

## EDITORIAL

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# Combining Epidermal Growth Factor Receptor Inhibitors and Radiation Therapy in Pancreatic Cancer: Small Step or Giant Leap?

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### Summary

Targeting the epidermal growth factor receptor (EGFR) with small molecule inhibitors or monoclonal antibodies in combination with chemotherapy and radiation is a theoretically appealing strategy in pancreatic cancer. EGFR inhibitors have shown efficacy as radiosensitizers and activity against metastatic pancreatic cancer when combined with gemcitabine. This paper examines the available clinical data, with a focus on locally advanced, unresectable disease. Further studies with a focus on understanding the basic biology of EGFR inhibition are needed to identify an optimal multi-modality regimen.

### Introduction

When overexpressed or inappropriately activated, epidermal growth factor receptor (EGFR) promotes a variety of oncogenic activities in human cells, including uncontrolled proliferation, angiogenesis, and inhibition of apoptosis. [1]. EGFR is frequently over expressed in pancreatic cancer [2] and overexpression is correlated with poor prognosis [3]. EGFR has been investigated as a target for systemic therapy in pancreatic cancer using both small-molecule tyrosine kinase inhibitors (TKI) and monoclonal antibodies against the extracellular domain of the EGFR. Inhibiting EGFR appears to sensitize tumor cells to ionizing radiation, either through increasing the proportion of cells in the radiosensitive G1 phase of the cell cycle while decreasing the proportion in the radioresistant S phase [4], or through restoration of apoptosis [5] or even anti-angiogenic mechanisms [6]. Preclinical data suggests that adding EGFR inhibitors can increase the activity of gemcitabine and radiation in pancreatic cancer cell lines and tumors [7, 8]. The

publication of the randomized clinical trial in locally-advanced head-and-neck squamous cell carcinoma by Bonner *et al.* in 2006 was a watershed event that provided clinical validation for the combination of EGFR inhibitors with radiation [9]. The addition of cetuximab to radiation therapy led to a 10% absolute increase in three-year survival (55% *versus* 45%) and increased local control (50% *versus* 41%) compared with radiation alone.

### A Ray of Hope?

In 2005, results of a National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) randomized study lead to the approval of erlotinib, a small-molecule inhibitor of EGFR, for use in combination with gemcitabine in unresectable, chemotherapy-naïve pancreatic cancer [10]. Although the NCIC-CTG trial was deemed successful, the 2-week survival benefit associated with the addition of erlotinib to gemcitabine was so modest that many oncologists questioned its clinical relevance. Furthermore, the rate of complete plus partial responses was only 8.6%, *versus* 8.0% in the gemcitabine-alone arm, suggesting that erlotinib has, at best, marginal anti-tumor activity. In light of the moderate incremental benefit of adding EGFR inhibition to chemotherapy and the known radiosensitizing properties of EGFR inhibitors, could combining EGFR inhibition, chemotherapy, and radiation therapy improve outcomes in localized pancreatic cancer?

### Radiation Therapy and Pancreatic Cancer

Pancreatic cancer patients generally receive radiation either in the adjuvant setting, following a definitive

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**Abbreviations** NCIC-CTG: National Cancer Institute of Canada Clinical Trials Group; TKI: tyrosine kinase inhibitors

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resection, or for locally advanced, non-metastatic disease, in which no such surgery is possible. Although there is considerable controversy as to the exact benefit of radiotherapy in pancreatic cancer, there is randomized phase III data to support the use of radiation and chemotherapy both in the adjuvant [11]

and locally advanced [12, 13] settings. In adjuvant therapy, the radiation fields typically encompass the tumor bed, the anastomoses and the regional lymphatics, in order to enhance locoregional control by sterilizing occult microscopic disease within the field. In treatment of locally advanced disease, some

