Metastatic melanoma: how do local treatment options compare with current standards of care? – Interview with Oncologist Dr Nicholas Refalo

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Breastfeeding is best for babies. You should always seek the advice of a doctor, midwife, health visitor, public health nurse, dietician or pharmacist on the need for and proper method of use of infant formulae and on all matters of infant feeding. Good maternal nutrition is important for the preparation and maintenance of breastfeeding. Introducing partial bottle-feeding may have negative effect on breastfeeding and reversing a decision not to breastfeed is difficult. Social and financial implications should be considered when selecting a method of infant feeding. Infant Formulae should always be prepared and used as directed. Inappropriate foods or feeding methods, or improper use of infant formula, may present a health hazard.
Actifed* oral solutions and tablets provide symptomatic relief of upper respiratory tract disorders. 1-7

**Actifed** DM COUGH LINCTUS
- relieves dry cough and nasal congestion 3,6

**Actifed** SYRUP AND TABLETS
- clears blocked and runny noses 2,5

**Actifed** EXPECTORANT
- clears chesty cough and nasal congestion 4,7

<table>
<thead>
<tr>
<th>DOSAGE</th>
<th>LIQUIDS</th>
<th>TABLETS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>children aged 2 to 5 years</strong> 3-4</td>
<td>2.5ml every 4-6hrs as required</td>
<td>1 tablet every 4-6hrs as required</td>
</tr>
<tr>
<td><strong>children aged 6 to 11 years</strong> 2-4</td>
<td>5ml every 4-6hrs as required</td>
<td></td>
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<tr>
<td><strong>adults (including the elderly)</strong> and children aged 12 years and over 5-7</td>
<td>10ml every 4-6hrs as required</td>
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OTC legal status applies for oral solutions in adults and children aged 12 years and over.

ACTIFED ABRIDGED PRESCRIBING INFORMATION: Please refer to full Summary of Product Characteristics (SPC) before prescribing. TRADE NAME: ACTIFED. ACTIVE INGREDIENT: Actifed DM Cough Linctus: Each 5ml contains Dextromethorphan Hydrobromide 10mg, Pseudoephedrine Hydrochloride 30mg and Triprolidine Hydrochloride 1.25mg; Actifed Syrup: Each 5ml contains Pseudoephedrine Hydrochloride 30mg and Triprolidine Hydrochloride 1.25mg; Actifed Expectorant: Each 5ml contains Triprolidine Hydrochloride 1.25mg, Pseudoephedrine Hydrochloride 30mg and Quaifeprone 100mg; Actifed Tablets: Each tablet contains Pseudoephedrine hydrochloride 30mg, Triprolidine hydrochloride 1.25mg, PHARMACEUTICAL FORM: Oral Solution and Tablets. INDICATIONS: Symptomatic relief of upper respiratory tract disorders which are benefited by a combination of Actifed DM Linctus: a nasal decongestant, an anti-histamine and an anti-tussive; Actifed Syrup: a nasal decongestant, and an anti-histamine; and Actifed Tablets: a nasal decongestant, and an anti-histamine. DOSAGE: please refer to full SPC. Actifed DM Cough Linctus, Actifed Syrup and Actifed Expectorant are authorised for use without the need of a medical prescription in Adults and Children over 12 years. In Children between 2-11 years of age, these products are authorised for use only against a medical prescription as recommended by your doctor. CONTRAINDICATIONS: Previous intolerance to any of the active substances, use of MAOIs in the preceding two weeks, severe hypertension or heart disease, concurrent use of pseudophedrine can cause a rise in blood pressure. PRECAUTIONS: May cause drowsiness, avoid concomitant use of alcohol or other centrally active sedatives, use with caution in patients with brain impairment or moderate to severe renal impairment. INTERACTIONS: Systemic antidepressants, MAOIs, ADVERSE EVENTS: Central nervous system depression or excitation with drowsiness being reported most frequently; sleep disturbance and nausea/halitosis have also been reported; skin rash, tachycardia, dryness of mouth, nose and throat and urinary retention have occasionally been reported especially in men with prostatic enlargement. PREGNANCY AND LACTATION: Administration should only be considered if the expected benefit to the mother outweighs the potential risks to foetus or child. PRESENTATION: DM Cough Linctus, Expectorant. Syrup: Amber glass bottle x 150ml. Tablets: Pack x 24 tablets. Marketing Authorisation Holder: GlaxoSmithKline UK Limited, Marketing Authorisation Number: MA 06706012/7. Legal category: POM – Actifed Tablets, POM – Actifed DM Cough Linctus, Actifed Syrup, Actifed Expectorant in Children between 2-11 years, OTC – Actifed DM Cough Linctus, Actifed Syrup, Actifed Expectorant in Adults and Children over 12 years. For further information and full prescribing information contact GlaxoSmithKline (Malté) Ltd. Tel: 21230131. Date of preparation: January 2015

In order to ensure that this product information reflects the most up-to-date clinical and post-marketing surveillance data, please always refer to the latest Summary of Product Characteristics (SPC) which is available from GlaxoSmithKline (Malté) Ltd [Tel: +356 21230131]

REPORTING ADVERSE EVENTS (AEs): If you become aware of any AEs, medication errors and/or use during pregnancy in association with GSK products, please report the event promptly to: GSK (Malté) Limited, 1, Dei di Azzurru Aveu, Gzira GVM 2408, Malta (Tel: +356 21230131). Alternatively, any suspected AEs and medication errors can also be reported via the national Adverse Drug Reactions (ADR) reporting system: Report forms can be downloaded from www.medicinesauthority.gov.mt/adrspatial and posted to the Malta Medicines Authority, Post-Banking Directorate, 203, Level 3, Rue D’Argens, Gzira GZR 1368, MALTA, or sent by email to postlicensing.medicinesauthority@gov.mt.


Job No: MLI_148199/01/05/06. Date of preparation: February 2016.
THOU SHALT NOT PRESCRIBE ANTIBIOTICS...

According to the report, Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations, it is estimated that at least 700,000 people succumb from microbial-resistant infections around the globe each year. It is indeed predicted that by 2050, antibiotic resistance will cost the world up to a staggering €88,000,000,000,000 as well as a reduction of 2% - 3.5% in global GDP. We are partly to blame for this, considering over-prescriptions, over-the-counter selling of antibiotics, as well as veterinary misuse. Interestingly, the Health at a Glance: Europe 2016, published in November, reports that of all EU countries, Malta has the highest proportion of second-line antibiotic use (32%). The EU27 average is 18%.

How can we tackle this problem, or at least part of it? Interestingly, Jason Doctor, director of health informatics at the University of Southern California’s Schaeffer Center for Health Policy and Economics, has been carrying out experiments to see whether it is possible to [at least] reduce over-prescriptions. He persuaded 248 physicians working in 47 primary care practices in Boston and Los Angeles to participate in a cluster randomized clinical trial. The interventions included:

1. Placing a poster in the examination room with the picture of the physician and signature showing a public commitment to not over-prescribe antibiotics;
2. Physicians had to explain their reasoning for the prescribed drugs;
3. Comparing physicians to other top-performing physicians within the cohort [those with the lowest inappropriate prescribing rates].

These interventions effectively reduced the number of antibiotic prescriptions. In fact, similar interventions are now being applied in health departments across the United States and even in the EU. However, if one were to completely eliminate over-prescribing [and illicit over-the-counter use of antibiotics], this would not solve the problem relating to antimicrobial resistance. The reason for this is very simple … there is an even bigger market of antibiotics. In 1950, a group of US scientists found that adding antibiotics to animal feed increases the growth rate of livestock. Ever since, antibiotics have been pumped in animals, even though we are all aware of the fact that bacterial resistance passes from animals to humans. On many occasions, any bans on growth-promoting antibiotics have been circumvented by using different labeling. Furthermore, it is envisaged that countries such as China, Brazil and Russia, will double their use of antibiotics by 2030. This has spurred researchers to try to source novel antibiotics from different sources such as the algae-filled fur of a three-toed sloth in Panama [at least this country is not only the home of tax evaders], the saliva of Komodo dragons, blood of alligators, bacteria in British Columbia caves and on the ocean floor off the coast of Panama.

