Advance reports

Included in this report are the highlights of 48th Annual Meeting of the American Society of Clinical Oncology (ASCO), Chicago and the 72nd Annual Scientific Sessions of the American Diabetes Association, Philadelphia, USA.

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New results in hepatocellular carcinoma

Tivantinib, a single-agent, investigational, second-line treatment in hepatocellular carcinoma (HCC) showed a statistically significant 56% improvement as compared to placebo in time to progression in an intent to treat population.

The results of the randomised, placebo-controlled, double-blind, phase 2 clinical trial with the selective MET inhibitor, tivantinib, were presented recently at the 48th Annual Meeting of the American Society of Clinical Oncology (ASCO) in Chicago, USA.

The 107 patients in the trial had unresectable HCC and had disease progression after first-line therapy or were unable to tolerate the first-line therapy. Patients were randomised to receive tivantinib at 360mg twice daily or 240mg twice daily or placebo (2:1 tivantinib). The primary endpoint was time to progression in the intent to treat population. Other study endpoints were disease control rate, progression free survival, overall survival, as well as safety for the ITT population and pre-defined MET-high or MET-low cohorts (as defined by immunohistochemistry).

Tivantinib is an orally administered, selective inhibitor of MET, a receptor tyrosine kinase. In healthy adult cells, MET is present in normal levels to support natural cellular function, but in cancer cells MET is inappropriately and continuously activated for unknown reasons. When abnormally activated, MET plays multiple roles in aspects of human cancer, including cancer cell growth, survival, angiogenesis, invasion and metastasis.

In the MET-high cohort, there were also statistically significant improvements in time to progression, progression free survival and overall survival. Median overall survival in the tivantinib arm was 7.2 months and 3.8 months in the placebo arm (HR = 0.38; log rank p-value = 0.01). Median time to progression was 2.9 months in the tivantinib arm and 1.5 months in the placebo arm (HR = 0.43, log rank p-value = 0.03).

Median progression free survival was 2.4 months in the tivantinib arm and 1.5 months in the placebo arm (HR = 0.45, log rank p-value = 0.02). Adverse events were reported at similar rates in the treatment and placebo arms of the trial, except for a higher incidence of fatigue and haematologic events, including neutropenia and anaemia, in tivantinib-treated patients. The incidence of haematologic events decreased following dose reduction of tivantinib from 360mg twice daily to 240mg twice daily. Due to the incidence of neutropenia in the 360mg treatment group, the tivantinib dose was reduced to 240mg twice daily for all patients.

Globally, liver cancer is the sixth most common cancer (749,000 new cases), accounting for 7% of all cancers, and is the third cause of cancer related death (692,000 cases). HCC represents more than 90% of primary liver cancers. Chronic hepatitis B and C are recognised as the major factors worldwide increasing the risk of HCC, with risk being even greater in the presence of coinfection with these viruses. Cirrhosis is also a risk factor for development of HCC.

Lorenza Rimassa, Deputy Director, Medical Oncology Unit, Humanitas Cancer Center, Milan, Italy, said: "Patients living with this disease need more options to slow progression. The findings from this tivantinib study represent the first randomized data reported in HCC with an investigational MET inhibitor, as single-agent therapy in second-line treatment. The data suggest that patients

significantly benefited in time to progression and, importantly, those in a biologically relevant MET-high subgroup had an additional significant advantage in overall survival."

Tivantinib is currently in phase 3 development and has not yet been approved for any indication. Tivantinib has the potential to be a first-in-class MET inhibitor for the treatment of non-small cell lung cancer (NSCLC) and is currently being studied for other indications including liver and colorectal cancers.

Safety and efficacy of tivantinib (ARQ 197) combined with sorafenib

The safety and efficacy of tivantinib plus sorafenib was presented in a series of posters at ASCO.

