APPENDIX

Sunitinib

In January 2007, the phase III clinical trial by Motzer et al. demonstrated improved quality of life (QOL), response rate, and progression free survival (PFS) with sunitinib over interferon-alpha for patients with mRCC.[4] Based on earlier phase data, sunitinib was approved by Health Canada ahead of the final phase III trial publication in August 2006, for patients with mRCC of clear cell histology who had failed prior cytokine therapy or were considered likely to be intolerant of cytokines. Similarly it was approved by the United States Food and Drug Administration (FDA) in January 2006, by the European Medicines Agency (EMA) in July 2006, and the Australian Therapeutic Goods Administration (TGA) in September 2006.

In the 2006 decision, sunitinib was approved by Health Canada for use after cytokine failure, but the study population received first line sunitinib. The CADTH report published April 2007 recommended that sunitinib not be publicly funded in Canada due to a combination of cost factors and lack of evidence for the specific patient population for which the drug was approved. Despite this recommendation, sunitinib was adopted for funding in many provinces soon after the phase III clinical trial publication. Of the available dates, British Columbia (BC) was the first province to adopt funding in July 2007. PEI was the last to adopt funding in February 2009. Health Canada later approved sunitinib for first line use in May 2008. Currently sunitinib is publicly available in all provinces and territories across Canada for patients meeting specific criteria. There was a 19 month lag in funding from the first province to offer the drug to the last.

Sorafenib

The phase III clinical trial by Escudier et al. demonstrating improved PFS with sorafenib vs. placebo in patients with mRCC after failing first line systemic therapy was published in January 2007.[5] Sorafenib was approved by Health Canada in July 2006, prior to final publication of the phase III trial data, for patients who failed or were intolerant of previous systemic therapy. Sorafenib was approved by the FDA in December 2005, by the EMA in July 2006, and the TGA in September 2006.

The CADTH report published February 2007 recommended that sorafenib not be publicly funded in Canada due to a lack of cost effectiveness.[6] However sorafenib was ultimately approved for funding in many provinces soon after the phase III clinical trial publication. BC was the first province to approve funding for sorafenib in July 2007. Alberta was the last to adopt funding in October 2009. Use of sorafenib has decreased over time given the availability of more effective options, and some funding decisions have since been reversed. Sorafenib is currently unfunded in Alberta, Saskatchewan, Manitoba, Quebec and the Yukon.

Temsirolimus

The phase III ARCC trial published in May 2007 showed improved PFS and overall survival (OS) with temsirolimus compared to interferon in patients with poorer-risk mRCC, and combination therapy with both agents did not provide any additional benefit.[7] Temsirolimus was

approved by Health Canada in December 2007 as first line therapy for patients with mRCC. It was similarly approved by the FDA in May 2007, EMA in November 2007 and TGA in June 2008.

There is no CADTH review of temsirolimus available on record. Temsirolimus is funded in most Canadian provinces. Of the available dates, BC was the earliest to adopt funding in November 2008, and Quebec the last in February 2012, representing a funding lag of 40 months. It is not publicly funded in PEI. However, due to availability of more effective options, temsirolimus is now rarely prescribed.

Everolimus

The phase III RECORD-1 trial published in July 2008 showed improved PFS with everolimus versus placebo in patients with mRCC who had failed previous sunitinib or sorafenib.[8] Non-inferiority was later rejected in the first line setting compared to sunitinib after the RECORD-3 trial. Health Canada approved everolimus in December 2009 as a second-line therapy for patients with mRCC. The drug was approved by the FDA in March 2009, EMA in August 2009, and TGA in July 2009.

There is no CADTH review of everolimus for mRCC available, but it is publicly funded in most Canadian provinces, with BC, Ontario and Alberta all announcing positive funding decisions in February 2011. The drug is not publicly available in PEI. There was an 11 month lag in the provinces ultimately approving reimbursement. Everolimus has also become less frequently prescribed due to the availability of more effective options, such as nivolumab which demonstrated superiority over everolimus in the CHECKMATE 025 study.

Pazopanib

The phase III clinical trial demonstrating improved PFS with pazopanib vs. placebo in both cytokine naive and refractory patients was published in February 2010.[9] Additionally, the 2013 Comparz clinic trial showed that PFS with pazopanib was non inferior to sunitinib as first line therapy in mRCC.[10] Health Canada approved pazopanib for use in patients with mRCC clear cell histology after cytokine failure in May 2010, and then as first line systemic therapy in July 2013.[11] It was approved by the FDA in October 2009, and both the EMA and TGA in June 2010.

