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Clinical Trial Results

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

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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.

Table 1. Adverse events (grade 3 or higher).

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.

Author disclosures and references available online.

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/m^2
Route	Continuous intravenous infusion (CIV)
Schedule of administration	Upfront chemoradiotherapy Panitumumab: 6 mg/kg on days 1, 15, and 29 of radiotherapy 5-fluorouracil (39 patients): 225 mg/m^2 per day as continuous infusion during radiotherapy OR Capecitabine (12 patients): 825 mg/m^2 PO twice daily during radiotherapy Post-radiotherapy chemotherapy Gemcitabine: 1000 mg/m^2 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/m^2
Route	Oral (p.o.)
Schedule of administration	Upfront chemoradiotherapy Panitumumab: 6 mg/kg on days 1, 15, and 29 of radiotherapy 5-Fluorouracil (39 patients): 225 mg/m^2 per day as continuous infusion during radiotherapy OR Capecitabine (12 patients): 825 mg/m^2 PO twice daily during radiotherapy Post-radiotherapy chemotherapy Gemcitabine: 1000 mg/m^2 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/m^2 per day as continuous infusion during radiotherapy OR Capecitabine (12 patients): 825 mg/m^2 PO twice daily during radiotherap
	Post-radiotherapy chemotherapy
	Gemcitabine: 1000 mg/m^2 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	**Gemcitabine**
Drug type	Cytotoxic
Drug class	Antimetabolite
Dose	1000 mg/m^2
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/m^2 per day as continuous infusion during radiotherapy OR Capecitabine (12 patients): 825 mg/m^2 PO twice daily during radiotherapy
	Post-radiotherapy chemotherapy
	Gemcitabine: 1000 mg/m^2 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
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

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:	

Outcome notes	
Overall response	3/51 (5.9%; 95% CI: 1.2-16.2%) (1 CR, 2 PR)
Stable disease	35/51 (68.6%)
Progressive disease	13/51 (25.5%)

Adverse Events

Table 1 shows adverse events of grade 3 or higher that were at least possibly related to treatment.

Assessment, Analysis, and Discussion

Completion	Study Completed
Investigator's Assessment	Poorly tolerated/not feasible

The prognosis of patients with locally advanced adenocarcinoma of the pancreas remains poor, and long-term survivors are rare.[1] 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.[1,3,4] 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.[5,6] 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.[2] 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 an option for patients who do not develop metastatic disease while on initial chemotherapy in the most recent National Comprehensive Cancer Network (NCCN) guidelines.[4]

Patients with locally advanced pancreatic adenocarcinoma should be evaluated by a multidisciplinary team at a large-volume center with substantial experience treating patients with this entity. Carefully selected patients with locally advanced tumors may be considered for aggressive upfront therapy with an eventual goal of resection. Neoadjuvant chemotherapy, typically with FOLFIRINOX, followed by chemoradiotherapy may result in sufficient downstaging for resection, often with complex vascular resections. Although not considered standard therapy, experience from single centers suggests that receipt of neoadjuvant chemotherapy, normalization of previously elevated CA 19-9 and pathological response is associated with more favorable outcomes, but prospective data are lacking.[7-10]

The EGFR pathway has been suggested as a potential target for systemic therapy in patients with pancreatic adenocarcinoma. Increased expression of EGFR has been associated with worse outcomes, but the incorporation of EGFR-directed therapy has yielded minimal improvement in survival and inclusion of EGFR-directed drugs is not recommended outside of clinical trials.[11-13] Based on the available evidence, EGFR-directed therapy is very unlikely to meaningfully improve outcomes of patients with advanced pancreatic adenocarcinoma.

The approach in the currently reported trial cannot be recommended for clinical practice for several reasons. Firstly, the studied regimen was associated with substantial toxicities, well in excess of what is seen with conventional systemic therapy. Secondly, EGFR-directed therapy has not been shown to improve outcomes such as PFS and OS and the survival outcomes of this study compare unfavorably with other trials done in similar patient populations. Thirdly, there has been 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.

