Biosimilars in Oncology

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CANCERCARE MANITOBA

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Presenter Disclosure

- Faculty/Speaker: Marc Geirnaert
- Relationships with financial sponsors:
- Grants/Research Support: None
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- Consulting Fees: None
- Other: Employee of CancerCare Manitoba

Mitigating Potential Bias

- Not applicable

Objectives

1. Recall the main differences between generics and biosimilars
2. Review the process of Health Canada's approval of biosimilars
3. Explain the terms: totality of the evidence, extrapolation and switching
4. Inform and counsel patient regarding the rationale for switching to a biosimilar
5. Review the upcoming use of biosimilars in oncology

Biosimilar

- A biosimilar biologic drug, or biosimilar, is a drug demonstrated to be highly similar to a biologic drug that was already authorized for sale (known as the reference biologic drug).
- Biosimilars are approved based on a thorough comparison to a reference drug and may enter the market after the expiry of reference drug patents and data protection.
- Biosimilars are not the same as generic drugs.
- Generic drug are small molecules that are chemically synthesized and contain identical medicinal ingredients to their brand name reference products.
- Due to size, complexity and natural variability of biologic drugs, and because biologic drugs are made in living cells rather than with chemicals, a biosimilar and it reference biologic drugs can be shown to be similar, but not identical.

Health Canada Fact Sheet on Biosimilars: https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/applications-submissions/guidance-documents/fact-sheet-biosimilars.html Accessed September 18th, 2019.

Differences between generics and biosimilars

Property	Biosimilar	Generic
Molecular Composition	High molecular weight, complex biologic agent	Small molecular weight, reproducible structure
Comparison with reference drug	Same amino acid sequence	Identical active ingredient
	May have different posttranslational modifications, protein folding, excipients	Same bioequivalence, purity
Manufacturing	Uses living cellular systems	Chemically synthesized
	Unique cell lines and production steps	Stepwise process of identified reactions

Harvey, D. Science of Biosimilars, Journal of Oncology Practice, Volume 13 (Sept 2017)

Costs of biologics in Canada

Biologics	Annual sales 2016 (in millions)
Trastuzumab	251M
Rituximab	241M
Filgrastim	128M
Bevacizumab	104M

Langu, E. and Warwick, G. Potential Savings from Biosimilars in Canada. PMPRB presentation In CADTH symposium 2017. Accessed online: https://www.cadth.ca/sites/default/files/symp-2017/presentations/april24-2017/Concurrent-Session-B4-Gary-Warwick.pdf (September 15th, 2019)

Health Canada Guidance

- Health Canada provides guidance to manufacturers in order for them to satisfy the information and regulatory requirements under the Food and Drugs Act for the authorization of biosimilars in Canada.

Guidance o Document: Informatin and Submission Requirements for Biosiilar biologic Drugs
https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/applications-submissions/guidance-documents/information-submission-requirements-biosimilar-biologic-drugs-1.html

Health Canada Approvals

- To obtain authorization as a biosimilar, the drug manufacturer must provide information to Health Canada to show that the biosimilar and the reference biologic drug are similar and there are no clinically meaningful differences in terms of safety and efficacy between them.
- Health Canada's decision to authorize a biosimilar for sale is based upon a benefit/risk assessment after considering all of the data submitted by the manufacturer.
- Health Canada's **rigorous standards** for authorization mean that patients and health care providers can rely upon the **quality**, **safety** and **efficacy** of a biosimilar, just as for any biologic drug.

Guidance o Document: Informatin and Submission Requirements for Biosiilar biologic Drugs
https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/applications-submissions/guidance-documents/information-submission-requirements-biosimilar-biologic-drugs-1.html

What is required to be submitted?

- Non-clinical evidence (pharmacokinetics, pharmacodynamics)
- Clinical – phase 3 trial comparing biosimilar to reference product in tumor type that reference product has been used.
- Safety
- Immunogenicity

Case example: Bevacizumab (Mvasi)

- Bevacizumab (Mvasi) approved by Health Canada in April 2018
- Bevacizumab (Mvasi) first oncology biosimilar to be authorized for sale in Canada and available on Canadian market since August 2019
- I will review how Health Canada reviewed and approved bevacizumab (Mvasi)

Pharmacokinetics

- Healthy men
- Age 18 to 45
- BMI equal to or greater than 18 and less than 30
- Excluded if they had hypertension or history of hypertension requiring medication

Markus R, Chow V, et al. *Cancer Chemother Pharmacol* 2017; 80:755-63

Pharmacokinetics

- Randomized, single-blind, single-dose, 3 arm, parallel group study in healthy male subjects.
- Primary objective of this study was to demonstrate the PK similarity of MVASI® to US reference bevacizumab (Avastin®) and EU reference bevacizumab (Avastin®) by the PK parameters AUC_{inf} and C_{max}.
- 202 patients received a single dose of MVASI® or bevacizumab refence (US or EU) in a ratio of 1:2. (therefore 1:1:1 MVASI® : Avastin® US: Avastin® EU
- Subjects returned periodically for safety evaluations, PK sample collections and anti-drug antibody (ADA) tests until day 85.

Markus R, Chow V, et al. *Cancer Chemother Pharmacol* 2017; 80:755-63.

Pharmacokinetics

- Linear kinetics over dosing range of 1 to 10 mg/kg; therefore single dose of 3 mg/kg considered appropriate and informative across the range of therapeutic doses while minimizing drug exposure in healthy subjects
- Participants given bevacizumab 3 mg/kg over 90 minutes
- Participants had to come to clinic on days 3, 5, 8, 11, 15, 22, 29, 36, 43, 50, 64, 78 and 85 (day 85 was end of study visit)
- Participants evaluated for safety, collection of PK samples and testing of anti-drug antibodies
- Participants also monitored throughout study for adverse events, clinical lab results, concomitant medication use and vital signs.

