Poster 184-P

nab-Paclitaxel Plus Gemcitabine for Patients With Advanced Pancreatic Cancer Who Have Cholestatic Hyperbilirubinemia Secondary to Bile Duct Obstruction: A Phase I Safety and Pharmacokinetic Study

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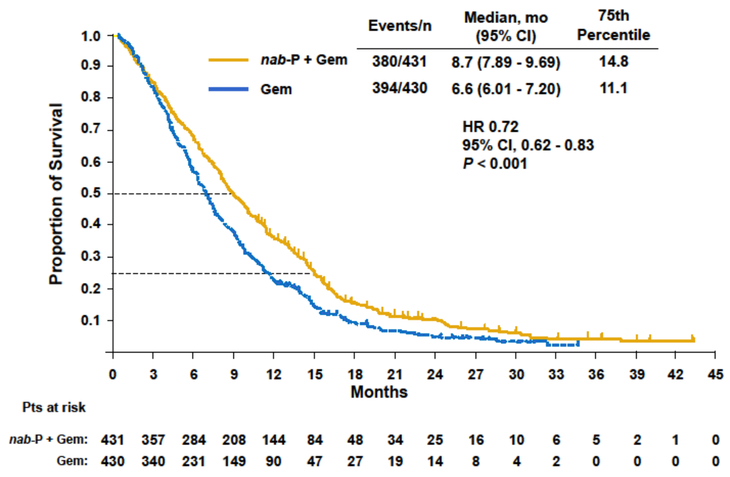
INTRODUCTION

- Pancreatic cancer (PC) frequently develops in the head of the pancreas, and subsequent bile duct compression can lead to cholestasis and elevated bilirubin[1]
- In patients (pts) with unresectable tumors and a life expectancy > 6 months, biliary stents offer palliative treatment of complications associated with obstructive jaundice[2,3]
- Paclitaxel is eliminated primarily through hepatic metabolism and biliary excretion[4,5]
- *nab*®-Paclitaxel (*nab*-P) + gemcitabine (Gem) is an approved treatment option for pts with metastatic PC (mPC) based on superior efficacy data vs Gem alone in the MPACT trial[6-8]
  - The MPACT trial, which demonstrated superior efficacy for *nab*-P + Gem vs Gem alone (Figure 1), did not include patients with elevated bilirubin[7,8]
  - The most frequent grade 3 - 4 AEs were neutropenia, leukopenia, fatigue, and neuropathy[7]
  - The MPACT trial excluded pts with bilirubin levels higher than the ULN; therefore, there are limited clinical data regarding this pt population and use of *nab*-P + Gem[7]
- Recommendations for treating pts with hepatic impairment are available in the current prescribing information:[6]
  - For pts with mild hepatic impairment (total bilirubin > ULN and ≤ 1.5 ULN and AST ≤ 10 ULN), no dose adjustments are required, regardless of indication
  - Pts with mPC and a total bilirubin > 1.5 ULN should not receive *nab*-P
- Information obtained from this study may provide insights into future dosing regimens for pts with PC and elevated bilirubin levels

Figure 1. OS in MPACT (as of updated cutoff May 9, 2013)[8]



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OBJECTIVES

Primary

- To evaluate the safety and PK profile of *nab*-P + Gem in pts with advanced adenocarcinoma of the pancreas who have cholestatic hyperbilirubinemia secondary to bile duct obstruction

