# FINAL RESULTS OF A PHASE II QUALITY OF LIFE RANDOMIZED, CROSS-OVER STUDY WITH GEMCITABINE AND NAB-PACLITAXEL IN LOCALLY ADVANCED OR METASTATIC PANCREATIC DUCTAL ADENOCARCINOMA: QOLINPAC

Chiritescu G[1], Dumon K[1], Verslype C[1], Houbiers G[2], Peeters M[3], Janssens J[4], Van Daele D[5], Laurent S[6], Arts J[7], Hendrickx K[8], Borbath I[9], Ferrante M[10], Bastin F[11], Goeminne JC[12], Van Laethem JL[13], Vanderstraeten E[14], Decaestecker J[15], Van Vaerenbergh W[16], Delhougne B[17], Van Cutsem E[1]

on behalf of the Belgian Group of Digestive Oncology (BGDO)

*1 UZ Leuven, 2 CHC St. Joseph Liege, 3 UZ Antwerp, 4 AZ Turnhout, 5 CHU Sart-Tilman Liege, 6 UZ Gent, 7 AZSL Bruges, 8 OLVZ Aalst, 9 CUSL Brussels, 10 AZSM Mechelen, 11 CHU Charleroi, 12 CMSE Namur, 13 Erasme Brussels, 14 AZMM Gent, 15 AZD Roeselare, 16 HH Lier, 17 CHRC Liege*

EudraCT 2013-004101-75; NCT02106884

## BACKGROUND

**ACCORD 11 trial[1,2]**
- Overall survival: FOLFIRINOX 11 months vs. Gem alone 6.8 months (HR=0.57, p<0.001)
- Better QOL with FOLFIRINOX compared to Gem: deterioration free rate of global health status at 3 months 83% with FOLFIRINOX vs. 69% with Gem; at 6 months 69% vs. 44%

**MPACT trial[3,4]**
- Overall survival: nab-Paclitaxel with Gem 8.7 months vs. Gem alone 6.6 months (HR=0.72, p<0.001)
- No QOL data for nab-Paclitaxel with Gem

## STUDY DESIGN

- Academic, multicentric study in Belgium, sponsored by UZ Leuven within the Belgian Group of Digestive Oncology network
- Phase II, randomized 1:1

**QOL INSTRUMENT**
- EORTC QLQ-C30 V. 3.0 QOL questionnaire[5,6] applied at baseline and q4wks until death or for a max of 12 months

**DEFINITION**
- Definitive deterioration of a QOL score: a decrease of at least 10 points (minimal clinically important difference) between the score at baseline and any timepoint without further recovery[7]

**HYPOTHESIS**
- A deterioration free rate of the global health score of 83% for nab-P + Gem arm and of 69% for Gem arm at 3 months (log-rank test)[1,2]

## ENDPOINTS

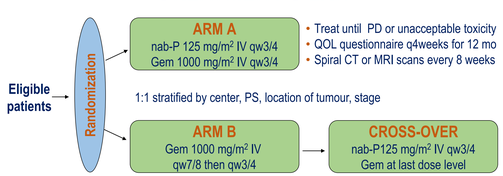
**MAIN**
- Deterioration free survival rates of QOL parameters at 3 months, comparatively in treatment groups

**SECONDARY**
- Time intervals to definitive deterioration for all QOL scores: global health, functional and symptom scales
- Efficacy: PFS, OS, best response and duration of response, disease control
- Safety: drug exposure, AEs/SAEs (NCI CTCAE version 4.0), deaths within 60 days and on study, incidence of lab abnormalities
- Descriptives of the relationship between time to progression and TR data

## TARGET POPULATION

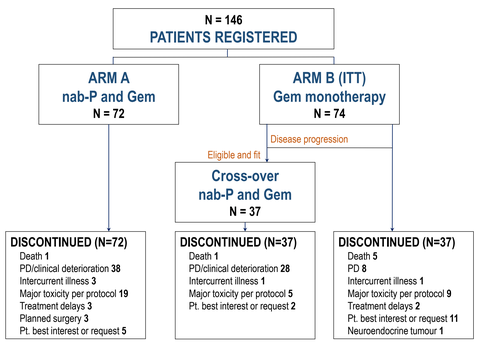
- Unresectable locally advanced or metastatic pancreatic adenocarcinoma
- Histologically or cytologically confirmed, valuable or measurable disease
- Consenting, previously untreated patients, able to receive nab-P and Gem

