N064A (Alliance): Phase II Study of Panitumumab, Chemotherapy, and External Beam Radiation in Patients with Locally Advanced Pancreatic Adenocarcinoma

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Abstract

Background: This North Central Cancer Treatment Group (NCCTG) N064A (Alliance) phase II trial evaluated upfront chemoradiotherapy incorporating the EGFR inhibitor panitumumab, followed by gemcitabine and panitumumab for unresectable, non-metastatic pancreatic cancer.

Methods: The treatment consisted of fluoropyrimidine and panitumumab given concurrently with radiotherapy followed by gemcitabine and panitumumab for 3 cycles followed by maintenance panitumumab. The primary endpoint was the 12-month overall survival (OS) rate and secondary endpoints included confirmed response rate (RR), OS, progression-free survival (PFS), and adverse events. Enrollment of 50 patients was planned and the study fully accrued.

Results: Fifty-two patients were enrolled, but only 51 were treated and included in the analysis. The median age of patients was 65 years and 54.9% were women. Twenty-two patients received at least 1 cycle of systemic therapy following radiotherapy, but 29 patients received chemoradiotherapy only without receiving subsequent chemotherapy after completion of chemoradiotherapy. The overall RR was 5.9% (95% CI: 1.2%-16.2%). The 12-month OS rate was 50% (95% CI: 38%-67%) which fell short of the per-protocol goal for success (51.1%). The median PFS was 7.4 months (95% CI: 4.5-8.6) and the median OS was 12.1 months (95% CI 7.9-15.9). Grade 3 or higher adverse events were reported by 88%.

Conclusion: The combination of panitumumab, chemotherapy, and external beam radiation therapy was associated with very high rates of grades 3-4 toxicities and survival results did not meet the trial’s goal for success. This regimen is not recommended for further study (ClinicalTrials.gov Identifier NCT00601627).

Key words: pancreatic adenocarcinoma; panitumumab; radiotherapy; locally advanced.

Lessons Learned

- The combination of panitumumab, cytotoxic chemotherapy, and external beam radiation therapy is associated with substantial toxicity and should not be used in clinical practice and is not recommended for further study.
- Progression-free survival and OS appear shorter than in studies utilizing upfront chemotherapy followed by chemoradiotherapy for selected patients.

Discussion

Locally advanced and unresectable pancreatic cancer constitutes more than 50% of newly diagnosed pancreatic adenocarcinoma. Overall survival is poor and median OS is generally <18 months.1,2 The optimal treatment of patients with unresectable pancreatic adenocarcinoma is not known, but patients are increasingly treated initially with systemic chemotherapy alone, with radiotherapy reserved for selected...
patients who do not have progressive disease after several months of chemotherapy.

The NCCTG N064A (Alliance) was a single arm phase II trial in patients with locally advanced and unresectable pancreatic adenocarcinoma. After written consent and registration, participants received radiotherapy with fluoropyrimidine as a radiosensitizer concurrent with panitumumab. The choice of radiosensitizing fluoropyrimidine, either 5-fluorouracil or capecitabine, was at the physician’s discretion. North Central Cancer Treatment Group is now part of the Alliance for Clinical Trials in Oncology.

Overall survival at 12 months, the primary endpoint of the trial, was 50% and fell just short of the pre-defined, per-protocol goal for success (51.1%). Twenty-two patients received at least 1 cycle of systemic therapy following radiotherapy. However, 29 patients received chemoradiotherapy alone without chemotherapy after completion of chemoradiotherapy, suggesting that the majority of patients received suboptimal therapy by current standards. Grade 3 or higher adverse events (at least possibly related to treatment) were reported by 88% of participants (Table 1).