Secondary

- To evaluate ORR, PFS, and OS

Exploratory

- To evaluate changes from baseline in serum CA19-9 levels

ENDPOINTS

Primary

- MTD for each cohort
- PK

Secondary

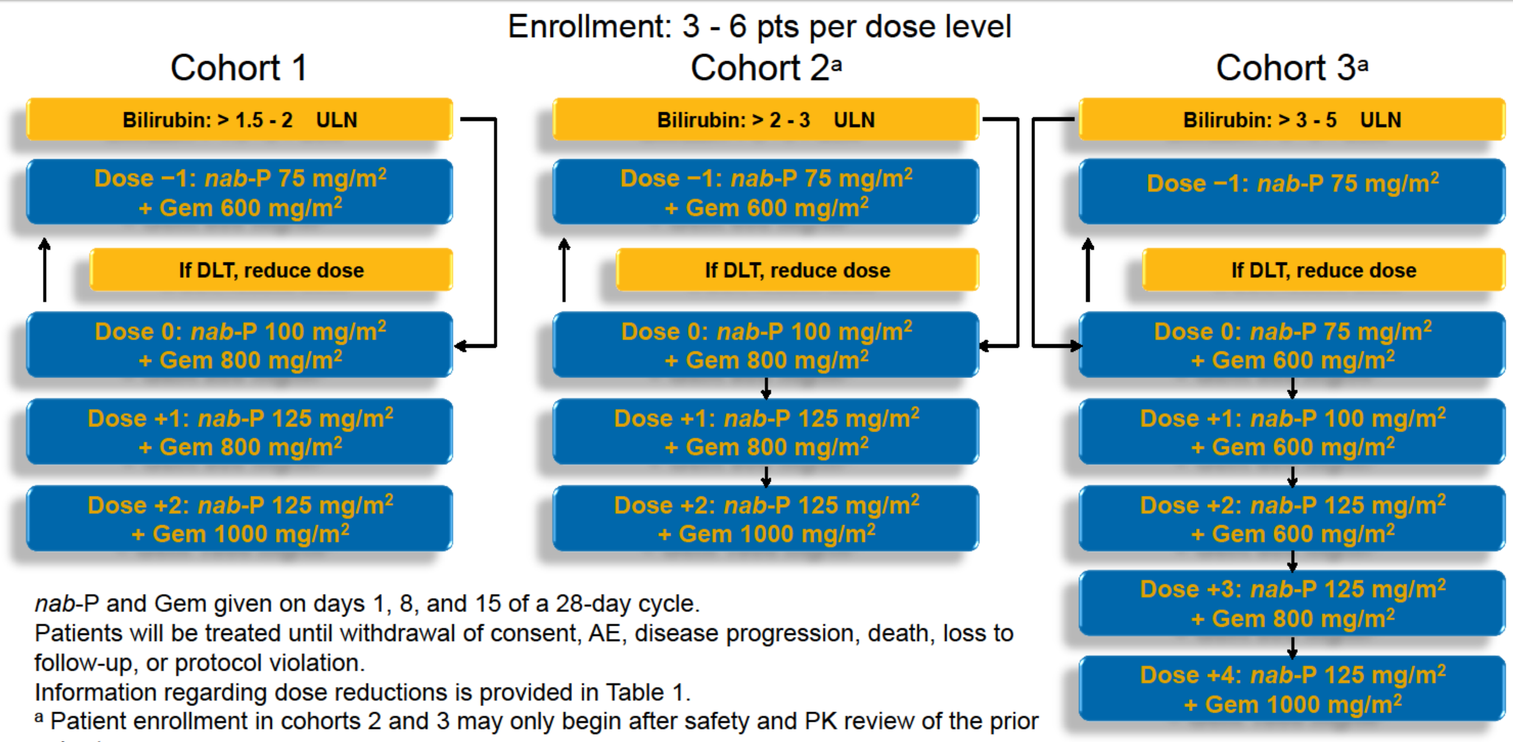
- Investigator-assessed objective tumor response (RECIST v1.1)
- Investigator-assessed PFS (RECIST v1.1)
- OS
- Safety

Exploratory

- Changes from baseline in serum CA19-9 levels

AE, adverse event; AST, aspartate aminotransferase; AUC, area under the curve; CA19-9, carbohydrate antigen 19-9; C_{max}, maximum concentration; CYP, cytochrome P450; DLT, dose-limiting toxicity; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HR, hazard ratio; KPS, Karnofsky performance status; MTD, maximum tolerated dose; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetic; RECIST, Response Evaluation Criteria In Solid Tumors; $t_{1/2}$, terminal half-life; ULN, upper limit of normal; Vss, volume of distribution at steady state.

STUDY DESIGN



nab-P and Gem given on days 1, 8, and 15 of a 28-day cycle.
Patients will be treated until withdrawal of consent, AE, disease progression, death, loss to follow-up, or protocol violation.
Information regarding dose reductions is provided in Table 1.
[a] Patient enrollment in cohorts 2 and 3 may only begin after safety and PK review of the prior cohort.

METHODS

Key Inclusion Criteria

- KPS ≥ 70
- Age ≥ 18 years
- Histologically or cytologically confirmed locally advanced unresectable PC or mPC with measurable disease per RECIST v1.1
- Confirmed cholestatic hyperbilirubinemia due to bile duct obstruction
- No prior therapy for mPC (adjuvant Gem is allowed provided tumor recurrence occurred ≥ 6 months after last Gem dose)
- If using biliary stent, 2 stable bilirubin readings within 48 - 72 hours of each other taken ≥ 5 days and ≤ 14 days after stenting must be obtained. No complications and 2 bilirubin readings within 20% of each other are required before first treatment
- Adequate organ function

