EDITORIAL

# Advancements in the Management of Pancreatic Cancer: 2015 ASCO Gastrointestinal Cancers Symposium

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### Introduction

Despite advances in chemotherapy regimens and improvement in radiation delivery, pancreatic cancer remains to be associated with a grim prognosis. Overall, the lifetime risk of pancreatic cancer is 1 in 67 individuals, with an expected incidence of 48,960 new cases for pancreatic cancer (24,840 men and 24,120 women) and expected 40,560 deaths from pancreatic cancer (20,710 men and 19,850 women) for the United States by the American Cancer Society in 2015. Although, pancreatic cancer will account for only 3% of all cancers diagnosed in the United States, it will be the cause of 7% of cancer deaths and is the 4$^{th}$ most common cause of cancer-related deaths behind much more common malignancies such as breast, colorectal, prostate and lung cancers [1].

The treatment of pancreatic cancer remains challenging; however, multiple areas of research including the development and testing of novel agents, optimization of multimodality treatment and combination chemotherapy regimens, utilization of genomic analysis to identify potential targets of therapies and assessment of response with tumor markers are being intensely pursued. In this article we review abstracts presented at the 2015 Gastrointestinal Cancers Symposium in San Francisco, California as they pertain to the management of pancreatic cancer.

### Studies in the Treatment of Advanced and Metastatic Pancreatic Cancer

After the impact of FOLFIRINOX [2] and gemcitabine plus nab-paclitaxel regimen [3] in patients with metastatic pancreatic cancer (mPAC), many studies were presented to share the investigators experience with modified versions of FOLFIRINOX regimen in advanced as well as in earlier stages of pancreatic cancer. Although no randomized phase III study was presented at this meeting for first-line treatment of mPAC, many novel agents were explored in the setting as summarized in Tables 1, 2, and 3.

Of the above studies, the novel agents that seem promising and deserve further discussion include Abstracts #336, #261, and #359.

IMM-101 is a heat killed whole-cell preparation of *mycobacterium obuense.* In combination with gemcitabine, IMM-101 provided a statistically significant improvement in overall survival by 1.6 months in advanced pancreatic cancer (Abstract #336) [4]. This agent is being developed by Immodulon Therapeutic, Ltd. (London, UK) and has been granted Orphan Drug Status by the USA and EU. IMM-101 has been shown in a murine model of pancreatic cancer to upregulate cytotoxic CD8+ T-cell activity, which in consequence resulted in improved survival [5]. It is thought that the CD8+ mediated effects overcome the relative immunosuppression within the tumor microenvironment, thus enhancing cancer cell destruction. This study appears promising due to the novel mechanism of effect and minimal additional toxicities of this agent.

Another immunomodulatory therapy (Abstract #261), by Aduro Biotech, Inc. (Berkeley, CA, USA) consists of GVAX which is a growth factor secreting allogeneic pancreatic cancer cell vaccine followed by treatment with CRS-207, a live attenuated *Listeria monocytogenes* vaccine which expresses mesothelin. Mesothelin is a cell surface antigen and has been shown to be upregulated in pancreatic cancer cells [7]. In murine models of pancreatic cancer, vaccines against mesothelin have been shown to decrease tumor volume and improve survival [8]. The pathway by which CRS-207 works is important as it presents an immune-mediated therapy that is targeted to a protein that is known to be over-expressed in pancreatic cancer cells. This treatment demonstrated improved overall survival

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of 2.2 months in patients with previously treated mPAC in a phase II study. These results had been previously reported, but an update at this year's Gastrointestinal Cancers Symposium presented follow-up survival data and correlation of mesothelin-specific CD8+ T-cell responses, T cell subsets and serum cytokines to overall survival. This agent appears to show promise as a non-chemotherapy agent which demonstrates activity against pancreatic cancer with no reported grade 3 or 4 toxicities. GVAX/CRS-207 is currently being further investigated in the phase IIb ECLIPSE trial (NCT02004262) with plans to enroll 240 adults with previously treated mPAC.