One poster looked at the safety and efficacy of tivantinib plus sorafenib in patients with renal cell carcinoma (RCC) from a phase I study and found that it was well tolerated and exhibited preliminary anticancer activity in patients with RCC, including patients pretreated with vascular endothelial growth factor (VEGF) inhibitors.

Inhibitors of VEGF and VEGF receptor are standard therapy for RCC, and the MET signalling pathway is implicated in tumor angiogenesis. Tivantinib is an oral, selective MET inhibitor. The phase I dose-escalation study assessed the safety of tivantinib plus sorafenib in patients with advanced solid tumors. Endpoints were safety, the recommended phase II dose (RP2D) of tivantinib plus sorafenib, and antitumor activity. Previously, dose escalation established the RP2D as tivantinib 360mg twice daily (BID) plus sorafenib 400mg BID. Extension cohorts enrolled ≤20 patients each with RCC or other tumors. Patients were treated until disease progression or unacceptable toxicity.

Another poster presentation looked at the safety and efficacy of tivantinib combined with sorafenib in patients with NRAS wild-type or mutant melanoma from a phase I study. Again, it found that tivantinib plus sorafenib combination therapy was well tolerated and exhibited preliminary anticancer activity in patients with melanoma. Dual inhibition of MET and angiogenesis may be an effective treatment strategy in NRAS-mutant melanoma. The MET receptor tyrosine kinase is implicated in tumor cell proliferation, invasion, and metastasis, and is activated in NRAS mutant melanoma.

The third poster presented at ASCO looked at tivantinib combined with sorafenib in patients with hepatocellular carcinoma (HCC) from a phase I study. The combination of tivantinib (360mg BID) plus sorafenib (240mg BID) was well tolerated. Best response was one complete response (CR), one partial response (PR), and 12 stable disease (SD). Overall response rate and disease control rate were 10% and 70%, respectively. Median progression-free survival (mPFS) was 3.5 months (95% CI, 2.8–11.1 months). Among eight patients previously treated with VEGF inhibitors (six sorafenib; one sunitinib; one sorafenib plus sunitinib), best response was one CR, one PR, and three SD, and mPFS was 15.9 months (95% CI, 1.6–15.9 months). Two patients are still on study.

A phase II study of tivantinib monotherapy in patients with previously treated advanced or recurrent gastric cancer

In the single-arm phase II study, presented at ASCO, the efficacy of tivantinib monotherapy in Asian patients with previously treated metastatic gastric cancer (MGC) was evaluated This is the first clinical trial evaluating the efficacy of a selective c-MET inhibitor for MGC.

Tivantinib was daily administered 360mg bid orally. The primary endpoint was disease control rate (DCR) defined as CR, PR or SD after eight weeks administration. Pretreatment tumor tissue collection was required to evaluate the relationship between biomarkers and efficacy. Pharmacokinetic (PK) evaluation was also conducted.

Tivantinib as a monotherapy showed only a modest efficacy in previously treated MGC, and further trial testing in combination would be warranted in MGC. It would be an important finding that gastrectomy do not affect PK profile of tivantinib.

Bevacizumab: extends overall survival

Results from a large, phase III clinical trial show that combination treatment with bevacizumab (Avastin) and standard chemotherapy in the second line setting in patients with advanced colorectal cancer who have received bevacizumab combination treatment first-line extends overall survival.

These findings were presented at ASCO. 820 patients with metastatic, inoperable colorectal cancer were treated with standard first-line chemotherapy (physician's

choice of oxaliplatin- or irinotecan-based) plus bevacizumab. Following disease progression, patients were randomised to receive the opposite chemotherapy drug plus bevacizumab or placebo. Researchers observed that both overall survival (11.2 months versus 9.8 months) and progression-free survival were significantly longer (5.7 versus 4.1 months) among patients who received bevacizumab.

