DIGESTIVE CANCERS EUROPE

POSITION PAPER

On the use of biosimilar medicines in colorectal cancer

June 2019

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DIGESTIVE CANCERS EUROPE'S POSITION ON BIOSIMILAR MEDICINES

We believe equality of access to medicines is a fundamental right for all patients. Partly due to the disparities in availability of biological medicines, there are wide ranging standards of care for colorectal cancer across Europe, which means that where someone lives is a crucial factor in their prognosis. We passionately believe that all patients with colorectal cancer should have access to the same high standard of care, regardless of where they live.

With this in mind, we believe there is an important role for biosimilar medicines to play in the treatment of colorectal cancer.

Because they are generally less expensive than the reference medicine, the introduction of biosimilar medicines could increase patient access to biologic therapies, without compromising quality. This in turn could generate cost savings that could be redistributed to expand patient access to other biologic therapies, or improve healthcare by providing services and care that are currently not provided.

Patient safety is the main priority and it is vital that biosimilars continue to be evaluated with the same exacting standards as the reference medicines. It is also important that patients are fully informed about the medicines available to be able to make an informed decision themselves. We also acknowledge that the companies that create the reference medicines invest millions into the research and development program of each medicine in extremely thorough clinical trial programs, have well-established manufacturing processes for these complex medicines, and well-established pharmacovigilance in place. The EMA has imposed similar pharmacovigilance programs for all biosimilars.

With the above in mind, Digestive Cancers Europe is supportive of the development and prescribing of biosimilar medicines, with the following considerations:

- **Patient safety must be the priority.** Access to medicines must never come at the cost of patient safety. It is essential that the full adverse event profile of each biosimilar is well established, and that it meets all regulatory requirements in terms of comparative quality, safety and efficacy to the reference medicine.

- **Pharmacovigilance is essential.** We accept there is an element of the unknown with all biological medicines, even after clinical trials and market authorization. Close tracking of biological medicines, including biosimilars, is therefore essential to gauge drug performance and adverse reactions.
- **Patient education and involvement is key.** The intention to prescribe a biosimilar instead of the reference product should always be discussed with the patient. Patients should be given a clear explanation of what biosimilars are, and how rigorously they are tested and regulated, to ensure they understand that they are not in any way 'inferior' drugs. The benefits that more affordable options like biosimilars can bring to the entire patient community should also be explained. However, individual patients' choices must ultimately always be respected. Healthcare professionals should ensure they make time for face-to-face patient education and encourage the patient to ask questions. We also recommend that hospitals engage with local patient organisations so that patient experts can educate recently diagnosed patients about what they can expect from their treatment, including the use of biosimilars.
- **Information should be clear and easily available.** Patients and health professionals must have the opportunity to access clear information about biosimilars, including the potential risks and benefits, and key relevant clinical evidence presented in a patient-friendly manner. This is essential for true shared decision making. Education and support materials should be designed to assist the transfer of information to patients so that they are well informed both about biological products and biosimilars. Where possible, patients also have a societal responsibility to help to improve access for other patients.
- **Patients should not be forced to switch.** We believe that if a patient is currently taking an original reference biological medicine, and is stable and responding well to treatment, then they should never be forced to switch to a biosimilar medicine. We believe the decision to switch should never be made on cost alone. However, if the patient has all the relevant information and, after consultation with their healthcare professional, actively chooses to switch, then that is their decision to make. Patients who do agree to switch should be closely supported throughout the process, usually by a nurse.

THE USE OF BIOSIMILAR MEDICINES IN COLORECTAL CANCER: A POSITION PAPER BY DIGESTIVE CANCERS EUROPE

Overview

There is significant disparity across Europe in terms of access to biological medicines for colorectal cancer. Biosimilars are medicines that are a version of other already approved biological medicines, which undergo the same rigorous level of regulatory assessment and approval, and are usually more affordable.

By providing competition, which in itself can result in significant cost reductions, the use of biosimilars has led to improved access to biological medicines in many European countries, and freed up finances for innovative new drugs or for other health services.

It is vital that patients are kept fully informed and involved in the decision-making about their treatment, as with any other medicine. It is also important to note there are some complexities and ongoing debates around these medicines that can make it a confusing topic for a patient.

