National Institute for Health Research

NIHR Innovation Observatory
Evidence Briefing: August 2017

Nivolumab (Opdivo) + Ipilimumab (Yervoy) for metastatic colorectal cancer patients with deficient DNA mismatch repair mechanism (dMMR) or high microsatellite instability (MSI-H)

NIHRIO (HSRIC) ID: 12638 NICE ID: 9658

LAY SUMMARY

Nivolumab and ipilimumab is a combination therapy to treat cancer of the large bowel (colon) or back passage (rectum) – these types of cancers (bowel and colon) are also known as colorectal cancer. Metastatic colorectal cancer occurs when the cancer has spread to another part of the body; this is most commonly to the liver. A small proportion of colorectal cancer cases develop due to deficiencies in a repair mechanism for DNA; this may contribute to an increase in potential faulty (mutated) DNA. A high rate of mutation is known as high microsatellite instability. These subsets of patients may have poorer outcomes which are worse than those observed in the overall metastatic colorectal cancer population.

The combination therapy of nivolumab and ipilimumab is currently being evaluated in phase II clinical trials. Treatment is administered via a drip directly into the bloodstream and works by altering the body's immune response to the cancer. It is being developed to improve patient survival, and some studies suggest that the combination of these two drugs may offer a new treatment option for patients with advanced dMMR/MSI-H metastatic colorectal cancer that has returned or spread to another part of the body.

TARGET GROUP

Metastatic colorectal cancer for patients with deficient DNA mismatch repair mechanism (dMMR) or high microsatellite instability (MSI-H).

TECHNOLOGY

DESCRIPTION

Nivolumab [BMS-936558; MDX-1106; Opdivo] is a fully-human IgG4 monoclonal antibody which targets and blocks the PD-1 (programmed death-1) receptor on the surface of T-cells. This action triggers a T-cell mediated immune response against cancer cells. Nivolumab is administered by intravenous (IV) infusion at 3mg/kg over 60 minutes every 2 weeks for its currently licensed indications. Ipilimumab [BMS-734016; MDX-101; Yervoy] is a recombinant human IgG1 monoclonal antibody directed against the human T-cell receptor cytotoxic T-lymphocyte-associated antigen 4 (CTLA4), with immune checkpoint inhibitory and antineoplastic activities. Ipilimumab is administered intravenously at 3 mg/kg over 90 minutes every 3 weeks.[1,2,3,4,5]

Nivolumab has been approved/licensed for use in the EU for the following indications:[5]

- First and second line locally advanced unresectable or metastatic melanoma (*monotherapy or in combination with ipilimumab*) in adults
- Locally advanced or metastatic (squamous and non-squamous) non-small cell lung cancer (*monotherapy*) after prior chemotherapy in adults
- Advanced renal cell carcinoma after prior therapy in adults (*monotherapy*)
- Relapsed or refractory classical Hodgkin's lymphoma after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin (*monotherapy*)
- Squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy (*monotherapy*)
- Locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy (*monotherapy*)

Ipilimumab has been approved/licensed for use in the EU for the following indication:[4]

- Treatment of advanced (unresectable or metastatic) melanoma in adults

Recognised very common adverse events ($\geq$1/10 frequency) of nivolumab in combination with ipilimumab include: hypothyroidism, decreased appetite, headache, colitis, diarrhoea, vomiting, nausea, abdominal pain, rash, pruritus, arthralgia, fatigue, and pyrexia, lymphopaenia, leucopoenia, neutropaenia, thrombocytopaenia, anaemia, hypocalcaemia, hyperkalaemia, hypokalaemia, hypomagnesaemia, hyponatraemia; and an increase in: AST, ALT, total bilirubin, alkaline phosphatase, lipase, amylase, creatinine.[5]

Nivolumab + ipilimumab is currently in phase II clinical trial (CheckMate-142 study; NTC02060188) for the treatment of recurrent and metastatic MSI-H and non-MSI-H colon cancer.

