

Cancer Drugs

NEW DRUGS AND INDICATIONS OVER THE PAST TEN YEARS

by KONG KHOO, ROSEMARY COLUCCI, DANIEL GILLESPIE, JAMES D. GOWING, PIERRE MAJOR, JOSEPH RAGAZ, DAVID SALTMAN, COLLEEN SAVAGE

Development of new drug therapies is progressing at an unprecedented rate with more than 800 new cancer agents in the pipeline. Over the past four CACC annual Report Cards, we have highlighted the increasing number of new drugs for cancer, many of them approved by Health Canada for specific cancer indications. However, listing on provincial formularies and coverage by private insurers may be variable in different parts of the country.

In last year's Report Card, we calculated that \$555 million was spent in 2007 for all take-home cancer drugs¹. The top 10 take-home cancer drugs accounted for more than 80 per cent of the expenditures. We documented the rising cost, with private insurers' costs increasing faster than public payers, and the shifting burden from public payers to employers and individual cancer patients during a time of significant economic downturn.

We were interested in exploring the impact of the loom-

ing influx of new cancer drugs, especially as it converges with the trend toward multiple cancer indications for each product. To understand the scope of the issue, we investigated the approved indications for cancer for the past 10 years (2000 to 2009).

Methodology

All Health Canada approved indications for all new cancer drugs or new indications for pre-existing cancer drugs were identified from Health Canada drug databases and website for 2000 to 2009².

Individual drugs used for cancer were identified, including oral and injectable drugs. Additional expanded cancer indications were identified from Jan 1, 2000 to December 31, 2009.

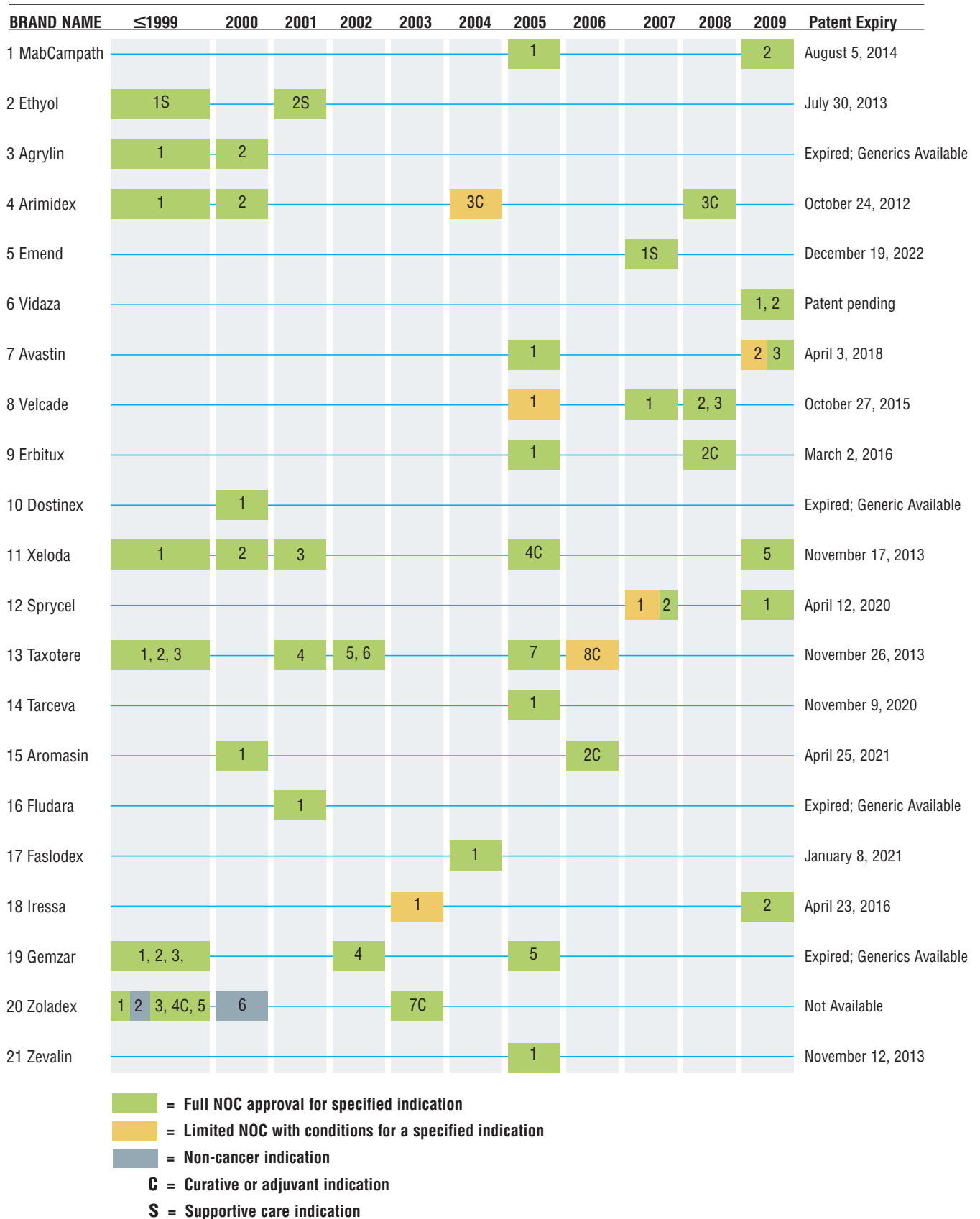
Patent expiry dates were determined from the Health Canada Patent Register³ for the cancer drugs identified.

