Selinexor

Horizons Infosheet
Clinical trials and novel drugs

This Horizons Infosheet contains information on selinexor, 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 novel 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 called 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.

The usual maximum dose of selinexor in current clinical trials is 80mg twice a week, or in some trials 100mg once a week.

What evidence exists to support the use of selinexor?

Early stage clinical trials to date are showing that selinexor can produce effective responses in myeloma patients who are relapsed and/or refractory to several prior treatments. Research is focusing on combinations of selinexor
and dexamethasone with other additional drugs, as the different drugs seem to have greater effects when used together.

The Phase I/II STOMP trial is investigating selinexor with low-dose dexamethasone in combination with various other myeloma treatments - the proteasome 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.

The selinexor, low-dose dexamethasone and low-dose bortezomib arm of the trial has been completed and published. 63% of patients (25 out of 40) responded, with a median length of time to progression of their myeloma of 9 months. There was a higher response rate of 84% (16 out of 19) in patients who had previously responded to (or had never been treated with) a proteasome inhibitor, and the median time to myeloma progression for this group of patients was 17.8 months. For patients who had previously been refractory (non-responsive) to proteasome inhibitors, the overall response in this group was 43% (9 out of 21 patients) and the time before progression of their myeloma was 6 months. Other treatment arms of the STOMP trial are still enrolling patients.

The Phase II STORM trial is investigating the use of selinexor in multiply relapsed patients.

In the first part of the trial, 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. The response rate among those patients who were refractory to daratumumab as well as the other four treatments was 20% (6 of 30 patients).

The second part of the STORM trial included 122 patients who were heavily pre-treated/refractory. The patients were treated with selinexor 80mg twice-weekly together with dexamethasone. The response rate was 26.2% (32 out of 122), and median time to disease progression was 3.7 months.
What are the possible known side effects of selinexor?

The most commonly observed side effects of selinexor include nausea, vomiting, loss of appetite, fatigue, infections, low platelet levels (thrombocytopenia) and other changes in blood cell counts.

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 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.

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 could have a place in treatment of multiply relapsed and/or refractory patients. Studies are continuing of selinexor in combination with other anti-myeloma drugs such as lenalidomide, daratumumab and pomalidomide in relapsed and/or refractory patients. A new trial developed with Myeloma UK started in 2018. It will look at the combination of selinexor with cyclophosphamide (a chemotherapy drug) and prednisolone (a steroid drug) to treat patients who have relapsed after two or more previous drug treatments.

Larger scale studies (called phase III studies) are now being carried out to follow up the preliminary trials, and to provide better evidence of effectiveness of selinexor in combination with different drugs. One of these is called the BOSTON trial, and includes centres in the UK. This trial is looking at whether selinexor added to bortezomib and dexamethasone is more effective than bortezomib and dexamethasone alone, in patients with relapsed and refractory myeloma.

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

**About this Infosheet**

The information in this 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 myeloma.org.uk/references

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To talk to one of our Myeloma Information Specialists about any aspect of myeloma, call our Myeloma 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 myeloma.org.uk
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