**Table 1.** Efficacy of EGFR inhibitors and radiation in pancreatic cancer.

| Author            | Patients                                       | Chemo  | EGFR Inhibitor   | RT   | Response   | Outcome  |
|-------------------|--|--|--|--|--|--|
| Czito [15]        | 4 locally advanced, unresectable. 6 resectable | Dose level 1:<br>Cape 650 mg/m <sup>2</sup> bid w/RT<br><br>Dose level 2:<br>Cape 825 mg/m <sup>2</sup> bid w/RT | Gefitinib<br>250 mg/day w/RT   | 1.8 Gy/d to tumor and LN to 45 Gy<br>Cone-down to 50.4 Gy to gross tumor                                   | 7/10 SD<br>3/10 PD<br><br>No locally advanced, unresectable patients became resectable                                 | NR   |
| Maurel [16]       | 18 locally advanced, unresectable.             | Gem 0/100/150/200 mg/m <sup>2</sup> /wk at FDR<br>10 mg/m <sup>2</sup> /min w/RT                                 | Gefitinib<br>250 mg/day w/RT then continued until progression  | 1.8 Gy/d to 45 Gy to tumor only w/2cm margins  | RECIST:<br>15 patients evaluable:<br>1/15 PR<br>7/15 SD<br>7/15 PD   | Median PFS: 3.7 mos<br>Median survival: 7.5 mos  |
| Ianitti [17]      | 13 locally advanced, unresectable. 4 PM        | Gem 75 mg/m <sup>2</sup> /wk.<br>Paclitaxel 40 mg/m <sup>2</sup> /wk for 6 wks                                   | Erlotinib<br>50/100/150 mg po qd w/RT then 150 mg/day until progression  | 1.8 Gy/d to 50.4 Gy to tumor and LN w/2-3 cm margins   | WHO:<br>6/13 PR  | Median survival: 14 mos for locally advanced, unresectable patients  |
| Duffy [18]        | 20 locally advanced, unresectable              | Gem 40 mg/m <sup>2</sup> twice/wk w/RT then 1,000 mg/m <sup>2</sup> on d1, d8 of 21d cycle for 4 cycles          | Erlotinib<br>100/125 mg qd w/RT then 100 mg/d for 12 wks   | 1.8 Gy/d to 50.4 Gy to tumor and LN w/2 cm margins   | RECIST:<br>17 patients evaluable:<br>6/17 PR<br>9/17 SD  | Median TTP: 13 mos<br>Median survival: 18.7 mos  |
| Cardenes [19]     | 10 resectable                                  | Gem 300 mg/m <sup>2</sup> /wk w/RT   | Erlotinib<br>100 mg/m <sup>2</sup> /day w/RT   | 3 Gy/d to 30 Gy  | 8 patients evaluable:<br>6 R0<br>2 R2 resections   | 7/8 alive at median follow-up 10.7 mos (range 6-19.5 mos).<br>3/8 with liver metastases  |
| Ma [20]           | 11 resected                                    | Cape 800 mg/m <sup>2</sup> bid w/RT then Gem for 4 mos   | Erlotinib<br>150/100 mg/d w/RT then for 4 mos  | 1.8 Gy/d to 50.4 Gy  | NR   | NR   |
| Robertson [21]    | 15 locally advanced, unresectable              | Gem 1,000 mg/m <sup>2</sup> /wk w/RT   | Erlotinib 100 mg/d w/RT  | 2 Gy/d to 30/34/38 Gy to tumor only w/1cm margin   | NR   | NR   |
| Chakravarthy [22] | 8 locally advanced, unresectable               | Gem 200 mg/m <sup>2</sup> /wk at FDR<br>10 mg/m <sup>2</sup> /min w/RT   | C225 400 mg/m <sup>2</sup> d1 then 250 mg/m <sup>2</sup> for wks 2-7   | 1.8 Gy/d to 50.4 Gy starting d8  | NR   | NR   |
| Munter [23]       | 66 locally advanced, unresectable              | Gem 300 mg/m <sup>2</sup> /wk w/RT then Gem 1,000 mg/m <sup>2</sup> /wk for 4 wks                                | Arm A:<br>C225 400 mg/m <sup>2</sup> d1 then 250 mg/m <sup>2</sup> /wk w/RT<br><br>Arm B:<br>C225 400 mg/m <sup>2</sup> d1 then 250 mg/m <sup>2</sup> /wk w/RT and for 12 wks after RT | Intensity-modulated radiation therapy<br>45 Gy to CTV and 54 Gy to GTV in 25 fractions                     | RECIST:<br>1.5% CR<br>34% PR<br>60% SD<br>4% PD<br><br>21% were able to undergo resection                              | Median survival 15 mos<br>1-year survival 61%<br>2-year survival 20%   |
| Demols [24]       | 25 locally advanced, unresectable              | Gem 300 mg/m <sup>2</sup> /wk w/RT   | C225 400 mg/m <sup>2</sup> d1 then 250 mg/m <sup>2</sup> /wk w/RT  | Group 1:<br>1.8 Gy/d to 36 Gy,<br><br>Group 2:<br>1.8 Gy/d to 45 Gy<br><br>Group 3:<br>1.8 Gy/d to 50.4 Gy | 20 patients evaluable:<br>5% CR<br>40% PR<br>30% SD<br>25% PD<br><br>1 patient from Group 1 had PR and then R0 surgery | Group 1:<br>Median TTP: 4.3 mos<br>Median survival: 9 mos<br><br>Group 2<br>Median TTP: 3.7 mos<br>Median survival: 10.7 mos<br><br>Group 3<br>Median TTP: 2.8 mos<br>Median survival: 3.7 mos |