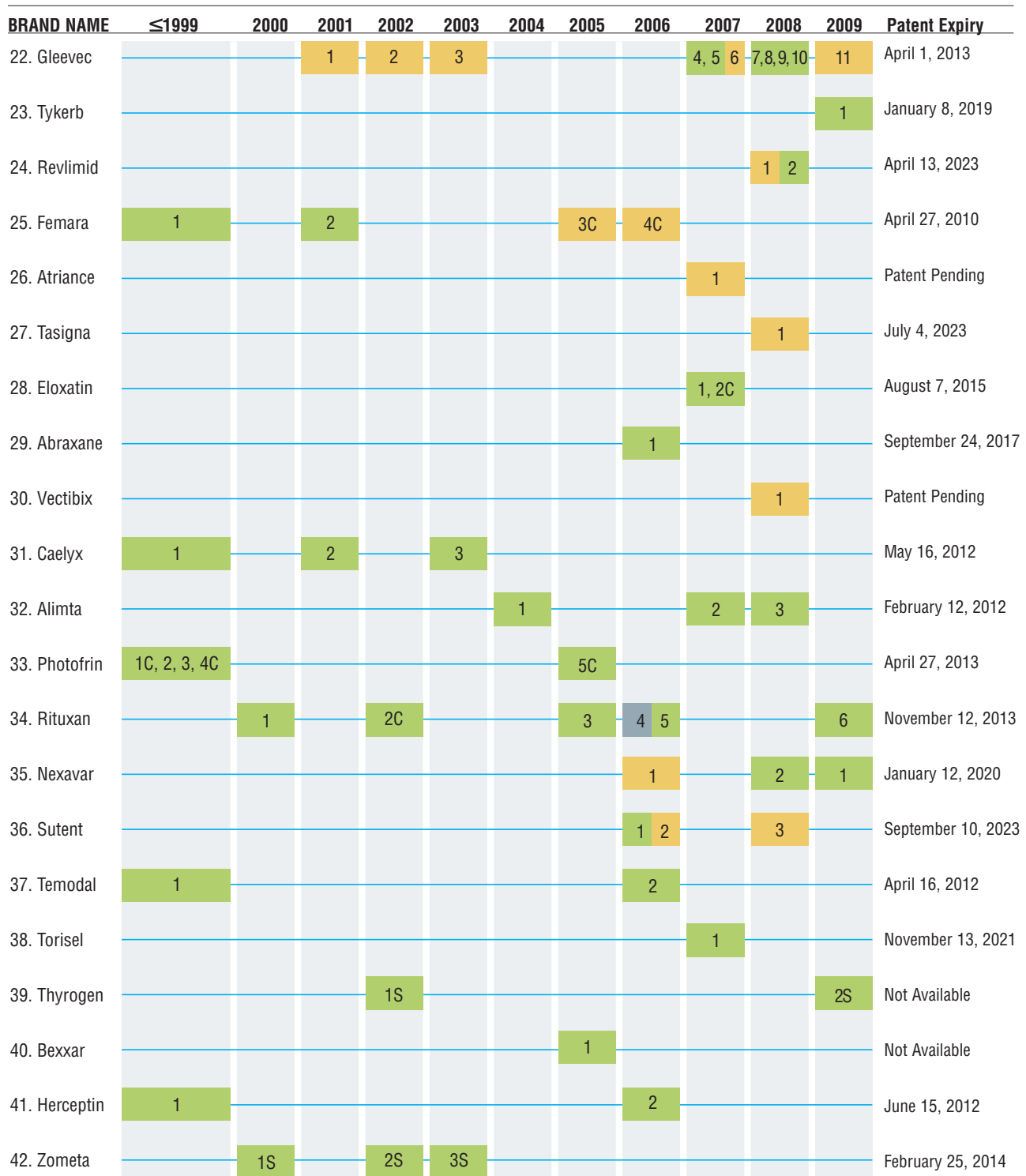
FIGURE 1
THE 42 DRUGS STUDIED

CHEMICAL	BRAND	CHEMICAL	BRAND
1. Alemtuzumab	MabCampath	22. Imatinib	Gleevec
2. Amifostine	Ethyol	23. Lapatinib	Tykerb
3. Anagrelide	Agrylin	24. Lenalidomide	Revlimid
4. Anastrozole	Arimidex	25. Letrozole	Femara
5. Aprepitant	Emend	26. Nelarabine	Atriance
6. Azacitidine	Vidaza	27. Nilotinib	Tasigna
7. Bevacizumab	Avastin	28. Oxaliplatin	Eloxatin
8. Bortezomib	Velcade	29. Paclitaxel-nab	Abraxane
9. Cetuximab	Erbix	30. Panitumumab	Vectibix
10. Cabergoline	Dostinex	31. Pegylated Liposomal Doxorubicin	Caelyx
11. Capecitabine	Xeloda	32. Pemetrexed	Alimta
12. Dasatinib	Sprycel	33. Porfimer	Photofrin
13. Docetaxel	Taxotere	34. Rituximab	Rituxan
14. Erlotinib	Tarceva	35. Sorafenib	Nexavar
15. Exemestane	Aromasin	36. Sunitinib	Sutent
16. Fludarabine	Fludara	37. Temozolomide	Temodal
17. Fulvestrant	Faslodex	38. Temsirolimus	Torisel
18. Gefitinib	Iressa	39. Thyrotropin-alfa	Thyrogen
19. Gemcitabine	Gemzar	40. I-131 tositumomab	Bexxar
20. Goserelin	Zoladex	41. Trastuzumab	Herceptin
21. Y-90 Ibritumomab Tiuxetan	Zevalin	42. Zoledronic acid	Zometa

CANCER DRUGS

FIGURE 2
CANCER DRUGS APPROVED BY HEALTH CANADA BETWEEN 2000–2009
SHOWING THE SEQUENCE OF APPROVED INDICATIONS, NOC STATUS AND DATE OF PATENT EXPIRY





= Full NOC approval for specified indication
 = Limited NOC with conditions for a specified indication
 = Non-cancer indication
C = Curative or adjuvant indication
S = Supportive care indication

Results

