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PEGPH20 in addition to nab-paclitaxel and gemcitabine for metastatic pancreatic ductal adenocarcinoma

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LAY SUMMARY

Pancreatic ductal adenocarcinoma is a common type of cancer in the pancreas. The cause of pancreatic cancer is not known, but factors such as smoking, drinking alcohol, poor diet and lack of exercise can increase the risk of developing the condition. In the early stages, pancreatic cancer does not usually cause any symptoms, and when symptoms do appear they are vague, including pain in the stomach area or back, jaundice and weight loss, making diagnosis difficult. Many people do not know they have pancreatic cancer until the disease is advanced, and three quarters of people die within a year of diagnosis. Treatment of pancreatic cancer with chemotherapy drugs such as nab-paclitaxel and gemcitabine is often difficult due to accumulation of hyaluronic acid in the cancer cells.

PEGPH20 is being developed to be added to nab-paclitaxel and gemcitabine for the treatment of hyaluronan-high stage 4 previously untreated pancreatic ductal adenocarcinoma. PEGPH20 breaks down the hyaluronic acid, allowing the cancer-killing drugs to be more effective. Some clinical studies have shown that adding PEGPH20 to nab-paclitaxel and gemcitabine increased overall survival of patients. If PEGPH20 is licensed, it could be used together with existing treatments as a first line treatment for advanced pancreatic cancer.

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TARGET GROUP

Pancreatic ductal adenocarcinoma (hyaluronan-high, stage 4) – first line; in combination with nab-paclitaxel (Abraxane) and gemcitabine

TECHNOLOGY

DESCRIPTION

PEGPH20 (Pegylated Recombinant Human Hyaluronidase PH20; pegvorhyaluronidase alfa) is a pegylated formulation of a recombinant form of human hyaluronidase with potential anti-tumour activity. Upon intravenous administration, pegylated recombinant human PH20 degrades hyaluronic acid (HA) coating tumour cells, which may result in the inhibition of tumour cell growth. In addition, the degradation of HA may result in a lowering of the interstitial fluid pressure (IFP), allowing better penetration of chemotherapeutic agents into the tumour bed. HA is a glycosaminoglycan found in the extracellular matrix (ECM) that is frequently overproduced by various tumour cell types. The presence of HA in tumours correlates with increased tumour cell growth, metastatic potential, tumour progression, increased resistance to chemotherapeutic agents, and an elevation in tumour IFP.[1]

By degrading accumulated HA in solid tumours, PEGPH20 has been shown to reduce tumour pressure, improve vascular perfusion, and decrease hypoxia, enabling increased access of anti-cancer therapeutics and immune cells. The increase access may allow more anti-cancer agents and immune cells to accumulate in the tumour, which may lead to increased tumour cell killing.[2,3]

PEGPH20 is being developed as a combination therapy with nab-paclitaxel and gemcitabine for the treatment of hyaluronan-high stage 4 previously untreated pancreatic ductal adenocarcinoma.[4]

In the phase III clinical trial (NCT02715804), PEGPH20 is administered as an intravenous (IV) infusion at 3.0 micrograms per kilograms (µg/kg) twice weekly for weeks 1 to 3 of cycle 1 (each cycle consisting of 4 weeks), then once weekly for weeks 1 to 3 of cycle 2 and beyond. It is given in combination with nab-paclitaxel which is administered as an IV infusion at 125 milligrams per square meter (mg/m^2) once weekly for weeks 1 to 3 of all treatment cycles and with gemcitabine which is administered as an IV infusion at 1,000 mg/m^2 once weekly for weeks 1 to 3 of all treatment cycles. The number of treatment cycles is not stated on the trial registry.[4]

PEGPH20 does not currently have Marketing Authorisation in the EU for any indication.[5]

INNOVATION and/or ADVANTAGES

The key innovation of PEGPH20 is that it breaks down hyaluronic acid (HA), making cancer easier to treat with other authorised therapies.[6]

Pancreatic cancers are notoriously resistant to virtually all forms of chemo and radiotherapies, partly due to very high interstitial concentrations of HA.[7] In a phase II trial, in patients with tumours with high HA levels, adding PEGPH20 to chemotherapy doubled progression-free survival to 9.2 months (compared to 5.2 months).[8] If licensed, PEGPH20 would offer an additional first line treatment option to patients with advanced pancreatic ductal adenocarcinoma.