## TREATMENT PLAN




## RESULTS

### PATIENT DISPOSITION – CONSORT




### PATIENT CHARACTERISTICS AT BASELINE

| BASELINE | Arm A nab-P+Gem N=72 (%) | Arm B (ITT) Gem N=74(%) | Total N=146 (%) |
|---|---|---|---|
| **Male sex** | 41 (57) | 42 (57) | 83 (57) |
| **Age (yrs)** | | | |
| Median | 64 | 65 | 65 |
| Range | 40-82 | 41-82 | 40-82 |
| **Site of pancreatic tumour** | | | |
| Head | 16 (22) | 19 (26) | 35 (24) |
| Body | 37 (51) | 34 (46) | 71 (49) |
| Tail | 19 (26) | 21 (28) | 40 (27) |
| **Locally advanced/Metastatic** | | | |
| Locally advanced | 37 (51) | 41 (55) | 78 (53) |
| Locally advanced and metastatic | 27 (38) | 30 (41) | 57 (39) |
| Metastatic | 62 (86) | 63 (85) | 125 (86) |
| **ECOG performance status** | | | |
| 0 | 27 (38) | 23 (31) | 50 (34) |
| 1 | 42 (58) | 49 (66) | 91 (62) |
| 2 | 3 (4) | 2 (3) | 5 (3) |

### TREATMENT EXPOSURE

| | Arm A nab-P+Gem N = 72 (%) | Arm B (ITT) Gem N = 37 (%) | Arm B (ITT) Cross-over nab-P+Gem N = 37 (%) |
|---|---|---|---|
| **Prior treatment** Adjuvant chemotherapy | 5 (7) | 2 (5) | 4 (11) |
| **Study treatment duration**[a] median weeks (range) | 24 (4 – 137) | 14 (1 – 105) | 43 (10 – 130) |
| **Relative dose intensity mean**[b] nab-P (%) | 73.5 | NA | 65.8 |
| Gem (%) | 74.5 | 67.9 | 71.0 |

[a]From start of treatment to EoT visit; [b]%sum of doses planned/sum of doses given.

### QUALITY OF LIFE

| QOL questionnaires completed | Arm A nab-P+Gem 1st line N=72 | Arm B (ITT) N=74 Gem | Arm B (ITT) N=74 Cross-over nab-P+Gem | All groups |
|---|---|---|---|---|
| Total QLQ completed | 716 | 528 | 232 | 1476 |
| Baseline QLQ completed N (%) | 72 (100%) | 73 (99%) | NA | 145 (99%) |
| At least 2 QLQ completed N (%) | 69 (96%) | 66 (89%) | NA | 135 (92%) |
| Pts. evaluable for QOL change N (%)[a] | 72 (100%) | 72 (97%)[b] | NA | 144 (97%) |

[a]At least 2 QLQ completed or baseline and survival data available; [b]Two patients were not evaluable: one did not complete any questionnaire, the second completed only one at baseline and was lost to FU for survival. All QOL analyses are based on evaluable patients for whom data was available.

**Correlations of baseline QOL scores with efficacy variables[a]**

**COX regression models:**
- **OS median time:** Global health status HR 0.98, 95%CI 0.98-0.99, p=0.001; Physical function HR 0.98, 95% CI 0.97-0.99, p=0.001; Pain HR 1.009, 95% CI 1.003-1.015, p=0.003; Appetite loss HR 1.006, 95% CI 1.002-1.011, p=0.009.
- **PFS median time:** Global health status HR 0.99, 95%CI 0.98-0.99, p=0.019; Social function HR 0.99, 95% CI 0.98-0.99, p=0.021; Pain HR 1.006, 95% CI 1.00-1.012, p=0.042;

**Bivariate correlation models:**
- **Disease control:** Nausea/vomiting (p=0.044); Insomnia (p=0.032); Appetite loss (p=0.042).