Figure 2 displays the drugs approved by Health Canada for the years 2000 to 2009 and the approved cancer indications, approval date, and whether full approval (Notice of Compliance or NOC) or conditional approval (NOC with conditions or NOC/c) was granted.

The approvals by year were charted in Figures 3 and 4 to illustrate the trends in number of new drugs and cancer indications by year as well as cumulative totals. Figure 5 summarizes the number of new cancer drugs (distinct drug entities) and expanded indications for already existing cancer drugs approved in the periods 2000–2004 and 2005–2009. Over these two consecutive five year periods, the total number of new cancer drug entities and the expanded indications for existing cancer drugs doubled.

In the 10 year period from 2000 to 2009, a total of 42 drug entities were approved for at least one cancer indication. Thirty of these were new drug entities, many representing landmark drugs in the treatment of different cancers. Twelve were older drugs approved in 1999 or earlier, but with new cancer indications approved in the decade studied. A total of 88 individual cancer indications were approved for these 42 individual drugs during this period. A significant number (20) of these 88 approvals were conditional approvals (NOC/c).

Many new drugs are described as “targeted” therapies as they inactivate a specific molecular target or its pathway, yet they can work for many different tumour types. For example Gleevec (imatinib), although initially discovered to treat one specific disease (chronic myelogenous leukemia), has been approved for a total of 11 separate indications involving seven different

