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MEETING SUMMARY
ASCO GI 2018, San Francisco, USA

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CANCERS OF THE LIVER, LOWER INTESTINE AND PANCREAS TRACT

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A PHASE IB/II RANDOMIZED STUDY OF mFOLFIRINOX (mFFOX) + PEGYLATED RECOMBINANT HUMAN HYALURONIDASE (PEGPH20) VERSUS mFFOX ALONE IN PATIENTS WITH GOOD PERFORMANCE STATUS METASTATIC PANCREATIC ADENOCARCINOMA (mPC): SWOG S1313

Ramesh K. Ramanathan. Abstract #208

STUDY DESIGN

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- PEGPH20 degrades hyaluronan (HA), a major component of the stroma, increases delivery of gemcitabine and prolongs survival in preclinical models
- This was a Phase IB/II randomized study of modified FOLFIRINOX (mFFX) with or without PEGPH20
- Eligibility
  - untreated mPC, ECOG PS 0-1
- mFFX regimen:
  - elimination of the 5FU bolus and use of G-CSF post treatment
- Following increase in thromboembolic events in another study with this agent, an amendment was passed to require enoxaparin treatment for all patients on the PEGPH20 arm
- Primary end point was OS
- Following the dose finding phase IB run-in phase, a phase II randomized study was initiated and 138 were accrued
- After a phase Ib run in a dose of 3mcg/Kg q 2 weeks given 24hr before mFFX was selected for phase II

Presented at ASCO GI 2018, Ramesh K. Ramanathan. Abstract #208

RESULTS

- Planned interim analysis was conducted after 35 deaths occurred and these results were reported at the meeting
- Significant increase in grade 3-4 toxicity, specifically GI toxicity was seen in the investigational arm with PEGPH20
  - HR for increased toxicity in the investigational arm of 2.7
- The results showed improved OS in the **standard** arm 14.4 months vs. 7.6 months
  - PFS was also lower in the experimental arm
- The study was closed early due to futility

Presented at ASCO GI 2018, Ramesh K. Ramanathan. Abstract #208

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- Although this is a negative study it demonstrates the highest reported OS with mFFX of 14.4 months
- Inferior results in the experimental arm could be due to less FFX exposure in this arm
- These results are in contrast to the reported data of improved PFS with the combination of PEGPH20 with gemcitabine/Nab-P in a phase II study which serves as the basis for an ongoing phase III study (HALO 301)

Hingorani et al. JCO 2017

PHASE II LAPACT TRIAL OF *nab*-PACLITAXEL (*nab*-P) PLUS GEMCITABINE (G) FOR PATIENTS WITH LOCALLY ADVANCED PANCREATIC CANCER (LAPC)

Hammel et al. Abstract #204

STUDY DESIGN

- International, multicenter, single arm phase II study for evaluation of the safety and efficacy of gemcitabine and abraxane (GA) for the treatment of untreated LAPC
- Patients received induction GA at standard dosing for 6 months
- At 6 months those with no evidence of progression or unacceptable adverse events were allowed to have one of the following by MD choice:
  - continued GA
  - chemoradiation
  - surgery
- Eligibility: chemotherapy naive, PS 0-1
- Primary end point was TTF
- Secondary end points: DCR, ORR, PFS, OS

Presented at ASCO GI 2018, Hammel et al. Abstract #204

LAPC, Locally Advanced Pancreatic Cancer; GA, Gemcitabine and Abraxane; TTF, Time to Treatment Failure; DCR, Disease Control Rate; ORR, Objective Response Rate; PFS, Progression Free Survival; OS, Overall Survival

RESULTS

- 107 patients enrolled, 106 were evaluable
- No new toxicities of this regimen were recorded
- 43% were able to have further therapy by MD choice:
  - 12% chemotherapy
  - 16% chemo XRT
  - 15% surgery
- TTF was 8.6 months
- PFS –10.2 months
- DCR –78%
- ORR –35%

Presented at ASCO GI 2018, Hammel et al. Abstract #204

TTF, Time to Treatment Failure; DCR, Disease Control Rate; ORR, Objective Response Rate; PFS, Progression Free Survival; OS, Overall Survival

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- The study shows the feasibility and tolerability of GA in the setting of LAPC, confirmation for ongoing and future clinical trials
- The outcome is reassuring, especially the fact that some patients proceeded to have surgical resection
- The main limitation is the non-uniform definition of LAPC across various centers that may have affected the results

Presented at ASCO GI 2018, Hammel et al. Abstract #204

LAPC, Locally Advanced Pancreatic Cancer; GA, Gemcitabine and Abraxane

CABOZANTINIB (C) VERSUS PLACEBO (P) IN PATIENTS (PTS) WITH ADVANCED HEPATOCELLULAR CARCINOMA (HCC) WHO HAVE RECEIVED PRIOR SORAFENIB: RESULTS FROM THE RANDOMIZED PHASE III CELESTIAL TRIAL

Abou-Alfa. Abst #207

STUDY DESIGN

- Cabozantinib is a tyrosine kinase inhibitor which inhibits VEGFR, MET and AXL with previously shown activity in HCC
- This was a RCT, international, double blind placebo controlled, for advanced HCC patients who received prior therapy with sorafenib
- Patients were randomized to cabozantinib vs placebo in a 2:1 fashion
- **Eligibility criteria** included: Child-Pugh score A, ECOG PS 0-1; must have received prior sorafenib; up to 2 prior therapies, must have progressed on at least one
- **Primary end point** OS
- **Secondary end point** PFS, ORR