References

1. Balaban EP, Mangu PB, Khorana AA, et al. Locally advanced, unresectable pancreatic cancer: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol*. 2016;34(22):2654-2668.
2. Hammel P, Huguet F, van Laethem JL, et al. LAP07 Trial Group. Effect of chemoradiotherapy vs chemotherapy on survival in patients with locally advanced pancreatic cancer controlled after 4 months of gemcitabine with or without erlotinib: the LAP07 randomized clinical trial. *JAMA*. 2016;315(17):1844-1853.
3. Ducreux M, Cuhna AS, Caramella C, et al. ESMO Guidelines Committee. Cancer of the pancreas: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2015;26(Suppl 5):v56-v68.
4. Pancreatic Adenocarcinoma. NCCN guidelines version 1.2020 (accessed 10/19/2020). 2020.
5. Huguet F, André T, Hammel P, et al. Impact of chemoradiotherapy after disease control with chemotherapy in locally advanced pancreatic adenocarcinoma in GERCOR phase II and III studies. *J Clin Oncol*. 2007;25(3):326-331.
6. Sultana A, Tudur Smith C, Cunningham D, et al. Systematic review, including meta-analyses, on the management of locally advanced pancreatic cancer using radiation/combined modality therapy. *Br J Cancer*. 2007;96(8):1183-1190.
7. Truty MJ, Kendrick ML, Nagorney DM, et al. Factors predicting response, perioperative outcomes, and survival following total neoadjuvant therapy for borderline/locally advanced pancreatic cancer. *Ann Surg*. 2019.
8. Gemenetzis G, Groot VP, Blair AB, et al. Survival in locally advanced pancreatic cancer after neoadjuvant therapy and surgical resection. *Ann Surg*. 2019;270(2):340-347.
9. Perri G, Prakash L, Qiao W, et al. Response and survival associated with first-line FOLFIRINOX vs gemcitabine and nab-paclitaxel chemotherapy for localized pancreatic ductal adenocarcinoma. *JAMA Surg*. 2020;155(9):832-839.
10. Pietrasz D, Turrini O, Vendrely V, et al. How does chemoradiotherapy following induction FOLFIRINOX improve the results in resected borderline or locally advanced pancreatic adenocarcinoma? an AGEO-FRENCH multicentric cohort. *Ann Surg Oncol*. 2019;26(1):109-117.
11. Korc M, Chandrasekar B, Yamanaka Y, Friess H, Buchier M, Beger HG. Overexpression of the epidermal growth factor receptor in human pancreatic cancer is associated with concomitant increases in the levels of epidermal growth factor and transforming growth factor alpha. *J Clin Invest*. 1992;90(4):1352-1360.
12. Moore MJ, Goldstein D, Hamm J, et al. National Cancer Institute of Canada Clinical Trials Group. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the national cancer institute of canada clinical trials group. *J Clin Oncol*. 2007;25(15):1960-1966.
13. Philip PA, Benedetti J, Corless CL, et al. Phase III study comparing gemcitabine plus cetuximab versus gemcitabine in patients with advanced pancreatic adenocarcinoma: southwest oncology group-directed intergroup trial S0205. *J Clin Oncol*. 2010;28(22):3605-3610.

Figures and Tables

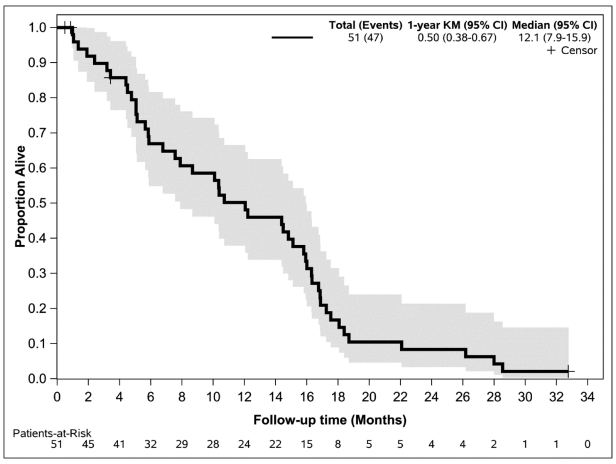

Figure 1. Overall survival.

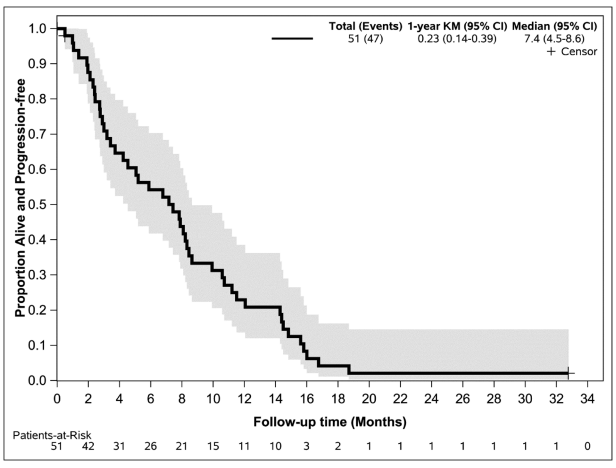

Figure 2. Progression-free survival.