REFERENCE
A maintenance bronchodilator treatment for patients with COPD who are breathless

Anoro® Ellipta® (umeclidinium bromide/vilanterol)
Abridged Prescribing Information

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 on SPC how to report adverse reactions.

Kindly consult the full Summary of Product Characteristics (SmPC) before prescribing.

Trade Name: Anoro® Ellipta®
Active Ingredients: 55 micrograms umeclidinium bromide and 22 micrograms vilanterol (as trifenatate).
Pharmaceutical Form: 55 micrograms/22 micrograms inhalation powder, pre-dispensed.

Indications: Maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD.

Dosage and administration: Inhalation only. One inhalation once daily of Anoro® Ellipta® at the same time of the day.

Contraindications: Hypersensitivity to the active substances or to any of the excipients (lactose monohydrate and any of the excipients).

Precautions: Anoro® Ellipta® should be used with caution in patients with severe cardiovascular disease. Avoid beta-adrenergic blockers since this may weaken or antagonize the effect of beta-adrenergic agonists. Caution is advised when co-administering with strong CYP3A4 inhibitors (e.g. ketoconazole, clarithromycin, itraconazole, ritonavir, telithromycin). Anoro® Ellipta® should not be used in conjunction with other long-acting muscarinic antagonists, long-acting beta-adrenergic agonists or medicinal products containing either of these agents. Caution is advised with concomitant use with methylxanthine derivatives, steroids or non-potassium-sparing diuretics as it may potentiate possible hypokalaemic effect of beta-adrenergic agonists. Fertility, pregnancy, and breast-feeding: No available data. Balance risks against benefits.

Side effects: Common: Urinary tract infection, sinusitis, nasopharyngitis, pharyngitis, upper respiratory tract infection, headache, cough, oropharyngeal pain, constipation and dry mouth. Uncommon: Atrial fibrillation, supraventricular tachycardia, rhythm idioventricular, tachycardia, supraventricular extrasystoles and rash. Legal category: POM. Presentation: Anoro® Ellipta®, 1 inhaler x 30 doses. Anoro® Ellipta® 55/22mcg. Marketing authorisation (MA) nos: 5522mcg 1x30 doses [EU/1/14/898/002]; MA holder: Glaxo Group Ltd, 980 Great West Road, Brentford, Middlesex, TW8 9GS, UK. Last date of revision: October 2014. Anoro® and Ellipta® are registered trademarks of the GlaxoSmithKline group of companies. All rights reserved. Anoro® Ellipta® was developed in collaboration with Theravance, Inc.

In order to ensure that this product information reflects the most up-to-date clinical and post-marketing surveillance data, please always refer to the latest Summary of Product Characteristics (SPC) which is available from GlaxoSmithKline (Malta) Ltd (Tel: +356 21238131).

REPORTING ADVERSE EVENTS (AEs):

Malta & Gibraltar: If you become aware of any AEs, medication errors and/or use during pregnancy in association with GSK products, please report the event promptly to: GSK (Malta) Limited, 1, De la Cruz Avenue, Qormi ORM 2458, Malta (Tel: +356 21238131)

Malta: alternatively, any suspected AEs and medication errors can also be reported via the national Adverse Drug Reactions (ADRs) reporting system:

Report forms can be downloaded from www.medicinesauthority.gov.mt/adportal and posted to the Malta Medicines Authority, Post-licensing Directorate, 203, Level 3, Rue D’Argens, Gżira GZR 1368, MALTA, or sent by email to postlicensing.medicinesauthority@gov.mt

Gibraltar: alternatively, any suspected AEs and medication errors can also be reported via the UK regulatory authority (MHRA): https://yellowcard.mhra.gov.uk/

ANORO ELLIPTA was developed in collaboration with Theravance.

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Anoro® Ellipta® (umeclidinium bromide/vilanterol)

**Trade Name:**

Anoro® Ellipta® (umeclidinium bromide/vilanterol)

**Inhalation only.** One inhalation once and administration:

55 micrograms/22 micrograms inhalation powder, pre-

vilanterol (as trifenatate)

55 micrograms umeclidinium bromide and 22 micrograms

magnesium stearate).

**Indications:**

Maintenance bronchodilator

**Presentation:**

Anoro® Ellipta®. 30 doses. Anoro® Ellipta® 55/22mcg.

**Maintenance bronchodilator**

**Interactions with other medicinal products:**

Avoid beta- adrenergic blockers since this may weaken

sparing diuretics as it may potentiate possible hypokalaemic

moderate hepatic impairment.

Acute symptoms:

**Wear:**

**Caution is advised when co-administering with strong**

Effects of beta-2 agonists therefore Anoro

paradoxical bronchospasm and alternative therapy initiated

disorders, thyrotoxicosis, hypokalaemia, hyperglycaemia

should be discontinued immediately in the event of

should be used with caution in patients

Common: Urinary tract infection,

Constipation and dry mouth. Uncommon: Atrial fi brillation,

tract infection, headache, cough, oropharyngeal pain,

sinusitis, nasopharyngitis, pharyngitis, upper respiratory

benefits.

Discontinue immediately in the event of

breast-feeding:

is not indicated for acute episodes of bronchospasm.

**Disclaimer:**

The information in this leaflet is not intended to replace medical advice.

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is currently in her fourth year reading for a PhD. In 2012 she obtained associateship of the Royal College of Pathologists (in chemical pathology). She harbours a strong interest in biochemical laboratory science.

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**ABSTRACT**

Colorectal cancer is the second most common cancer in Malta. On average, between 2012-2014, 259 persons have been diagnosed with colorectal cancer and 110 persons died each year. It is a disease of the Western world. The need to target colorectal cancer from prevention through physical exercise and healthy eating, to earlier diagnosis and treatment, through organised screening programmes and fast track referral systems and advanced treatment protocols is crucial to reduce incidence and improve survival.

**INTRODUCTION**

Colorectal cancer accounts for 9.7% of all cancers worldwide (excluding non-melanotic skin cancer). It is the second most common cancer in Europe and third most common cancer in the world. It is far more common in the Western world with age standardised incidence rates being highest in Europe and North America (Table 1) and lowest in Africa and Central America. There is variation in the trends in incidence and mortality of colorectal cancer in different countries with three main patterns being observed:

- Increase in incidence and mortality is being seen in rapidly transitioning regions such as Eastern Europe, Asia and South America;
- Increase in incidence with a decrease in mortality is being seen in some European countries such as Denmark, Sweden, United Kingdom and Malta amongst others as well as Canada and Singapore;
- In countries such as the United States, Japan and other Western countries both incidence and mortality have stabilised or have even started to decline.

Colorectal cancer is associated with a number of modifiable risk factors including diets rich in animal fat and protein, obesity and lack of physical activity, smoking and excessive alcohol consumption. Inherited conditions such as familial adenomatous polyposis (FAP) as well as a personal history of inflammatory bowel diseases are associated with a high risk of developing colorectal cancer. The latter risk conditions account for only a small proportion of all colorectal cancer cases.

