

The 2010 Gastrointestinal Cancers Symposium

Oral Abstract Session: Cancers of the Pancreas, Small Bowel and Hepatobiliary Tract

Abstract #131: Phase I study of MK-0646 (dalotuzumab), a humanized monoclonal antibody against IGF-1R in combination with gemcitabine or gemcitabine plus erlotinib for advanced previously untreated pancreatic cancer

Speaker: Milind Javle, MD – University of Texas, MD Anderson Cancer Center

IGF-1R

- The insulin-like growth factor 1 receptor (IGF-1R) pathway plays an important role in cellular proliferation and resistance to therapy.
- Data suggests IGF-1R is crucial in cancer pathogenesis and is an attractive target in cancer research.
- IGF-1R is activated by its ligands: IGF1 and IGF2

IGF-1R Targeting and Pancreatic Cancer

- Activation of IGF-1R predicts an aggressive disease course in pancreatic cancer.
- IGF-1R activation is associated with acquired resistance to EGFR-targeted therapies like erlotinib.
- Preclinical studies presented at 2009 AACR proceedings showed the addition of IGF-1R monoclonal antibody R1507 to cetuximab was synergistic against pancreatic cell lines.

MK-0646

- MK-0646 is a humanized IGF-1R directed antibody. It preferentially binds to IGF-1R.
- Elicits antibody-dependent cell-mediated cytotoxicity (ADCC) activity.
- Inhibits IGF-1 and 2 stimulation of the IGF-1R.
- Down regulates IGF-1R expression in tumor models and has antitumor activity in xenografts.

MK-0646 : Phase I Single Agent Data

- Single agent MK-0646 is well tolerated.
- Maximum tolerated dose (MTD) not reached at 20 mg/kg weekly and 15 mg/kg bi-weekly.
- Hyperglycemia is easily controlled with oral hypoglycemic agent.
- All doses >10 mg/kg resulted in trough concentration (plasma level of a pharmaceutical product measured just before the next dose) above the target.
- Pharmacodynamic effect: down regulation of IGF-1R, 4-EBP1, eIF4-E, pS6 seen at all dose levels

Primary Objectives

- Phase I - determine the MTD of:
 - MK-0646 + gemcitabine
 - MK-0646 + gemcitabine + erlotinib
- Phase II - assess progression free survival in the two study arms

Secondary Objectives

- Assess overall response rate, treatment toxicity and overall survival.
- Correlate Progression Free Survival (PFS) and Overall Survival (OS) with IGF-1, IGFBP-3 levels and the expression of p-IRS, IGF-1R, Akt and Erk in tissue. SNPs of the IGF-1R genes correlation with clinical and pathologic endpoints.

Inclusion Criteria

- Stage IV pancreatic adenocarcinoma.
- Greater than six months since adjuvant therapy.
- Greater than 18 years of age.
- ECOG performance status 0-1.
- Blood work including fasting glucose of ≤ 160 mg/dl.

Phase I Study had Two Arms

- Non-randomized, sequential enrollment: Arm A1, A2, then Arm B1, B2
- **Arm A**
 - 1: FDR Gem 1000 mg (day 1, 8, 15) + MK-0646 5mg (day 1, 8, 15, 22)
 - 2: FDR Gem 1000 mg (day 1, 8, 15) + MK-0646 10mg (day 1, 8, 15, 22)
- **Arm B**
 - 1: FDR Gem 1000 mg (day 1, 8, 15) + erlotinib 100 mg+ MK-0646 5mg (day 1, 8, 15, 22)
 - 2: FDR Gem 1000 mg (day 1, 8, 15) + erlotinib 100 mg + MK-0646 10mg (day 1, 8, 15, 22)

Demographics (N=28)

- 27 patients (96%) had ECOG performance status of 1
- 22 patients (78%) were male
- All patients (n=28) had stage IV disease
- 2 patients (7%) had prior Whipple

Accrual per Dose Level

Dose Level	Therapy	# of patients
A1	Gem + MK-0646 (5 mg/kg)	3
A2	Gem + MK-0646 (10 mg/kg)	6
B1	Gem + Erlotinib + MK-0646 (5 mg/kg)	6
B2	Gem + Erlotinib + MK-0646 (10 mg/kg)	6