Pegylated recombinant human hyaluronidase (PEGPH20), developed by Halozyme Therapeutics (San Diego, CA, USA), was investigated in a phase I study (NCT01453153) (Abstract #359) [9]. The desmoplastic reaction of the pancreatic cancer extracellular matrix is one mechanism by which pancreatic tumor cells are physiologically protected from cytoxic agents. This reaction includes buildup of the glycosaminoglycan hyaluronan, resulting in decreased penetration of chemotherapy due to increased interstitial edema and lymphatic system dysfunction [10]. Therapy with PEGPH20 seeks to abrogate this protective environment by depleting hyaluronan within the tumor microenvironment. Interestingly, in this phase I study, patients with high levels of tumor hyaluronan had comparatively improved PFS and OS in relation to patients with low levels of tumor hyaluronan. Of note, there were thromboembolic events reported in 28.6% of patients on the study. PEGPH20 has been granted Orphan Drug designation and there are currently two ongoing clinical trials in mPAC. The phase II study evaluating PEGPH20 in combination with gemcitabine/abraxane or gemcitabine (NCT01839487), had been placed on temporary hold, subsequently lifted, by the FDA and underwent revision of protocol to include evaluation for thromboembolic events and prophylactic low molecular weight heparin to prevent thromboembolism [11]. There is also an ongoing phase I/II study of PEGPH20 with mFOLFIRINOX (NCT01959139). Although the mechanism of action targeting the tumor microenvironment appears promising for this drug, this enthusiasm is tempered by concerns over the above mentioned thromboembolic events.

We were encouraged to see data presented for second line treatments in mPAC, as almost all patients will progress on first line therapy chemotherapy. Chen *et al*. (Abstract #234) presented the expanded analyses of NAPOLI-1 (NCT01494506), a phase III study of MM-398 (nal-IRI), with or without 5-fluorouracil (5-FU) and leucovorin (LV), versus 5-fluorouracil and leucovorin, in mPAC previously treated with gemcitabine-based therapy (Figure 1) [12]. MM-398 is a nanoliposomal form of irinotecan. In this study, patients with previously treated mPAC were randomized 1:1:1 to receive either MM-398 (120 mg/m$^2$ i.v. over 90 minutes) q3weeks or 5-FU (2000 mg/m$^2$ over 24 hours) plus LV (200 m/m$^2$ over 30 min) for 4 weeks or a combination of the two with MM-398 (80 mg/m$^2$ i.v. over 90 minutes) prior to 5-FU (2,400 mg/m$^2$ over 46 h) and LV (400 mg/m$^2$ over 30 min) every 2 weeks (Figure 1). The previously reported intention to treat (ITT) analysis showed that there was a significant difference in survival in MM-398 + 5-FU/LV arm of 6.1 months *versus* 4.2 months in the 5-FU/LV arm (HR 0.67, p-value = 0.012). The updated results presented at this meeting were from the Per Protocol group, which included patients who received at least 80% of the target dose in the first 6 weeks. Results in this group showed a median overall survival of 8.9 months versus 5.1 months in the MM-398 + 5-FU/LV arm compared to the 5-FU/LV arm (HR 0.57, P=0.011). The grade 3/4 adverse effects more prevalent in the MM-398 arm included neutropenia, fatigue, and gastrointestinal effects.

Ettrich *et al*., (Abstract #352) in a study sponsored by the University of Ulm in Germany, presented the results of DocOx study (AIO-PK0106) [13]. This was a phase II trial investigating the use of combination doxetaxel 75 mg/m$^2$ over 60 minutes day 1 and oxaliplatin 80 mg/m$^2$ over 120 minutes day 2 of a 21 day cycle in patients previously treated for mPAC, the majority of whom received prior gemcitabine based therapy. Among the 22 patients enrolled, the primary endpoint of tumor response was obtained in 7 (15.9%) by achieving partial remission. No complete remissions were seen and stable disease was seen in 31.8% of patients. Median progression free survival was 7 weeks and overall survival was 40 weeks. Although significant grade 3 and 4 toxicities were seen, including neutropenia (63.6%), febrile neutropenia (4.6%), GI (29.6%) and infectious (18.2%), this study does suggest activity of this regimen which warrants further investigation in phase III studies. However, the efficacy of this regimen in patients who have previously received gemcitabine/abraxane or FOLFIRINOX first line regimens is not clear, especially in terms of neurotoxicity as a common side effect of both agents.