A reduction in colorectal cancer incidence and mortality is achievable through a number of measures which include primary prevention through improved nutrition and increased physical activity, and organised population-based cancer screening programmes. New and advanced treatments are also contributing towards improvements in the outcomes of colorectal cancer care. There are wide variations worldwide in the state of implementation of colorectal screening with countries such as the United States and Japan having organised screening programmes since the 1990s. On the other hand, by 2008, only 19 out of the 27 EU countries had or were developing a screening programme. By 2015, this implementation figure has gone up to 24 out of 28 EU countries. However, to date there are still several countries worldwide with no organised screening programme in place despite having a high incidence and mortality from the disease.
Colorectal cancer is the second commonest cancer for Malta in both genders combined following breast cancer. On average, 146 males and 113 females (3 year average of 2012-2014) are diagnosed each year with colorectal cancer. The incidence of colorectal cancer increases with age (Figure 1) and age-specific incidence rates in males are much higher than those in females for most age groups.6

The standardised incidence rate of colorectal cancer in Malta has remained relatively stable in females (Figure 2) but seems to show a rising trend in males. Incidence rates in Malta in both males and females are lower than the EU average (Malta: M: 42.1, F: 35.2; EU-27 average: M: 59.0, F: 36.1 in 2012 per 100,000 pop (ESP)).7

On average there are 61 male deaths and 49 female deaths due to colorectal cancer each year (average of 2012-2014). Colorectal cancer is the second most common cause of cancer death in both sexes combined following lung cancer. Average age at death for both genders is 73 years (2012-2014). The age standardised mortality rate has remained relatively stable in males over the past years (Figure 3) but is showing a downward trend in females.6 Mortality rates in Malta in both males and females are slightly above the EU average (Malta: M: 23.9, F: 15.9; EU-27 average: M: 23.8, F: 14.2 in 2012 per 100,000 pop (ESP)).7

The one-year and 5-year relative survival for patients with invasive colon cancer who were diagnosed between the years 2000-2007 was 77.6 and 57.0 respectively in Europe.8 Malta observed one of the highest increases in colon cancer 5-year relative survival from 53% for patients diagnosed between 1999-2001 to 61% in patients diagnosed with colon cancer in 2005-2007.8 As presented in the tables below, one-year relative survival of patients with rectal cancer is higher than those with colon cancer in all regions. However, the same does not always apply for the 5-year relative survival. In Malta, between the periods 1999-2001 and 2005-2007, the 5-year relative survival for patients with rectal cancer fell from 60% to 50% (European average increased by 6 percentage points to 58%).8

Prior to the introduction of the colorectal screening programme in Malta in November 2012, screening for colorectal cancer by faecal occult blood tests (FOBT) and other means was only performed on an opportunistic basis and activity rates were very low. Only 2.6% of persons aged between 50 and 74 years interviewed in the European Health Interview Survey carried out in 2008 reported as having had a FOBT in the previous two years.9

The National Colorectal Cancer Screening programme was launched in November 2012. During its first screening cycle, persons aged between 60-64 years were invited to undergo colorectal cancer screening. The colorectal cancer screening programme is now in its second cycle and persons aged 55 to 66 years are invited to undertake an iFOBT (immunochemical-faecal occult blood test) every 2 years. Clients that obtain a positive iFOBT result are referred for a colonoscopy. The aim is to eventually reach the age cohorts 50 to 74 years recommended in the EU Council Recommendation of 2003 on Cancer Screening.10

Apart from the screening route, patients can also enter the colorectal cancer care pathway from the symptomatic route. A number of measures are being planned and introduced to ensure that patients with suspicious signs and symptoms gain access to specialist care in hospital in the shortest time possible. One of these measures involves the introduction of a fast-track referral system. A pilot system relating to the fast-track referral system for colorectal cancer was introduced in early 2016 whereby participating family physicians can complete an electronic referral form that has been specifically designed for this purpose. A surgeon with a special interest in colorectal surgery vets these referrals. When the indication for a fast-track...
referral is confirmed, the family physician is instructed on how best to prepare their patient and an expedited appointment for a colonoscopy is given.

Measures are also being planned to ensure continuity and seamless care for patients navigating the cancer pathway from diagnosis to palliative care and survivorship. The aims are to improve patients’ experience and outcomes and also to assist patients during this challenging journey. These include the planned and incremental introduction of cancer care pathway navigators. These navigators will most often be nursing professionals and they will be appointed to act as care-coordinators for patients with various cancers. Navigators will be assigned to different groups of cancer patients so that they will be able to develop specific expertise in assisting patients with similar conditions.

The diagnostic and treatment plan of patients suspected or diagnosed with colorectal cancer is discussed during multidisciplinary team (MDT) meetings which are held once every fortnight at Mater Dei Hospital. Support for the operations of these MDTs will be reinforced to improve their effectiveness and to ensure inclusivity for all patients diagnosed with colorectal cancer. Plans also envisage that the MDTs will eventually assume the role of a tumour management group which will have the responsibility of developing and overseeing the implementation of relevant national care guidelines and monitor and evaluate selected performance outcome indicators.

**DISCUSSION AND CONCLUSION**

There is large variation in trends in mortality from colorectal cancer in the different European countries, with an average reduction in mortality in EU 27 falling by 13% in men and 27% in women between 1989 and 2011.11 Countries including the United Kingdom, Austria, Germany and Ireland amongst others showed major reductions in mortality while other countries especially central European countries showed either a small decline or no decline at all.11 In Malta the overall mean change in mortality in females fell by 15.9% while in males it increased by 5.2% from between 1989 and 2011.11 Implementation of and participation rates in national screening programmes varies considerably between countries and this is considered to be an important factor in reducing mortality.11

The need to target colorectal cancer from prevention, through to earlier diagnosis and advanced treatment protocols is key to improved survival11 and requires financial resources and well planned cancer strategies.
FEEL RELIEVED
from the symptoms of dry eye

Advanced Hydration
for longer lasting relief

NOT ALL DRY EYE DROPS
ARE CREATED EQUAL
Systane family of products are formulated with HP Guar1-4

Systane
Family of Products

Cancer control services require a comprehensive approach for the planning, acquisition and governance of the necessary organisational, human, technological and financial resources for the sustainability and further development of the services needed to meet the increasing demand and the dynamic and evolving domains of cancer care. A new National Cancer Plan for Malta is currently being collated and this strategy will include several measures aimed at generating quality improvements at the multiple different phases of the cancer care pathways. Measures will include generic upgrades that will affect all cancer patients such as the implementation of a comprehensive ICT infrastructure that will closely document an individual patient’s trajectory, improve connectivity between different care providers and allow the generation of more timely and detailed cancer intelligence. The new National Cancer Plan will also include specific developments that will target the accessibility of increasingly more advanced levels of expertise and technology (including cancer care medicines) for specific cancer groups.

In 2015 the Ministry for Health set up the Cancer Care Pathways Directorate. The aim of this directorate is to develop individualized pathways of excellence in cancer care where the journey of both patients and their families is facilitated in a safe and integrated manner through the provision of holistic care. It also supports, recommends and implements changes within cancer services to ensure high quality services that are delivered in a timely manner.

Support for the patients and their families during this time is an important factor that helps people cope with this challenging condition. The Malta ColoRectal Cancer Awareness Group (MCRCAG - http://www.crc.org.mt/GetSupport) has been set up in February of this year with the aim of creating awareness and education about colorectal cancer as well as support to the patients and their families and caregivers.