Presented at ASCO GI 2018, Abou-Alfa. Abst #207

VEGFR, Vascular Endothelial Growth Factor Receptor; HCC, HepatoCellular Carcinoma; RCT, Randomized Controlled Trial; OS, Overall Survival; PFS, Progression Free Survival; ORR, Objective Response Rate

RESULTS

- 773 patients enrolled
- Balanced patients' characteristics between the arms
- About 40% of patients had HBV, and 20% had HCV
- The results of the study showed significant improvement in OS 10.6 vs 8 months in favor of cabozantinib (HR – 0.76, p=0.0049)
- mPFS was 5.2m vs. 1.9m in favor of cabozantinib (HR – 0.44, p<0.001)
- ORR was 4% vs. 0.4% (for C) p=0.0086
- OS + PFS survival benefit was seen in most of the sub groups analyzed
- Adverse events from cabozantinib were seen in most patients
  - most common: HTN, hand foot syndrome, fatigue and diarrhea

Presented at ASCO GI 2018, Abou-Alfa. Abst #207

HBV, Hepatitis B Virus; HCV, Hepatitis C Virus; OS, Overall Survival; HR, Hazard Ratio; ORR, Objective Response Rate; C, cabozantinib; PFS, Progression Free Survival; HTN, hypertension

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- This study establishes a new treatment option for patients with HCC post treatment with sorafenib

Presented at ASCO GI 2018, Abou-Alfa. Abst #207
HCC, HepatoCellular Carcinoma

KEYNOTE-224: PEMBROLIZUMAB IN PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA PREVIOUSLY TREATED WITH SORAFENIB

Andrew X. Zhu. Abst #209

STUDY DESIGN

- Phase II study – evaluating the efficacy of pembrolizumab in advanced HCC post sorafenib therapy
- Treatment regimen was pembrolizumab 200 mg Q3wk
- Eligibility included patients with Child Pugh A, PS 0-1, predicted life expectancy > 3 months
- Primary end point ORR
- Secondary end point DCR, PFS, OS

Presented at ASCO GI 2018, Andrew X. Zhu. Abst #209

HCC, HepatoCellular Carcinoma; ORR, Objective Response Rate; DCR, Disease Control Rate; PFS, Progression Free Survival; OS, Overall Survival

RESULTS

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- 104 patients enrolled, 23 patients still on treatment
- ~20% HCV, ~20% HBV
- ORR was 16.3% and similar across the different sub groups
- Median time to response 2.1 months
- >90% of patients that responded had a respond for over 6 months
- DCR 61.5%
- PFS 4.8 months; OS not reached
- 6 month PFS and OS were 43.1% and 77.9% respectively
- AEs typical for IOs. No flare of HCV/HBV was seen

Presented at ASCO GI 2018, Andrew X. Zhu. Abst #209

HBV, Hepatitis B Virus; HCV, Hepatitis C Virus; ORR, Objective Response Rate; DCR, Disease Control Rate; PFS, Progression Free Survival; OS, Overall Survival; AE, Adverse Event; IO, immunotherapy

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- Results of this study are consistent with the prior data with nivolumab in patients with HCC post sorafenib therapy
- This further confirms the activity of immunotherapy in this disease

RANDOMIZED, OPEN LABEL, MULTICENTER, PHASE II TRIAL COMPARING TRANSARTERIAL CHEMOEMBOLIZATION (TACE) PLUS SORAFENIB WITH TACE ALONE IN PATIENTS WITH HEPATOCELLULAR CARCINOMA (HCC): TACTICS TRIAL

Masatoshi Kudo. Abst #206

STUDY DESIGN

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- Phase II open label study in patients with unresectable HCC treated with TACE with or without sorafenib. Conducted in Japan
- **Eligibility**: Child-Pugh score ≤7; no more than 2 prior TACE; no macro-vascular invasion; no extra-hepatic disease; no more than 10 tumors, none of them more than 10cm in size
- Patients on the sorafenib arm received 400mg once daily for 2-3 weeks prior to TACE. Then 800mg once daily after TACE
- Sorafenib was paused for 2 days before and 3 days after each TACE
- Patients remained on study until they became refractory to TACE, or developed untreatable progression, due to deterioration of liver function, development of vascular involvement or extra-hepatic disease
- New disease in the liver was not considered progressive disease
- **Primary end point** – PFS (defined as time to unTACEable progression, TACE failure or death) and OS

Presented at ASCO GI 2018, Masatoshi Kudo. Abst #206

HCC, HepatoCellular Carcinoma; TACE, TransArterial ChemoEmbolization; PFS, Progression Free Survival; OS, Overall Survival

RESULTS

- 156 patients enrolled
- The study met its primary end point median PFS was significantly improved with the addition of sorafenib to TACE (13.5m vs. 25.2m; HR=0.59; p=0.006)
- The benefit was noted in all sub groups
- OS data was not mature
- No unexpected toxicities were noted on this trial

Presented at ASCO GI 2018, Masatoshi Kudo. Abst #206

PFS, Progression Free Survival; TACE, TransArterial ChemoEmbolization; OS, Overall Survival

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- This is the first study to show efficacy of the combination of sorafenib and TACE in patients with HCC
- The TACTICS study had novel end point of time to unTACEable disease progression which has not been previously evaluated
- This end point requires further validation to determine if it is a good surrogate of survival
- These data are not mature yet to change the standard practice, and require further validation from Western countries

TACE, TransArterial ChemoEmbolization; HCC, HepatoCellular Carcinoma

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