CADTH issued a recommendation for public funding January 2012. Pazopanib is publicly funded in all provinces and territories across Canada for patients with mRCC meeting criteria. BC was the first province to offer funding in September 2011 before the final CADTH recommendation was published. Manitoba was the last province in July 2013, representing a funding lag of 22 months.

Axitinib

The AXIS phase III clinical trial published November 2011 showed improved PFS with axitinib compared to sorafenib in the second line setting.[12] Axitinib was approved by Health Canada in July 2012 for patients with clear cell mRCC second line after failing previous cytokine or TKI

therapy.[13] The drug was approved by the FDA in January 2012, EMA in September 2012, and TGA in July 2012.

CADTH issued an initial recommendation for funding in January 2013, with a final followup report in March 2013. Monotherapy with axitinib is publicly funded in all Canadian provinces, data is not available for the territories. Ontario and Saskatchewan were first to offer funding in December 2013 and PEI was the last in August 2018, representing a funding lag of 57 months.

Nivolumab

Nivolumab is the first immunotherapy checkpoint inhibitor to be used for mRCC. The pivotal November 2015 CHECKMATE 025 trial demonstrated superior response rates and OS with nivolumab compared to everolimus in the second or third line setting regardless of prognosis or previous therapies.[14] Improved QOL and less toxicity was also experienced in the nivolumab group. Health Canada approved nivolumab monotherapy in April 2016 for patients who had received prior anti-angiogenic therapy. It was approved by the FDA in November 2015 and EMA in February 2016, and TGA in August 2017.

CADTH issued its recommendation for funding in September 2016. Nivolumab monotherapy is now funded in all Canadian provinces and territories, with BC, Saskatchewan, Manitoba, Ontario and Quebec all announcing funding in March 2017. PEI was the last province in August 2018, representing a 17 funding lag.

Ipilimumab plus nivolumab

The CheckMate 214 phase 3 clinical trial, published in April 2018, showed improved OS and objective response rate with ipilimumab plus nivolumab compared to sunitinib in the first line setting for patients with intermediate or poor risk metastatic and advanced RCC.[15] Health Canada published a notice of compliance approving ipilimumab in combination with nivolumab in patients with mRCC and poor/intermediate performance status in December 2018. It was approved by the FDA in April 2018, EMA in November 2018, and TGA in September 2018.

pCODR published a pre-NOC recommendation for funding in November 2018. British Columbia, Ontario, and Quebec began publicly funding this regimen in May 2019; Saskatchewan, Manitoba and New Brunswick implemented funding in June 2019; and Alberta, Nova Scotia and Newfoundland in July 2019.[16-18] PEI was the last to approve funding, date of approval unclear.[19]

Cabozantinib

Health Canada approved cabozantinib in September 2018 based on results from the phase III METEOR trial which randomized previously treated patients to cabozantinib vs. everolimus.[20] pCODR recommended reimbursement in February 2019 if cost-effectiveness was improved to an acceptable level. It is currently funded in all Canadian provinces. There was a two year lag in funding decisions, with the earliest province to reimburse cabozantinib being Quebec in December 2019, and last being PEI in December 2021.[21-23]

Lenvatinib plus everolimus

Lenvatinib was approved by Health Canada in September 2017 for use as a second line agent in combination with everolimus, based on the results of a phase II open-label trial.[24] It was approved by the FDA in May 2016 and EMA in August 2016. Lenvatinib plus everolimus was approved by the TGA but date is unclear. pCODR published its review in January 2019, with a recommendation to not publicly fund lenvatinib given the lack of high quality data to support its benefit. Lenvatinib plus everolimus is not currently funded in any Canadian province.[25]

Pembrolizumab plus axitinib

The KEYNOTE-426 trial published in March 2019 showed significantly improved OS, PFS and higher objective response rate with the combination of pembrolizumab and axitinib in previously untreated patients with advanced RCC compared to sunitinib.[26] Based on this data, it was approved by Health Canada for first line treatment in combination with axitinib in December 2019. It was approved by the FDA in April 2019, EMA in July 2019, and TGA in June 2020.

The regimen was initially conditionally recommended for funding by pCODR in January 2020, and final conditional recommendation in April 2020 if cost effectiveness criteria could be met.[27] Of available dates, Quebec was first to publish a positive funding decision in December 2020, and Newfoundland last in May 2021. This regimen appears to be reimbursed in all provinces except PEI.