The observed survival, which compares unfavorably with more recently reported results, and the very high rates of significant adverse events support that this regimen should not be used in practice or recommended for further study.

| Event           | All AEs, % | AEs related to therapy\(^a\), % |
|-----------------|------------|---------------------------------|
| Overall AEs     | 92.2       | 88.2                            |
| Hematologic     | 41.2       | 41.2                            |
| Anemia          | 10         | 10                              |
| Neutropenia     | 14         | 14                              |
| Thrombocytopenia| 6          | 6                               |
| Thrombosis      | 10         | 6                               |
| Non-hematologic | 88.2       | 84.3                            |
| Anorexia        | 27         | 25                              |
| Dehydration     | 25         | 24                              |
| Diarrhea        | 20         | 16                              |
| Fatigue         | 37         | 33                              |
| Hypotension     | 6          | 6                               |
| Nausea          | 35         | 29                              |
| Rash            | 16         | 16                              |
| Vomiting        | 22         | 16                              |

\(^a\)Adverse events at least possibly related to treatment.
**Trial Information**

| **Disease**       | pancreatic cancer               |
|-------------------|---------------------------------|
| **Stage of disease/treatment** | metastatic/advanced           |
| **Prior therapy** | none                            |
| **Type of study**  | phase II, single arm            |
| **Primary endpoint** | 12-month OS                   |
| **Secondary endpoints** | overall RR, OS, PFS, toxicity |
| **Additional details of endpoints or study design** | The study was open to accrual from June 19, 2009 to August 6, 2010. The study was permanently closed on August 6, 2010. The primary endpoint was the 12-month OS rate and secondary endpoints included RR, OS, PFS, and adverse events. The study had 91% power to detect a 12-month OS rate of 60%, with a 9% significance level when the true 12-month OS rate was 40%. An observed 12-month OS rate of 51.1% was needed for success. For time-to-event data (OS, PFS), a Kaplan-Meier analysis was performed, where medians and 95% confidence intervals were reported. For categorical data (ie, response, adverse events), the frequencies and percentages were reported, including 95% confidence intervals, as needed. |

**Investigator’s analysis** poorly tolerated/not feasible

**Drug Information**

| **Generic/working name** | **5-Fluorouracil** |
|--------------------------|-------------------|
| **Drug type**            | Cytotoxic         |
| **Drug class**           | Antimetabolite    |
| **Dose**                 | 225 mg/m²         |
| **Route**                | Continuous intravenous infusion (CIV) |

**Schedule of administration**

Panitumumab: 6 mg/kg on days 1, 15, and 29 of radiotherapy
5-Fluorouracil (39 patients): 225 mg/m² per day as continuous infusion during radiotherapy OR Capecitabine (12 patients): 825 mg/m² PO twice daily during radiotherapy
Post-radiotherapy chemotherapy
Gemcitabine: 1000 mg/m² on days 1, 8, and 15 on a 28-day cycle
Panitumumab: 6 mg/kg i.v. on days 1 and 15 on a 28-day cycle
Maintenance therapy
Panitumumab: 6 mg/kg i.v. on days 1 and 15 on a 28-day cycle

| **Generic/working name** | **Capecitabine** |
|--------------------------|------------------|
| **Drug type**            | Cytotoxic        |
| **Drug class**           | Antimetabolite   |
| **Dose**                 | 825 mg/m²        |
| **Route**                | Oral (p.o.)      |

**Schedule of administration**

Panitumumab: 6 mg/kg on days 1, 15, and 29 of radiotherapy
5-Fluorouracil (39 patients): 225 mg/m² per day as continuous infusion during radiotherapy OR Capecitabine (12 patients): 825 mg/m² PO twice daily during radiotherapy
Post-radiotherapy chemotherapy
Gemcitabine: 1000 mg/m² on days 1, 8, and 15 on a 28-day cycle
Panitumumab: 6 mg/kg i.v. on days 1 and 15 on a 28-day cycle
Maintenance therapy
Panitumumab: 6 mg/kg IV on days 1 and 15 on a 28-day cycle

| **Generic/working name** | **Panitumumab** |
|--------------------------|-----------------|
| **Drug type**            | Antibody        |
| **Drug class**           | EGFR            |
| **Dose**                 | 6 mg/kg         |
| **Route**                | i.v.            |
Schedule of administration

**Upfront chemoradiotherapy**
- Panitumumab: 6 mg/kg on days 1, 15, and 29 of radiotherapy
- 5-fluorouracil (39 patients): 225 mg/m² per day as continuous infusion during radiotherapy
  - OR Capecitabine (12 patients): 825 mg/m² PO twice daily during radiotherapy
- Post-radiotherapy chemotherapy
  - Gemcitabine: 1000 mg/m² on days 1, 8, and 15 on a 28-day cycle
  - Panitumumab: 6 mg/kg i.v. on days 1 and 15 on a 28-day cycle