Key Exclusion Criteria

- Brain metastases
- Any other active malignancy
- Any active, uncontrolled infection(s) requiring systemic therapy
- Nondiagnostic surgical procedure ≤ 4 weeks before study initiation
- History of a myocardial infarction
- HBV/HCV or HIV infection or use of medications that would increase risk of serious neutropenic complications
- Any condition, abnormality, or illness that may prevent study participation
- Medication known to be strong inducer of CYP3A4 and CYP2C8
- History of or suspected allergy or hypersensitivity to *nab*-P, Gem, or any of their excipients

DLT Definitions

- Grade 4 (< 0.5 10^9/L) neutropenia lasting for ≥ 5 days
  - In pts with grade 4 neutropenia for ≥ 5 days without administration of colony-stimulating growth factor, 1 further rechallenge with growth factor support is permitted
- Grade 4 neutropenia (< 0.5 10^9/L) associated with fever > 38.5 C or neutropenic infection
- Grade 4 thrombocytopenia (< 25 10^9/L) or grade 3 (< 50 10^9/L) with hemorrhage
- Any grade ≥ 3 drug-related or serious nonhematologic toxic effects attributable to either or both study drugs (except untreated nausea, vomiting, or diarrhea)

Table 1. Dose Reduction Guidelines

Dose Level[a]	*nab*-P, mg/m²	Gem, mg/m²
Study dose	Per assigned dose level in cohort	Per assigned dose level in cohort
First dose-level reduction	Reduce 1 dose level from current cohort group dose level	Reduce 1 dose level from current cohort group dose level
Second dose-level reduction	Reduce 2 dose levels from current cohort group dose level	Reduce 2 dose levels from current cohort group dose level

[a] Dose reductions may or may not be concomitant; [b] A maximum of 2 dose-level reductions are allowed, and reductions below *nab*-P 75 mg/m² and Gem 600 mg/m² are not allowed.

STATISTICAL ANALYSIS

- This trial will enroll and treat ≈ 18 to 60 pts at sites in the United States and European Union
- Safety analyses
  - DLT-evaluable population includes pts receiving ≥ 1 dose of study treatment and completion of cycle 1 or discontinuation of cycle 1 due to AEs
  - Safety population includes pts receiving ≥ 1 dose of study treatment and having ≥ 1 postdose safety assessment
- Secondary endpoint efficacy analysis based on the treated population
  - ORR tabulated by dose cohort and dose levels
  - Survival estimates by the Kaplan-Meier method: medians and 2-sided 95% CIs provided by dose cohorts and levels
- PK parameters (C_{max}, AUC, clearance, Vss, and $t_{1/2}$) will be summarized across dose levels by baseline categorical bilirubin cutoffs

Data Monitoring

- A data monitoring committee will be responsible for the safety of study pts and for monitoring the conduct of the study

CONCLUSIONS

- Elevated bilirubin levels frequently occur in pts with advanced PC
- The current, ongoing study will
  - Examine *nab*-P + Gem dosing in pts based on their bilirubin levels at baseline: > 1.5 - 2 ULN, > 2 - 3 ULN, and > 3 - 5 ULN
  - Evaluate the safety and PK profile of *nab*-P + Gem in pts with advanced PC who have cholestatic hyperbilirubinemia secondary to bile duct obstruction
- The results of this trial will be informative for the treatment of pts with advanced PC and hyperbilirubinemia

ACKNOWLEDGMENTS

This study was supported by Celgene Corporation, Summit, NJ. The authors received editorial and production support in the preparation of this poster from MediTech Media, Ltd, funded by Celgene Corporation. The authors are fully responsible for all content and editorial decisions for this poster.

DISCLOSURES

HR: consultant or advisory role and speakers bureau, Celgene, Roche, GlaxoSmithKline, and Bayer; VK: consultant or advisory role, Celgene; PP: consultant or advisory role, honoraria, speakers bureau, and research funding, Celgene; TS: consultant or advisory role, Lilly, Merck Serono, Celgene, Roche; research funding, Boehringer, Celgene, Sanofi; travel, accommodations, and expenses, Bayer, Sanofi, Merck, Roche; DM: employment or leadership position and stock ownership, Celgene; PC: employment or leadership position and stock ownership, Celgene; AR: employment or leadership position and stock ownership, Celgene; RKR: consultant or advisory role and research funding, Celgene.

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Poster presented at the European Society for Medical Oncology 17th World Congress on Gastrointestinal Cancer; July 1 - 4, 2015; Barcelona, Spain

WCGC 2015 184--P
Clinical Pancreatic Cancer
Hanno Riess
DOI: 10.3252/pso.eu.17wcgc.2015
Poster presented at: ESMO Imedex 17th World Congress on Gastrointestinal Cancer 1–4 JULY 2015 BARCELONA, SPAIN