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Ibrutinib for the treatment of relapsed or refractory Follicular Lymphoma

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LAY SUMMARY

Follicular Lymphoma (FL) is the most common type of non-Hodgkin lymphoma (a type of B-cell cancer) and accounts for 10-20% of all immune cell cancers. The most common symptoms of FL is painless swelling in the neck, armpit or groin, tiredness, weight loss, night sweats and fever. non-Hodgkin lymphoma is most common in adults >65 years and in women. FL is treated using different combinations of chemotherapy drugs, however if this treatment does not work the FL is said to be relapsed (the cancer has regrown) or refractory (treatment has failed to treat the cancer).

Ibrutinib is a drug which blocks signals in cancer cells which helps the cancer cell survive and grow resulting in the cells death and preventing the cancer from growing. Early clinical trials of ibrutinib in FL patients suggest it may reduce symptoms and ongoing clinical trials will determine if ibrutinib will extend life and slow the progression of FL compared to placebos and current offered treatment.

If licenced in the UK, Ibrutinib could provide a novel alternative option for the treatment of patients with relapsed or refractory FL which may improve FL symptoms.

TARGET GROUP

Follicular Lymphoma: relapsed or refractory; second line; adults

TECHNOLOGY

DESCRIPTION

Ibrutinib; CRA-032765; ibrutinib (capsule); ibrutinib (tablet); Imbruvica; JNJ-54179060; PCI-32765) is an orally active, small molecule, selective Bruton's Kinase (Btk) inhibitor developed originally for the treatment of B-cell lymphomas but also licenced and in clinical trials for a variety of other conditions. Ibrutinib works by irreversibly blocking cell signals by specifically blocking Bruton's tyrosine kinase (Btk) involved in the pathway which aids cancer cell survival and growth. Blocking this pathway promotes the death of the cell, preventing it from dividing and the cancer growing.[1]

The proposed dosing of Ibrutinib for treatment of Follicular Lymphoma is for oral administration as 140mg capsules given 4x per day (total dose: 560mg/day).[1] [2]In the phase II clinical trial, Ibrutinib is administered orally at 560mg daily in 21 day treatment cycles until disease progression or unacceptable toxicity.[3]

Ibrutinib has been licenced for the use the following indications in the EU:

- Chronic Lymphocytic Leukaemia; adults with previously untreated or received 1 prior therapy
- Mantle Cell Lymphoma (MCL); adult patients with relapsed/refractory MCL with at least 1 prior treatment
- Waldenstrom's Hypergammaglobulinaemia (WM); adults with WM who received at least 1 prior treatment or first line for patients unsuitable for chemo-immunotherapy

Recognised common adverse events (>10%) of Ibrutinib in the currently licence indications include: Infections (incl. Pneumonia, Upper respiratory Tract Infections, Sinusitis and skin infections), Neutropenia, Thrombocytopenia, Headache, Haemorrhage, Bruising, Diarrhoea, Vomiting, Stomatitis, Nausea, Constipation, Rash, Arthralgia, Muscle spasm, Musculoskeletal pain, Pyrexia (fever) and Peripheral oedema.[4]

Ibrutinib is in phase III clinical trials for the following indications:

- Diffuse large B cell lymphoma
- Non-Hodgkin's lymphoma
- Pancreatic Cancer

Ibrutinib is in phase II clinical trials for the following indications:

- B-cell Lymphoma
- Myeloma
- Acute Myelogenous Leukaemia
- Breast Cancer
- Non-small cell lung cancer
- Renal Cancer
- Colorectal Cancer
- Stomach Cancer

- Genitourinary Cancer
- Unspecified solid Cancer

INNOVATION and/or ADVANTAGES

If licensed, Ibrutinib will offer a novel, alternative treatment option for patients with refractory or relapsed Follicular Lymphoma.

DEVELOPER

Pharmacyclics (part of AbbVie); Johnson & Johnson; Jassen-Cilag

AVAILABILITY, LAUNCH or MARKETING

Ibrutinib is a designated orphan drug in the EU and USA and has been designated Breakthrough Therapy and Fast Track status by the FDA. Ibrutinib is currently in phase III clinical trials.