DEVELOPER

Halozyme Therapeutics

REGULATORY INFORMATION/ MARKETING PLANS

PEGPH20 was designated an orphan drug in the USA for pancreatic cancer in October 2014.[9]

PEGPH20 was designated an orphan drug in the EU for pancreatic cancer in December 2014.[10]

PEGPH20 in combination with nab-paclitaxel and gemcitabine was granted Fast Track designation for pancreatic cancer by FDA in September 2014.[11]

At the time of writing this briefing note, no information regarding EU/UK licensing plans could be obtained.

PATIENT GROUP

BACKGROUND

Most pancreatic cancers are the exocrine type (start in cells that product pancreatic digestive juices). More than 8 out of 10 exocrine pancreatic cancers are adenocarcinomas, and nearly all of these are ductal adenocarcinomas (start in the cells lining the ducts of the pancreas).[12] Pancreatic ductal adenocarcinoma is typically characterised by a dense desmoplastic stroma containing a large amount of HA. This abnormal accumulation correlates with worsened prognosis.[13]

The cause of pancreatic cancer is not known. However, some factors increase the risk of developing this condition, including smoking, drinking alcohol, diet, overweight/obesity, previous cancer or radiotherapy and genetic factors. The risk of pancreatic cancer is increased with a history of long term inflammation of the pancreas (chronic pancreatitis), hereditary pancreatitis, stomach ulcers, diabetes, infection with hepatitis B virus, and tooth or gum disease. Pancreatic cancer is uncommon in people under 40 years of age, and almost half of all new cases are diagnosed in people aged 75 years and over.[14]

In the early stages, pancreatic cancer does not usually cause any symptoms, and when symptoms do appear they are vague, including pain in the stomach area or back, jaundice and weight loss, making diagnosis difficult.[15] Despite progress in diagnostic imaging, surgical techniques and radiation therapies, the prognosis for pancreatic cancer is poor. Cytotoxic treatment has been associated with modest benefits in the advanced disease setting, and survival for patients with stage 4 disease has not exceeded a year.[8]

CLINICAL NEED and BURDEN OF DISEASE

In England in 2016 there were 8,455 registrations of newly diagnosed cases of malignant neoplasm of pancreas (ICD-10 code C25).[16] Across the UK, the incidence rate for pancreatic cancer is expected to increase from 19.5 per 100,000 European age-standardised rate (EASR) (9,616 cases) in 2014 to 20.65 per 100,000 EASR (15,157 cases) in 2035.[17]

In England and Wales in 2016 there were 8,315 deaths with malignant neoplasm of pancreas (ICD-10 code C25) recorded as the underlying cause.[18] The latest published survival statistics for pancreatic cancer (2016, patients diagnosed in 2011-2015) report 1-year survival rate of 23.7% and 5-year survival rate of 6.9% (age-standardised).[19]

In England in 2016/2017 there were 28,204 hospital admissions with a primary diagnosis of malignant neoplasm of pancreas (ICD-10 code C25), resulting in 91,409 bed days and 20,029 day cases.[20]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Paclitaxel as albumin-bound nanoparticles with gemcitabine for adjuvant treatment of pancreatic cancer (GID-TA10329). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Pancreatic cancer - capecitabine (GID-TAG394). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Pancreatic cancer (locally advanced, metastatic) - masitinib (GID-TAG330). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Pancreatic cancer (metastatic) - nimotuzumab (1st line) (GID-TAG363). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Pancreatic cancer (metastatic, untreated) - liposomal cisplatin (with gemcitabine) (GID-TAG494). Expected date of issue to be confirmed.
- NICE technology appraisal. Paclitaxel as albumin-bound nanoparticles with gemcitabine for untreated metastatic pancreatic cancer (TA476). September 2017.
- NICE technology appraisal. Everolimus and sunitinib for treating unresectable or metastatic neuroendocrine tumours in people with progressive disease (TA449). June 2017.
- NICE guideline. Pancreatic cancer in adults: diagnosis and management (NG85). February 2018.
- NICE quality standard in development. Pancreatic cancer (GID-QS10061). Publication anticipated December 2018.
- NICE interventional procedure guidance. Irreversible electroporation for treating pancreatic cancer (IPG579). May 2017.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.