Here we outline the key facts around biosimilar medicines and provide our organisation's position on their role in colorectal cancer.

What are biological medicines?

Most medicines are made by chemical processes. But biological medicines – also known simply as biologics – are made with living cells or organisms. These might be micro-organisms (like bacteria or yeast), animal cells or human cells. The development of biological medicines requires a sterile manufacturing process, which also differs from the chemical drug synthesis process.

Biological medicines are much more complicated than traditional chemical medicines. They generally cannot be made as pills and need to be given by injection or an intravenous drip. Many biological medicines are made using the very latest cutting-edge technology.

The complex manufacturing process, and the fact they are made with living cells or organisms, results in slightly variable outcomes for ALL biological medicines, even between different batches of the same biological medicines.

Biological medicines are used to treat several different conditions, including diabetes, psoriasis, rheumatoid arthritis, inflammatory bowel diseases and cancers.

What are biosimilar medicines?

The European Medicines Agency (EMA) defines a biosimilar medicine as "a biological medicine highly similar to another already approved biological medicine (the 'reference medicine')."[1] Sometimes they are referred to as a "follow-on biological medicine".

In other words, they are similar – but not exact – copies of already existing biological medicines.

This is because biological molecules are so complex, and by their nature variable. However, to gain EMA approval, a company developing a biosimilar has to prove that there are no meaningful differences in patients' clinical outcomes compared to the reference medicine.

Companies are allowed to make biosimilars when the patent or the market exclusivity of the original medicine expires, usually around 10 years after its launch. Although developing biosimilar medicines requires large investment in cutting-edge technology to produce them, companies are usually able to produce and sell the biosimilar at a lower cost than the original reference medicines. This is because the company producing the biosimilar does not have to invest in all the original research and development for the drug. The lower prices make biosimilar medicines appealing to healthcare systems and may help to improve access for patients. Furthermore, because of their lower cost, biosimilars may be prescribed to broader patient groups and at earlier stages of treatment, enabling better disease management.

It is important to note that biosimilar medicines are different to generic medicines. Generic medicines are exact copies of much simpler, chemically-made medicines, such as aspirin or paracetamol.

Biological medicines and colorectal cancer

Biological medicines are widely used for treating colorectal cancer, particularly for patients with a more advanced state of the disease.

The latest treatment guidelines from ESMO (European Society for Medical Oncology) state that biological medicines are indicated for the first-line treatment of patients with metastatic colorectal cancer (advanced cancer that has spread from the original site in the body). There are exceptions: for example, if the patient has reduced organ function or cardiovascular insufficiency, but generally, the advice is to start treatment with a biological medicine, usually in combination with chemotherapy.[2]

Treatment with biological medicines in combination with chemotherapy has been shown to significantly improve overall survival compared to chemotherapy alone. Before the introduction of biological medicines into treatment algorithms for metastatic colorectal cancer, median survival in phase III trials never exceeded 24 months.[3] The introduction of biological medicines has improved median survival in metastatic colorectal cancer to more than 30 months in phase III trials.

Biological medicines used in colorectal cancer include:

- aflibercept (Zaltrap®)
- bevacizumab (Avastin®)
- cetuximab (Erbitux®)
- panitumumab (Vectibix®)
- ramucirumab (Cyramza®)

Please note that the names in brackets are the brand names of the original biological medicine.

Cetuximab (Erbitux®) and panitumumab (Vectibix®) are EGFR (epidermal growth factor receptor) inhibitors. With these treatments, each patient is required to take a test to see if the treatment is likely to work. The test assesses the RAS gene – if this gene is mutated, these treatments are unlikely to be effective. But if the RAS gene is not mutated (wild-type), patients are more likely to benefit.

Aflibercept (Zaltrap®), bevacizumab (Avastin®) and ramucirumab (Cyramza®) work by targeting what's known as angiogenic pathways. This helps to deprive the tumour of oxygen and nutrients to stop it growing and spreading.

In countries where these medicines are available, patients may be prescribed more than one biological therapy over the course of their disease. The optimal treatment order has not been firmly established.

The key issue – access and availability of biological medicines

There is quite significant disparity across Europe in terms of patient access to biological medicines.