PATIENT GROUP

BACKGROUND

Follicular Lymphoma (FL) is the most common type of non-Hodgkin lymphoma (NHL) (a type of B-cell lymphoma) and accounts for 10-20% of lymphomas.[5] The most common symptoms of FL is painless swelling in the neck, armpit or groin (due to build-up of lymphoma cells in the lymph nodes), tiredness, weight loss, night sweats and fever.[6] Risk factors for all NHLs including FL are: medical conditions which weaken the immune system (e.g. HIV), immunosuppressant medication, autoimmune conditions (e.g. rheumatoid arthritis, lupus, Sjogrens syndrome and coeliac disease), previous exposure to the Epstein Barr virus Human T-cell lymphotropic virus, previous Helicobacter pylori infection and previous chemotherapy/radiotherapy. NHL is also more common in adults >65 years and in women.[7] FL is usually diagnosed by obtaining biopsies of enlarged lymph nodes and assessing it for lymphoma cells, followed by blood and bone marrow samples, x-rays and scans to determine how many lymph nodes are affected and if the cancer has spread elsewhere. During diagnosis, the stage of the FL (defined by the number of lymph nodes affected and spread of the cancer) will be determined, according to the following criteria:[6]

- Stage 1: One group of lymph nodes affected e.g. armpit, groin or one side of the neck;
- Stage 2: More than one group of lymph nodes affected but all effected nodes either in the upper half (above the diaphragm) or lower half (below the diaphragm) of the body;
- Stage 3: Affecting lymph nodes throughout the whole body;
- Stage 4: Lymphoma has metastasised beyond the lymph nodes to e.g. bones, liver or lungs;
- A or B symptoms: letters can be added to each stage to indicate the presence of any symptoms. B indicates the presence of symptoms and A indicated no symptoms.

FL is classed as low grade lymphoma, meaning it develops slowly, often over a number of years,[8] so often treatment is not initial required. Treatment for FL depends on the stage and current treatment options for each stage are summarised in the current treatment section below.

CLINICAL NEED and BURDEN OF DISEASE

The exact population likely to be eligible to receive ibrutinib, refractory or relapsed FL, could not be estimated from available published sources. Overall data for NHLs and FL, however are summarised below.

For the UK, the incidence of NHLs (ICD Code: C82-86) was 22.9 per 100,000 population in 2014.[9] For the UK, the prevalence of NHLs (ICD Code: C82-86 and C96) at 1, 5 and 10 years was 7591, 29, 052 and 45, 772 in 2006.[9]

Survival statistics were obtained by the Haematological Malignancy Research Network (HMRN) from 2004-2011 of 5 year crude survival by FL grade at diagnosis, as follows:[10]

- Stage 1: 90.5% patients survive 5 years after diagnosis
- Stage 2: 86.5% patients survive 5 years after diagnosis
- Stage 3: 78.5% patients survive 5 years after diagnosis
- Stage 4: 79% patients survive 5 years after diagnosis

FL survival can also be predicted according to risk which is calculated by the number of prognostic factors (which predict response to treatment) the patient possesses, called the Follicular Lymphoma International Prognostic Index (FLIPI). There are 5 prognostic factors in the FLIPI, including:[11]

- >60 years old
- Stage 3-4 FL
- Low red blood cell (RBC) level
- >4 areas of lymph nodes affected by lymphoma
- High serum level of lactate dehydrogenase (LDH)

Presence of each prognostic factor is given a score of 1 so the patient is score 0 to 5. Low risk patients score 0 to 1, Intermediate risk patients score 2 and high risk patients score >3. The 5 and 10 year survival for FL patients based on risk:[11]

- Low risk group: 90% patients survive >5 years and 70% patients survive >10 years after diagnosis
- Intermediate risk group: 80% patients survive >5 years and 50% patients survive >10 years after diagnosis
- High risk group: 50% patients survive >5 years and 35% patients survive >10 years after diagnosis

A total of 4296 deaths from NHL were registered in England and Wales during 2014 (ICD-C82-C85).[12]

In 2015, there were 22,668 admissions for Follicular Lymphoma (ICD Code C82) in England, resulting in 12,933 bed days and 23,325 finished consultant episodes.[13]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE Technology appraisal guidance. Lymphoma (follicular, rituximab-refractory) – obinutuzumab (with bendamustine) (ID841). Expected date of issue to be confirmed.