[a]Intent to treat (all patients, both treatment arms); [b]For functional scales, a higher reported score indicates a better function; for symptom scales, a higher reported score indicates worse symptoms.

| Deterioration free rates of QOL scores[a,b] | Arm A nab-P+Gem 1st line N=72 | | | Arm B Gem N=74 (72)[c] | | | Arm B subgroups Gem N=44[d] | | | Arm B subgroups Cross-over nab-P+Gem 2nd line N=28[e] | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 3mo | 6mo | 9mo | 3mo | 6mo | 9mo | 3mo | 6mo | 9mo | 3mo | 6mo | 9mo |
| **FUNCTIONAL SCALES** | | | | | | | | | | | | |
| Global health status | 85% | 68% | 44% | 75% | 64% | 47% | 59% | 46% | 30% | NA | 93% | 75% |
| Physical function | 81% | 60% | 39% | 71% | 56% | 42% | 52% | 39% | 27% | NA | 82% | 64% |
| Role function | 81% | 65% | 43% | 71% | 54% | 40% | 54% | 39% | 28% | NA | 81% | 62% |
| Emotional function | 90% | 76% | 54% | 76% | 67% | 51% | 61% | 49% | 35% | NA | 93% | 76% |
| Cognitive function | 86% | 71% | 49% | 78% | 64% | 50% | 66% | 49% | 32% | NA | 92% | 84% |
| Social function | 85% | 65% | 43% | 74% | 61% | 46% | 58% | 44% | 27% | NA | 89% | 78% |
| **SYMPTOM SCALES** | | | | | | | | | | | | |
| Fatigue | 85% | 69% | 41% | 74% | 57% | 46% | 56% | 42% | 30% | NA | 79% | 69% |
| Nausea/vomiting | 90% | 71% | 51% | 74% | 63% | 51% | 58% | 42% | 33% | NA | 96% | 82% |
| Pain | 96% | 71% | 50% | 76% | 67% | 51% | 61% | 46% | 32% | NA | NA | 82% |
| Dyspnea | 90% | 72% | 47% | 78% | 63% | 53% | 64% | 47% | 38% | NA | 89% | 78% |
| Insomnia | 92% | 79% | 52% | 79% | 67% | 54% | 66% | 46% | 34% | NA | NA | 86% |
| Appetite loss | 88% | 63% | 43% | 78% | 57% | 47% | 64% | 40% | 29% | NA | 85% | 78% |
| Constipation | 93% | 76% | 56% | 76% | 68% | 53% | 61% | 48% | 34% | NA | NA | 82% |
| Diarrhea | 93% | 72% | 56% | 81% | 64% | 56% | 69% | 49% | 40% | NA | 89% | 82% |
| Financial problems | 90% | 75% | 55% | 81% | 71% | 57% | 68% | 55% | 39% | NA | 96% | 86% |

83% with FOLFIRINOX[1,2] · 69% with Gem alone[1,2]

[a]Kaplan-Meier (log-rank); [b]Definitive deterioration on the QOL scale or death if no QOL deterioration occurred are considered as "events"; [c]Percentages based on 72 evaluable pts; [d]Pts receiving Gem monotherapy at time of event; [e]Pts in cross-over receiving nab-P+Gem in 2nd line at time of event.