Additionally nivolumab + ipilimumab is currently in phase III trials for the following indications:

- Non-small cell lung cancer
- Previously untreated, unresectable or metastatic melanoma; advanced melanoma; advanced melanoma following resection; melanoma brain metastases
- Small cell lung cancer

- Renal cell carcinoma
- Gioblastoma
- Esophageal cancer
- Stomach cancer
- Mesothelioma
- Urothelial cancer
- Head and neck cancer

INNOVATION and/or ADVANTAGES

If licensed, nivolumab + ipilimumab will offer an additional treatment option for patients with deficient DNA mismatch repair mechanism or high microsatellite instability metastatic colorectal cancer.

DEVELOPER

Bristol-Myers Squibb

AVAILABILITY, LAUNCH or MARKETING

Nivolumab was designated priority review status by the FDA for mismatch repair deficient or microsatellite instability high metastatic colorectal cancer after prior fluoropyrimidine-, oxaliplatin- and irinotecan- based chemotherapy in April 2017. It was subsequently granted accelerated FDA approval for for the treatment of adult and paediatric patients 12 years and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan in July 2017.[6]

PATIENT GROUP

BACKGROUND

Colorectal cancer is a malignant tumour arising from the lining of the large intestine (colon and rectum); almost two-thirds (62%) of all bowel cancers arise from the colon and nearly one-third (29%) arise from the rectum (including the anus).[7] There are a number of different histological types of colorectal cancer including: adenocarcinoma, squamous cell carcinoma, carcinoid tumour, sarcoma, and lymphoma.[8]

Symptoms of colorectal cancer may include: bleeding from the rectum or blood in the stools, a change in normal bowel habits, a lump in the rectum or abdomen, weight loss, pain in the abdomen or rectum, and anaemia.[9] Sometimes a tumour may obstruct the bowel, which can result in symptoms including abdominal pains, feeling bloated, constipation, and vomiting.[10] Individuals with colorectal cancer may exhibit a number of disease related symptoms such as weight loss, fatigue, and appetite loss with research suggesting that such symptoms may predict shortened survival.[11]

The cause of colorectal cancer in most people remains unknown, although lifestyle-related factors such as physical inactivity, obesity, smoking and high alcohol intake are believed to increase risk.[12,13] A diet high in fibre and low in saturated fat may reduce risk, whilst a diet high in red or processed

meats may increase risk.[9,11] Family history, age (over 65 years), and inherited conditions or related bowel conditions may greatly increase an individual's risk of colorectal cancer.[9,11]

Up to one in five colorectal cancers show high-level microsatellite instability (MSI-H). Microsatellites are short repetitive segments of DNA sequences, which are prone to mismatch during replication. Microsatellite instability arises from germline (inherited – Lynch Syndrome) or somatic (sporadic; acquired) mutations. DNA mismatch errors are normally repaired by mismatch repair protein complexes. Functional loss of the mismatch repair system results in accumulation of DNA errors, a condition of genetic hypermutability, i.e. microsatellite instability (MSI). Patients with MSI-H colorectal cancers have better prognosis at early stages of disease than those with microsatellite stable (MSS) or low-level microsatellite instability (MSI-L) colorectal cancer.[14,15] However accumulating evidence suggests that once with metastatic disease, dMMR/MSI-H patients experience outcomes which are worse than that of the overall metastatic CRC population with proficient DNA mismatch repair mechanism (pMMR) since they respond poorly to current chemotherapies.[16,17]

CLINICAL NEED and BURDEN OF DISEASE

Bowel cancer is the fourth most common cancer in the UK (2014), accounting for 11% of all new cases. It is the third most common cancer in both males (12% of the male total) and females (10%) separately. In 2014, there were 41,265 new cases of bowel cancer in the UK: 22,844 (55%) in males and 18,421 (45%) in females, giving a male:female ratio of 12:10. The crude incidence rate shows that there are 72 new bowel cancer cases for every 100,000 males in the UK and 56 for every 100,000 females.[18]