C225: Cetuximab; Cape: capecitabine; Chemo: chemotherapy; CR: complete response; CTV: clinical tumor volume; FDR: fixed dose-rate; Gem: gemcitabine; GTV: gross tumor volume; Gy: Gray; NR: not reported; PD: progressive disease; PFS: progression-free survival; PM: positive margin after resection; PR: partial response; RECIST: Response Evaluation Criteria In Solid Tumors; RT: radiation therapy; SD: stable disease; TTP: time to progression; WHO: World Health Organization criteria for solid tumor response

institutions have adopted a strategy of highly conformal therapy, treating only the gross tumor with a margin [14] while omitting the uninvolved lymphatics. Systemic therapies are generally thought to enhance the efficacy of radiation in two ways: by increasing the ability of radiation to kill tumor cells in the radiation field (radiosensitization), and by eliminating micro-metastatic disease outside of the field (spatial cooperation). Given the potential of EGFR inhibitors as radiosensitizing agents, it makes sense that the benefits of combination therapy in pancreatic cancer should be evident in terms of increased local disease control.

### Clinical Trials of EGFR Inhibitors and Radiation in Pancreatic Cancer

Tables 1 and 2 summarize the efficacy and toxicity, respectively, of different combinations of EGFR inhibitors, radiation, and chemotherapy in pancreatic cancer. The principal small-molecule EGFR inhibitors to be investigated in pancreatic cancer are gefitinib and erlotinib. Gefitinib was studied in combination with capecitabine and radiation by Czito *et al.* in pancreatic

and rectal cancer patients [15]. Capecitabine was dose-escalated from 650 mg/m<sup>2</sup> *bid* to 825 mg/m<sup>2</sup> *bid*, but dose-limiting gastrointestinal toxicity became apparent even at the lower dose level. Four patients were unable to complete chemoradiation and two required prolonged breaks. There were no radiographic responses and no locally advanced patients were rendered resectable. Maurel *et al.* tested gefitinib with radiation and escalating doses of gemcitabine in a cohort of locally advanced patients, and reported moderate acute toxicity [16]. However, three patients died before they could be evaluated. Out of the 15 evaluable patients, there was a single partial response. No patients were able to undergo surgery, and the median survival was only 7.5 months.

The Brown University group reported results of a combination of escalating doses of erlotinib with gemcitabine, paclitaxel and radiation followed by maintenance erlotinib in a mixed population of locally advanced and margin-positive patients [17]. The main toxicities were gastrointestinal and hematologic, and a maximum tolerated dose of 50 mg/day of erlotinib was