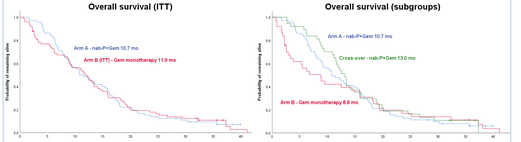
| Median time to definitive deterioration or death[a] months [95% CI] | Arm A nab-P+Gem 1st line N=72 | Arm B Gem N=74 (72)[b] | Arm B subgroups Gem N=44[c] | Arm B subgroups Cross-over nab-P+Gem 2nd line N=28[d] |
|---|---|---|---|---|
| **FUNCTIONAL SCALES** | | | | |
| Global health status | 7.9 [6.0-9.9] | 8.5 [6.0-10.4] | 4.6 [1.5-7.7] | 11.6 [9.0-14.2] |
| Physical function | 7.5 [5.9-9.1] | 6.5 [4.8-8.2] | 3.2 [0.2-6.2] | 9.8 [7.8-11.8] |
| Role function | 7.9 [5.8-10.0] | 6.7 [3.8-9.6] | 4.4 [1.7-7.2] | 10.3 [7.5-13.2] |
| Emotional function | 9.2 [7.7-10.6] | 9.0 [5.6-12.4] | 5.5 [3.4-7.5] | 12.5 [9.2-15.8] |
| Cognitive function | 8.9 [7.0-10.7] | 9.0 [5.5-12.5] | 5.8 [2.7-9.0] | 13.0 [11.2-14.9] |
| Social function | 7.9 [6.2-9.7] | 8.2 [5.4-11.1] | 5.5 [2.9-8.0] | 12.5 [10.4-14.6] |
| **SYMPTOM SCALES** | | | | |
| Fatigue | 7.2 [5.3-9.1] | 8.6 [5.3-11.9] | 4.9 [1.6-8.2] | 11.5 [9.5-13.6] |
| Nausea/vomiting | 9.1 [7.1-11.2] | 11.2 [7.0-15.4] | 4.6 [1.8-7.4] | 13.4 [11.6-15.2] |
| Pain | 8.9 [7.0-10.8] | 9.0 [5.6 -12.5] | 5.3 [3.5-7.0] | 12.5 [11.5-13.6] |
| Dyspnea | 8.0 [6.6-9.4] | 8.5 [6.9-12.0] | 5.5 [2.9–8.1] | 13.4 [11.4-15.3] |
| Insomnia | 9.1 [7.1-11.1] | 9.8 [6.3-13.3] | 5.4 [3.6-7.1] | 13.4 [11.9-14.8] |
| Appetite loss | 7.7 [6.2-9.2] | 7.8 [3.2-12.3] | 4.6 [2.7-6.5] | 13.6 [11.0-16.2] |
| Constipation | 10.1 [7.0-13.2] | 11.0 [7.4-14.6] | 5.6 [3.0-8.2] | 13.4 [11.3-15.5] |
| Diarrhea | 10.1 [7.9-12.3] | 10.3 [7.5-13.2] | 5.7 [3.0-8.5] | 13.4 [11.8-15.0] |
| Financial problems | 9.9 [7.4-12.4] | 11.5 [8.2-14.8] | 6.2 [4.9-7.5] | 13.6 [11.6-15.6] |

[a]Kaplan-Meier (log-rank); [b]Analysis based on 72 evaluable patients; [c]Patients receiving Gem monotherapy at time of event; [d]Patients in cross-over receiving nab-P+Gem in 2nd line at time of event.

### EFFICACY

| | Arm A nab-P+Gem N = 72 (%) | Arm B Gem N = 37 (%) | Arm B Cross-over nab-P+Gem N = 37 (%) |
|---|---|---|---|
| **Best response** | | | |
| Complete response | - | - | 2 (5) |
| Partial response | 31 (43) | 7 (19) | 7 (19) |
| Stable disease | 28 (39) | 19 (51) | 25 (68) |
| Progressive disease | 11 (15) | 6 (16) | 3 (8) |
| Not evaluable (no scans) | 2 (3) | 5 (14) | - |
| **Response rate ORR** (%)[a] [95% CI] | 43% [31-55] | 19% [6-32] | 24% [10-39] |
| **Disease control rate DCR** (%)[b] [95% CI] | 82% [73-91] | 70% [55-86] | 92% [83-100] |
| **Duration of response median** (months) [95% CI] | 3.5 [1.4-5.7] | 1.6 [1.5-1.8] | 3.3 [0.0-6.7] |
| **PFS** | | | |
| Median time months, [95% CI][c] | 7.4 [6.4-8.4] | 7.2 [0.8-13.6] | 5.4 [3.6-7.1] |
| Median time months, [95% CI][d] | 7.4 [6.4-8.4] | 7.2 [0.8-13.6] | 10.8 [9.8-11.8] |
| **Overall survival**[e,f] | | | |
| Median time months, [95% CI] | 10.8 [7.9-13.7] | 8.8 [3.9-13.7] | 13.0 [11.5-14.5] |
| Median time months, [95% CI][g] | 10.8 [7.9-13.7] | 11.9 [8.6-15.2] | |