As the need for further understanding and research in pre-clinical arena is a major mandate in this deadly disease, multiple abstracts presented developing markers that may not only aid in diagnosing pancreatic cancer at earlier stages, but can also assess treatment response (Table 4).

Mitsunaga *et al*. (Abstract #265) [14] evaluated the role of S100P in assessing efficacy of chemotherapy. S100P is a calcium binding protein P that has been shown to be upregulated in pancreatic cancer and has been associated with adverse tumor biology characteristics such as metastasis and resistance to chemotherapy, as well as being investigated as a target of novel therapies [15]. In the study by Mitsunaga *et al*., serum levels of S100P were monitored in patients treated with chemotherapy for advanced pancreatic cancer, and patients who had at least a 25% reduction in S100P had better PFS and OS on univariate analysis. Although this correlation did not hold up on multivariate analysis, the role of S100P as a tumor marker in assessing response and correlation with patient outcomes merits further study in larger trials.

**Table 1.** Experimental details of few studies in treatment of advanced and metastatic pancreatic cancer.

| Abstract | Agent | Mode of action | Study type (phase) | No. of Pts | Ref. |
|---|---|---|---|---|---|
| **#344** | Pimasertib (Pim) + gemcitabine *vs.* Placebo + gemcitabine | Selective, non-competitive MEK 1/2 inhibitor | II | 44 *vs.* 44 | [17] |
| **#336** | IMM-101 + gemcitabine *vs.* gemcitabine monotherapy | Immunotherapy | II | 75 *vs.* 35 | [4] |
| **#352** | Docetaxel and oxaliplatin 2nd line therapy | - | II | 44 | [13] |
| **#359** | Gemcitabine + PEGPH20 | PEGylated recombinant human hyaluronidase | Ib | 28 | [9] |
| **#467** | Enzalutamide + gemcitabine/abraxane | Androgen receptor antagonist | I | 8 | [18] |
| **#240** | Chimeric monoclonal antibody NEO102 (NPC-1C) | Monoclonal antibody directed against MUC5AC | Ib/IIa | 26 | [19] |
| **#261** | GVAX pancreas and CRS-207 immunotherapy *vs.* GVAX alone | Immunotherapy | II | 61 *vs.* 29 | [6] |
| **#234** | MM-398 (nal-IRI) *vs.* 5-FU/LV *vs.* Combination of MM-398 prior to 5-FU/LV | MM-398 is a nanoliposomal irinotecan | III | 117 *vs.* 149 *vs.* 151 | [12] |

5-FU: 5-fluorouracil; LV: leucovorin; MEK: mitogen-activated protein kinase/extracellular signal-regulated kinase kinase; MUC5AC: mucin 5AC; PEGPH20: PEGylated recombinant human hyaluronidase; Pim: pimasertib; Pts: patients

**Table 2.** Efficacy of few studies in treatment of advanced and metastatic pancreatic cancer.

| Abstract | Agent | Response rate (RR) | Median PFS | Median OS |
|---|---|---|---|---|
| **#344** | Pimasertib (Pim) + gemcitabine *vs.* Placebo + gemcitabine | 9.1% both arms | 3.7 months *vs.* 2.8 months (HR: 0.883, 95% CI: 0.549–1.42; P=0.608) | 7.3 months *vs.* 8.3 months |
| **#336** | IMM-101 + gemcitabine *vs.* gemcitabine monotherapy | NR | 4.4 months *vs.* 2.4 months (P=0.003) | 7.2 months *vs.* 5.6 months (P=0.022) |
| **#352** | Docetaxel and oxaliplatin 2nd line therapy | SD: 31.8%<br>PR: 15.9%<br>CR: 0% | 7 weeks | 40 weeks |
| **#359** | Gemcitabine + PEGPH20 | SD: 45.8%<br>PR: 29.2%<br>CR: 0% | All Pts: 154 days<br>HA high: 219 days<br>HA low: 108 days | All Pts: 200 days<br>HA high: 395 days<br>HA low: 174 days |
| **#467** | Enzalutamide + gemcitabine/abraxane | SD in 3 of evaluated Pts | NR | NR |
| **#240** | Chimeric monoclonal antibody NEO102 (NPC-1C) | Stable disease in 42% | NR | 4.5 months |
| **#261** | GVAX pancreas and CRS-207 immunotherapy *vs.* GVAX alone | NR | NR | 6.1 months *vs.* 3.9 months (HR=0.54, P=0.011) |
| **#234** | MM-398 (nal-IRI) + 5-FU/LV *vs.* 5-FU/LV | 16% *vs.* 1% (P<0.001) | 3.1 months *vs.* 1.5 months (P=0.0001) | **ITT groups:** 6.1 months *vs.* 4.2 months (HR=0.67, P=0.012)<br>**Per protocol [a]:** 8.9 months *vs.* 5.1 months (HR=0.57, P=0.011) |