Treatment Delivery

- Median cycles delivered = 2 (min 1, max 12+)
- Of 28 patients enrolled, 82% required dose modification of gemcitabine.
- Five patients (35%) in Arm B discontinued erlotinib but none withdrew because of toxicity.
- Study discontinuation for toxicity = 0 pts

Agent Dose Modified	Patients
Gemcitabine	23 (82%)
Erlotinib	7 (50%) <i>This was a surprise give the dose was only 100mg/day</i>
MK-0646	0 (0%)

Dose Limiting Toxicity (DLT)

- Hematologic DLT included:
 - Grade 4 thrombocytopenia
 - Grade 4 neutropenia lasting ≥ 7 days
 - Grade 3 or greater neutropenia with fever

- Non-hematologic toxicities were grade 3 or 4 events excluding hyperglycemia and rash (caused by erlotinib)

Grade 3 or 4 Non-Hematological Toxicities

Toxicity	Patients
Hyperglycemia	5 (18%)
Fatigue	5 (18%)
ALT/AST	4 (14%)
Increased Magnesium	4 (14%)
Decreased Lipase	1 (3%)
Dehydration	1 (3%)
Muscle weakness	1 (3%)

Grade 3 or 4 Hematological Toxicities

Toxicity	Patients
Decreased Neutrophils	14 (50%)
Decreased platelets	5 (18%)
Anemia	2 (7%)
Hemorrhage	1 (3%)

Response Data (from 24 evaluable patients)

- Partial Responses (PR): 6 patients (25%)
- Stable Disease (SD): 8 patients (33%)
- Progressive Disease (PD): 10 patients (42%)
- Dr. Javle stated the responses occurred equally in both arms and he believed the responses were sustained. Five out of six patients experienced long responses as outlined in this table.

Study Arm	Patient Number	Duration of PR (weeks)
A	1	44+
B	5	14
A	8	44+
A	9	32
B	17	28+
B	21	20+

Where do we go From Here?

- Long history of failed phase III trials in pancreatic cancer.
- Plan to develop MK-0646 in pancreatic cancer in two ways:
 1. Narrow down the predictive markers for this disease. Look at SNPs, tissue correlates and IGF-1: IGFBP-3 ratios.
 2. Randomized phase II study (n=80 patients) currently ongoing.
 - a. Primary Objective: PFS.
 - b. Three arms:
 - i. Arm A – gemcitabine + MK-0646
 - ii. Arm B – gemcitabine + MK-0646 + erlotinib
 - iii. Arm C – gemcitabine + erlotinib
 - c. Includes correlative studies to identify predictive markers.

Conclusions

- For Arm A, MK-0646 + gemcitabine was tolerable. MTD not reached at 10 mg/kg.
- For Arm B, the addition of erlotinib to MK-0646 + gemcitabine was associated with toxicity. MTD of MK-0646 was 5 mg/kg.
- Sustained partial response occurred in some patients.
- Phase II randomized study (with gemcitabine + erlotinib as a control arm) is ongoing.
- Correlative studies to identify predictive markers included in phase II study.

Discussant for Abstract #131: Philip Philip, MD, PhD, FRCP
Karmanos Cancer Institute, Wayne State University

Background – Targeted Therapies in Pancreatic Cancer

- Several agents tested in combination with gemcitabine have shown no improvement in clinical outcome, except for a marginal benefit with erlotinib.
- Dr. Philip noted that over the last 10 years, the research community has learned there are multiple genetic abnormalities and genetic changes that occur during the progression of pancreatic cancer that necessitate multi-targeted approaches and very importantly biomarker driven patient selection.