[a]Arm A/Gem alone (p=0.012), [b]Gem alone/CO (p=0.017); [c]PFS in first line from start of treatment to 1st progression; [d]PFS from start of treatment to 1st progression in Arm A and Gem alone and to 2nd progression in CO; [e]Differences between groups were not statistically significant, [f]No effects of covariates such as gender, PS, site were seen in a COX proportional analysis model, [g]Arm B ITT analysis.




### SAFETY

| | Arm A nab-P+Gem N (%) | | Arm B Gem[a] N (%) | | Arm B nab-P+Gem[b] N (%) | |
|---|---|---|---|---|---|---|
| **At least one treatment related SAE**[c] | 27 (38) | | 17 (46) | | 4 (11) | |
| **Selected most common[d] AEs** | **Gr. ≥ 3** | **All** | **Gr. ≥ 3** | **All** | **Gr. ≥ 3** | **All** |
| Diarrhea | 5 (7) | 39 (54) | - | 23 (31) | 2 (5) | 15 (41) |
| Nausea | 5 (7) | 50 (69) | 4 (5) | 37 (50) | 1 (3) | 18 (49) |
| Vomiting | 6 (8) | 46 (64) | 4 (5) | 27 (36) | - | 10 (27) |
| Anorexia | 7 (10) | 45 (63) | 5 (7) | 38 (51) | 10 (27) | 16 (43) |
| Abdominal pain | 3 (4) | 33 (46) | 6 (8) | 31 (42) | 2 (5) | 10 (27) |
| Bile duct stenosis | 2 (3) | 2 (3) | 5 (7) | 5 (7) | 1 (3) | 1 (3) |
| Fatigue | 15 (21) | 60 (83) | 10 (14) | 41 (55) | 10 (27) | 20 (54) |
| Weight loss | 2 (3) | 8 (11) | - | 9 (12) | 2 (5) | 4 (11) |
| Peripheral sensory neuropathy | 5 (7) | 27 (38) | - | 4 (5) | 2 (5) | 12 (32) |
| Dyspnea | 6 (8) | 18 (25) | 4 (5) | 27 (36) | - | 8 (22) |
| Hemolytic uremic syndrome | 3 (4) | 3 (4) | 3 (4) | 3 (4) | - | - |
| Lung infection | 6 (8) | 8 (11) | 2 (3) | 6 (8) | 1 (3) | 1 (3) |
| Sepsis | 2 (3) | 2 (3) | 1 (1) | 1 (1) | 2 (5) | 2 (5) |
| Myocardial infarction | - | - | 3 (4) | 3 (4) | - | - |
| Thromboembolic event | 5 (7) | 10 (14) | 6 (8) | 21 (28) | - | 3 (8) |
| **Severe laboratory abnormalities** | **Gr. ≥ 3** | | **Gr. ≥ 3** | | **Gr. ≥ 3** | |
| Anemia | 9 (13) | | 8 (22) | | 5 (14) | |
| Neutropenia | 31 (43) | | 11 (30) | | 20 (54) | |
| Leukopenia | 21 (29) | | 2 (6) | | 9 (24) | |
| Thrombocytopenia | 12 (17) | | 5(14) | | 7(19) | |
| Hyperglycemia | 6 (8) | | 7 (19) | | 3 (8) | |
| Hypomagnesemia | 2 (3) | | - | | 3 (8) | |
| Creatinine increased | - | | 1 (3) | | - | |
| Bilirubin increased | 3 (4) | | 2 (5) | | 6 (16) | |
| ALT increased | 13 (18) | | 2 (5) | | 6 (16) | |
| AST increased | 7 (10) | | 5 (14) | | 3 (8) | |
| ALP increased | 9 (13) | | 3 (8) | | 8 (22) | |

[a]Events occurring before CO, %calculated ITT over 74 pts; [b]Events occurring after CO if worst grade per pt, % calculated over 37 pts; [c]Total of 184 SAEs in 98 unique pts, all expected; [d]Incidence ≥ 5% for gr. ≥ 3 worst grade per patient.