- NICE Technology appraisal guidance. Lymphoma (follicular non-Hodgkins – advanced) – bortezomib (ID407). Expected date of issue to be confirmed.
- NICE Technology appraisal guidance. Obinutuzumab for untreated advanced follicular lymphoma (ID1020). Expected date of issue to be confirmed.
- NICE Technology appraisal guidance. Idelalisib for treating follicular lymphoma that is refractory to 2 prior treatments (terminated appraisal) (TA328). December 2014.
- NICE Technology appraisal guidance. Rituximab for the first-line treatment of stage III-IV follicular lymphoma (TA243). January 2012.
- NICE Technology appraisal guidance. Rituximab for the first-line maintenance treatment of follicular non-Hodgkin's lymphoma (TA226). June 2011.
- NICE Technology appraisal guidance. Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma (TA137). February 2008.
- NICE Technology appraisal guidance. Rituximab for the treatment of follicular lymphoma (TA110). September 2006 Withdrawn.
- NICE Technology appraisal guidance. The clinical effectiveness and cost effectiveness of rituximab for follicular lymphoma (TA37). March 2002 Withdrawn.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. Clinical Commissioning Policy: Haematopoietic Stem Cell Transportation. NHSCB/B04/P/a. April 2013.

CURRENT TREATMENT OPTIONS

Treatment of FL depends on the grade at which it is diagnosed. NICE currently recommend the following treatments:[14, 15]

- First Line Treatment (early stage 1 to 2 FL):
    - Local radiotherapy : recommended for patients with Stage 2A FL
    - Observation (no therapy)
    - Proceed to advanced stage treatment: recommended for patients with symptomatic stage 2B FL and for those whom radiotherapy is not suitable.
- Treatment for advanced (Stage 3 to 4), asymptomatic FL:
    - Rituximab induction therapy
- Treatment of advanced (Stage 3 to 4) symptomatic FL:
    - Rituximab in combination with:
        - Cyclophosphamide, Vincristine and Prednisolone (CBP)
        - Cyclophosphamide, Doxorubicin, Vincristine and Prednisolone (CHOP)
        - Mitoxantrone, Chlorambucil and Prednisolone (MVP)
        - Cyclophosphamide, Doxorubicin, Etoposide, Prednisolone and interferon-α (CHVPi)
        - Chlorambucil
    - Rituximab maintenance therapy: recommended for FL which has responded to first line induction therapy with rituximab in combination with chemotherapy.
- Treatment of advanced (Stages 3 to 4) relapsed or refractory FL:
    - Rituximab in combination with chemotherapy: recommended for inducing remission in advance FL patients
    - Rituximab monotherapy: recommended for treatment of relapsed FL with remission induced by rituximab + chemotherapy

- Rituximab monotherapy: recommended for treatment of relapsed or refractory FL when all other treatment option have been exhausted.
- Autologous (using stem cells from the patient) stem cell transplantation: for patients with FL in >2nd remission and who are fit for transplantation.
- Allogenic (using stem cell from a donor) stem cell transplantation: recommended for patients with FL in 2nd remission and for who autologous stem cell transplantation has not resulted in remission or is inappropriate.