Markus R, Chow V, et al. *Cancer Chemother Pharmacol* 2017; 80:755-63.

Pharmacokinetics

- Primary objective of study to demonstrate PK bioequivalence determined by comparing AUC_{inf} and C_{max} in subjects treated with biosimilar bevacizumab to those treated with reference bevacizumab (US and EU)
- Secondary objectives: safety, tolerability, immunogenicity in the biosimilar group compared to the reference groups

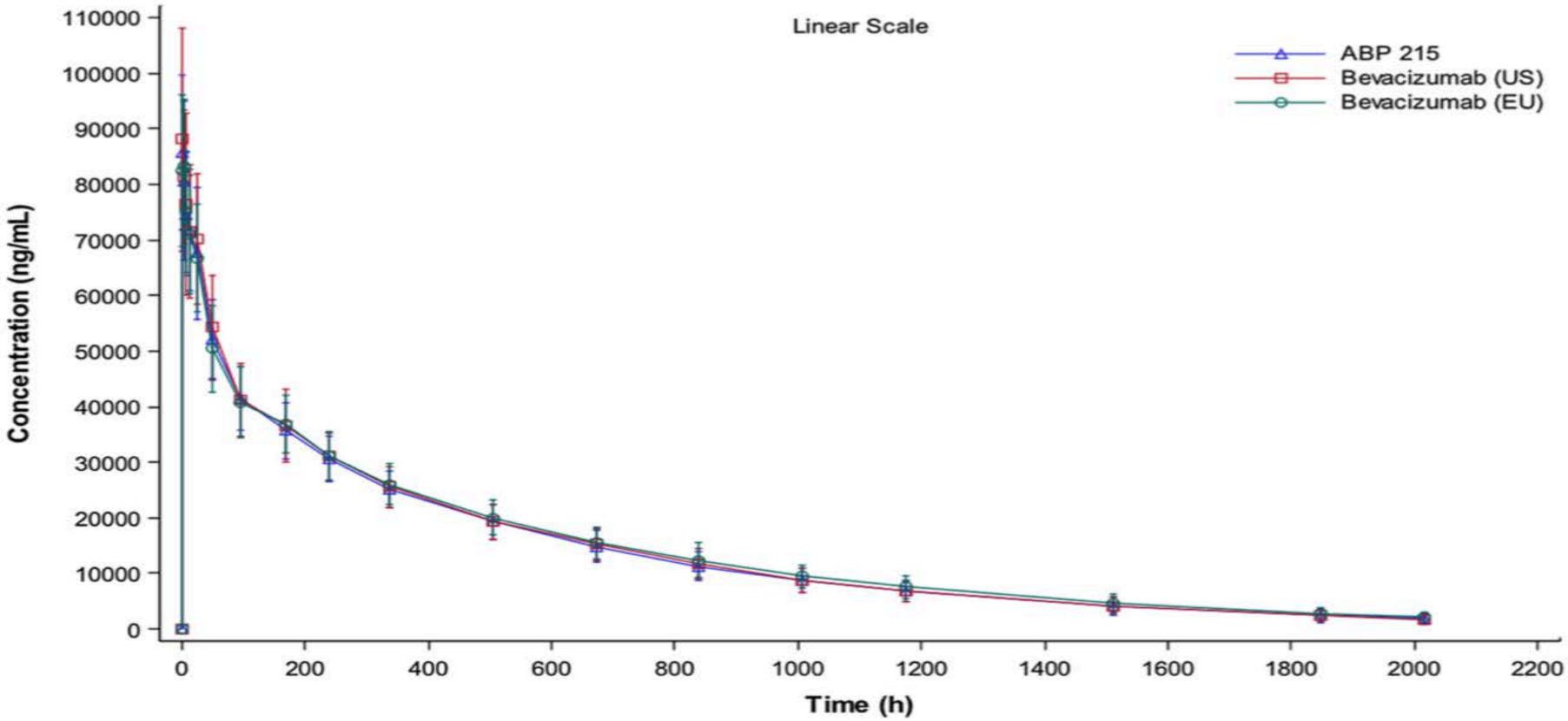
Markus R, Chow V, et al. *Cancer Chemother Pharmacol* 2017; 80:755-63.

Pharmacokinetics

- 202 patients enrolled
- 68 randomized to biosimilar bevacizumab, 67 patients randomized to US Avastin®, and 67 patients randomized to EU Avastin®
- 94.5% of participants completed the study.

Markus R, Chow V, et al. *Cancer Chemother Pharmacol* 2017; 80:755-63.