### Table 2: 1-year and 5-year relative survival for adult patients with invasive colon cancer diagnosed in 2000-2007

<table>
<thead>
<tr>
<th>Region/Country</th>
<th>1 year</th>
<th>5 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Northern Europe</td>
<td>79.3 (78.9-79.6)</td>
<td>59.0 (58.5-59.5)</td>
</tr>
<tr>
<td>Ireland and UK</td>
<td>72.6 (72.4-72.8)</td>
<td>51.8 (51.5-52.1)</td>
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<tr>
<td>Central Europe</td>
<td>80.5 (80.3-80.7)</td>
<td>60.5 (60.2-60.8)</td>
</tr>
<tr>
<td>Southern Europe</td>
<td>78.6 (78.4-78.9)</td>
<td>58.5 (58.1-58.8)</td>
</tr>
<tr>
<td>Malta</td>
<td>74.9 (72.0-78.0)</td>
<td>58.1 (53.7-62.7)</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>69.7 (69.4-70.1)</td>
<td>49.4 (48.9-49.8)</td>
</tr>
</tbody>
</table>

### Table 3: 1-year and 5-year relative survival for adult patients with invasive rectum cancer diagnosed in 2000-2007

<table>
<thead>
<tr>
<th>Region/Country</th>
<th>1 year</th>
<th>5 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Northern Europe</td>
<td>83.4 (83.0-83.8)</td>
<td>59.5 (58.9-60.2)</td>
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<tr>
<td>Ireland and UK</td>
<td>78.5 (78.2-78.7)</td>
<td>53.7 (53.3-54.1)</td>
</tr>
<tr>
<td>Central Europe</td>
<td>83.7 (83.5-84.0)</td>
<td>80.1 (59.7-60.5)</td>
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<tr>
<td>Southern Europe</td>
<td>80.4 (80.1-80.7)</td>
<td>55.4 (54.9-55.9)</td>
</tr>
<tr>
<td>Malta</td>
<td>82.1 (78.5-85.8)</td>
<td>52.8 (47.0-59.3)</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>72.4 (72.0-72.8)</td>
<td>44.6 (41.1-45.1)</td>
</tr>
</tbody>
</table>

Acknowledgements: Ms Danika Marmara & Dr Stephanie Xuereb


4. Most common adverse effects are diarrhoea, nausea, vomiting and mucocutaneous candidiasis.

5. Prepared for use in adults & adolescents aged ≥16 years; 2 tablets BD for 7-10 days.

References:
5. Augmentin SR, April 2015.

Spread the infectious liveliness!
Amoxicillin/Clavulanate Potassium
Powder for oral suspension

✓ Provides extended antibacterial coverage to include the most penicillin-resistant strains.\(^1\)
✓ Recommended by leading Guidelines as first line treatment in AOM.\(^{2,3}\)
✓ Most common adverse effects are diarrhoea, nausea, vomiting and mucocutaneous candidiasis.\(^4\)
✓ Indicated for children <40 kg and older than 3 months; dosed at 90/6.4 mg/kg/day in 2 divided doses.\(^4\)

Spreading infectious energy!

Mini Abridged Prescribing Information: Please refer to the full Summary of Product Characteristics (SPC) before prescribing. TRADE NAMES: Augmentin ES. ACTIVE INGREDIENTS: Amoxicillin (as trihydrate) and potassium clavulanate. PRESENTATIONS: Supplied in 100 ml glass bottle with a dosing spoon. INDICATIONS: Treatment of acute otitis media and community-acquired pneumonia infections in children aged at least 3 months and less than 40 kg body weight, caused or thought likely to be caused by penicillin-resistant *Streptococcus pneumoniae*. POSOLGY & ADMINISTRATION: Oral use; recommended dose of 90/6.4 mg/kg/day in two divided doses. CONTRAINDICATIONS: Hypersensitivity (and past history of) to the active substances, to any penicillins or to any of the excipients. SPECIAL WARNINGS & PRECAUTIONS: Before initiating therapy careful enquiry of previous hypersensitivity reactions to beta-lactams. Where an infection is proven to be due to an amoxicillin susceptible organism, a switch to an amoxicillin-only preparation should be considered. Convulsions may occur in patients receiving high doses or who have impaired renal function. Concomitant use of allopurinol increase likelihood of allergic skin reactions. Prolonged use may occasionally result in overgrowth of non-susceptible organisms. Augmentin ES contains aspartame (E951), a source of phenylalanine. The suspension also contains maltodextrin (glucose). Refer to the SPC for full list of precautions.

INTERACTIONS: Penicillins may reduce the excretion of methotrexate causing a potential increase in toxicity. Concomitant use of probenecid is not recommended. If co-administration with oral anticoagulants is necessary, the prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of amoxicillin. Moreover, adjustments in the dose of oral anticoagulants may be necessary. PREGNANCY & LACTATION: Use should be avoided unless considered essential by the physician. UNDESIRABLE EFFECTS: Very common (≥ 1/10): diarrhoea. Common (≥ 1/100, < 1/10): mucocutaneous candidosis, nausea, abdominal pain. Refer to the SPC for full list of undesirable effects. AUTHORISATION NUMBER: AA 1051/0010. MARKETING AUTHORISATION HOLDER: GlaxoSmithKline Bulgaria EOOD. LEGAL CATEGORY: POM. DATE OF PREPARATION: May 2016 In order to ensure that this product information reflects the most up-to-date clinical and post-marketing surveillance data, please always refer to the latest Summary of Product Characteristics (SPC) which is available from GlaxoSmithKline (Malta) Ltd (Tel: +356 21238131) REPORTING ADVERSE EVENTS (AEs): If you become aware of any AEs, medication errors and/or use during pregnancy in association with GSK products, please report the event promptly to GSK (Malta) Limited, 3, De la Cruz Avenue, Orion GBM 2458, Malta (Tel: +356 21238131) Alternatively, any suspected AEs and medication errors can also be reported via the national Adverse Drug Reactions (ADRs) reporting system: Report forms can be downloaded from www.medicinesauthority.gov.mt/adportal and posted to the Malta Medicines Authority, Post-licensing Directorate, 203, Level 3, Rue D’Argens, Gzira GZR 1368, MALTA, or sent by email to postlicensing@medicinesauthority@gov.mt

References:

Prepared: November 2016 Job No: MLT_GIB/AES/0001/15(3)
Chemical Pathology in the Movies: ‘Lorenzo’s Oil’

Michelle Muscat

Director: George Miller
Writer: George Miller & Nick Enright
Stars: Nick Nolte, Susan Sarandon, Peter Ustinov
Runtime: 129 min
Release date: 1992

The 1992 medical drama ‘Lorenzo's Oil’, directed by George Miller, is at the same time a tragic and uplifting movie which deals with one of the lesser known diseases, adrenoleukodystrophy (ALD), which forms part of a subset of diseases of interest to the chemical pathologist. The movie follows the quest and struggle of Michaela and Augusto Odone to save their very own child, Lorenzo, who is found to have this rare condition. The events narrated in this movie are based on a true story, albeit with some alterations made for a movie adaptation.

Adrenoleukodystrophy is an X-linked disorder, hence primarily affecting males, due to a mutation in the ABCD1 gene. This gene encodes a protein in the peroxisomal membrane which is responsible for very long chain fatty acid (VLCFAs) transmembrane transport. In this condition we find elevated levels of VLCFAs. Over the years this disease has also been referred to as Siemerling-Creutzfeld disease, bronzed Schilder's disease, encephalitis periaxialis diffusa, melanodermic type of leukodystrophy, as well as other nomenclature variations that were historically applied. The clinical spectrum may vary significantly, hence making diagnosis more difficult. Males may range from having just adrenocortical insufficiency, adrenomyeloneuropathy, or the childhood cerebral form, for example.1-7 This last form of the disease is the one illustrated in the film.

Lorenzo is initially depicted in the movie as a bright and vivacious young boy. The very first indication in the film that something is amiss is when the teacher points out to his mother that he is throwing tantrums at school and having ‘disturbed behavior’. One of the teachers even recommends he receives special education classes, which his mother insists will be provided at home. In later incidents he falls off his bike, and also falls when reaching out for a decoration on the Christmas tree. The constellation of events leads his parents to seek medical advice. Initial investigations revealed a normal CT scan and EEG and no gross visible neurological abnormality. Later on his mother finds him listening to very loud music and it is discovered that he has hearing impairment. Again, after referral to the appropriate medical specialist, an auditory processing difficulty is confirmed. Further inpatient investigations included tuning fork testing for conductive and sensorineural hearing loss, fundoscopy and further...
imaging amongst others. The escalating sense of his parents’ desperation is depicted, and climaxes when the diagnosis is provided without equivocation. This is especially so given they were told it is a progressive and relentless disease with a bleak prognosis, and there was no known treatment whatsoever that could be provided to their son at the time. Lorenzo had significantly elevated VLCFAs in his blood. In the movie it is stated that there is a defective enzyme for metabolizing these fats, however this is no longer entirely correct since it is the peroxisomal membrane protein that is defective in ALD patients. The parents are told what ‘myelin’ is, and are also explained briefly the concept of demyelination. Distraught and in search for answers the father is seen reading literature on the pathology of adrenoleukodystrophy as well as individual case studies. Numerous medical terms were enlarged on screen. Dysphagia, seizures, spasticity, deafness, coma and death were amongst the words highlighted to the viewer on the screen.