OTHER GUIDANCE

- National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology: Pancreatic Adenocarcinoma. Version 2. August 2017.[21]
- European Society for Medical Oncology. Cancer of the Pancreas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. August 2015.[22]

CURRENT TREATMENT OPTIONS

Pancreatic cancer is difficult to treat. It rarely causes any symptoms in the early stages, so it is often not detected until the cancer is fairly advanced. If the tumour is large or has metastasised it will be more difficult to treat.[23]

NICE guidelines for the first line treatment of metastatic pancreatic cancer recommend: [24]

- Offer FOLFIRINOX to people with metastatic pancreatic cancer and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1.
- Consider gemcitabine combination therapy for people who are not well enough to tolerate FOLFIRINOX. For guidance on combination therapy with gemcitabine and nab–paclitaxel, see the NICE technology appraisal guidance on paclitaxel as albumin-bound nanoparticles with gemcitabine for untreated metastatic pancreatic cancer.
- Offer gemcitabine to people who are not well enough to tolerate combination chemotherapy.

The NICE guidelines state that although the use of FOLFIRINOX was common at the time of publication (February 2018), FOLFIRINOX did not have a UK marketing authorisation for this indication. Also, the use of many gemcitabine combination therapies was common at the time of publication (February 2018) but do not have a UK marketing authorisation covering the first-line treatment of adults with metastatic pancreatic cancer. In both these instances, the prescriber should follow relevant professional guidance, taking full responsibility for the decision to prescribe. Informed consent should be obtained and documented.[24]

EFFICACY and SAFETY

Trial	HALO-109-301, NCT02715804; PEGPH20 vs placebo, both in combination with nab-paclitaxel and gemcitabine; phase III
Sponsor	Halozyme Therapeutics
Status	Ongoing
Source of Information	Trial registry[4]
Location	EU (incl UK), USA, Canada and other countries.
Design	Randomised, placebo-controlled, double-blind, parallel assignment
Participants	N=570 (planned); aged 18 yrs and older; pancreatic ductal adenocarcinoma; hyaluronan-high; stage 4; at least 1 tumour metastasis; previously untreated
Schedule	Randomised to PEGPH20 given as intravenous (IV) infusion at a dose of 3.0 µg/kg twice wkly for wks 1 to 3 of cycle 1 (each cycle consisting of 4 wks), then once wkly for wks 1 to 3 of cycle 2 and beyond in combination with nab-paclitaxel administered as an IV infusion at a dose of 125 mg/m^2 once wkly for wks 1 to 3 of all treatment cycles and with gemcitabine administered as an IV infusion at a dose of 1,000 mg/m^2 once wkly for wks 1 to 3 of all treatment cycles; vs matching placebo given as intravenous (IV) infusion twice wkly for

	wks 1 to 3 of Cycle 1 (each cycle consisting of 4 wks), then once wkly for Wks 1 to 3 of Cycle 2 and beyond in combination with nab-paclitaxel administered as an IV infusion at 125 mg/m^2 once wkly for wks 1 to 3 of all treatment cycles and with gemcitabine administered as an IV infusion at 1,000 mg/m^2 once wkly for wks 1 to 3 of all treatment cycles
Follow-up	Active treatment period not reported; follow-up 2 yrs
Primary Outcomes	• Progression-free survival (PFS) [Time Frame: approx. 12 mths] • Overall survival (OS) [Time Frame: approx. 24 mths]
Secondary Outcomes	• Objective response rate (ORR) [Time Frame: approx. 12 mths] • Duration of response [Time Frame: approx. 12 mths] • Incidence of adverse events and serious adverse events [Time Frame: approx. 12 mths] • Change from Baseline in potential biomarkers of PEGPH20 activity [Time Frame: Baseline to approx. 12 mths] • Peak plasma concentration of PEGPH20 in combination with nab-paclitaxel plus gemcitabine [Time Frame: concentration at 24 hours post-dose on day 1, day 2 and day 4 of cycle 1 for PEGPH20 treatment; concentrations after the end of infusion on day 2 of cycle 1 through cycle 3 for nab-paclitaxel plus gemcitabine treatment] • Patient reported quality of life [Time Frame: approx. 12 mths]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Primary completion date reported as Oct 2018.