## CONCLUSIONS

- Patients receiving the combination nab-P/Gem seem to report better quality of life scores and for longer duration compared to patients on Gem monotherapy.
- In an intent to treat analysis, deterioration free rates of all QOL domains were higher in the combination arm than in the Gem arm at 3, 6 and 9 months. In subgroup analyses, deterioration free rates were higher in combination groups (1st and 2nd line) than in the Gem monotherapy group, some reaching statistical significance.
- A trend of longer time intervals from baseline to definitive deterioration of most QOL scores was observed in the nab-P groups.
- Baseline reported scores of global health status, physical function, pain and appetite loss showed some statistical effect on survival median time in univariate COX regression models. Global health status, social function and pain baseline scores correlated with progression free survival times. The value of baseline QOL scores as indicators of survival probability will be further explored in multivariate analyses including clinical variables.
- Median survival was long in all groups. Patients receiving nab-P in combination had better outcomes than those receiving Gem monotherapy, without reaching statistical significance. The effect of covariates will be further explored.
- Response rates were significantly higher in the combination groups. Two complete responses were seen in the cross-over group. Two patients were successfully resected post treatment with long survival.
- Treatment related toxicity was moderate but manageable with slightly higher incidences in the combination groups. As expected neutropenia, gastrointestinal symptoms, anorexia, fatigue and abdominal pain were the most common. Thromboembolic events were noted.
- Translational studies are ongoing.

Conducted with financial support and study medication from Celgene

ACKNOWLEDGEMENTS:

**Participating sites, investigators, co-investigators and coordinators**

01 - UZ Leuven - Prof. Dr. Eric Van Cutsem, Prof. Dr. Chris Verslype; 02 - UZ Antwerpen - Prof. Dr. Marc Peeters ; 03 - UCL Saint-Luc Bruxelles - Prof. Dr. Ivan Borbath; 04 - UZ Gent - Prof. Dr. Stéphanie Laurent; 05 - AZ Sint-Maarten Mechelen - Dr. Michel Ferrante, Dr Leen Mortier; 06 - CHU Charleroi - Dr. Fabienne Bastin; 07 - AZ Turnhout - Dr. Jos Janssens; 08 - CHR Citadelle Liege - Dr. Bernard Delhoughe; 09 - AZ Maria Middelares Gent - Dr. Erik Vanderstraeten; 10 - AZ St Lucas Brugge - Dr. Joris Arts; 11 - CHC St-Joseph Liege - Dr. Ghislain Houbiers;12 - CHU Sart-Tilman Liege - Dr. Daniel Van Daele; 13 - Clinique Ste-Elisabeth Namur – Dr. Jean-Charles Goeminne; 14 - AZ Delta Roeselare - Dr. Jochen Decaestecker; 16 - OLV Ziekenhuis Aalst - Dr. Koen Hendrickx; 17 - CUB Hôpital Erasme - Prof. Dr. Jean-Luc Van Laethem; 18 - AZ Klina - Dr. Willem Van Vaerenbergh

**BGDO: Mrs. Micheline Stempin and Ine De Bruyn** for site monitoring and continuous support

**UZ Leuven: Mrs. Kristien Dumon** for site monitoring, data management and continuous support; **Mrs. Anne Baggerman** for administrative and logistic support.

**The 146 patients and their families.**

ABBREVIATIONS:

nab-P – nab-Paclitaxel; Gem – gemcitabine; QOL – quality of life; QLQ – Quality of life questionnaire; mo – months; TR – translational research; EoT – end of treatment; TUDD – time interval to definitive deterioration; AE – adverse event; SAE – serious adverse event;

REFERENCES:

[1]Conroy, et al., 2011; [2]Gourgou-Burgade et al, 2013; [3]Von Hoff et all, 2013; [4]Goldstein, et al., 2015; [5]Aaronson, et al., 1993; [6]Fayers, et al., 2001; [7]Hamidou, et al., 2016.

CONTACT: gabriela.chiritescu@uzleuven.be