The search for a world expert on the leukodystrophies leads them to Professor Gus Nikolais, who was working on a diet for the disease. He suggests enrolling Lorenzo in a trial, and explains to his mother the nature of the genetic transmission of this effect which was described in the movie as ‘a beautiful piece of biochemistry’. This is another movie which shows a personal journey to a medical breakthrough. The author personally highly recommends this movie to those practicing within her medical discipline of chemical pathology or clinical biochemistry as well as those interested in the more research-based pure biochemistry.

not seem to improve any further. The boy’s clinical condition later takes an acute turn for the worse, but he miraculously survives the acute episode and the family look further into the literature, and even make a model using different paper clips as carbon atoms. They determine that erucic acid would be a better candidate therapy, however there were challenges in sub-fractionating this from rapeseed oil and getting it approved for human consumption. Finally, after obtaining the desired substance, they tested it out on Michaela’s sister, termed jokingly, ‘the family rat’, and subsequently gave it to Lorenzo. The treatment consisted of an oil containing specific combinations of the triacylglycerol forms of both oleic and erucic acid [hence the name of the movie, Lorenzo’s oil]. Upon blood sampling and testing, they were contacted by the laboratory querying possible mislabeling of the specimen, given that the levels of the VLCFAs C24 and C26 were assayed twice and were within normal limits. This held great scientific potential, however in the setting of neurological damage that had already occurred. The movie ends on the note that the father was meeting a group of specialists who were looking into methods to re-myelinate ‘the shaking puppy dogs’, and the mother tells her child ‘if they ever give you back your myelin, you will be able to tell your brain to tell your toes … to do what you want them to do…’. The real life Lorenzo Odone lived up to age 30, which was significantly longer than originally predicted.

Persistence and desperation leads the Odone family to fabricate their very own miracle. The family writes a paper to this effect which was described in the movie as ‘a beautiful piece of biochemistry’. This is another movie which shows a personal journey to a medical breakthrough. The author personally highly recommends this movie to those practicing within her medical discipline of chemical pathology or clinical biochemistry as well as those interested in the more research-based pure biochemistry.

**REFERENCES**


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Relvar & Glibenclamid: If you become aware of any AEs, medication error and/or use during pregnancy in association with SAE events, please report the event promptly to GSK (Maltese Units, 9, Deo Dr. Ghasa, Birkirkara, Malta. Tel: +356 21281315). Make alternatively, any suspected AEs and medication errors can also be reported via the national Adverse Drug Reactions (ADR) reporting system.

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The FLAME study is a 52-week, head-to-head trial comparing ULTIBRO® BREZHALER® with Serevent® Accuhaler® (RAPIKIN, a long-acting 

## References

2. Novartis Europharm Ltd. ULTIBRO Brezhaler Summary of product characteristics.

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Report forms can be downloaded from www.medicinesmonitoring.gov.mt available and posted to the Malta Medicines Authority, Port Lincoln Directories, 205/207, Level 3, 248, Victoria, Gzira, 1688, MALTA, as soon by email to prescribing.medicines@att.net.mt

Gibraltar, alternatively, any suspected AEs and medication errors can also be reported via the UK regulatory authority (MHRA): https://www.gov.uk/report-ADR

References:
1. Relvar Ellipta Summary of Product Characteristics, GlaxoSmithKline 2011
3. ICS/LABA: A Novel Combination Therapy for COPD. Available at: www.gsk.com
4. Reports of Severe Gastrointestinal Events in Patients on Long-term Treatment with long-acting bronchodilators. Data on file with GlaxoSmithKline

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For Update on previous maintenance inhalers. Multa/Malta/UK/EU/USA/France (COPD):

SUGGESTED ADDITIONAL INFORMATION

"Patient" is a current or previous maintenance inhaler. Multa/Malta/UK/EU/USA/France (COPD):

Multa Therapy:

1. Relvar Ellipta Summary of Product Characteristics, GlaxoSmithKline 2011
3. ICS/LABA: A Novel Combination Therapy for COPD. Available at: www.gsk.com
4. Reports of Severe Gastrointestinal Events in Patients on Long-term Treatment with long-acting bronchodilators. Data on file with GlaxoSmithKline

GSK theravance

For Update on previous maintenance inhalers. Multa/Malta/UK/EU/USA/France (COPD):
A recent widely publicised Lancet review of statin efficacy and safety data generated more controversy than it resolved.1 Led by Professor Rory Collins of Oxford University, the review claimed that the benefits of statins have been underestimated and the risks exaggerated. Claims of statin intolerance in up to 20% of patients, the review argues, are not supported by large-scale evidence from randomised trials. In fact, Collins et al. claim that statin therapy is no less well tolerated than placebo.

Collins further claimed that the controversy about statin intolerance and myopathy rates emerged only in the past 2 or 3 years as manufacturers began marketing newer and “very expensive” cholesterol-lowering agents, such as, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors for patients classified as statin intolerant. He also pointed out that industry has funded reports on statin intolerance, as in the case of the European Atherosclerosis Society’s report2 which, not only had funding from makers of PCSK9 inhibitors, but also had its meetings coordinated by a commercial entity funded by the manufacturers.

Collins claimed that one could expect that 5 years of a statin regimen that lowered LDL cholesterol by 2mmol/L would prevent major vascular events in about 1000 of 10,000 secondary-prevention patients and about 500 of 10,000 primary-prevention patients, with a bigger benefit to be expected with lifelong statin use. Moreover, he added, whereas many of the adverse effects (such as myopathy) can be reversed with no residual ill-effects by stopping the statin, the effects of a heart attack or stroke are often irreversible.

Dr Harlan Krumholz (Yale University), commenting on the review in the BMJ,3 said that while the findings strongly support the benefits of statins in comparison to modest risks, there is little consideration of the limitations of the trial evidence, most notably a lack of robust data on elderly patients, individual trials whose design prevented detection of many relevant harms, and inconsistent methods for adverse event data collection.

A vocal critic of the review, and an author of one of the 2013 BMJ papers,4 Dr Aseem Malhotra (Lister Hospital, Stevenage, UK) claims that the Clinical Trials Service Unit at Oxford has received hundreds of millions of pounds in funding from statin manufacturers and that Collin’s group has not released raw data on the major statin randomised controlled trials for independent scrutiny. He adds that by using predominantly industry-sponsored trials designed for the purpose of determining the benefits of statins but minimising side-effects, this review simply adds false precision to biased estimates. He also noted that Pfizer’s own patient leaflet on atorvastatin states that common side-effects possibly affecting up to one in 10 people include sore throat, nausea, digestive problems, muscle and joint pains.

Malhotra has also co-authored a recent systematic review revealing that in those patients over age 60, LDL-cholesterol is not associated with cardiovascular disease and is inversely correlated
with all-cause mortality. He is quick to admit that statins have a benefit, but adds that focusing on LDL lowering as if this was the end in itself is counterproductive, especially when insulin resistance is a more important risk factor for myocardial infarction. He concludes that in his view, the Lancet review is a total whitewash, and agrees with the BMJ’s editor-in-chief, Fiona Godlee, who described it as “the trialists making their own homework.”