Dirk Arnold, of the German AIO Colorectal Cancer Collaborative Study Group (which initiated the trial) said: "These findings confirm what many physicians and researchers have long suspected—that extended bevacizumab treatment provides meaningful benefits for patients with advanced colorectal cancer, without adding significant side effects. But the findings also provide an important new insight about the biology of advanced colorectal cancer, showing us that if the disease develops resistance to chemotherapy, it does not necessarily mean that tumors become resistant to anti-angiogenic therapy. By simply switching chemotherapy drugs when the cancer progresses and continuing with bevacizumab, we can make second-line treatment even more powerful. This finding will likely spur research into other cancer types that are sensitive to both bevacizumab and chemotherapy."

Bevacizumab is known as an anti-angiogenic targeted therapy, meaning it works by blocking the development of blood vessels that tumors need to grow and spread. This is the first randomised trial to evaluate the combination regimen second-line in patients who have previously been treated with a bevacizumab regimen in the first-line setting.

New investigational drug for breast cancer

A phase III randomised study of the investigational agent trastuzumab emtansine (T-DM1) versus standard therapy using capecitabine (Xeloda) and lapatinib (Tykerb) found significant and clinically meaningful improvement in progression-free survival for T-DM1 in women with HER2-positive locally advanced or metastatic breast cancer previously treated with a taxane and trastuzumab.

T-DM1 is an experimental antibody-drug conjugate that consists of the antibody trastuzumab (Herceptin) linked to the cytotoxic drug emtansine (DM1). T-DM1 has not been approved by the Food and Drug Administration, and is not yet available outside of clinical trials.

The international study, called EMILIA, randomised nearly 1,000 patients to receive either T-DM1 or XL every three weeks until their disease progressed or they experienced unmanageable toxicity.

The median progression-free survival for patients receiving T-DM1 was 9.6 months, compared to 6.4 months in the group receiving capecitabine and lapatinib (a regimen known as XL)—a difference that was statistically significant.

After two years, 65.4% of the T-DM1 patients were alive, compared to 47.5% of the XL patients. This difference in statistical significance did not meet the trial's predetermined statistical survival threshold for the first analysis. The second planned survival analysis planned for later in the study will provide additional information.

The most common adverse events of Grade 3 or above for T-DM1 included thrombocytopenia (12.9% versus 0.2%) and elevation in liver function tests.

Kimberly Blackwell, Professor of medicine and assistant professor of radiation oncology at Duke Cancer Institute at Duke University said: "The drug worked. It was significantly better than a very effective approved therapy for HER2 overexpressing metastatic breast cancer. Also, as a clinician who takes care of a lot of breast cancer patients, I'm pleased that this drug has very little dose-limiting toxicity. Patients don't lose their hair from this drug. For patients facing metastatic breast cancer, this is a breakthrough."

Liraglutide: real world data on weight loss and cost-effectiveness in type 2 diabetes

New data show that liraglutide provided greater reductions in HbA1c compared to exenatide and DPP-4 inhibitors, with weight loss and cost-effectiveness, when used in routine primary care according to current UK type 2 diabetes treatment guidelines.

The study presented at the 72nd Annual Scientific Sessions of the American Diabetes Association (ADA) in Philadelphia also shows that more patients appeared to favour a drug with a liraglutide-like profile, which is given by injection, over a drug with a sitagliptin-like profile, which is given orally (62.5% versus 37.5%, $p<0.05$).

The study looked at data from 1114 type 2 diabetes patients from primary care practices in the UK

and assessed the clinical efficacy and patient preference with respect to liraglutide, exenatide and DPP-4 inhibitors.

Marc Evans, Study Investigator from Llandough Hospital, Cardiff, Wales said: "This study shows us that the results we've seen with liraglutide in clinical trials are reflected in day-to-day, real world use. Key to managing diabetes is choosing treatments that patients will adhere to. So, as physicians, we can help to get the best outcomes by prescribing treatments, like liraglutide, that both work well and which patients like."