In metastatic colorectal cancer the tumour has spread beyond the confines of the bowel and locoregional lymph nodes to other parts of the body. Between 20-55% of people presenting with colorectal cancer have metastatic disease at diagnosis, and an estimated 50-60% of patients who have undergone surgery for early stage colorectal cancer will eventually develop metastatic disease, most commonly in the liver.[19] Approximately 55% of patients will progress to metastatic disease following first line treatment[19] (comprising around 15% of early stage CRC cases[15,20]) but only around 4% (3.5%-5.0%) of patients with metastatic disease (equal to approximately 930 patients in the UK).[21,17,22] Due to lack of dMMR/MSI-H specific treatments these patients are currently treated as the overall pMMR population despite evidence of poor response to these therapies.[16,17,22,23,24] According to NICE clinical pathway treatment options currently include FOLFOR or FOLFIRI combination with cetuximab or panutimumab as first line (subject to *EGFR* and *RAS* mutation status), followed by FOLFIRI or FOLFOX as second line whereas subsequent lines of therapy include trifluridine/tipiracil or best supportive care.[27]

Approximately 59% of patients diagnosed with bowel cancer in England and Wales survive the disease for five years of more, while ~57% survive their disease for ten years or more; however, large differences in duration of survival exist according to the stage of disease at diagnosis.[7,19]

Hospital Episode Statistics for England for 2015 to 2016 indicate that malignant neoplasms of the colon and rectum (ICD C18-C21) accounted for a combined 174,118 finished consultant episodes (FCE), 157,739 admissions and 385,813 FCE bed days.[25]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Pembrolizumab for previously treated metastatic colorectal cancer that has high microsatellite instability or mismatch repair deficiency [ID1071]. Expected date of issue to be confirmed.
- NICE technology appraisal. Nivolumab for previously treated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency [ID1136]. Expected April 2018.
- NICE technology appraisal. Cetuximab and panitumumab for previously untreated metastatic colorectal cancer (TA439). March 2017.
- NICE technology appraisal. Trifluridine–tipiracil for previously treated metastatic colorectal cancer (TA405). August 2016.
- NICE technology appraisal. Nivolumab in combination with ipilimumab for treating advanced melanoma (TA400). July 2016.
- NICE technology appraisal. Aflibercept in combination with irinotecan and fluorouracil-based therapy for treating metastatic colorectal cancer that has progressed following prior oxaliplatin-based chemotherapy (TA307). March 2014.
- NICE technology appraisal. Cetuximab, bevacizumab and panitumumab for the treatment of metastatic colorectal cancer after first-line chemotherapy: Cetuximab (monotherapy or combination chemotherapy), bevacizumab (in combination with non-oxaliplatin chemotherapy) and panitumumab (monotherapy) for the treatment of metastatic colorectal cancer after first-line chemotherapy (TA242). January 2012.
- NICE technology appraisal. Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer (TA118). January 2012.
- NICE technology appraisal. Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the treatment of metastatic colorectal cancer (TA212). December 2010.
- NICE clinical guideline. Colorectal cancer: diagnosis and management (update, CG131). Expected October 2019.
- NICE clinical guideline. Colorectal cancer: diagnosis and management (CG131). August 2016.
- NICE quality standard. Colorectal cancer (QS20). August 2012.
- NICE diagnostics guidance. Molecular testing strategies for Lynch syndrome in people with colorectal cancer (DG27). February 2017.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. National Cancer Drugs Fund list. V1.31. 15 June 2017.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Children, Teenagers and Young Adults). B12/S/b.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.
- NHS England. 2013/14 NHS Standard Contract for Colorectal: Distal Sacrectomy (Adult). A08/S/b.
- NHS England. 2013/14 NHS Standard Contract for Colorectal: Transanal Endoscopic Microsurgery (TEMS) (Adult). A08/S/e.
- NHS England. 2013/14 NHS Standard Contract for Colorectal: Cytoreductive Surgery (Adult). A08/S/f.