It turns out that Godlee and Collins have been at odds ever since Collins called on the BMJ to correct and ultimately withdraw the two 2013 studies that repeated claims made in a paper by Abramson et al.4 that side-effects of statins occur in 18% to 20% of people. The BMJ corrected the statements in the two studies, but Godlee passed the decision, on whether to retract, on to an independent expert panel, which rejected Collins’s request for retraction in June 2014. In October 2014, Collins and other co-authors of the new Lancet review, sent a letter of complaint about the BMJ’s handling of the two papers to the UK’s Committee on Publication Ethics (COPE). In April 2016, COPE determined that the BMJ acted with due diligence and in line with the expectations under the COPE Code of Conduct.

The Lancet editor-in-chief Dr Richard Horton, however, in a comment accompanying the statin review,7 calls into question the independence of the COPE-appointed panel’s judgement, noting that the chair had previously written critically about statin use among older patients. Horton observed that more than 200,000 patients were estimated to have stopped taking a statin in the 6 months after adverse media coverage following publication of the disputed research, and drew parallels between “this statin scare” and the MMR vaccine scare that began with a now-retracted research paper that had led to widespread vaccine hesitancy.

Horton’s comment about COPE’s conduct prompted Godlee’s rapid response letter8 of 14th September 2016, that COPE did not decline to act but deliberated on the concerns raised by Collins et al., and on the BMJ’s response, and came to a clear conclusion that the BMJ had acted appropriately. Godlee has also written to England’s chief medical officer asking for an inquiry into the statins saga and for an independent review of the evidence on statins. She claims that an independent third-party scrutiny of the statins trial data remains an essential next step if this increasingly bitter and unproductive dispute is to be resolved.

TAKE HOME MESSAGES
1. Apart from the above claims of drug-company funding and dubious research quality, the Lancet review in question, penned by several professors of medicine and cardiology, is flawed for at least another two reasons. One is the fact that all the data is based on routine LDL measurements. Previous instalments in this Synapse series have put forward evidence for LDL having two biologically different sub-fractions – a large light particle LDL and a small dense particle LDL – with only the latter being related to atherosclerosis. Routine LDL measurements do not indicate whether moderately raised LDL is due to a raised large or small sub-fraction. The surrogate marker for a raised small LDL sub-fraction is raised triglyceride (TRG) combined with low HDL – the higher the TRG/HDL ratio, the higher the risk for atherosclerotic disease.

2. Another flaw in the review is the persistent belief that the benefit of statins is via their blood lipid-lowering action. It is now well-established that the essence of atherosclerosis is an inflammatory disease of arteries. Statins are now recognised to be potent anti-inflammatory-cytokine agents, and their clinical benefit is mainly via this anti-inflammatory route. The high-sensitivity C-reactive protein (HsCRP) is the other valuable measurement of possible atherosclerotic inflammatory activity, particularly when combined with the TRG/HDL ratio.

3. As pointed out above by Dr Aseem Malhotra, insulin resistance (chronic hyperinsulinaemia) is a more potent indicator of myocardial infarction risk than LDL. This has been highlighted in a previous instalment of this Synapse series, which also pointed out that the TRG/HDL ratio is a surrogate marker for insulin-resistance/hyperinsulinaemia. Some private laboratories in Malta will be adopting the TRG/HDL ratio and the HsCRP as the main markers of atherosclerotic activity risk.

REFERENCES
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Seretide™ (salmeterol xinafoate and fluticasone propionate)  

4. Seretide Accuhaler® (fluticasone propionate/salmeterol xinafoate)  


References
3. Seretide Evohaler® (fluticasone propionate/salmeterol xinafoate)  

In order to ensure that this product information reflects the most up-to-date clinical and post-marketing surveillance data, please always refer to the latest Summary of Product Characteristics which is available from GlaxoSmithKline (Malta) Ltd (Tel: +356 21238131)

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Gibraltar: any suspected AEs and medication errors can also be reported via the UK regulatory authority (MHRA): https://yellowcard.mhra.gov.uk

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1 Novartis Europe Ltd. Galvus® Summary of Product Characteristics
2 Novartis Europe Ltd. Eucreas® Summary of Product Characteristics
HIV AND AIDS

HIV
HIV (human immunodeficiency virus) is a virus that gradually attacks the immune system. The body finds it harder and harder to fight off common infections as the disease gradually progresses. The virus destroys white blood cells (CD4). These cells are responsible for combating infections; another name for them is T-lymphocytes.

There are many different strains, someone who is infected may carry different strains in their body. The two main types are HIV-1 and HIV-2. HIV-1 is the most common type found worldwide whereas HIV-2 is limited to Western Africa, with very few cases in India and Europe. Symptoms may take around 10-15 years to emerge and by then the HIV would have already caused significant harm to the immune system.

HIV is found in the following body fluids of an infected person: semen, blood, vaginal secretions and breast milk. Risk of infection is increased when using infected needles, syringes or any other methods which include the crossover of blood. It is spread primarily by unprotected sex. HIV, however, cannot be transmitted through saliva, sweat or urine.

AIDS
AIDS (acquired immune deficiency syndrome) is a syndrome caused by the HIV virus. AIDS develops when the HIV infection has significantly progressed. This is the last stage of HIV infection where the body can no longer defend itself and may thus develop various diseases. These include pneumonia, fungal infections and any type of opportunistic infection. There is also an increased risk of developing other life-limiting conditions including cancer and brain illnesses.

Methods of prevention: safe sex; no sharing of any instruments in contact with blood.

There is currently no cure for HIV or AIDS. However with the right treatment and support, patients can live long and healthy lives.

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O
f all skin cancers, metastatic melanoma is the deadliest form. Early diagnosis allows it to be cured with surgery alone; later presentations considerably limit successful treatment options. Dr Nicholas Refalo, Consultant Oncologist at Mater Dei Hospital, explains to Dr Gabriel Ellul the toll which metastatic melanoma has on the Maltese population, and the current treatment options available.

**TS: WHAT IS METASTATIC MELANOMA?**

Melanoma is the malignant proliferation of melanocytes. As in all malignant growths, it is classified into stages depending on its degree of spread. Metastatic melanoma relates to stage IV of the disease, with metastatic spread to multiple organs, most notably lungs, liver, brain and bone. Spread occurs primarily via the lymphatic system, with haematogenous spread either arising secondary to the lymphatic dissemination of the tumour, or else once the tumour directly invades the vascular system.

A distinguishing and morbid aspect of stage IV melanoma is its poor survival rate with the 10-year survival rate being, at best, less than 10%. At this advanced stage of disease, the role of surgery and radiation is limited, and the only viable options are systemic treatment modalities.

**TS: WHAT CAUSES THE DISEASE?**

The aetiology of melanoma is a widely studied subject, with the principal causative factors being exposure to UV light and a genetic predisposition, amongst others. Additionally, there are a multitude of risk factors which decrease the overall survival rate, including older age, poor performance status at time of diagnosis, male gender, multiple metastatic sites, shorter disease-free intervals, leukocytosis, and neutrophilia prior to initiation of treatment.

Melanoma, in its aetiology, may arise from a number of different sites, with this forming the basis in the genetic variability of melanoma. Four distinct genetic types have in fact been identified: melanoma arising from normal skin without any preceding sun exposure; that arising from skin which had undergone chronic exposure to UV irradiation; melanoma arising from the soles of feet or the palms of the hands; and melanoma derived from mucosal surfaces.

This distinction has served to direct certain gene-based treatment modalities.

**TS: HOW DOES ADVANCED MELANOMA MANIFEST ITSELF AND HOW COMMON IS IT?**

These patients usually present with multi-organ involvement, mostly with metastases to the lungs, liver, brain and bone. Locally, metastatic melanoma accounts for up to 10 new cases a year. They are usually referred with curative intent, but current treatment options provided by the public health care system allow only palliation at the very best.