**Table 2.** Toxicity of EGFR inhibitors and radiation in pancreatic cancer.

| Author            | Patients   | Toxicity  | Notes  |
|-------------------|--|---|--|
| Czito [15]        | 4 locally advanced, unresectable<br>6 resectable | Dose level 1 (7 patients). Grade 3-4: diarrhea 3/6, nausea 1/6, vomiting 1/6, dehydration 1/6, anorexia 1/6<br>Dose Level 2 (3 patients). Grade 3-4: diarrhea 1/3, nausea 1/3, vomiting 1/3, dehydration 2/3  | No recommended phase II dose for this combination of gefitinib, Cape and RT.<br>Dose-limiting toxicity seen in 6/10 patients                             |
| Maurel [16]       | 18 locally advanced, unresectable                | Gem 0 mg/m <sup>2</sup> (6 patients). G rade 3-4: toxicity 0/6.<br>Gem 100 mg/m <sup>2</sup> (3 patients). G rade 3-4: toxicity 0/3.<br>Gem 150 mg/m <sup>2</sup> (6 patients). G rade 3-4: asthenia 1/6.<br>Gem 200 mg/m <sup>2</sup> (3 patients). Grade 3-4: neutropenia 2/3, anemia 1/3.                | Toxicity acceptable but modest activity  |
| Ianitti [17]      | 13 locally advanced, unresectable<br>4 PM        | Erlotinib 50 mg/day (6 patients). Grade 3-4: cholestasis 1/6.<br>Erlotinib 100 mg/day (5 patients). Grade 3-4: diarrhea 1/5, dehydration 1/5, rash 1/5, bowel stricture, 1/5 neutropenia 1/5.<br>Erlotinib 150 mg/day (6 patients). Grade 3-4: diarrhea 1/6, dehydration 2/6, nausea 1/6, fatigue 1/6.      | 50 mg/day erlotinib is maximum tolerated dose with concurrent Gem, Paclitaxel and RT   |
| Duffy [18]        | 20 locally advanced, unresectable                | Erlotinib 100 mg/day (14 patients). Grade 3: hematologic 14/14. Grade 4: neutropenia 1/14. Grade 3: fatigue 1/14, rash 2/14, diarrhea 3/14.<br>Erlotinib 125 mg/day (6 patients). Grade 3: hematologic 6/6.<br>Erlotinib 100 mg/day maintenance. Grade 3: lymphopenia 8/14, neutropenia 3/14, fatigue 1/14. | 100 mg/day erlotinib is maximum tolerated dose with RT and bi-weekly Gem   |
| Cardenes [19]     | 10 resectable                                    | 8/10 completed protocol. Grade 3-4: liver dysfunction 1/10, nausea 1/10, vomiting 1/10, neutropenia 1/10 during chemoradiation  | No pathologic complete responses.<br>2/8 were downstaged   |
| Ma [20]           | 11 resected                                      | 4/7 patients completed treatment with erlotinib 150 mg/day. Grade 3 rash, diarrhea, neuropathy and neutropenia were observed; erlotinib dose was therefore lowered to 100 mg/day.<br>4/4 patients completed treatment with erlotinib 100 mg/day.  | Erlotinib 150 mg/day with Cape 800 mg <i>bid</i> and RT is too toxic.<br>Protocol amended to erlotinib 100 mg/day with Cape 800 mg <i>bid</i> M-F and RT |
| Robertson [21]    | 15 locally advanced, unresectable                | 30 Gy (7 patients), 34 Gy (3 patients), 38 Gy (5 patients).<br>Grade 3 leg pain from rash in 1/15.<br>Grade 3 anorexia 1/5 at 38 Gy.  | Maximum tolerated dose not yet determined  |
| Chakravarthy [22] | 8 locally advanced, unresectable                 | 2/8 patients had grade 4 allergy during C225 loading.<br>1/8 had hepatic toxicity and CVA during C225 loading.<br>5/8 patients completed chemoradiation.<br>3/5 had grade 3-4 GI toxicity or pneumonitis.<br>1 patient died 43d after chemoradiation.   | No recommended phase II dose for this combination of C225, RT, and Gem   |
| Krempien [35]     | 36 locally advanced, unresectable                | Grade 3: diarrhea 14%, nausea 17%, vomiting 11%, fatigue 11%, neutropenia 28%, thrombocytopenia 11%.<br>34/36 developed rash.<br>1 patient died of tumor bleeding.  | No patients required cessation of C225.<br>No difference between arm A and B.<br>Excellent local control and survival                                    |
| Demols [24]       | 25 locally advanced, unresectable                | Group 1 (6 patients). No grade 3 toxicity<br>Group 2 (6 patients). Grade 3: 1 heme and 3 non-heme<br>Group 3 (13 patients). Grade 3: 2 heme and 11 non-heme<br>Overall 19 developed grade 1-2 rash.   | 45 Gy selected as RT dose to combine with Gem 300 mg/m <sup>2</sup> /wk and C225 250 mg/m <sup>2</sup> /wk.<br>6/6 in Group 2 completed chemoradiation   |