In some countries, certain biological medicines are not available at all. In some, they are available but only at full or part cost to the patient. In others, they are reimbursed in full and available for free to patients.

The accessibility of any medicine is dependent upon a range of factors, including licensing (which in Europe is unified by the European Medicines Agency), procurement by government, insurers or hospitals, and subsidisation or reimbursement. Cost is a key determining issue.

Biological medicines are generally considerably more expensive than other types of cancer treatment (e.g. chemotherapy), partly due to the complexity of researching, developing and manufacturing them.

A study by ESMO, the Union for International Cancer Control, the Institute of Cancer Policy of King's College London, and the European Society of Oncology Pharmacy, compared the availability and costs across Europe for licensed drugs to treat 14 common cancer settings, including colorectal cancer.

The results showed a clear divide for newer biological and targeted drugs between western European countries, where there was widespread availability either free of charge or at subsidised cost, and eastern Europe, where many of these drugs were either unavailable or available only at full cost to patients. The results also differed quite considerably between different biological medicines.

For example, bevacizumab (Avastin®) is widely available in Western Europe. However, it is only accessible to patients if they pay for it themselves at full cost in many countries in Eastern Europe (and some countries in Western Europe, e.g. the UK).

Meanwhile, aflibercept (Zaltrap®) is less widely available than other medicines in Western Europe and almost never available other than at full cost in Eastern Europe.

The most significant discrepancies were observed for cetuximab (Erbitux®) and panitumumab (Vectibix®). While they are almost universally available and fully subsidised in Western Europe, in Eastern Europe they are rarely subsidised, other than in Bulgaria, the Czech Republic, Montenegro, Poland, Slovenia, Slovakia and the Ukraine.[4]

Please see the following pages for a full breakdown of formulary availability and actual availability for cetuximab and panitumumab in each country in Europe.

It is because of these inequalities to access that biosimilar medicines – which are more affordable – are appealing to many stakeholders.

RAS/RAF wild-type metastatic colorectal cancer: formulary availability and out-of-pocket costs[4]

COLORECTAL CANCER: Formulary and cost		
Country	**Cetuximab**	**Panitumumab**
Austria		
Belgium		
Cyprus		
Denmark		
Finland		
France		
Germany		
Greece		
Holland		
Iceland		
Ireland		
Israel		
Italy		
Luxembourg		
Norway		
Portugal		
Spain		
Sweden		
Switzerland		
Turkey		
United Kingdom		
Albania		
Armenia		
Belarus		
Bosnia and Herzegovina		
Bulgaria		
Croatia		
Czech Republic		
Estonia		
Georgia		
Hungary		
Kazakhstan		
Kosovo, Republic of		
Kyrgyzstan		
Latvia		
Lithuania		
Macedonia		
Malta		
Montenegro		
Poland		
Romania		
Russian Federation		
Serbia		
Slovenia		
Slovakia		
Turkmenistan		
Ukraine		
Uzbekistan		

- Free
- <25% cost
- 25-50% cost
- Discount >50% and <100%
- Full cost
- Not available
- Missing data

RAS/RAF wild-type metastatic colorectal cancer: actual availability.[4]

COLORECTAL CANCER: Actual availabity		
Country	**Cetuximab**	**Panitumumab**
Austria		
Belgium		
Cyprus		
Denmark		
Finland		
France		
Germany		
Greece		
Holland		
Iceland		
Ireland		
Israel		
Italy		
Luxembourg		
Norway		
Portugal		
Spain		
Sweden		
Switzerland		
Turkey		
United Kingdom		
Albania		
Armenia		
Belarus		
Bosnia and Herzegovina		
Bulgaria		
Croatia		
Czech Republic		
Estonia		
Georgia		
Hungary		
Kazakhstan		
Kosovo, Republic of		
Kyrgyzstan		
Latvia		
Lithuania		
Macedonia		
Malta		
Montenegro		
Poland		
Romania		
Russian Federation		
Serbia		
Slovenia		
Slovakia		
Turkmenistan		
Ukraine		
Uzbekistan		

- Always
- Usually
- Half the time
- Occasionally
- Never
- Not available
- Missing data

Are biosimilars as safe and effective as the reference biological medicines?