Insulin-Like Growth Factor-1 Receptor (IGF1-R) Targeting in Pancreatic Cancer

- Activation of IGF-1R induced cell proliferation, survival, angiogenesis and invasion in multiple cancers. Targeting IGF-1R in preclinical models leads to tumor growth inhibition and may reverse drug resistance.
- Single anti-IGF-1R agent +/- gemcitabine is unlikely to succeed given the multiple genetic abnormalities and changes that occur during disease progression, especially in an unselected patient population.
- Dr. Philip said Dr. Javle's study is a scientifically rational study design but the activity demonstrated does not constitute an anti-tumor signal for MK-0646. Further, pre-clinical models and clinical validation must be undertaken.
- Eligibility criteria included stage IV disease only; this is in line with the thinking that metastatic disease should be separated from locally advanced unresectable disease.

MTD of MK-0646

- Dr. Philip said the pancreatic community sometimes thinks a phase I trial is not necessary when combining three drugs; however, Dr. Javle's trial reflected its importance. While there were no problems adding MTD MK-0646 (10 mg) to gemcitabine, the addition of the third drug erlotinib posed problematic to patients.
 - Researchers could not give the full dose of the drug. There were dose limiting toxicities. One third of patients discontinued erlotinib because of toxicity.

Hyperglycemia in Targeting IGF-1R in Pancreatic Cancer

- Dr. Philip spoke about hyperglycemia which is a typical side effect in this class of agents.
- IGF-1R is present on normal cells with 84% homology to insulin receptor. There is overlap between IGF-1R and insulin receptor when targeting IGF-1R.
- Up to 40% of patients with pancreatic cancer have diabetes mellitus.

Anti-tumor Activity of MK-0646 + Gemcitabine +/- Erlotinib (N=24)

Objective response (%)	25
Response duration (weeks)	14-44+
Stable disease (%)	33
Progressive disease (%)	42
Median Time to progression	<10 weeks

Conclusion

- Dr. Philip said he is pleased to see that Dr. Javle is collecting maximum data to understand the underlying mechanisms of this treatment.
- Hyperglycemia may not be a dose limiting toxicity to MK-0646 in this study.
- It is too early to determine whether there is a signal for anti-tumor activity for MK-0646 but Dr. Philip encouraged researchers to pursue further development of an anti-IGF-1R strategy in pancreatic cancer.
- Further preclinical and clinical validation of an IGF-1R based multi-targeted strategy in pancreatic cancer must be undertaken.
- Predictive biomarkers must be developed for patient selection and stratification and to understand if a treatment fails.
- Dr. Philip concluded that the pancreatic cancer community needs more data before they are ready to design a phase III study of an anti-IGF-1R in pancreatic cancer. He referred the audience to read the *JCO* 2009 whitepaper concerning the future of clinical trials in pancreatic cancer.
 - *Journal of Clinical Oncology*, Vol 27, No 33 (November 20), 2009: pp. 5660-5669
Consensus Report of the National Cancer Institute Clinical Trials Planning Meeting on Pancreas Cancer Treatment

Abstract #132: Multi-institutional phase II trial of induction cetuximab, gemcitabine and oxaliplatin followed by radiotherapy with concurrent capecitabine and cetuximab for locally advanced pancreatic adenocarcinoma

Speaker: Christopher Crane, MD – The University of Texas, MD Anderson Cancer Center

Background

- Pancreatic cancers are resistant to treatment.
- EGFR inhibition is a proven chemosensitizing and radiosensitizing strategy.
- Induction gemcitabine based chemotherapy followed by chemoradiation is an emerging preferred treatment sequence.
- The combination of gemcitabine/oxaliplatin/cetuximab has yielded promising phase II data; has not yet been evaluated in phase III setting.

Trial Eligibility

- Locally advanced pancreatic adenocarcinoma
 - T4, N0-1 (n=67)
 - Celiac axis or SMA involvement
 - Including borderline resectable
 - Advanced regional adenopathy (n=2)
- No prior therapy

- ECOG PS 0-1
- No unequivocal metastases
- Adequate biliary drainage

Schema

- Two months of gemcitabine/oxaliplatin/cetuximab
- Followed by capecitabine/radiation/cetuximab
- Maintenance therapy of gemcitabine/cetuximab was used for patients whose disease remained localized after restaging until progression.
- Dosing
 - Gemcitabine: FDR 1000 mg/m² over 100 min Q2wk
 - Oxaliplatin: 100mg/m² over 2 hours Q2wk
 - Cetuximab 400 mg/m² then 500mg/m² q2wk
 - Radiotherapy: 50.4 Gy (3DCRT to gross tumor only)