**TS: HOW SO? WHICH TREATMENTS ARE AVAILABLE LOCALLY?**

Locally we make use of dacarbazine, an alkylating agent approved by the FDA in 1975 - more than 4 decades ago. Patients on this drug only have a one-in-eight chance of tumour shrinkage. In fact, an analysis of a total of 23 RCTs concluded that the objective response rate for monotherapy with dacarbazine hovers around 15%. Consequently, the primary purpose of dacarbazine is palliation, not treatment, of metastatic melanoma.

Despite these shortcomings, dacarbazine remains the only form of chemotherapy funded by our healthcare system here in Malta. All other options, available abroad, require private funding.

**TS: HOW DOES THIS COMPARE TO CURRENT STANDARDS OF CARE?**

In view of the poor survival rates with the available chemotherapeutic modalities, as evidenced by data supporting dacarbazine, there has been a shift towards immune-mediated therapies and targeted therapies in Europe.

Over the past decade, with an enriched understanding of the pathogenesis of melanoma, novel therapies have been adopted in a multitude of European countries, which have had a profound impact on the survival rates of patients with metastatic melanoma.
These most notably include a drug called ipilimumab, an immunomodulator targeting the function of cytotoxic T-lymphocyte associated antigen-4 (CTLA-4).

Activated T-lymphocytes express this antigen, which in turn hinders positive stimulatory signals directed towards them. Thus, CTLA-4 acts negatively, to inhibit T-cell activation in the healthy individual.

Ipilimumab acts against CTLA-4. As a monoclonal antibody, it inhibits it and thus obviates its inhibitory effect on T-cell activation, thereby indirectly prompting the T-cell mediated immune system to counter cancer more effectively.

Response rates to ipilimumab are encouraging. A phase III trial on previously treated, unresectable advanced melanoma showed an overall rate of survival of 45.6% after 12 months of therapy, and 23.5% after 24 months of ipilimumab monotherapy. Such trials also compared the efficacy of this monoclonal antibody when given in combination with vaccination strategies, producing even more favorable results.4

These results have prompted the FDA to expedite its approval of ipilimumab as a treatment modality for metastatic melanoma in March 2011, after more than a decade without any pharmaceutical innovation in the field.

The response rates to dacarbazine pale in comparison to the results achieved through this novel treatment.

And while these results are encouraging, the same can be said to another treatment strategy which is currently being given much attention through research and clinical trials. As outlined previously, melanoma has been classified into four distinct genetic subtypes. Of those melanomas developing from normal skin, like the thighs and trunk, which has not been exposed to chronic insolation, around 60% have a mutation in the B-RAF gene.

The B-RAF gene acts as a proto-oncogene, with gain-of-function mutations allowing it to promote cell growth and division unchecked. The rationale behind targeted therapies is to shut down these genes, thereby nulling their positive effect on tumour growth.

The results obtained with such an approach are astounding: major shrinkage of advanced melanoma tumours was obtained through the use of a drug called PLX4032, with positive response rate in over 80% of treated patients.5 And while most of these patients eventually suffered from melanoma recurrences, prompting the need for future studies of possible combination therapies making use of this novel drug, the results speak for themselves.

Similar approaches are also being adopted for the different genetic subtypes, with ongoing research on potential inhibitors of the KIT proto-oncogene, which also plays a significant role in the aetiology of advanced melanoma.

REFERENCES

TS: WHAT ARE YOUR VIEWS ABOUT THE DIFFERENCE IN RESPONSE AND SURVIVAL RATES BETWEEN THESE NOVEL THERAPIES AND THE ONES ON THE GOVERNMENT FORMULARY?

To this day, dacarbazine remains the only systemic therapy available for advanced melanoma patients on the government formulary. And as discussed previously, the response rates for dacarbazine do not, in any way, match those obtained through the novel treatments available today.

As things stand, I feel confronted with the difficult situation of informing my patients that the only available “cure” afforded to them through the public health system is one which has nowadays been all but superseded by drugs which are not part of the formulary. The best I can offer them, presently, is dacarbazine, a drug which is palliative and not curative.

The price for immunotherapy or targeted therapy ranges in the tens of thousands of euro a month, with an estimated yearly cost of more than €120,000 for 12 months of therapy, despite discounts by the local pharmaceutical companies.

We are currently in a situation where advanced melanoma patients in Malta, who have a modest level of income, cannot afford basic curative treatment, which is otherwise available in other European countries.

Oncological centres across Europe, from well-established centres in Western Europe to less developed countries such as Albania, have made the necessary shift: they are treating their patients with these novel drugs for advanced melanoma, thus affording them a better chance of recovery.

TS: WHAT ARE YOUR CONCLUDING REMARKS?

The situation is in a dire need for change.

In the present state of affairs, all Maltese patients diagnosed with advanced melanoma have only two options: either buy this costly medication or else ask for help from local charitable institutions.

The former is a viable alternative only to those who are insured or else have the necessary financial means. With regards to the latter option, we cannot constantly rely on charity to provide for the needs of these patients. If these two options fail, the chances of successful recovery from advanced melanoma remain very, very slim.

The annual incidence rates of advanced melanoma may not be as high as in other, more well-known forms of cancer. However, we have a duty to each of our patients.

I believe that this situation warrants more public exposure; there is a need for greater public advocacy on the issue. That is why I have decided to speak up.

"cure" afforded to them through the public health system is one which has nowadays been all but superseded by drugs which are not part of the formulary. The best I can offer them, presently, is dacarbazine, a drug which is palliative and not curative.
Diabetes Control
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Ectopic pregnancy is defined as the presence of a gestational sac outside the uterine cavity and has a prevalence of approximately 2%. Ninety-five percent of ectopic pregnancies occur in the non-interstitial portion of the fallopian tube (infundibulum, ampulla or isthmus) (Fig 1). The main presenting features of an ectopic gestation are vaginal bleeding and abdominal/pelvic pain occurring during the first trimester of pregnancy; a prevalence of ectopic pregnancy of up to 18% has been reported for women presenting with these symptoms. Transvaginal Ultrasound (TVUS) combined with serial measurement of serum Human Chorionic Gonadotrophin (HCG) are the tools used for the diagnosis and management of ectopic pregnancy.

The possible locations of an ectopic pregnancy follow the normal course of the developing oocyte / fertilised ovum starting in the ovary, followed by release into the peritoneal cavity through ovulation and subsequent transit through the fallopian tube to reach the uterine cavity. In addition, an ectopic pregnancy may occur in the cervix or in a cesarean scar.

There are no reliable findings on pelvic ultrasound during the first 5 weeks of gestation. At 5 weeks gestational age, a 2-3mm gestational sac is generally seen in the endometrial lining of the uterus (Fig 2); the endometrial lining during gestation is known as the decidua and the presence a sac within it is called the intradecidual sac sign. At 5.5 weeks, a yolk sack appears (Fig 3). At 6 weeks, a 10mm gestational sac, a foetal pole and cardiac pulsations are generally evident (Fig 4). If none of these findings are present in a patient with a positive pregnancy test, serial Beta HCG testing and a repeat ultrasound in 7 days are indicated until the location of the pregnancy is identified.

An intradecidual sac may also occur with an early ectopic pregnancy, where it is known as a pseudogestational sac; this represents a small fluid collection within the decidua that mimics a gestational sac. A more reliable ultrasound finding to help differentiate a pseudogestational sac from a gestational sac is the presence of the double decidual sac sign; this sign is the result of minimal fluid present between the decidual capsularis and the decidual parietalis around the portion of the sac that is opposite the foetal pole (Fig 5).

Decidual cysts are the result of degeneration of decidual cells producing a thin walled, fluid filled cavity (Fig 6). A decidual cyst is located at the myometrial/endometrial
junction in early first trimester pregnancy, which contrasts with a pseudogestational sac that lies centrally within the endometrium. Decidual sacs may occur in intrauterine and extrauterine pregnancies and in non-pregnant women. They may also occur centrally within the placenta in later pregnancy frequently close to the point of cord attachment; they are only of concern when measuring >3cm in diameter, when they must be distinguished from villous infarcts.

