PRIMER-1: A randomised phase II trial of Perioperative pembrolizumab and lenvatinib in resectable Hepatocellular Carcinoma (HCC)

Tim Meyer 1,2, Laura White 1, Marian Oggioni 2, Michelle Hung 2, Valeria Mocca-Dodola 6, Paul Ross 2, Daniel Palmer 2, Yun Ting Ma 2, Jeff Evans 3, Joseph Matti 1, Brian Davidson 2, Alberto Quaglia 2, Dominic Vujic 2, Lizzie Lloyd-Dehler 6, Josep M Llovet 4,5,6,24,25,26,37,27,28,32,33,48,7,13,13, Tony Chen 3,28,9, Teresa Marafioti 3, Nathalie Schmidt 13, Giorgio Anzidei Mich-13,13, Mala K Maini 23

1 UCL Cancer Institute, University College London, London, UK, 2 Royal Free London NHS Foundation Trust, Pond Street, London, UK, 3 Cancer Research UK & UCL Cancer Trials Centre, London, UK, 4 Comprehensive CTI at UCL, London, UK, 5 Guy’s and St Thomas’ NHS Foundation Trust, London, UK, 6 University of Liverpool, Liverpool, UK, 7 University of Birmingham, Birmingham, UK, 8 University of Glasgow, Glasgow, UK, 9 Pfizer and Public Involvement and Engagement, 10 Translational Research in Hepatic Oncology, Liver Unit, CIBM, Hospital Clinic, Universitat de Barcelona, Barcelona, Spain, 11 Mount Sinai Liver Cancer Program, Division of Liver Disease, Translational Institute, Mount Sinai, New York, New York, USA, 12 Institute Calabona De Recerca: Estudis Avançats, Barcelona, Catalonia, Spain, 13 UCL Division of Infection and Immunity, University College London, London, UK.

Background

The only potentially curative options for HCC are transplantation, surgical resection and ablation. Both surgical resection and ablation are associated with a high rate of recurrence and 70% of resected patients relapse within 5 years. To date, no standard adjuvant therapies have been approved; the international phase III STORM trial evaluating adjuvant sorafenib failed to show an improvement in relapse free survival (1) and chemotherapy, chemoembolization, internal radiotherapy have also failed to improve survival in the adjuvant setting. The only intervention that has shown some evidence of benefit is adoptive immunotherapy with cytokine activated lymphocytes which improved relapse free survival and overall survival in two randomized trials conducted in Asia (2, 3). These studies provide evidence that immunotherapy may address a significant unmet need in the management HCC.

Rationale for Perioperative therapy

Pembrolizumab and Lenvatinib in advanced disease (4)

Key Eligibility Criteria

Inclusion

1. Resectable HCC (diagnosis confirmed by imaging or history and excluding fibrolamellar and mixed hepatocellular/cholangiocarcinoma)
2. Measurable disease by RECIST 1.1
3. Non-cirrhotic or Child-Pugh A liver disease
4. Performance status 0 or 1
5. Low risk of surgical morbidity and mortality from liver surgery
6. HBV < 900 IU/ml, ANC > 1.5 x 10^9/l, Platelets > 75 x 10^9/l
7. AST/ALT < 5.0 x ULN, Albumin >32g/l, GFR >40mls/min
8. HCV allowed but if treated must have completed >1 month before start of study
9. HBV must have been on antiviral for >4 weeks and have viral load <500 IU/ml

Exclusion

1. Any prior therapy for HCC
2. Oesophageal or gastric variceal bleeding within the last 6 months
3. Active autoimmune disease that has required systemic treatment in past 2 years
4. A diagnosis of immunodeficiency or is receiving systemic steroid therapy (>10mg daily prednisolone equivalent)
5. Has a known additional malignancy that is progressing or has required active treatment within the past 3 years
6. Uncontrolled blood pressure (Systolic BP>150 mmHg or diastolic BP >90 mmHg) in spite of an optimised regimen of antihypertensive medication
7. Proteinuria >1+ unless <1g/24hours

Surgical criteria

Low risk of surgical morbidity and mortality from liver surgery as defined by the following criteria:

• Single tumour
• No requirement for vascular resection
• Expected residual liver volume 40%
• Non-cirrhotic
• Single tumour any size
• Cirrhotic
  • Major resection (up to 5 segments) only with good liver function as to lenvatinib primary rate for treatment - intervals Major resection (up to 5 segments) only with good liver function as to lenvatinib primary rate for treatment - intervals

Endpoints

Primary Endpoint

• Major pathological response rate, defined as the proportion of patients with less than 10% viable tumour at resection

Secondary Endpoints

• Radiological response rate RECIST 1.1 and mRECIST
• 12 months Relapse Free Survival
• Rate of surgical delay (% patients delayed >4 weeks due to IMP related AEs)
• 30 day post-op complication rate (Clavien-Dindo classification)
• Safety and Feasibility

Exploratory Endpoints

• Biology: therapy induced changes in immune microenvironment

Study Design

2 cycles of pre-op and 17 cycles of post-op Pembrolizumab

60 Patients with Resectable HCC (30 per cohort)

Cohort 1 Pembrolizumab

Cohort 2 Lenvatinib

Cohort 3 Pembrolizumab + Lenvatinib

Tissue collection for biomarker research

8 weeks Surgery and B-D 12 week recovery 12 months

Statistics

All patients who receive at least one dose of pembrolizumab (arm 1), lenvatinib (arm 2), or the combination of pembrolizumab and lenvatinib (arm 3) will be included in the safety population, which will be used for the analysis of the primary (main) endpoint.

Major pathological response rate is defined as the proportion of patients with less than 10% viable tumour at resection. Patients who do not undergo surgery will be classified as non-responders for the primary endpoint. This approach will also apply to radiological response rate.

The number and percentage of patients with major pathological response will be presented by treatment arm, with 95% two-sided confidence intervals for the percentage.

The margin of practical equivalence is 5% (5 percentage points). If the major pathological response rate of one arm is ≥ 5% greater than that of the other arms, this will be taken as evidence that this arm can be selected for further testing in subsequent trials. The study was powered to have 85% chance to observe at least 5 percentage points difference in favour of arm 3, assuming that the true difference between arm 3 and arms 1 and 2 is 20 percentage points (40% vs 20%).

References