CURRENT TREATMENT OPTIONS

The management of metastatic colorectal cancer is largely palliative, combining specialist treatments (palliative surgery, chemotherapy and radiation) with control of symptoms and psychosocial support.[19] The majority of patients with metastases have disease that is initially not suitable for potentially curative resection; therefore the aim of treatment is to convert initially unresectable disease to resectable disease with combination chemotherapy.[26] Treatment may include:

Chemotherapy[26,27,28]

- FOLFOX (folinic acid, 5-fluorouracil and oxaliplatin) as first or second line treatment
- XELOX (capecitabine and oxaliplatin) as first line or second line treatment
- Irinotecan as second line treatment
- FOLFIRI (folinic acid, 5-fluorouracil and irinotecan) as first or second line treatment
- Raltitrexed – for patients who are intolerant to folinic acid, 5-fluorouracil, or for whom these drugs are not suitable
- Trifluridine/tipiracil

Biological agents[27]

According to current NICE guidance:

- Cetuximab is recommended, within its marketing authorisation, as an option for previously untreated EGFR-expressing, RAS wild-type metastatic colorectal cancer in adults in combination with FOLFOX or FOLFIRI
- Panitumumab is recommended, within its marketing authorisation, as an option for previously untreated RAS wild-type metastatic colorectal cancer in adults in combination with FOLFOX or FOLFIRI

Other licensed biologics include bevacizumab and aflibercept.[29,30]

EFFICACY and SAFETY

Trial	Checkmate 142, NCT02060188; adults or seniors eighteen years or older; phase II
Sponsor	Bristol-Myers Squibb
Status	Ongoing
Source of Information	Trial Registry[31], Press release[32]
Location	EU (excluding UK), USA, Canada and other countries
Design	Non-randomized, parallel assignment, no masking
Participants	n = 340 (estimated); aged 18 years or older; ECOG performance status 0 to 1; histologically confirmed recurrent or metastatic colorectal cancer; measurable disease by CT or MRI; testing for MSI status (by an accredited lab)
Schedule	• Nivo 3mg/kg IV every 2 wks until disease progression (informs ongoing ID1136); or • Nivo 3mg/kg IV with Ipi 1 mg/kg IV every 3 wks for 4 doses followed by Nivo 3mg/kg IV every 2wk until progression; or • Nivo IV dosed every 2wk with Ipi IV dosed every 6wk; or Nivo IV dosed every 2wk, with Ipi IV dosed every 6wk, combined with cobimetinib dosed orally once daily 21 days on/7 days off; or • Nivo IV dosed every 2wk with BMS-986016 dosed every 2 wk; or

	• Daratumumab IV dosed weekly for week 1-8; then every 2 wks from Week 9-24; then every 4 wks on week 25; with Nivo dosed every 2 wks starting at week 3 and every 4 wks starting at week 25
Follow-up	-
Primary Outcomes	Objective response rate (ORR) in all MSI-High and non-MSI-High subjects as determined by Investigators (approximately up to 34 months)
Secondary Outcomes	• ORR in all MSI-H and non-MSI-H subjects based on IRRC determination (approximately up to 34 months) • Progression free survival • Overall survival • Health related quality of life • Adverse events
Key Results	• investigator-assessed ORR was 25.5% (95% CI: 15.4-38.1) for nivolumab monotherapy and 33.3% (95% CI: 18.6-50.9) for the nivolumab and ipilimumab combination regimen • six-month progression-free survival (PFS) rates were 45.9% (95% CI: 29.8-60.7) for nivolumab monotherapy and 66.6% (95% CI: 45.5-81.1) for the nivolumab and ipilimumab combination
Adverse effects (AEs)	Safety profile of nivolumab alone or in combination with Ipilimumab was consistent with other tumour types and prior combination studies
Expected reporting date	Study Completion Date: December 2019

ESTIMATED COST and IMPACT

COST

Nivolumab is already marketed in the UK; the list price of nivolumab is £439 per 4 ml (40 mg) vial and £1,097 per 10 ml (100 mg) vial.[33]

Ipilimumab is already marketed in the UK; the list price of ipilimumab is £3,750 per 10 ml (50 mg) vial and £15,000 per 40 ml (200 mg).[34]

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☒ Increased use of existing services