C225: Cetuximab; Cape: capecitabine; Gem: gemcitabine; Gy: Gray; NR: not reported; PM: positive margin after resection; RT: radiation therapy

defined. Notably, the partial response rate was 46% and the median survival for locally advanced patients was 14 months. Recently, Duffy *et al.* described promising results of a combination of escalating doses of erlotinib with radiation and bi-weekly gemcitabine followed by maintenance weekly gemcitabine and erlotinib [18]. Although only 55% completed all protocol therapy, and one patient died of gastrointestinal bleeding during maintenance therapy, 53% had stable disease, and 35% had partial responses, with one patient later undergoing an R0 resection. The median survival was 18.7 months. Preliminary results of several small series combining erlotinib with radiation and chemotherapy in the neoadjuvant and adjuvant settings are shown in Table 1 [19, 20, 21].

Early reports from several trials of the monoclonal antibody cetuximab in combination with radiation against pancreatic cancer have shown mixed results. Preliminary results of a phase I study conducted at Vanderbilt University have been published in abstract form. Weekly cetuximab and 50.4 Gy radiation were combined with weekly fixed dose-rate gemcitabine beginning at 200 mg/m<sup>2</sup>/week to treat 8 patients with locally advanced disease. Two patients had grade 4 allergic reactions and a third patient had liver toxicity and a stroke after the loading dose of cetuximab. The chemoradiation regimen was associated with substantial gastrointestinal toxicity, and one patient died of aspiration after completing the regimen [22]. In contrast, the University of Heidelberg has conducted a large phase II randomized study of gemcitabine, intensity-modulated radiation therapy and cetuximab, followed by consolidation gemcitabine plus or minus cetuximab in locally advanced, unresectable patients. While no difference was seen between the two arms, the regimens had manageable toxicity. The rate of complete plus partial response was 35.5%, and the median survival for all patients was an encouraging 15 months. Twenty-one percent of patients were eventually able to undergo a potentially curative surgery [23]. Demols *et al.* treated 25 locally advanced patients with cetuximab, gemcitabine, and escalating radiation doses. One complete and 8 partial responses were seen, and one patient was able to undergo an R0 resection. A moderate dose of 45 Gy yielded the best survival and all 6 patients enrolled at this dose were able to complete treatment [24].

### More Questions than Answers

Oncologists are right to be frustrated with the current state of affairs in pancreatic cancer. Articles reviewing progress made in pancreatic cancer typically begin by citing the incidence (37,680 cases expected in 2008 in the U.S. [25]), which continues to be nearly identical to the yearly death rate. The 11-month median survival for locally advanced pancreatic cancer patients in the E4201 trial [12], reported in 2008, is not markedly different from the 10-month median survival seen in the best arm of the Gastrointestinal Tumor Study Group (GITSG) trial from 1988 [13]. The success of

erlotinib with gemcitabine in metastatic disease, however modest, marks the arrival of an additional therapeutic agent with proven activity against pancreatic cancer. The studies reviewed above represent the first tentative steps down a path that will hopefully lead us to new regimens with improved efficacy against pancreatic cancer.

What conclusions can be drawn so far from the published data? The heterogeneity of the data presented above makes it difficult to draw firm conclusions. The gefitinib trials used a fixed dose of gefitinib and escalating chemotherapy doses, while the larger erlotinib trials used fixed chemotherapy doses and escalating doses of erlotinib. Most patients were classified as having locally advanced disease, but the staging methods used were variable. Nonetheless, the published investigations of gefitinib with radiation and chemotherapy in locally advanced disease suggest little activity and the possibility for severe toxicity. In contrast, it seems that the combination of erlotinib, gemcitabine, and standard-dose and volume radiation is tolerable, with encouraging rates of response. The randomized cetuximab data reported by Munter *et al.* [23] demonstrated a high rate of response (35.5%) and intriguing resection data in a larger group of patients. Median survival was impressive at 15 months. Interestingly, the addition of consolidation cetuximab did not improve outcomes, although the trial was likely underpowered for this purpose. The Heidelberg group used intensity-modulated radiation therapy, which may have contributed to the tolerability of this regimen [26]. In contrast, Demols *et al.* found that the best survival rates were obtained with a moderate radiation dose of 45 Gy, whereas 50.4 Gy was more toxic and resulted in inferior survival [24].