Pharmacokinetics



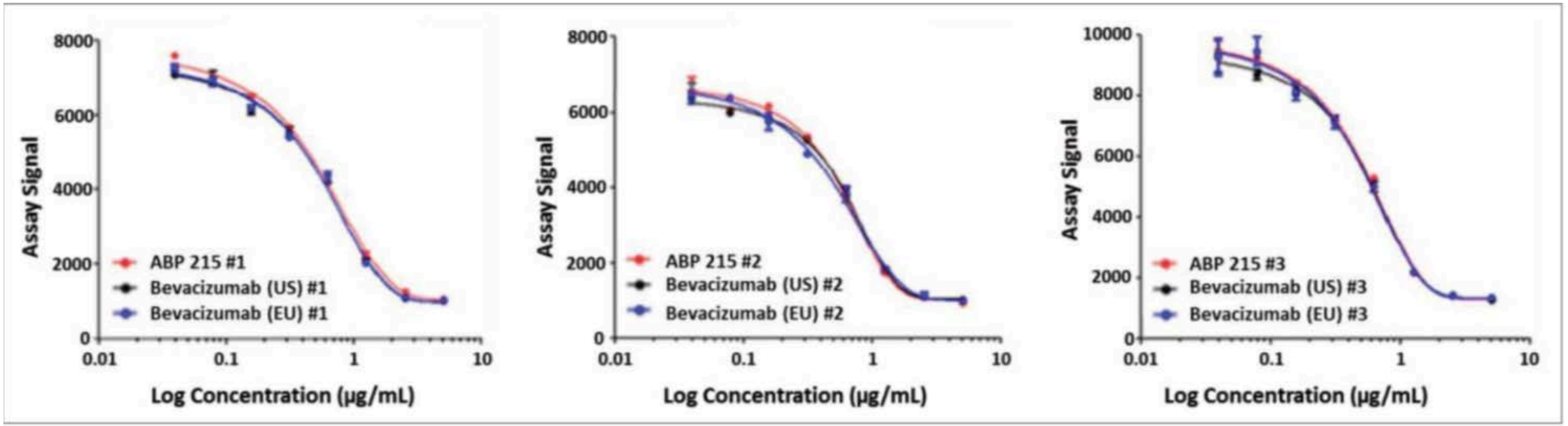
Markus R, Chow V, et al. *Cancer Chemother Pharmacol* 2017; 80:755-63.

Pharmacodynamics

- Bevacizumab binds to vascular endothelial growth factor A (VEGF-A) and prevents the binding of VEGF-A to VEGF receptors on the surface of endothelial cell proliferation and new blood vessel formation.
- Analytical and functional similarity of Amgen biosimilar ABP 215 (MVASI®) to bevacizumab (Avastin®) published in 2018
- The analytical similarity assessment plan was designed to assess structural/physicochemical and functional similarity and ensure understanding of whether any differences between MVASI® and bevaziumab (Avastin®) had the potential to impact clinical performance.

Seo, N, Polozova A, et al. *MABS* 2018; 10(4):678-91

Pharmacodynamics



Seo, N, Polozova A, et al. *MABS* 2018; 10(4):678-91

MAPLE study

- Phase 3 randomized study comparing efficacy, safety, immunogenicity and pharmacokinetic profiles of MVASI® compared to reference bevacizumab (Avastin®) in patients with advanced non-squamous NSCLC – "MAPLE" study
- Randomized, double-blind, active-controlled study in adult patients with non-squamous NSCLC receiving 1st line chemotherapy with CARBOplatin and PACLitaxel.
- Study conducted at 101 study centers in 17 countries in Asia Pacific, Europe, North America and Latin America
- Primary objective compare efficacy of MVASI® to Avastin®
- Secondary objectives: assessment of safety, pharmacokinetics, and immunogenicity of biosimilar bevacizumab compared to Avastin®

Thatcher N, Goldschmidt JH, et al. *Clin Cancer Res* 2019; 25(7):2088- 95

MAPLE study

- 1:1 randomization to receive IV bevacizumab biosimilar:IV bevacizumab reference 15 mg/kg IV every 3 weeks for cycles (in combination with CARBOplatin and PACLitaxel) for 4 to 6 cycles.
- Patients remained on the treatment phase until 21 days after the last dose of IP or study-specified chemotherapy.
- Patients were followed for disease progression and overall survival after completing the end-of-treatment visit until the end of the clinical study, lost to follow-up, withdrawal of consent, lost to follow-up death or receipt of prescribed therapy, including non-study anticancer treatment.

Thatcher N, Goldschmidt JH, et al. *Clin Cancer Res* 2019; 25(7):2088- 95

MAPLE study

- 820 patients screened
- 642 patients randomized as follows: 328 to biosimilar bevacizumab arm and 314 patients to reference Avastin® arm
- 324 patients in biosimilar arm and 309 patients in the reference product arm received at least 1 dose of bevacizumab and were included in safety analysis
- Groups well balanced
- Median time since original diagnosis with NSCLC was 4 weeks in both

Thatcher N, Goldschmidt JH, et al. *Clin Cancer Res* 2019; 25(7):2088- 95

Table 1. Patient demographics and baseline characteristics (ITT population)

	ABP 215 (*N* = 328)	Bevacizumab (*N* = 314)
Age, mean (SD)	61.6 (9.09)	61.6 (8.88)
< 65 years, *n* (%)	199 (60.7)	191 (60.8)
≥ 65 years, *n* (%)	129 (39.3)	123 (39.2)
Weight, mean (SD)	71.2 (14.7)	73.5 (15.3)
Race, *n* (%)		
White	315 (96.0)	300 (95.5)
Black	2 (0.6)	5 (1.6)
Asian	6 (1.8)	7 (2.2)
Other	7 (2.1)	2 (0.6)
Sex		
Male	196 (59.8)	188 (59.9)
Geographic region, (%)		
Eastern Europe	189 (57.6)	186 (59.2)
Western Europe	78 (23.8)	76 (24.2)
North America	31 (9.5)	26 (8.3)
Asia Pacific/	30 (9.1)	26 (8.3)
Other		
Smoking status, *n* (%)		
Never	65 (19.8)	76 (24.2)
Former	163 (49.7)	158 (50.3)
Current	100 (30.5)	80 (25.5)
Staging of original diagnosis, *n* (%)		
≤ Stage IIIA	23 (7.0)	25 (8.3)[a]
Stage IIIB	2 (0.6)	7 (2.2)
Stage IV	303 (92.4)	281 (89.5)
Disease stage at baseline, *n* (%)		
Stage IV	309 (94.2)	290 (92.4)
Recurrent disease	19 (5.8)	24 (7.6)
Weight loss in past 6 months, *n* (%)		
0%–5%	289 (88.1)	276 (87.9)[a]
> 5%–10%	39 (11.9)	37 (11.8)
ECOG performance status, *n* (%)		
Grade 0	127 (38.7)	117 (37.3)
Grade 1	201 (61.3)	197 (62.7)

[a]One patient with missing data.