**Post-radiotherapy chemotherapy**
- Gemcitabine: 1000 mg/m² on days 1, 8, and 15 on a 28-day cycle
  - Panitumumab: 6 mg/kg i.v. on days 1 and 15 on a 28-day cycle

**Maintenance therapy**
- Panitumumab: 6 mg/kg i.v. on days 1 and 15 on a 28-day cycle

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**Generic/working name**

**Gemcitabine**

| Drug type | Cytotoxic |
|-----------|-----------|
| Drug class | Antimetabolite |
| Dose | 1000 mg/m² |
| Route | i.v. |

Schedule of administration

**Upfront chemoradiotherapy**
- Panitumumab: 6 mg/kg on days 1, 15, and 29 of radiotherapy
- 5-Fluorouracil (39 patients): 225 mg/m² per day as continuous infusion during radiotherapy
  - OR Capecitabine (12 patients): 825 mg/m² PO twice daily during radiotherapy
- Post-radiotherapy chemotherapy
  - Gemcitabine: 1000 mg/m² on days 1, 8, and 15 on a 28-day cycle
  - Panitumumab: 6 mg/kg i.v. on days 1 and 15 on a 28-day cycle
- Maintenance therapy
  - Panitumumab: 6 mg/kg i.v. on days 1 and 15 on a 28-day cycle

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**Patient Characteristics**

- **Number of patients, male**: 23
- **Number of patients, female**: 28
- **Stage**: Locally advanced
- **Age**: Median (range): 65 years
- **Number of prior systemic therapies**: 0
- **Performance status: ECOG**
  - 0—20
  - 1—31
  - 2—0
  - 3—0
  - Unknown—0
- **Cancer types or histologic subtypes**: Adenocarcinoma of pancreas, 51

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**Primary Assessment Method**

| Title | 12-month survival |
|-------|-------------------|
| Number of patients screened | 52 |
| Number of patients enrolled | 52 |
| Number of patients evaluable for toxicity | 51 |
| Number of patients evaluated for efficacy | 51 |
| Evaluation method | RECIST 1.0 |
| Response assessment CR | n = 1 |
| Response assessment PR | n = 2 |
| Response assessment SD | n = 35 |
| Response assessment PD | n = 13 |
| (Median) duration assessments PFS | 7.4 months, CI: 4.5-8.6 |
| (Median) duration assessments OS | 12.1 months, CI: 7.9-15.9 |

**Outcome notes**

- **12-month survival**: 50% (95% CI 38%-67%)
- **Median OS**: 12.1 months (95% CI 7.9-15.9; Fig. 1)
- **Median PFS**: 7.4 months (95% CI 4.5-8.6; Fig. 2)

**Confirmed response:**
The prognosis of patients with locally advanced adenocarcinoma of the pancreas remains poor, and long-term survivors are rare. Current treatment guidelines recommend upfront cytotoxic chemotherapy for patients with adequate performance status, typically a multi-agent regimen such as either FOLFIRINOX or gemcitabine with nab-paclitaxel. External beam radiotherapy or stereotactic body radiation therapy (SBRT) is commonly used after initial 4-6 months of systemic therapy assuming disease stability or an objective response, but the contribution of additional radiotherapy, including its effect on survival, remains unclear. In this trial, the radiation consisted of 50.4 Gy in 28 fractions using 3-dimensional treatment planning, as was the standard at the time of conducting this trial. In fact, available evidence suggests that there is little if any survival advantage of including radiotherapy following chemotherapy. In patients who either have a partial response or stable disease after 4-6 months of systemic therapy, concurrent chemoradiotherapy followed by a period of observation is not unreasonable and is supported as a paradigm change with regard to the management of locally advanced adenocarcinoma of the pancreas over recent years. Upfront chemoradiotherapy is no longer recommended but can be considered after an initial phase of systemic therapy in cases where no metastases have developed. For those reasons, the approach reported in this trial is not recommended for further study or for clinical practice.

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Conflict of Interest

The authors indicated no financial relationships.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.
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Figures and Tables

Figure 1. Overall survival.

Figure 2. Progression-free survival.