[a] Pts with ≥80% target dose in 6 weeks

5-FU: 5-fluorouracil; CR: complete response; SD: stable disease; HA: hyaluronic acid; ITT: intention to treat; LV: leucovorin; NR: not reported; OS: overall survival; PEGPH20: PEGylated recombinant human hyaluronidase; Pim: pimasertib; PR: partial response; Pts: patients; RR: response rate; PFS: progression-free survival

Hingorani *et al*. (Abstract #300) [16] in their phase Ib study of PEGPH20 plus gemcitabine discussed above, also examined levels of soluble hyaluronic acid (sHA) as a marker of chemotherapy response. They also studied dynamic enhanced magnetic resonance imaging (DCE-MRI) and FDG-PET as methods of response assessment. They

**Table 3.** Toxicity of few studies in treatment of advanced and metastatic pancreatic cancer.

| Abstract | Agent | Grade 3 and 4 adverse events |
|---|---|---|
| **#344** | Pimasertib (Pim) + gemcitabine *vs.* Placebo + gemcitabine | Thrombocytopenia: 20.0 *vs*. 0%<br>Vomiting: 15.6 *vs*. 4.8%<br>Fatigue: 15.6 *vs*. 7.1%<br>Stomatitis: 13.3 *vs*. 0%<br>Diarrhea: 11.1 *vs*. 2.4% |
| **#336** | IMM-101 + gemcitabine *vs.* gemcitabine monotherapy | Asthenia: 10.8% *vs*. 2.9%<br>Abdominal : 8.1% *vs*. 2.9% |
| **#352** | Docetaxel and oxaliplatin 2$^{nd}$ line therapy | Neutropenia: 63.6%<br>Febrile neutropenia: 4.6%<br>GI symptoms: 29.6%<br>Infections: 18.2% |
| **#359** | Gemcitabine + PEGPH20 | Peripheral edema: 3.6%<br>Muscle : 7.1%<br>Thrombocytopenia: 7.1%<br>Fatigue: 7.1%<br>Anemia: 21.4%<br>Abdominal pain: 3.6%<br>Asthenia: 3.6%<br>Extremity pain: 3.6%<br>Hypokalemia: 7.1%<br>Pulmonary embolism: 10.7% |
| **#467** | Enzalutamide + gemcitabine/abraxane | Grade 3:<br>Febrile neutropenia: 12%<br>Neutropenia: 12%<br>ALT elevation: 12% |
| **#240** | Chimeric monoclonal antibody NEO102 (NPC-1C) | Grade 3:<br>Hyperbilirubinemia: 15.4%<br>Anemia: 3.8% |
| **#261** | GVAX pancreas and CRS-207 immunotherapy *vs.* GVAX alone | No grade 3 adverse events reported |
| **#234** | MM-398 (nal-IRI) + 5-FU/LV *vs.*5-FU/LV | Neutropenia: 20% *vs*. 2%<br>Fatigue: 14% *vs*. 4%<br>Vomiting: 11% *vs*. 3%<br>Diarrhea: 13% *vs*. 5%<br>Nausea: 8% *vs*. 3% |

5-FU: 5-fluorouracil; LV: leucovorin; PEGPH20: PEGylated recombinant human hyaluronidase; Pim: pimasertib