Thatcher N, Goldschmidt JH, et al. *Clin Cancer Res* 2019; 25(7):2088- 95

MAPLE study

	Biosimilar bevacizumab	Reference bevacizumab
Mean # of doses (SD)	4.8 (1.76)	5 (1.61)
Patients completing 6 doses of bevacizumab	59%	65.4%
# of patients who had at least 1 dose delay	22.2%	22.7%
Doses withheld at least once	1.9%	3.2%
At least 1 dose interruption	0.9%	0%
Mean # of PACLitaxel doses (SD)	4.5 (1.69)	4.7 (1.56)
Mean # of CARBOplatin doses (SD)	4.6 (1.67)	4.7 (1.57)

Thatcher N, Goldschmidt JH, et al. *Clin Cancer Res* 2019; 25(7):2088- 95

MAPLE study

Table 2A. Summary of primary efficacy results (ITT Population)

	ABP 215 (*N* = 328)	Bevacizumab (*N* = 314)
Best overall response, *n* (%)		
Complete response	2 (0.6)	2 (0.6)
Partial response	126 (38.4)	129 (41.1)
Stable disease	144 (43.9)	137 (43.6)
Progressive response	21 (6.4)	18 (5.7)
Not evaluable	35 (10.7)	28 (8.9)
ORR, *n* (%)[a]	128 (39.0)	131 (41.7)
PFS, *n* (%)[b]	197 (60.1)	189 (60.2)
OS, *n* (%)	281 (86.7)	273 (88.3)

[a]On the basis of RECIST v1.1.

[b]Patients who were alive and progression-free at the end of the study.

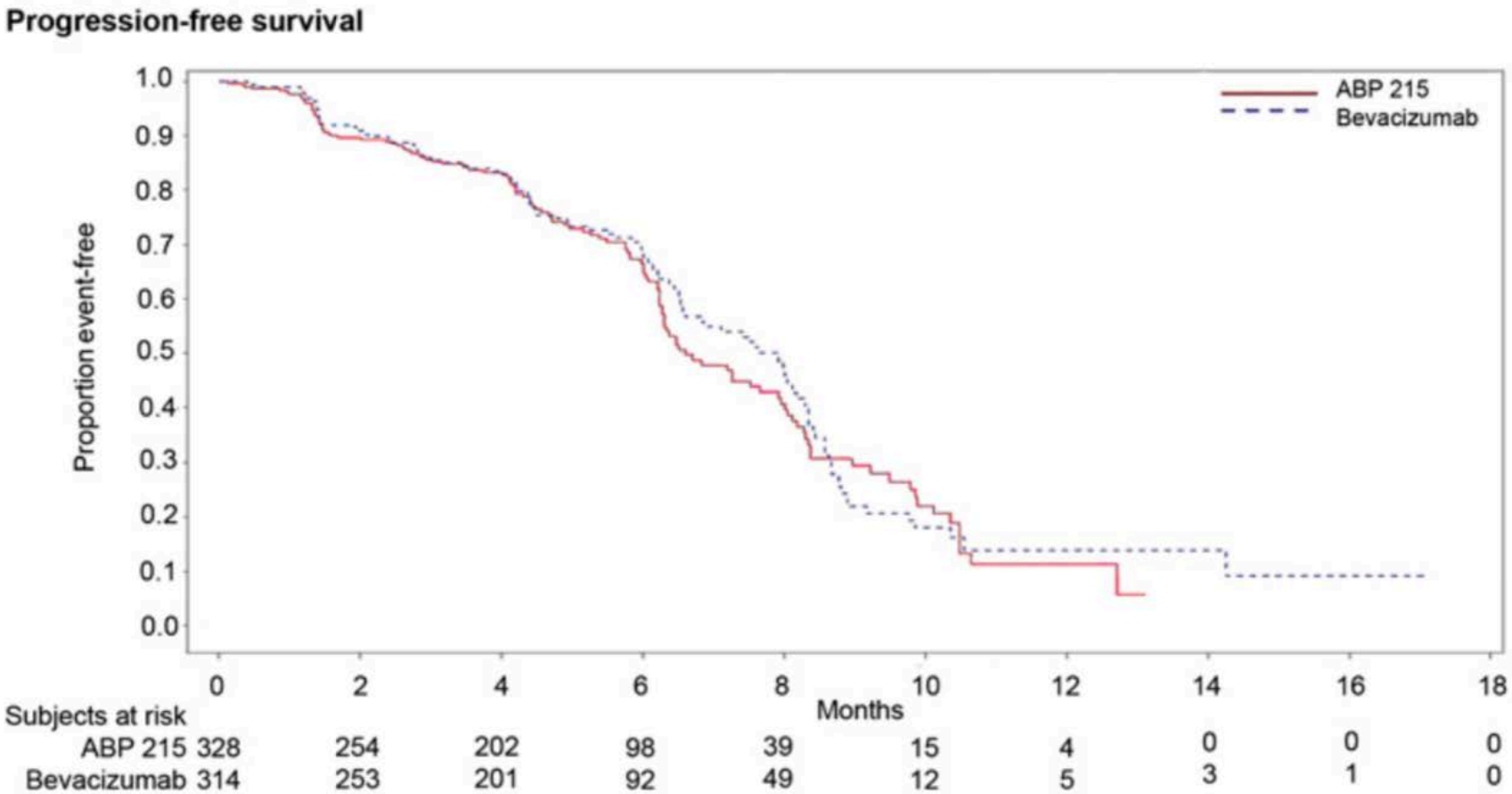
Thatcher N, Goldschmidt JH, et al. *Clin Cancer Res* 2019; 25(7):2088- 95

