Selinexor (KPT-330)

This Horizons Infosheet contains information on selinexor (originally known as KPT-330), a drug being investigated for the treatment of myeloma.

The Horizons Infosheet series provides information relating to novel drugs and treatment strategies that are currently being investigated for the treatment of myeloma. The series also aims to highlight the considerable amount of research currently taking place in the field of myeloma.

The drugs and treatment strategies described in the Horizons Infosheets may not be licensed and/or approved for use in myeloma. You may, however, be able to access them as part of a clinical trial.

What is selinexor?

Selinexor is the first in a new family of drugs known as Selective Inhibitor of Nuclear Export (SINE™) compounds. Selinexor works by blocking the action of a protein called XPO1 within the nucleus (centre compartment) of myeloma cells.

What is XPO1?

XPO1 (also known as Exportin 1) is a protein responsible for moving other proteins between different parts of the cell.

Cells are made up of two compartments, the cytoplasm and the nucleus, which are separated by a plasma membrane. Some proteins involved in the life cycle of the cell, for example tumour suppression proteins, are active only when located within the nucleus. Other proteins must be moved from the nucleus into the cytoplasm to become active. The compartment in which different proteins are located can therefore affect the growth and survival of the cell.

XPO1 is a transport protein responsible for moving proteins out of the nucleus of a cell into the cytoplasm. One of the characteristics of myeloma cells that makes them different from healthy cells is their high level of XPO1, which has been found to be essential for myeloma cell survival. Myeloma cells use XPO1 to move tumour suppression proteins from the nucleus into the cytoplasm. This deactivates them and allows the myeloma cells to multiply uninhibited.

How does selinexor work?

Selinexor is the first myeloma drug developed to block the action of XPO1. By blocking XPO1, selinexor prevents myeloma cells from moving tumour suppression proteins out of the nucleus and into the cytoplasm. The tumour suppression proteins are then activated as normal within the nucleus of the myeloma cell, leading to controlled death of the myeloma cells.

How is selinexor given?

Selinexor is given in tablet form. It can be given on its own as a monotherapy but it has shown to be most effective when used in combination with other myeloma treatments such as dexamethasone.

A series of Phase I trials of selinexor in myeloma patients have recommended a dose of 80mg twice a week when given in combination with dexamethasone. When given in combination with bortezomib (Velcade®) and dexamethasone the recommended dosage is 100mg, 1.3mg/m^2 bortezomib and 40mg dexamethasone once a week.

What evidence exists to support the use of selinexor?

Early stage clinical trials to date

have shown that selinexor can produce effective responses in myeloma patients who are relapsed and/or refractory to several prior treatments.

The Phase I/II STOMP trial is investigating selinexor with low-dose dexamethasone in combination with various other myeloma treatments - the protesome inhibitors bortezomib and carfilzomib (Kyprolis®); the immunomodulatory drugs lenalidomide (Revlimid®) and pomalidomide (Imnovid®); and the monoclonal antibody daratumumab (Darzalex®). These combinations are being investigated in patients who have relapsed after one or more treatments.

In the selinexor, low-dose dexamethasone and low-dose bortezomib arm, 63% of patients (25 out of 40) responded, with a median progression free survival (length of time following treatment before the myeloma returns and further treatment is required) of 9.2 months. There was a higher response rate of 84% (16 out of 19) in patients who had not been previously treated with a proteasome inhibitor, and the median progression free survival for this group of patients was 17.8 months.

In the selinexor, low-dose dexamethasone and daratumumab arm, the response rate was 74% (14 out of 19 patients), increasing to 88% (14 out of 17 patients) for those who had not been treated with daratumumab before.

In the selinexor, low-dose dexamethasone and pomalidomide arm, the response rate was 38% (3 out of 8) for patients who were refractory to pomalidomide and lenalidomide and they had the median progression free survival of 4.8 months. The response rate increased to 55% (12 out of 22) in patients who were not previously treated with pomalidomide and they had a longer median progression free survival of 11.6 months.

