.6 months. iPFS rate is 62% at 6 months and 19% at 1 year. Seven patients at cut-off are still receiving treatment. Median OS is 12.6 months (95% CI not estimable) with 42% of OS events (Figure 3b). 6-month survival rate is 71% and 1-year survival rate is 55%.

Efficacy NSCLC

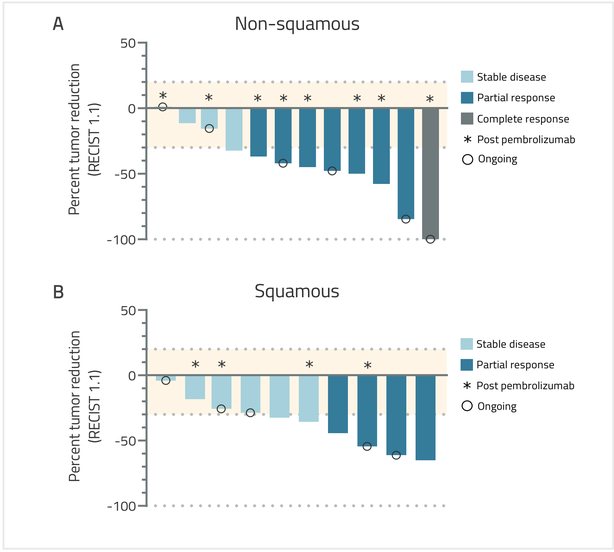

Figure 4. Waterfall plots for tumor reduction in non-squamous and squamous NSCLC

The plots in Figure 4 are based on largest percent tumor reduction (target lesions) and best overall response during study assessed as per RECIST1.1. For non-squamous NSCLC, 75% of patients post-pembrolizumab achieved response, versus 25% of squamous NSCLC patients.

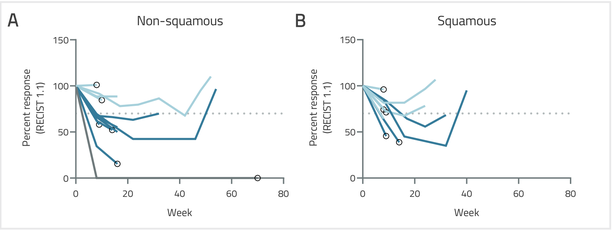

Figure 5. Individual tumor growth curves for non-squamous and squamous NSCLC

The plots in Figure 5 show individual growth curves for target lesions of patients with non-squamous (a) and squamous (b) NSCLC. Dotted line indicates cut-off (30% tumor reduction) between partial response and stable disease. Colors and symbols indicate the same categorization of patients as in Figure 4.

A summary of the NSCLC patient response parameters is disclosed in Table 4.

Table 4. Response parameters in non-squamous and squamous NSCLC

Response parameter	NSCLC (n=27)	Non squamous (n=15)	Squamous (n=11)
ORR per investigator	48% (13 PR)	53%	36%
Disease control rate (CR+PR+SD)	85%	80%	90%
Median duration of response	5.8 months (range 1.7 to 22.1)	NA	NA
PFS	7.2 months	NA	NA

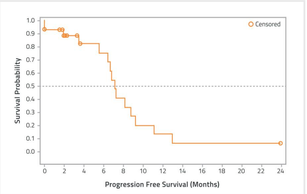

Figure 6. PFS for NSCLC

Median PFS is 7.2 months (95% CI 5.6-9.2) with 54% of events (Figure 6). Probability for 6-month PFS is 75% and 1-year is 14%. Enrollment is ongoing at cut-off.

Conclusions

- CAN04 combined with standard of care chemotherapy shows promising efficacy in NSCLC and PDAC:
  - In PDAC, iPFS and OS is longer than historical controls (von Hoff et al, 2013)
  - A subgroup of PDAC patients showed clear benefit beyond RECIST1.1 PD with long iPFS
  - In NSCLC, early data shows ORR well above historical control (Scagliotti et al, 2008), and at a similar level as platinum doublets plus pembrolizumab (Paz-Ares et al, 2018; Gandhi et al, 2018)
  - In NSCLC, trends show more pronounced effects in non-squamous histology
  - Non-squamous NSCLC patients pretreated with pembrolizumab showed the greatest response benefit
- Occurrence of neutropenia seems to be higher than historical control but is manageable by dose modifications and/or G-CSF
- Notably, no grade ≥3 neuropathy was observed in the trial
- The findings are incorporated in the next clinical phase of CAN04 combination therapy in PDAC/NSCLC patient groups
- Additional trials investigating CAN04 chemosensitization is performed in PDAC, NSCLC, triple negative breast cancer, colorectal cancer and biliary tract cancer

References

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