EFFICACY and SAFETY		
Trial	Ibrutinib, NCT01779791, UKCRN ID: 1504, 2012-1513, 2013-0173, AAAL3026, CR100956, DAWN, EudraCT Number: 2012-004097-26, FLR 2002, FLR2002, NCRN483, PCI-32765FLR2002, RECF2221, REec-2013-0215, TrialTroveID-181220, UPCI 13-058, UW12043; adults >18 years; single arm; phase II clinical trial	Ibrutinib; NCT02947347, COH 16400, EudraCT Number: 2016-003202-14, NCI-2017-00193, PCYC-1141-CA, PERSPECTIVE, TrialTroveID-289495; adults >60 years; randomised; phase III clinical trial
Sponsor	Pharmacyclics (AbbVie), Johnson & Johnson, Jassen-Cilag	Pharmacyclics (AbbVie),
Status	complete and published in abstract	Ongoing
Source of Information	Poster[16], trial registry[17]	trial registry[18, 19]
Location	EU (including UK), USA, Australia and Russia	EU (including UK), USA, Australia, Brazil, China, Israel, New Zealand, Russia, South Korea
Design	Non-randomised, single arm	Randomised; Placebo-controlled
Participants	N=111; aged >18 years; Grade 1,2 or 3a follicular lymphoma; refractory or relapsed despite previous treatment with at least 2 prior lines of therapy including at least 1 rituximab-containing and anti-CD20 monoclonal antibody containing chemotherapy regimen	N=440 (planned); adults >60 years; treatment naïve follicular lymphoma (grade 1, 2 or 3a)
Schedule	Initial screening phase up to 30 days before first dose. Treatment with 560mg capsule of Ibrutinib taken orally in 21 day treatment cycles until disease progression or unacceptable toxicity	4 study arms as follows: 1. Ibrutinib + Rituximab: 560mg oral Ibrutinib and 375mg IV rituximab 2. Placebo comparator: Placebo capsule and 375mg IV rituximab 3. Ibrutinib only: 560mg oral Ibrutinib 4. Placebo comparator Placebo capsule
Follow-up	Post treatment follow up until death, withdrawal or study end (2 years after last patient is enrolled).	Not Reported

	Visits performed every 21 days for 12 months following enrolment and every 42 days after till treatment discontinuation.	
Primary Outcomes	Overall Response rate (ORR): Complete Response (CR) and Partial Response (PR) of Ibrutinib	Progression Free Survival (PFS)
Secondary Outcomes	Overall Survival (OS), Progression Free Survival (PFS), Duration of response, Time to Response, Number of patients experiencing resolution of lymphoma-related B symptoms, Number of participants identified with blood biomarkers that alter B-cell receptor signalling or activate alternative signalling pathways, Minimum plasma concentration of Ibrutinib, Oral volume of distribution at steady state of Ibrutinib, Area under the plasma-concentration time curve of Ibrutinib, Number of participants affected by an Adverse Event No quality of life measurement included in trial outcomes	Complete Response (CR) rate, Overall response rate (ORR), Overall Survival (OS), frequency, severity and relatedness of adverse events (AEs).
Key Results	Mean Ibrutinib exposure was 11.2 (9.9) months. The ORR was 20.9% (23/110) and CR rate was 10.9% (12/110). Mean duration of response was 19.4 months. Median PFS was 4.6 months and OS was not reached in this study, with the 24 month OS 63% (95% CI: 0.53 to 0.72). In patients with lymphoma related symptoms at baseline (n=39), resolution of symptoms was seen in 66.7% patients (n=26). The median duration of symptoms resolution was 10.4 months.	-
Adverse effects (AEs)	Common AEs were: diarrhoea (50.9%), fatigue (40%) and cough (35.5%). Serious AEs occurred in 48% patients and included major haemorrhage (3.65) and atrial fibrillation (9.1%). 6.4% (n=7) patients discontinued Ibrutinib use due to an AE.	-
Expected reporting date	-	January 2022

ESTIMATED COST and IMPACT

COST

Ibrutinib is already marketed in the UK a 90x 140mg capsule pack costs £4599/a pack or 120 x 140mg capsule pack costs £6132. This equates to £51.10 per capsule.[20]

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: *specify*

☒ None identified

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