☐ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other reduction in costs

☒ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

INFORMATION FROM

Bristol-Myers Squibb

UK PharmaScan ID number 645697

REFERENCES

[1] Cancer Research UK. *Nivolumab (Opdivo)*. 2015. Available from: http://www.cancerresearchuk.org/about-cancer/cancers-in-general/treatment/cancer-drugs/nivolumab [Accessed 07 August 2017]

[2] National Cancer Institute. *Nivolumab*. NCI dictionary. 2017. Available from: https://www.cancer.gov/publications/dictionaries/cancer-drug?CdrID=539733 [Accessed 07 August 2017]

[3] National Cancer Institute. *Ipilimumab*. NCI dictionary. 2017. Available from: https://www.cancer.gov/publications/dictionaries/cancer-drug?cdrid=38447 [Accessed 07 August 2017]

[4] European Medicines Agency. *Ipilimumab – Summary of Product Characteristics*. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002213/WC500109299.pdf [Accessed 07 August 2017]

[5] EMC. *Opdivo 10mg/ml concentrate for solution for infusion*. 2017. Available from: https://www.medicines.org.uk/emc/medicine/30476 [Accessed 07 August 2017]

[6] US Food & Drug Administration. *FDA grants nivolumab accelerated approval for MSI-H or dMMR colorectal cancer*. 2017. Available from: https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm569366.htm [Accessed 17 August 2017]

[7] Cancer Research UK. *Bowel cancer statistics*. 2017. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bowel-cancer [Accessed 07 August 2017]

[8] Cancer Research UK. *Types of bowel cancer*. 2017. Available from: www.cancerresearchuk.org/about-cancer/type/bowel-cancer/about/types-of-bowel-cancer [Accessed 07 August 2017]