Greater reductions in HbA1c were seen in patients treated with liraglutide compared to exenatide or DPP-4 inhibitors (1.23% = (±0.14), 0.79% (±0.19) and 0.72% (±0.23), respectively, $p<0.05$, n=1114). Significantly greater weight loss was seen in patients treated with liraglutide (n=256) compared to DPP-4 inhibitors (n=710) ((-3.9kg (±5.7) versus -0.8 kg (±3.1), $p<0.05$,) and greater weight loss was seen in patients treated with liraglutide (n=256) compared to exenatide (n=148) (-3.9kg (±5.7) versus -2.9kg (±5.8)).

The calculated life-years gained per patient was 0.12, 0.08 and 0.07 for those receiving liraglutide, exenatide or a DPP-4 inhibitor, respectively, compared to their respective baselines.

ORIGIN trial: insulin glargine delays progression from pre-diabetes to type 2 diabetes

Results from the landmark ORIGIN trial (Outcome Reduction with Initial Glargine Intervention) were also announced at the ADA. It found that Lantus® (insulin glargine [rDNA] injection) had no statistically significant positive or negative impact on cardiovascular (CV) outcomes versus standard care during the study period.

Results also showed that insulin glargine delayed progression from pre-diabetes to type 2 diabetes and there was no association between insulin glargine use and increased risk of any cancer.

ORIGIN was a six-year randomised clinical trial designed to assess the effects of treatment with insulin glargine versus standard care on CV outcomes. The study involved over 12,500 participants worldwide with pre-diabetes or early type 2 diabetes mellitus and high CV risk, with 6,264 participants randomised to receive insulin glargine titrated to achieve fasting normoglycemia. The co-primary endpoints were the composite of CV death, or non-fatal myocardial infarction, or nonfatal stroke; and the composite of CV death, or non-fatal myocardial infarction, or non-fatal stroke, or revascularisation procedure, or hospitalisation for heart failure.

Dr Hertzel Gerstein, McMaster University, Hamilton, Ontario/ Canada and Principal Investigator of the ORIGIN trial said: "We now know more about insulin glargine than about any other glucose lowering drug with respect to future health outcomes. Specifically, it maintains excellent glycemic control, slows progression of dysglycemia and has no long-term serious health effects."

The study demonstrated that achieving fasting normoglycaemia did not affect CV outcomes in these participants with early dysglycaemia during the study period (first co-primary endpoint: Hazard Ratio [HR]: 1.02; p = 0.63, NS; and second co-primary endpoint: HR: 1.04; p = 0.27, NS).

Insulin glargine achieved targeted long-term glycaemic control (median fasting plasma glucose 5.2mmol/L and HbA1c 6.2%), which was sustained over the 6.2 years of follow-up.

There was no association between insulin glargine and increased risk of any cancer (HR: 1.00; p =0.97, NS). Neither analysis of all cancers combined, nor analysis of any organ-specific type of cancer, suggested an increased risk for the users of insulin glargine.

Results showed that insulin glargine delayed progression from pre-diabetes (IFG or IGT) to type 2 diabetes mellitus by 28% (HR: 0.72; p=0.006). Other secondary outcomes included a composite microvascular outcome (metrics of kidney or eye disease; (HR: 0.97; p= 0.43), and all-cause mortality (HR: 0.98; p= 0.70).

ORIGIN (Outcome Reduction with Initial Glargine Intervention) is a unique, six-year landmark cardiovascular (CV) outcomes trial, evaluating insulin glargine versus standard care in over 12,500 individuals who are at high CV risk with pre-diabetes or early type 2 diabetes mellitus. The extension of the observations of ORIGIN will be called ORIGINALE (Outcome Reduction with an Initial Glargine Intervention and Legacy Effect).

Lixisenatide in combination with insulin demonstrates significant reductions in HbA1C

New data on once-daily Lyxumia® (lixisenatide) presented at the ADA shows that it achieved the primary efficacy endpoint of significantly reducing HbA1c in combination with Lantus® (insulin

glargine). There was also an associated significant reduction in post-prandial glucose (PPG), in patients with uncontrolled type 2 diabetes on oral anti-diabetics.