To safeguard a possible wanted pregnancy, the Society of Radiologists in Ultrasound established criteria in 2013 for a nonviable first trimester pregnancy. Primarily they state that any round or oval fluid collection in a woman with a positive pregnancy test result is most likely, and should be reported as, an intrauterine pregnancy. Findings indicative of a non-viable pregnancy include (1) an embryonic crown-to-rump length ≥7mm and no heartbeat, (2) a mean gestational sac diameter of 25mm and no embryo, (3) absence of a heartbeat ≥2 weeks after detection of a decidual sac (4) absence of a heartbeat ≥11 days after detection of a decidual sac containing a yolk sac. These criteria may also be used to identify a pseudogestational sac in the presence of a rising beta HCG level.

An ectopic pregnancy usually presents around 5-6 week following the last menstrual period with vaginal bleeding and abdominal or pelvic pain if it is in a tubal location. Intraabdominal, ovarian or interstitial ectopic pregnancy may present later. More than 50% of women with tubal pregnancy present with tubal rupture resulting in haemoperitoneum and shock. Spontaneous resolution of a tubal pregnancy has been reported to occur in 5-24% of cases.

The absence of an intrauterine gestational sac at 5-6 weeks gestation should prompt measurement of serum beta HCG levels. Beta HCG levels increase more slowly in the case of ectopic pregnancy. In the case of a viable pregnancy, a rise beta HCG levels of at least 66% should be observed within 48 hours. An increase in beta HCG level of <53% in 48 hours is usually a sign of a non-viable pregnancy with a 99% sensitivity. Despite the increase in beta HCG levels during the first trimester, there is a wide range of normal values (Fig 7). Therefore, a single beta HCG value is of no value for diagnosing a viable, non-viable or ectopic pregnancy. Serial beta HCG measurements are required.

Figure 1: Ectopic pregnancies most frequently occur in the non-interstitial portion of the fallopian tube, which is composed of the infundibulum, ampulla or isthmus. Less commonly, an ectopic pregnancy may occur in the interstitial (intramyometrial) portion of the tube, in the ovary, in the cervix, in a caesarean scar or in the abdominal cavity.

Figure 2: TVUS showing a 5-week gestational sac (arrow) measuring 3mm in diameter located in the endometrium (positive intradecidual sac sign).

Figure 3: TVUS showing a 5.5-week intrauterine gestational sac containing a yolk sac (arrow).

Figure 4: TVUS showing a 6-week intrauterine gestation containing a yolk sac (large arrow) and a foetal pole (small arrow).

Figure 5: TVUS showing a decidual cyst (arrow) showing thin walls and located at the endometrial/myometrial junction.
Risk factors for developing an ectopic pregnancy include a previous ectopic gestation, prior tubal surgery or ligation, a prior cesarean section, previous myometrial or endometrial surgery, in vitro fertilisation, a history of endometriosis, the presence of an intrauterine contraceptive device, pelvic inflammatory disease, congenital uterine anomalies (may occur with a history of intrauterine diethylstilboestrol exposure) and smoking.

The most specific (100% specificity) for an extrauterine pregnancy is the finding of an extraovarian mass containing a sac with a live embryo (with heartbeat), however this is rarely seen. More commonly a tubal ectopic pregnancy presents on TVUS as an extraovarian extrauterine mass containing a gestational sac surrounded by an echogenic ring (Fig 8); there is increasing specificity if a yolk sac, embryo and a heartbeat are present. Increased vascularity around the sac on Doppler ultrasound (known as the Ring-of-Fire sign) and the presence of small amount of ascites are not reliable signs. The presence of more abundant peritoneal fluid containing blood components is a more reliable sign of an ectopic gestation.

An interstitial tubal ectopic pregnancy refers to a pregnancy located in that portion of the fallopian tube that runs through the myometrium. This portion of the tube has greater dispensability, so sign of an interstitial ectopic pregnancy may present later (as late as 16 weeks). The signs of an interstitial ectopic pregnancy include a thin myometrial cover and an eccentrically located gestational sac (Fig 9). However, this must be distinguished from an angular pregnancy, which is in the uterus close to the entry point of the fallopian tube and is viable pregnancy.

Cervical pregnancies occur about 3-4 times more frequently following vitro fertilisation treatment than in normally conceived pregnancies. The gestational sac is usually located in the proximal cervical canal (Fig 10) and must be distinguished from a spontaneous abortion in progress. On TVUS, pressure applied on the cervix by the endovaginal probe results in a sliding movement of the gestational up and down the cervical canal in the case of an abortion in progress. This movement is absent in a cervical ectopic pregnancy.

Heterotopic pregnancies are multiple pregnancies that occur simultaneously in both an intrauterine and an ectopic location (Fig 11). These are most commonly seen in women receiving assisted reproductive treatments. In such cases, the ectopic gestation sac may be treated with laparoscopic removal or image-guided ablation.

Understanding the imaging findings in women with ectopic pregnancies is crucial as it helps guide early management. The risk of incorrect diagnosis of an ectopic pregnancy are high and may result in maternal exsanguination and death.

Figure 6. TVUS showing a thin film of fluid (FL) separating the decidua capsularis from the decidual parietalis and forming the double decidual sac.

Figure 7. Range of normal beta HCG values at different stage of gestation. Not the increasing values occurring during the first trimester.

Figure 8. TVUS showing the uterus to the left (UT), left ovary to the right (L OV) and an tubal ectopic gestation (Ectopic). Note the echogenic ring (arrow) surrounding the sac.

Figure 9. TVUS showing an interstitial ectopic pregnancy (arrow) with thin overlying myometrium (curved arrow). Note the normal endometrium (arrowheads).

Figure 10. TVUS showing a gestational sac (arrow) in the proximal cervical canal.

Figure 11. TVUS showing a normal intrauterine gestational sac (arrow) and a tubal gestational sac (arrowhead).

Figure 12. TVUS showing a normal intrauterine gestational sac (arrow) and a tubal gestational sac (arrowhead).
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DUAC (CLINDAMYCIN/BENZOYL PEROXIDE) IS AN EFFECTIVE TREATMENT THAT HELPS YOUR MILD TO MODERATE ACNE PATIENTS TO SEE IMPROVEMENTS FAST.\(^1,3\)

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- Duac is a once daily treatment\(^2\)
- Duac is generally well-tolerated\(^2,5\)

**YOUR EXPERT ADVICE CAN SHOW ON THEIR FACE**

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- The gel contains added moisturisers, glycerin and dimethicone, for better tolerability\(^1\)

**DUAC HAS A DUAL MODE OF ACTION\(^2\)**

<table>
<thead>
<tr>
<th>Clindamycin</th>
<th>Benzoyl Peroxide</th>
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<tr>
<td>Bactericidal action against (P.) (acnes) strains(^2)</td>
<td>Keratolytic(^2)</td>
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<tr>
<td>Suppresses (P.) (acnes)</td>
<td>Treats comedones(^2) and inflammatory lesions(^2)</td>
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<td>Anti-inflammatory action(^2)</td>
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**UNBLOCKS FOLLICLES**

- Reduces the potential for bacterial resistance
- Kills bacteria

**REDUCES INFLAMMATION**

- Treats comedones\(^2\)

**KILLS FLORA.**

**TIPS**

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**TIPS**

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**FOR MORE INFORMATION:**

www.hcp.gsk.com.mt/products/list/duac.html

**REFERENCES:**


**DATE OF PREPARATION:** October 2016

**DATE CLINICAL AND POST-MARKETING SURVEILLANCE DATA, PLEASE ALWAYS REFER TO THE LATEST SPC, WHICH IS AVAILABLE FROM GSK (MALTA) LIMITED (TEL: 21238131)