Study Endpoints

- Primary: 1 year Overall Survival (OS)
- Secondary: Tumor response, safety
- Correlative studies: serum cytokines, correlative genomic analysis

Accrual

- 69 total patients (60 at MD Anderson and 9 at Brown University)
 - 51 unresectable
 - 18 borderline resectable
 - The treatment was reasonable and well tolerated in patients with ECOG PS 0 of 1.
 - Dr. Crane commented that some of the borderline patients with ECOG PS between 1 and 2 were not great candidates for this systemic therapy.
 - Fatigue and GI related toxicities were the most significant side effects.
 - The chemoradiation phase of treatment was well tolerated with only 2% experiencing grade 3 toxicity.
 - In 23% with grade 3 toxicity, dose adjustments were made of capecitabine. Grade 2 fatigue was the other toxicity seen.

Radiographic Response (measured 6 weeks after chemo XRT)

- Partial Response (PR)= 19%
- Minor Response (MR)= 17%
- Stable Disease (SD)= 45%
- Progressive Disease (PD)= 18%
 - 2 local progression after chemotherapy
 - 2 distant progression after chemotherapy
 - 7 distant progression after chemoradiation

Maintenance Chemotherapy

- 57% of patients received maintenance chemotherapy with stable or responding disease.
- Median start of maintenance chemotherapy – 4 months (range 1-20)
- Regimens given:

- Gemcitabine/cetuximab 52%
- Gemcitabine/erlotinib 24% (given to patients who lived far from the center and couldn't come in for IV therapy)
- Other 26%
- 57% of patients received chemotherapy at progression.

Overall Survival (OS) – All Patients (Intent-to-Treat)

- Median survival 18.8 months
- 1 year 67.8%
- 2-year 30.9%
- 3 year 18.5%
- Median PFS of 12.3 months

Survival According to Rash

- Any rash (grade 1, 2, or 3) n=42 pts
- No rash n=27 pts
- Overall Survival was not statistically significant between the two groups but Dr. Crane noted that the study was not powered for that endpoint.

Survival According to Resectability

- The 18 patients originally deemed borderline resectable had similar survival to the 51 patients who had unresectable disease.

Surgical Resection

- 7 patients underwent surgical resection
- All R0 resections
- Current status:
 - None are alive with no evidence of disease
 - 2 alive with progressive disease at 32.5 months and 29.9 months
 - 2 died with perioperative complications at 10.2 months and 9.7 months

Overall Survival –Unresected Patients

- 60 patients were unresected
- Median survival: 18.8 months
- 1 year OS 68.7%
- 2 year OS 25.6%
- 3 year OS 10.2%

Pattern of Disease Progression (First site)

- 30/69 patients distant metastases only 43%
- 9/69 local progression only 13%
- 3/60 synchronous local and distant 4%
- 27/69 progression-free 39%
- Dr. Crane pointed out that when one looks at the actuarial curve of local failure an interesting trend emerges.

- Local control was very good for about 16 months with patients passing from distant disease within first 16 months.
- But after 16 months, there was a lot of late local failures between 16 and 31 months. He feels there are two subsets of patients:
 - 1) Those with the rapid aggressive biology typically seen in this disease.
 - 2) Those with only the local pattern of disease progression.

Conclusion

- This regimen appears to be effective.
- The primary endpoint was met.
 - 68.7% 1-year OS.
 - 18.8 months median survival in unresected patients.
- Survival between the unresectable patients (n=51) and the borderline (n=18) were similar between the two groups.
- Small but significant subset of patients:
 - Disease controlled at 3 years without surgery (~10%).
 - Late local only progression 10-30%.

What Next?

- Both gemcitabine/cetuximab and gemcitabine/oxaliplatin showed negative results in prior phase III trial.
- Need hypotheses from translational data
 - Genomic tumor marker or profile predictive of localized disease phenotype or predictive of outcome to cetuximab-based therapy.
- Multi-institutional single arm trial of a patient subset.