Trial	HALO-109-202, NCT01839487; PEGPH20 in combination with nab-paclitaxel and gemcitabine vs nab-paclitaxel and gemcitabine; phase II
Sponsor	Halozyme Therapeutics
Status	Ongoing
Source of Information	Trial registry,[25] Publication[26]
Location	USA
Design	Randomised, placebo-controlled, open label, parallel assignment
Participants	N=279; aged 18 yrs and older; pancreatic ductal adenocarcinoma; stage 4; metastatic with liver and/or lung metastases; previously untreated
Schedule	Randomised to PEGPH20 given as intravenous (IV) infusion at a dose of 3.0 µg/kg twice wkly for wks 1 to 3 of Cycle 1 (each cycle consisting of 4 wks), then once wkly for wks 1 to 3 of Cycle 2 and beyond in combination with nab-paclitaxel administered as an IV infusion at 125 mg/m^2 once wkly for wks 1 to 3 of all treatment cycles and with gemcitabine administered as an IV infusion at 1,000 mg/m^2 once wkly for wks 1 to 3 of all treatment cycles (PAG treatment); nab-paclitaxel administered as an IV infusion at 125mg/m^2 once wkly for wks 1 to 3 of all treatment cycles and with gemcitabine administered as an IV

	infusion at 1,000 mg/m^2 once wkly for wks 1 to 3 of all treatment cycles (AG treatment). All pts received dexamethasone 8 mg orally 2 hrs before and 8 to 12 hrs after each PEGPH20 dose to manage musculoskeletal events, and pts in stage 2 of the trial received daily enoxaparin prophylaxis (40mg/d initial dose, later amended to the recommended 1mg/kg/d, per updated guidelines).
Follow-up	Active treatment period and follow-up period not reported. Stage 1 of study lasted 13 mths (Mar 2013 - Apr 2014). Stage 2 of study lasted 18 mths (Aug 2014 - Feb 2016).
Primary Outcomes	• Estimate the PFS duration of PEGPH20 combined with nab-paclitaxel with gemcitabine [Time Frame: 12 mths] • To evaluate the thromboembolic (TE) events in subjects treated in the experimental arm [Time Frame: Ongoing]
Secondary Outcomes	• Estimate relative benefit of PAG treatment vs AG treatment [Time Frame: 1 yr] • Estimate relative benefit of PAG vs AG treatment as assessed by the PFS hazard ratio based on subject tumour-associated hyaluronan levels [Time Frame: 1 yr] • Estimate ORR as defined by RECIST 1.1 of PAG treatment and the relative benefit of PAG treatment vs AG treatment [Time Frame: 1 yr] • Estimate the OS duration of PAG treatment and the relative benefit of PAG treatment vs AG treatment, ass assessed by the OS hazard ratio [Time Frame: 16 mths] • Evaluate the safety and tolerability profile of PAG and AG treatment groups [Time Frame: 1 yr] • Characterise the plasma pharmacokinetics of PEGPH20 when given in combination with nab-paclitaxel and gemcitabine [Time Frame: various visits and timepoints]
Key Results	PFS was significantly improved with PAG treatment overall (hazard ratio [HR], 0.73; 95% CI, 0.53 to 1.00; P = .049) and for patients with HA-high tumours (HR, 0.51; 95% CI, 0.26 to 1.00; P = .048). In patients with HA-high tumours (PAG v AG), the objective response rate was 45% versus 31%, and median overall survival was 11.5 versus 8.5 months (HR, 0.96; 95% CI, 0.57 to 1.61).
Adverse effects (AEs)	The most common treatment-related grade 3/4 adverse events with significant differences between arms (PAG v AG) included muscle spasms (13% v 1%), neutropenia (29% v 18%), and myalgia (5% v 0%). TE events were comparable after enoxaparin initiation (14% PAG v 10% AG).
Expected reporting date	Study completion date reported as Sep 2018.

ESTIMATED COST and IMPACT

COST

The cost of PEGPH20 is not yet known.

Nab-paclitaxel (Abraxane) is already marketed in the UK (Celgene Ltd). A vial of 100mg powder for suspension in infusion costs £246.00.[27]

Gemcitabine is already marketed in the UK by a number of companies. Examples of quantities and costs are:[28]

- 200mg/2ml concentrate for solution for infusion vial costs £6.40 (Accord Healthcare Ltd)
- 1g/25ml concentrate for solution for infusion vial costs £13.09 (AAH Pharmaceuticals Ltd, Activis UK Ltd)
- 1g/26.3ml concentrate for solution for infusion vial costs £162.00 (hospital use only, Pfizer Ltd)
- 1.2g/120ml infusion bag costs £120.00 (Sun Pharmaceuticals UK Ltd)

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☐ Reduced symptoms or disability

☐ Other

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☐ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other

☒ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☒ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs

☐ Other reduction in costs

☐ Other

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

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