In Europe under the jurisdiction of the EMA, biosimilar medicines are approved according to the same standards of pharmaceutical quality, safety and efficacy that apply to all biological medicines.[5] Developers of biosimilars are required to demonstrate through comprehensive comparability studies with the 'reference' biological medicine that their follow-on biological medicine (the biosimilar) is highly similar to the reference medicine and there are no clinically meaningful differences in terms of safety, quality and efficacy. This means if a biosimilar is approved in the EU, it has demonstrated comparable safety, quality and efficacy to the available biological medicines.

The demonstration that the biosimilar molecule is the same as the reference molecule on an analytical level, allows avoiding the unnecessary repetition of clinical trials already carried out with the reference medicine, which would neither progress cancer research nor be ethical.

It is also important to note that ALL biological medicines (the reference medicines and biosimilars) are associated with inherent variability and complex manufacturing. Therefore, even when the original company remanufactures the reference product, structural variability can be found – meaning it could be considered almost a 'biosimilar' of the original reference medicine.

A key factor that impacts the efficacy and the safety of biological medicines is their immunogenicity (this refers to their ability to provoke – for most medicines in rare cases – an immune response in the body). All studies performed up to now have convincingly shown that this factor doesn't appear to be any different for biosimilars as compared with their reference medicines.[6]

So, the evidence shows that if a biosimilar medicine has been approved by the EMA, then it has demonstrated comparable efficacy and safety to the reference medicine without any compromise on quality.

Conclusion

The current inequalities in terms of access to essential biological medicines mean that biosimilars are an appealing option, as the increasing competition and associated lower price may help to improve access. In Europe, biosimilars must meet all the same exacting regulatory requirements in terms of quality, safety and efficacy as the reference medicine. For these reasons, we are fully supportive of the use of biosimilar medicines in colorectal cancer.

We believe the patient should be front and centre of the decision-making process around biosimilars. This means having access to comprehensive and clear information about biosimilars and the original biological medicines and, crucially, never being put under pressure to choose or switch to a biosimilar medicine for cost reasons alone.

We believe that, wherever possible, patient advocates and organisations such as ours also have a responsibility to help improve access for other patients.

If implemented widescale, we are optimistic that biosimilars could help to close the inequality gap in access to the highest standards of care in colorectal cancer.

Digestive Cancers Europe is the umbrella organisation, in Europe, representing the voice of patients with digestive cancers (oesophageal, gastric, colon, rectum, pancreatic and rare cancers), their families and their carers. Currently the Organisation has a Membership of 30 and is still growing.

Every year more than 800,000 people in Europe get a diagnosis of a digestive cancer and approximately 500,000 of them die.

It is the Mission of Digestive Cancers Europe to contribute to the early diagnosis and decreased mortality from digestive cancers and to increase overall survival and quality of life.

In order to achieve this the Organisation is active in:

- Building stronger capacity at national level
- Coaching individual patients to deal with both medical and non-medical needs
- Organising information campaigns on prevention and better screening
- Advocating for the identification and application of best practices
- Lobbying for the early adoption of innovative technologies
- Raising digestive cancers on the political agenda
- Introduction of better healthcare policies and increased research investments

Digestive Cancers Europe aspiration is to save an additional 250,000 lives per year by 2028 in Europe. We believe, that with the necessary investments and commitment amongst all stakeholders, this aspiration is feasible. Only by applying current best practices can this figure be reached.

Patient Advisory Committee (PAC) was launched in Barcelona in July 2018 at ESMO GI. It is a dedicated group of 7 patients and carers from different countries in Europe.

“We have all experienced some form of colorectal cancer (CRC) and it is through our own experience that we try to help other patients who are suffering this disease.

Treatments and procedures for CRC vary tremendously in each country and we acknowledge that there are financial restrictions. However there is much to be learnt from the personal experience of the patient that can improve the experience for others in the future and even prevent incidence.

We aim to help the patient to learn how to be part of their own healthcare team and to make decisions that affect their life. We do this by producing documents in patient language. We also feel that in relating our experiences, we can help the decision makers to prioritise what is of importance to the patient and their family.”

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