Table 2B. Overall summary of AEs

AE category, *n* (%)	ABP 215 (*N* = 324)	Bevacizumab (*N* = 309)
Any AE	308 (95.1)	289 (93.5)
Any grade ≥ 3 AE	139 (42.9)	137 (44.3)
Any fatal AE	13 (4.0)	11 (3.6)
Any serious AE	85 (26.2)	71 (23.0)
Any AE leading to discontinuation of IP	61 (18.8)	53 (17.2)
Any AE leading to discontinuation of any component of chemotherapy	74 (22.8)	59 (19.1)
Any AE leading to dose delay of IP	73 (22.5)	69 (22.3)
Any AE leading to dose delay of any component of chemotherapy	86 (26.5)	83 (26.9)
Any AE leading to dose reduction of any component of chemotherapy	48 (14.8)	49 (15.9)

NOTE: Only treatment-emergent AEs are summarized. For each category, patients are included only once, even if they had multiple events in that category.

Thatcher N, Goldschmidt JH, et al. *Clin Cancer Res* 2019; 25(7):2088- 95



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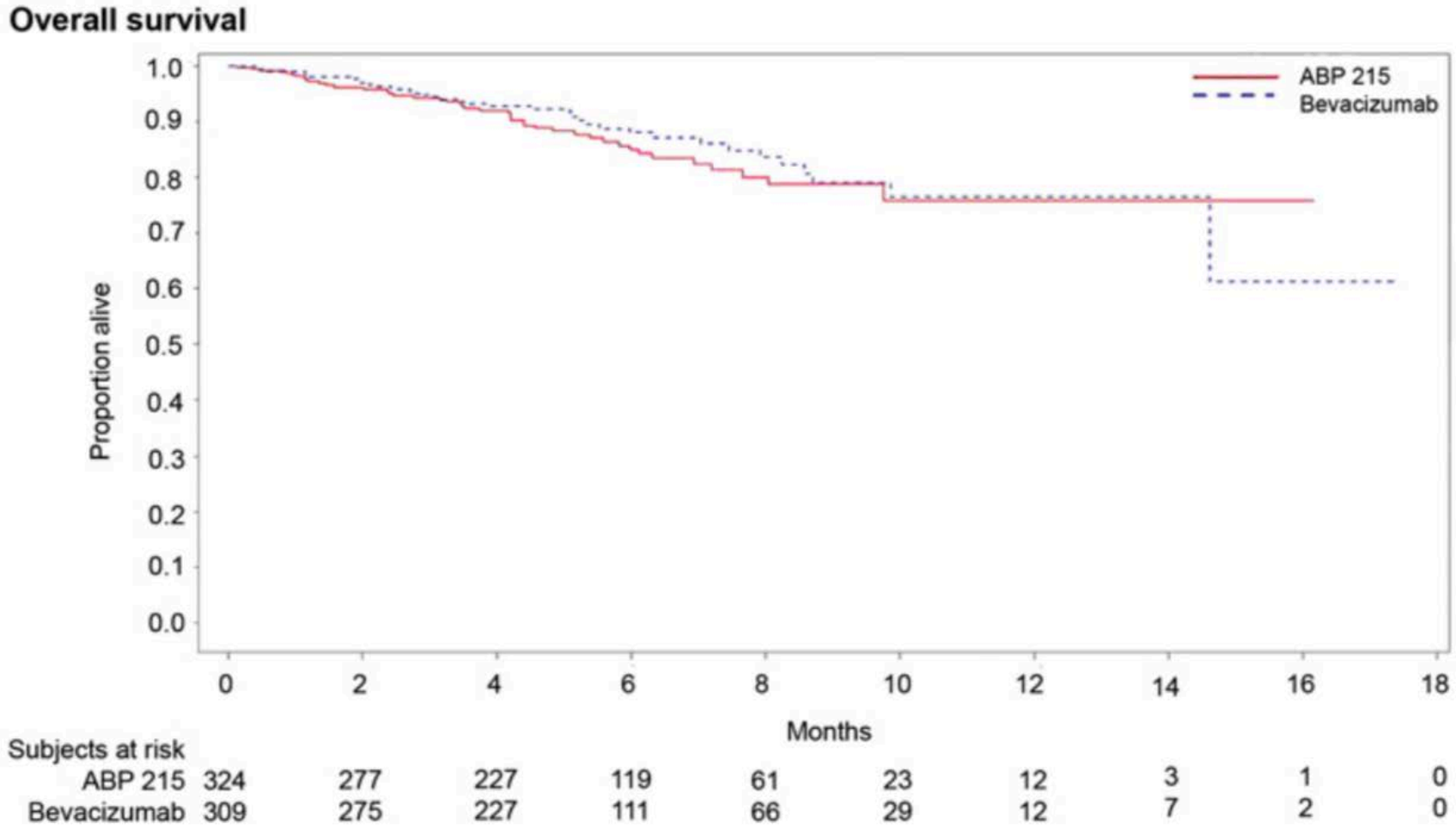

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Adverse events of interest

Thatcher et al.