The Phase II STORM trial investigated the use of selinexor in multiply relapsed patients. Preliminary data have shown that around 21% (10 out of 48) of patients refractory to four prior treatments, including at least one immunomodulatory drug and one proteasome inhibitor, responded to a combination of selinexor with low-dose dexamethasone. This is a similar result to early data from other novel drugs that have gone on to prove highly promising in myeloma, including daratumumab (Darzalex®).

Furthermore, 20% of patients (6 out of 30) on the trial who were refractory to daratumumab as well as the four other treatments responded to selinexor. No other

novel treatment to date has shown any response in this population of patients, and as such the trial has been expanded to include more patients in this group.

Of the 41 patients taking part in the STORM trial, 18 patients (44%) had high-risk genetic abnormalities. Typically, 'high-risk' patients have a more active or difficult to treat myeloma which may relapse more quickly after treatment. The overall response rate of high-risk patients treated with selinexor was 33% (6 out of 18 patients), compared to 17% (4 out of 23) of 'standard-risk' patients, potentially making it a promising treatment for this harder-to-treat group of patients.

What are the possible known side effects of selinexor?

The most commonly observed side effects of selinexor include nausea, vomiting, loss of appetite and fatigue. Some patients also experience low platelet levels (thrombocytopenia).

Is selinexor currently available in any UK clinical trials?

For an up-to-date list of UK clinical trials involving selinexor, visit the **Myeloma Trial Finder** on **www.myeloma.org.uk**

To be enrolled on a clinical trial, patients have to meet certain conditions known as eligibility criteria. You should speak to your doctor in the first instance if you are interested in taking part in a trial.

Availability of selinexor in the UK

Before a drug can be widely used, it must first be licensed as a safe and effective treatment. This is usually done by the regulatory authorities at a European level and involves a review of evidence from large-scale clinical studies.

Normally, the licensed drug must then be approved by a UK drug appraisal body before it can be routinely prescribed by NHS doctors. The drug appraisal process differs from licensing - it compares how effective the newly-licensed drug is to existing drugs already in use on the NHS and decides whether it offers the NHS good value for money.

The main body responsible for carrying out drug appraisals in England and Wales is the National Institute for Health and Care Excellence (NICE). NICE recommendations are usually adopted in Northern Ireland. Scotland's drug appraisal body is the Scottish Medicines Consortium (SMC).

For more information, see the Health Technology Assessment (HTA) Infosheet from Myeloma UK

In 2014, selinexor was granted "orphan drug designation" by the European Medicines Agency (EMA) for myeloma. This means that the EMA will offer the drug company certain financial incentives throughout the development and licensing process to enable selinexor to become available to patients sooner. The final results of the STORM trial (expected early 2018), if consistent with the preliminary results, will be submitted to the EMA for potential conditional approval of selinexor.

Therefore, selinexor is not currently licensed for use in myeloma in the UK and is only accessible to patients as part of a clinical trial.

Future directions

Selinexor continues to be studied in different patient groups and in different combinations. It has an entirely different way of working from other anti-myeloma drugs, and therefore offers hope for multiply relapsed and/or refractory patients. Selinexor has also shown promising initial results in high-risk patients whose myeloma is particularly resistant to the effects of treatment.

In addition to low-dose dexamethasone and bortezomib, selinexor is also being studied in combination with other anti-myeloma drugs such as lenalidomide, daratumumab and pomalidomide in relapsed and/or refractory patients.

These trials will provide information about the safest and most effective way to use selinexor in myeloma.

About this Horizons Infosheet

The information in this Horizons Infosheet is not meant to replace the advice of your medical team. They are the people to ask if you have questions about your individual situation.

For a list of references used to develop our resources, visit **www.myeloma.org.uk/references**

To provide feedback about this publication, email **myelomauk@myeloma.org.uk**

Other information available from Myeloma UK

Myeloma UK has a range of publications available covering all areas of myeloma, its treatment and management.

To order your free copies or to talk to one of our Myeloma Information Specialists about any aspect of myeloma, call our Myeloma UK Infoline on **0800 980 3332** or **1800 937 773** from Ireland.

The Infoline is open from Monday to Friday, 9am to 5pm and is free to phone from anywhere in the UK and Ireland.

Information and support about myeloma is also available around the clock at **www.myeloma.org.uk**

Notes

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