The results from the GetGoal Duo study showed that HbA1c decreased on average from 8.60% to 7.60% during the run-in period with insulin glargine. The addition of lixisenatide led to a further significant HbA1c decrease to 6.96% after 24 weeks, compared to 7.3% in patients receiving placebo ($p<0.0001$). A significantly higher percentage of patients achieved target HbA1c of <7.0% with lixisenatide, compared to placebo (56.3% versus 38.5%, respectively, $p=0.0001$). Results also showed a beneficial effect on body weight.

In order to achieve complete glycaemic control in type 2 diabetes, both fasting plasma glucose (FPG) and PPG components need to be addressed. PPG is the term used to define plasma glucose concentrations after eating. A patient's PPG profile is determined by carbohydrate absorption, insulin and glucagon secretion, and their co-ordinated effects on glucose metabolism in the liver and peripheral tissues.

Dr Martin Hadley Brown, Chair of the Primary Care Diabetes Society and GP from Norfolk said: "This is a useful step towards meeting the demand for a combination therapy to address the needs of some uncontrolled type 2 diabetes patients who fail to meet HbA1c targets despite controlled fasting plasma glucose. These results suggest that once-daily lixisenatide in combination with Lantus® could be an innovative therapeutic option by addressing post-prandial glucose levels in a simple and convenient once-daily regimen which reduces the chance of weight gain."

This randomised, double-blind, placebo-controlled study included a 12-week run-in period with insulin glargine initiated and titrated to reach a target fasting plasma glucose of 80–100mg/dL (4.44–5.56mmol/l) followed by a 24-week randomised period where 446 patients with HbA1c ≥7%—despite controlled fasting plasma glucose—received either lixisenatide once-daily or placebo while insulin glargine and metformin were continued.

Also presented at ADA were results from the GetGoal-L study, which showed that lixisenatide added to a variety of non-optimised basal insulin ± metformin, also significantly reduced HbA1c, PPG and body weight versus placebo. This 24-week randomised, double-blind multicentre, placebo-controlled study concluded that lixisenatide achieved its primary efficacy endpoint of significantly reducing HbA1c versus placebo ($p=0.0002$). The GetGoal programme also undertook an elderly subanalysis which found that the efficacy and safety profile of lixisenatide is similar regardless of age, with comparable decreases in HbA1C, adverse event rates and the incidence of hypoglycaemia.

Dr Richard Brice, a GP from Eastern and Coastal Kent PCT, said: "It is refreshing to see that this trial reflected real life, with patients over the age of 70 included in the randomisation. These results show that this product appears to be equally effective and equally safe in the elderly as in the general adult population on basal insulins who have raised HbA1c levels, but with FPG at goal."

In addition, results of the GetGoal-P study were presented at the meeting, which showed that lixisenatide provides significantly greater reductions in HbA1C compared with placebo in patients with type 2 diabetes insufficiently controlled on pioglitazone ± metformin.

Global survey finds one in four type 2 diabetes patients do not take basal insulin as prescribed

One in four people with type 2 diabetes missed or did not dose their long-acting (basal) insulin correctly in the previous 30 days, according to a new global survey funded by Novo Nordisk presented at the ADA.

The GAPP2™ (Global Attitudes of Patients and Physicians) survey also found that more than a third experienced a self-treated low blood sugar event, called hypoglycaemia. It found that dosing irregularities are not uncommon in people with type 2 diabetes taking basal insulin. In the previous 30 days, 22% missed a dose, 24% mis-timed a dose by more than two hours, and 14% reduced a basal insulin dose. In addition, self-treated hypoglycaemia remains a significant management challenge in type 2 diabetes and 36% of those surveyed experienced an event in the previous 30 days.

There is a correlation between hypoglycaemia and dosing irregularities. Those who missed a basal insulin dose in the previous 30 days were significantly more likely to report self-treated hypoglycaemia over the same period as well (41% compared to 34%).