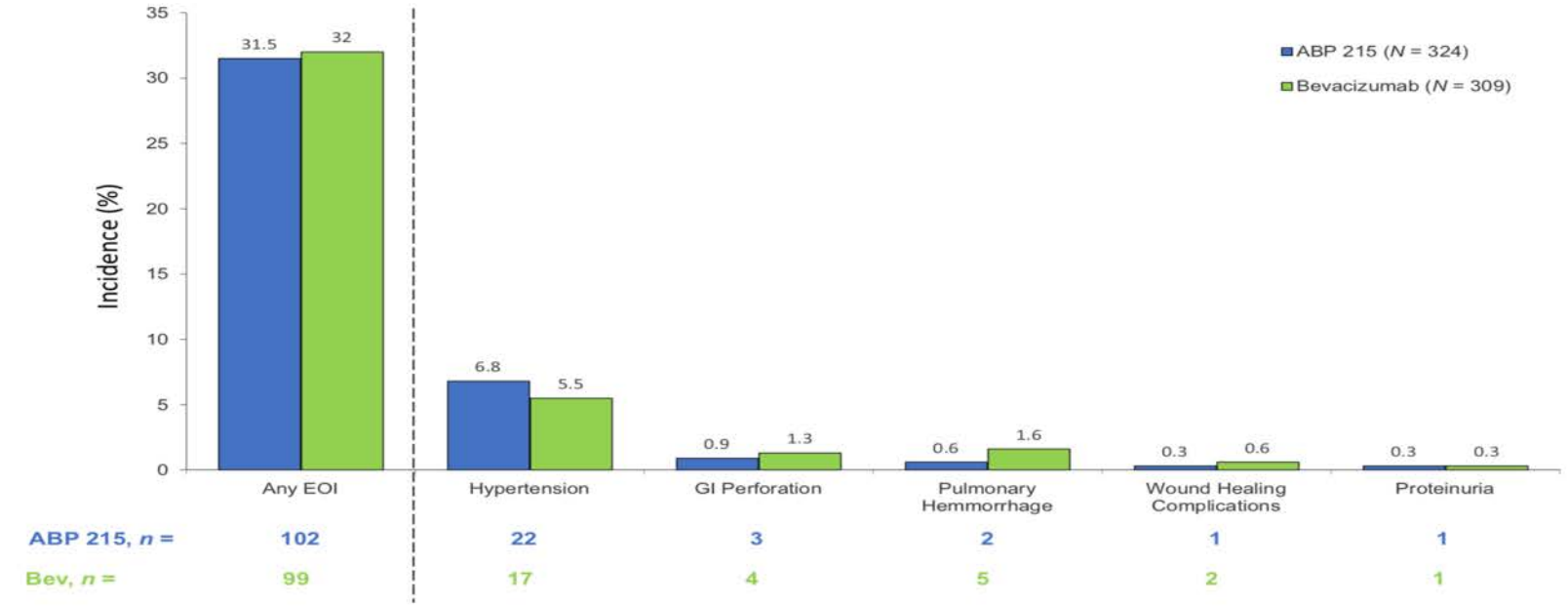


Figure 4.
Grade ≥3 adverse events of interest and anti-VEGF toxicities. EOI, event of interest; GI, gastrointestinal.

Thatcher N, Goldschmidt JH, et al. *Clin Cancer Res* 2019; 25(7):2088- 95

Immunogenecity

- Note: all biologics have potential of immunogenicity.
- 324 patients in MVASI® arm and 309 patients in Avastin® arm were administered for up to 19 weeks.
- Immunogenicity was evaluated at baseline, week 7, week 13 and week 19.
- The incidence of subjects developing binding antibodies at any time during the study was 1.4% for those receiving MVASI® and 2.5% for those receiving Avastin®.
- Among those with positive binding ADAs, no subject in either treatment group tested positive for neutralizing antibodies

Thatcher N, Goldschmidt JH, et al. *Clin Cancer Res* 2019; 25(7):2088- 95

Extrapolation

- Once studies show that biosimilar is highly similar to the reference biologic drug with no clinically meaningful differences, Health Canada can authorize the biosimilar for the same indications as the reference biologic drug, based on the previously-established efficacy and safety of the reference biologic drug in each indication. This concept is called extrapolation and. It avoids repetition of clinical studies.

Health Canada Fact Sheet on Biosimilars: https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/applications-submissions/guidance-documents/fact-sheet-biosimilars.html Accessed September 18th, 2019.

What indications get approved?

- Indications authorized for a particular biosimilar depend on factors such as:

i) Indications can be patented at different times. Indications under intellectual property cannot be authorized until the protection expires.

ii) Biosimilar manufacturer chooses which indications they wish to seek for their product.

Note: Health Canada cannot grant approval for an indication in which the reference product does not have. For example, bevacizumab (Avastin) does not have indication of metastatic cervix, so Health Canada cannot grant approval for that indication to any biosimilar manufacturer (Mvasi or Zirabev)

Health Canada Fact Sheet on Biosimilars: https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/applications-submissions/guidance-documents/fact-sheet-biosimilars.html Accessed September 18th, 2019.