[9] Cancer Research UK. *Bowel cancer symptoms*. 2017. Available from: www.cancerresearchuk.org/about-cancer/type/bowel-cancer/about/bowel-cancer-symptoms [Accessed 07 August 2017]
[10] National Health Service. *Bowel cancer – Symptoms*. 2017. Available from: http://www.nhs.uk/Conditions/Cancer-of-the-colon-rectum-or-bowel/Pages/Symptoms.aspx [Accessed 17 August 2017]
[11] Quinten C, Coens C, Mauer M *et al*. *Baseline quality of life as a prognostic indicator of survival: a meta-analysis of individual patient data from EORTC clinical trials*. The Lancet Oncology 2009;10(9):865-71.
[12] Macmillan Cancer Support. *Age, lifestyle, diet and other conditions – Diagnosing cancer*. 2014. Available from: http://www.macmillan.org.uk/information-and-support/bowel-cancer/colon/diagnosing/causes-and-risk-factors [Accessed 07 August 2017]
[13] Haggar F and Boushey R. *Colorectal cancer epidemiology: incidence, mortality, survival, and risk factors*. Clinics in Colon and Rectal Surgery 2009;22(4):191.
[14] Wang M, Kanehira K and Chen F. Screening for microsatellite instability in colorectal cancer and Lynch syndrome – a mini review. North American Journal of Medicine and Science 2016;9(1):5-11.
[15] Boland, C.R. and A. Goel, *Microsatellite instability in colorectal cancer.* Gastroenterology, 2010. 138(6): p. 2073-2087 e3.
[16] Sinicrope FA, Yang ZJ. Prognostic and predictive impact of DNA mismatch repair in the management of colorectal cancer. Future Oncology. 2011;7(3):467-74.
[17] Koopman M, Kortman GA, Mekenkamp L, et al. Deficient mismatch repair system in patients with sporadic advanced colorectal cancer. Br J Cancer. 2009;100(2):266-73.
[18] Cancer Research UK. *Bowel cancer incidence statistics*. 2017. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bowel-cancer/incidence [Accessed 07 August 2017]
[19] National Institute for Health and Clinical Excellence. *Cetuximab, bevacizumab and panitumumab for the treatment of metastatic colorectal cancer after first-line chemotherapy: Cetuximab (monotherapy or combination chemotherapy), bevacizumab (in combination with non-oxaliplatin chemotherapy) and panitumumab (monotherapy) for the treatment of metastatic colorectal cancer after first-line chemotherapy*. Technology appraisal TA242. London: NICE; January 2012
[20] Xiao, Y. and G.J. Freeman, *The microsatellite instable subset of colorectal cancer is a particularly good candidate for checkpoint blockade immunotherapy.* Cancer Discov, 2015. 5(1): p. 16-8
[21] Fujiyoshi, K., et al., *Metastatic Pattern of Stage IV Colorectal Cancer with High-Frequency Microsatellite Instability as a Prognostic Factor.* Anticancer Res, 2017. 37(1): p. 239-247.
[22] Venderbosch, S., et al., *Mismatch repair status and BRAF mutation status in metastatic colorectal cancer patients: a pooled analysis of the CAIRO, CAIRO2, COIN, and FOCUS studies.* Clin Cancer Res, 2014. 20(20): p. 5322-30.
[23] Goldstein J, Tran B, Ensor J, et al. Multicenter retrospective analysis of metastatic colorectal cancer (CRC) with high-level microsatellite instability (MSI-H). Ann Oncol. 2014;25(5):1032-8.
[24] Tran B, Kopetz S, Tie J, et al. Impact of BRAF mutation and microsatellite instability on the pattern of metastatic spread and prognosis in metastatic colorectal cancer. Cancer. 2011;117(20):4623-32.
[25] National Health Services Digital. *Hospital Episode Statistics for England. Admitted Patient Care statistics, 2015-16*. Available from http://www.content.digital.nhs.uk/catalogue/PUB22378 [Accessed 07 August 2017]
[26] Van Cutsem E, Cervantes A, Nordlinger B *et al. Metastatic colorectal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up*. Annals of Oncology 2014;25(3):1-9.
[27] National Institute for Health and Clinical Excellence. *Managing advanced and metastatic colorectal cancer*. NICE Pathways. 2017. Available from: https://pathways.nice.org.uk/pathways/colorectal-cancer#content=view-node%3Anodes-chemotherapy&path=view%3A/pathways/colorectal-cancer/managing-advanced-and-metastatic-colorectal-cancer.xml [Accessed 07 August 2017]
[28] National Institute for Health and Clinical Excellence. *Trifluridine–tipiracil for previously treated metastatic colorectal cancer*. Technology appraisal TA405. London: NICE; August 2016.
[29] European Medicines Agency. *Avastin.* 2017. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000582/human_med_000663.jsp&mid=WC0b01ac058001d124 [Accessed 07 August 2017]
[30]European Medicines Agency. *Zaltrap.* 2017. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002532/human_med_001617.jsp&mid=WC0b01ac058001d124 [Accessed 07 August 2017]

[31] ClinicalTrials.gov. *An Investigational Immuno-therapy Study of Nivolumab, and Nivolumab in Combination With Other Anti-cancer Drugs, in Colon Cancer That Has Come Back or Has Spread (CheckMate142).* Available from: https://clinicaltrials.gov/ct2/show/NCT02060188 [Accessed 07 August 2017]
[32] Bristol-Myers Squibb. Media release. *First Presentation of Phase 2 CheckMate -142 Study Evaluating Opdivo® (nivolumab) Alone or in Combination with Yervoy® (ipilimumab) Demonstrates Encouraging Clinical Activity in MSI-High Metastatic Colorectal Cancer*. Available from: https://news.bms.com/press-release/asco2016/first-presentation-phase-2-checkmate-142-study-evaluating-opdivo-nivolumab-al [Accessed 07 August 2017]
[33] British National Formulary – Medicines Complete. *Nivolumab*. 2017. Available from https://www.medicinescomplete.com/mc/bnf/current/PHP202754-nivolumab.htm [Accessed 07 August 2017]
[34] British National Formulary – Medicines Complete. *Ipilimumab*. 2017. Available from: https://www.medicinescomplete.com/mc/bnf/current/PHP5475-ipilimumab.htm [Accessed 07 August 2017]