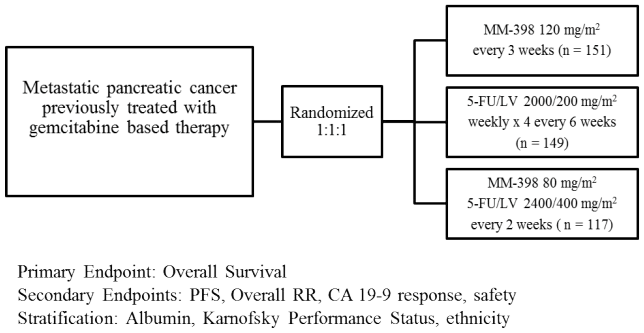


**Figure 1.** NAPOLI-1 Study Schema

found that increases in plasma sHA correlated with rising doses of chemotherapy, DCE-MRI tumor perfusion was increased at 24 hours, and FDG-PET avidity was reduced an average of 37% at the end of cycle 1. These responses suggest that sHA is indeed a marker of PEGPH20 mediated hyaluronic acid degradation and further investigation into how levels of sHA, tumor perfusion by DCE-MRI and FDG-PET correlate with response to treatment with PEGPH20 is indicated; especially if PEGPH20 shows further efficacy in future studies. Larger studies are needed to further elucidate the correlation between serum hyaluronic acid levels and response to PEGPH20 therapy. This study underscores the importance of investigating beyond drugs and developing better methods or diagnostic tools to select patients for optimal therapy and prevent toxicity.

Finally, 3 more studies evaluating treatment of advanced and metastatic pancreatic cancer were presented (Abstract #344 [17]; Abstract #467) [18]; Abstract #240[19]) (Tables 1, 2 and 3).

## Discussion

Despite the multiple modalities of therapy available to patients with pancreatic cancer, this disease disproportionately results in a larger burden of morbidity and mortality relative to its incidence compared to other more common malignancies. This is true regardless of the stage at which pancreatic cancer patients present. In the abstracts presented at the 2015 Gastrointestinal Cancers Symposium, we see progress being made in regards to further characterizing the genomic characteristics of this disease as it relates to prognosis and response to therapy. Existing combination chemotherapy agents continue to be investigated in conjunction with radiation therapy to improve resectability rates, although the survival benefit of this approach remains to be fully appreciated. Additionally, there are a multitude of novel therapeutic agents being investigated, such as new formulations of chemotherapy (MM-398), immunomodulatory therapies (IMM-101, GVAX CRS-207), monoclonal antibody therapy (NEO102), agents targeting the cell cycle pathway (pimasertib), androgen receptor blockade (enzalutamide) and agents targeting the tumor microenvironment (PEGPH20, PF-04136309).

**Table 4.** Translational correlates.

| Abstract | Marker | Setting | Validation | Ref. |
|---|---|---|---|---|
| **#265** | Serum S100P tumor marker | Patients undergoing first line chemotherapy for mPAC with liver mets | Response of S100P correlated with longer PFS (HR: 0.47, P=0.02) and OS (8.4 months *vs*. 3.7 months, P=0.04) | [14] |
| **#300** | Soluble hyaluronic acid (sHA) | Patients with mPAC treated with PEGPH20 plus gemcitabine | sHA increased within 2-3 days after 1.0, 1.6, or 3.0 μg/kg of PEG, with correlated early increase in tumor perfusion on dynamic contrast enhanced MRI (n=6) and average reduction in SUVmax of 37% by PET/CT with partial metabolic response by EORTC criteria in 4/5 patients | [16] |

mPAC: metastatic pancreatic cancer; OS: overall survival; PFS: progression free survival; sHA: soluble hyaluronic acid

Although some of these outcomes may appear to be of small incremental benefit in terms of progression free survival and overall survival, the hope is that the knowledge gained from these studies will translate into a better understanding of pancreatic cancer and substantially improved outcomes in the future. Investigators need to combine their efforts to bring basic science to the clinic quickly. In addition to developing novel drugs and new regimens we must explore pathways and markers to guide us towards patient specific treatments in the personalized medicine era. Selecting the right therapy for the patient, being able to better predict outcomes and incur less toxicity will be most beneficial in this setting of pancreatic cancer as the window of opportunity is so small due to short survival.

## Conflict of Interest

Authors declare to have no conflict of interest.

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