Switching

- Refers to a change from one biologic brand to another brand.
- Usually refers to switching from reference product to a biosimilar.
- For example, switching a patient who is currently on treatment with bevacizumab (Avastin) for metastatic colorectal cancer to bevacizumab (Zirabev) or bevacizumab (Mvasi)

Health Canada

"Biosimilars are authorized by Health Canada for the indications listed in the Product Monograph. Patients and health care providers can have confidence that biosimilars are effective and safe for each of their authorized indications. No differences are expected in efficacy and safety following a change in routine use between a biosimilar and its reference biologic drug in an authorized indication."

Health Canada Fact Sheet on Biosimilars: https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/applications-submissions/guidance-documents/fact-sheet-biosimilars.htm Accessed September 18th, 2019.

Switching

- Decision is left at the discretion of each Jurisdictions.
- When discussing with patients about switching:
- Health Canada statement
- Monitored for side effects
- Pharmacovigilance
- Lot # and expiry tracking

From the non-oncology side

JIM Journal of Internal Medicine
Founded in 1863

Original Article | Open Access

Long-term efficacy and safety of biosimilar infliximab (CT-P13) after switching from originator infliximab: open-label extension of the NOR-SWITCH trial

G. L. Goll, K. K. Jørgensen, J. Sexton, I. C. Olsen, N. Bolstad, E. A. Haavardsholm ... See all authors

First published: 14 February 2019 | https://doi.org/10.1111/joim.12880 | Cited by: 6

Registration:: ClinicalTrials.gov NCT-02148640
EudraCT Number: 2014-002056-40

Conclusion

The NOR-SWITCH extension showed no difference in safety and efficacy between patients who maintained CT-P13 and patients who switched from originator infliximab to CT-P13, supporting that switching from originator infliximab to CT-P13 is safe and efficacious.

In Canada – non-oncology

B.C. to become first province to force patients to switch from biologics to less expensive biosimilar drugs

Globe and Mail, May 27th, 2019

Practical considerations

Position Statements for the Implementation of Oncology Biosimilars from the pan-Canadian Clinical Operations Working Group

Version: 1 Aug 2019

Authors: Pan-Canadian Clinical Operations Working Group Core Writing Team, Jessica Arias, Dr. Vishal Kukreti, Sean Hopkins,

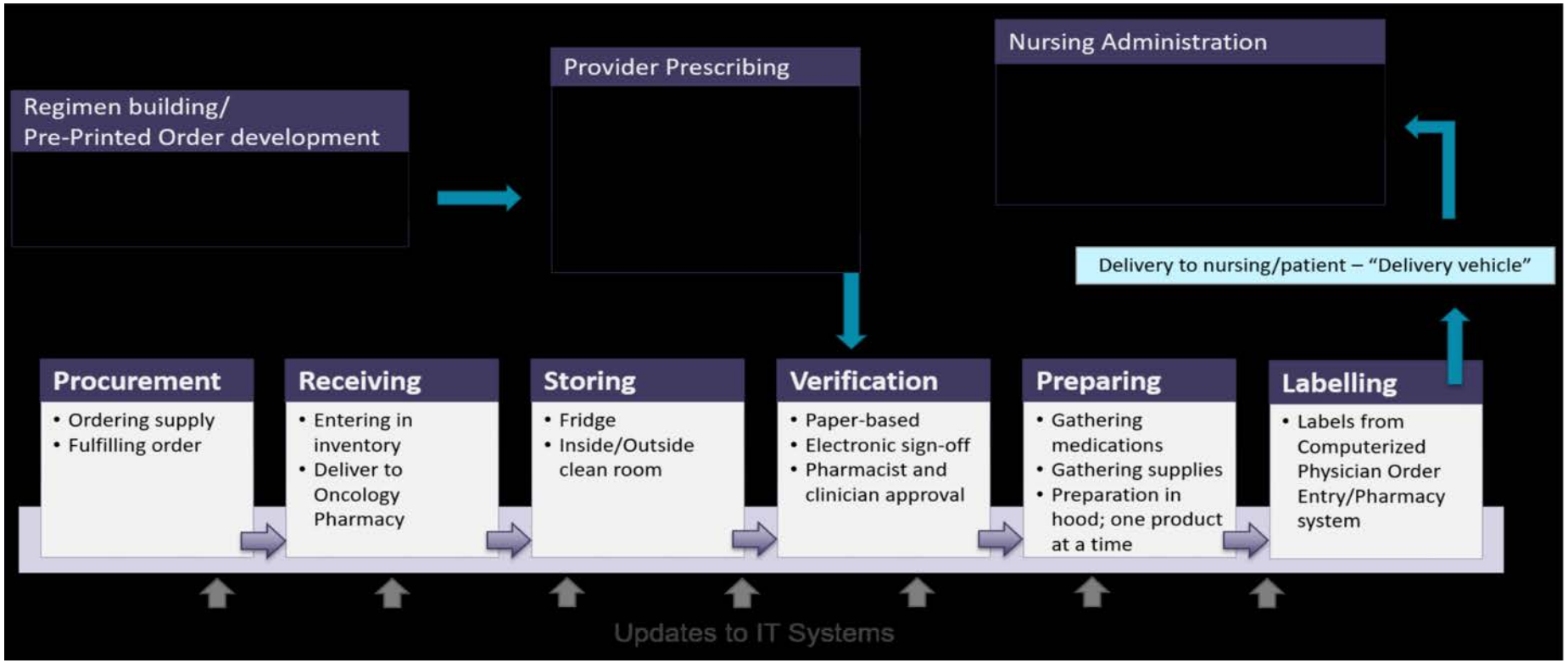
Guideline Objective

The objective of the Position Statement is to provide recommendations to assist hospitals and cancer centers appropriately prepare for the implementation of oncology biosimilars.