Some would argue that, given the controversy surrounding the use of radiation in pancreatic cancer, efforts to add EGFR inhibition to radiation represent not a giant leap or even a small one, but a misstep. We would suggest that this is not the proper way to approach the issue. The theoretical benefits of radiosensitization and the clinical data published so far regarding radiation and EGFR inhibition in locally advanced pancreatic cancer offer sufficient promise to merit additional phase II investigation, at the least. In the pre-operative and adjuvant settings, more data and longer follow-up are needed to make an assessment.

It is not clear which EGFR inhibitor should be combined with radiation. Cetuximab has the stronger clinical record as a radiosensitizer, and has approval specifically for this indication in head-and-neck cancer. Regarding the potential for controlling metastases, erlotinib has well-documented activity in advanced pancreatic cancer. A recent phase III randomized trial failed to show a statistically significant survival benefit to adding cetuximab to gemcitabine in advanced disease, although the absolute survival benefit (median survival of 6.4 *versus* 5.9 months) was similar to that seen in the NCIC trial with erlotinib [27]. In terms of tolerability, it is important to remember that even so

called “targeted agents” can have significant systemic toxicity (particularly diarrhea), and that this is additive to the toxicity of “standard” chemotherapy and radiation. Maintenance or consolidation EGFR inhibition in conjunction with gemcitabine is an appealing concept, given the prevalence of metastatic disease, but unproven, and would also add to toxicity. The optimal radiation dose and volumes for locally advanced disease (tumor alone *versus* tumor and draining lymph nodes) remain additional unknown quantities. Finally, Lawrence *et al.* have published pre-clinical data suggesting that the sequencing of chemotherapy, EGFR inhibition and radiation may be clinically significant [28]. Given the number of factors in play, further phase I and II studies should be performed, and indeed a number are underway. Data from these studies should be studied carefully before moving into a cooperative group setting.

Efforts to define molecular markers that can select a cohort of pancreatic patients who will benefit from EGFR inhibition are ongoing. In the NCIC study, the intensity of immunohistochemical staining for EGFR did not predict response to erlotinib [10]. There is evidence to suggest that mutations in EGFR and increased EGFR gene copy number are related to tumor response to EGFR inhibition in certain tumor types. EGFR mutations appear to be rare in pancreatic cancer, and although increased EGFR copy number is relatively common finding, the implication of this finding with regard to EGFR inhibitor therapy has not yet been elucidated [29]. Researchers continue to evaluate other components of the EGFR signaling pathway, such as activated EFGR, in the search for a marker that will predict the response of pancreatic tumors to EGFR inhibition [30]. There is strong data to indicate that mutation of the *K-ras* gene, a downstream signaling intermediary of the EGFR family, predicts for a lack of response to cetuximab in colorectal cancer [31]. Likewise, non-small cell lung cancer patients with mutated *K-ras* do not respond to EGFR inhibition by TKIs [32]. A subset analysis of available samples from the NCIC trial showed that 76% had mutated *K-ras*, and there was a non-significant trend towards response to erlotinib in patients with wild-type *K-ras* [33]. While up to 90% of pancreatic tumors have *K-ras* mutations [34], the high response rates seen in Table 1 suggest that the biology of pancreatic cancer may be different with regard to the interaction of *K-ras* and EGFR. Alternatively, the mechanisms through which the combination of radiation, chemotherapy and EGFR inhibitors attack tumors may be different from those involved when chemotherapy and EGFR inhibitors are combined. Only 181 of the 569 patients enrolled on the NCIC trial had adequate tissue for retrospective molecular analysis [33]. Future studies should make every effort to incorporate prospective tissue banking and consider repeat biopsies to evaluate molecular responses during treatment to improve our understanding of the biology of EGFR inhibition in the setting of chemoradiation.

Ultimately, improved patient selection through the use of biomarkers could greatly increase the chances for success of future phase III efforts.

## Conclusions

The combination of EGFR inhibition with concurrent chemoradiation in locally advanced pancreatic cancer has shown promising tumor response rates in the range of 30-40% with acceptable toxicity and median survival times in excess of 14 months. Further prospective studies are needed to determine the optimal combination and schedule of EGFR inhibitor, chemotherapy, and radiation and to validate molecular markers that can identify a set of patients who are most likely to respond.

**Conflict of interest** The authors have no potential conflicts of interest

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