Intended Guideline Users

CancerCare Ontario website: https://www.cancercareontario.ca

Summary of clinical process flow



CancerCare Ontario website: https://www.cancercareontario.ca

Labelling

- That computer physician orders that incorporate a biosimilar in the regimen:
- Generic name followed by trade name in parentheses
- (i.e. bevacizumab (Mvasi); bevacizumab (Zirabev); bevacizumab (Avastin)

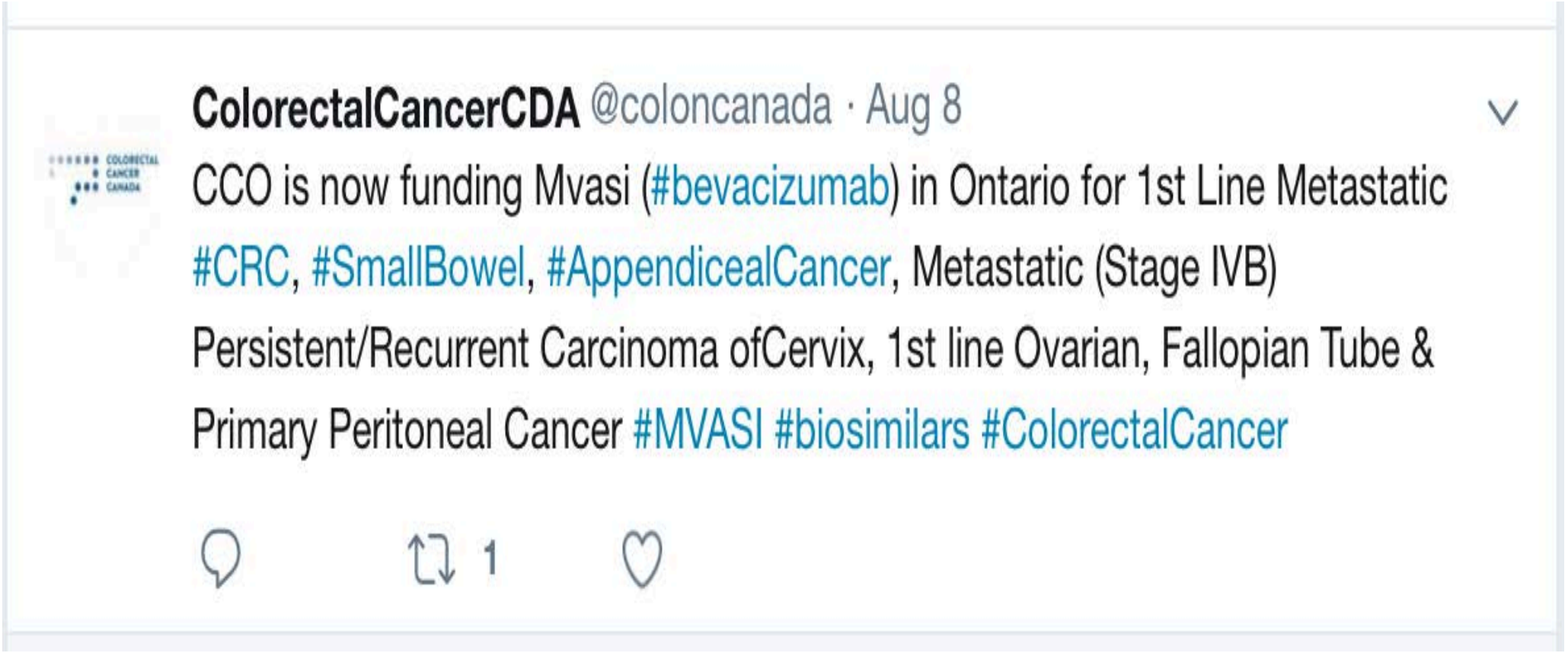
Infusion Times

- If the reference biologic has off-label administration evidence (e.g. infusion rate) that has been incorporated into clinical practice, these same practices may be used for the biosimilar in the same situations (ie. First dose vs subsequent doses)
- i.e. bevacizumab 0.5 mg/kg/min
- i.e. rituximab rapid infusion

Pharmacovigilance

- Eqch manufacturer must report any adverse events and safety reports to Health Canada
- It would be no different than other biologics

Bevacizumab



Colorectal Cancer Canada Twitter: https://twitter.com/coloncanada?lang=en (Accessed: September 14th, 2019)

Upcoming.....

Biosimilar	Reference Product	Health Canada status
Bevacizumab (Zirabev)	Bevacizumab (Avastin)	Health Canada approved
Trastuzumab (Trazimera)	Trastuzumab (Herceptin)	Health Canada approved
Trastuzumab (Herzuma)	Trastuzumab (Herceptin)	Health Canada approved
Trastuzumab (Ogivri)	Trastuzumab (Herceptin)	Health Canada approved
Rituximab (Truxima)	Rituximab (Rituxan)	Health Canada approved
Rituximab biosimilar (from Pfizer)	Rituximab (Rituxan)	Under review Health Canada

Useful Links

- CancerCare Ontario website: https://www.cancercareontario.ca

- Health Canada Guidance on biosimilars: Health Canada Fact Sheet on Biosimilars: https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/applications-submissions/guidance-documents/fact-sheet-biosimilars.html

Conclusions

- This year, we will see our first biosimilar introduced for the treatment of cancers.
- We are anticipated more biosimilars in the upcoming year
- Policies on switching and extrapolation are currently left to the Jurisdictions to decide

Questions?