FIGURE 3
TOTAL NEW CANCER DRUGS AND INDICATIONS
APPROVED IN CANADA, 2000–2009

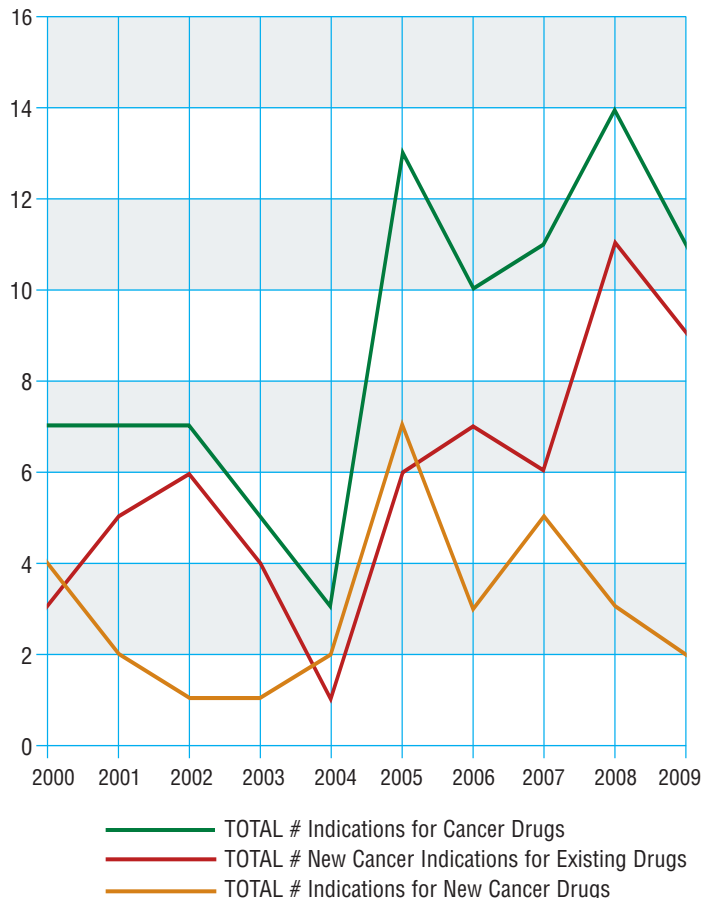
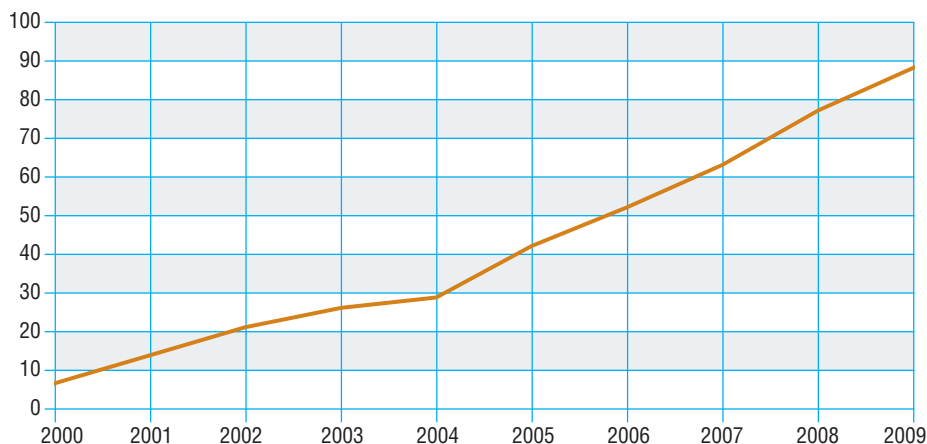


FIGURE 4
CUMULATIVE CANCER DRUG INDICATIONS



types of cancer (CML, certain forms of acute lymphoblastic leukemia, gastrointestinal stromal tumour, certain forms of myelodysplastic syndromes, dermatofibrosarcoma protuberans, systemic mastocytosis, and hypereosinophilic syndrome).

Most of the 42 drugs were used for palliative treatment of advanced and/or metastatic cancer, although 10 drugs also had curative or adjuvant indications. Four were supportive care drugs for cancer: aprepitant (an anti-emetic), amifostine (cytoprotectant to protect normal tissues and organs), thyrotropin hormone (used to prevent hypothyroidism in thyroid cancer patients), and zoledronic acid (used to reduce risk of bony complications of various cancers metastatic to bone and to treat hypercalcemia of malignancy). Two of the 42 drugs were also approved for non-cancer indications: rituximab for rheumatoid arthritis and goserelin for endometriosis.

Patent protection has expired for only four of the 42 drugs, with generic formulation(s) now available in Canada (anagrelide, cabergoline, fludarabine, gemcitabine).

Figure 6 summarizes cancer drugs that are not approved and not commercially available in Canada.

FIGURE 5
TREND OF NEW CANCER DRUGS AND NEW/EXPANDED CANCER INDICATIONS FOR THE PERIODS 2000–2004 AND 2005–2009

	5-year period 2000–2004	5-year period 2005–2009
# New cancer drugs	10	20
# New/expanded cancer drug indications	19	39
Totals	29	59

FIGURE 6
CANCER DRUGS NOT APPROVED IN CANADA BUT AVAILABLE, UNFUNDED, THROUGH HEALTH CANADA SPECIAL ACCESS PROGRAM (as of Dec.31, 2009)

	Drug	Brand Name	Indication
1	Arsenic Trioxide	Trisenox	Acute promyelocytic leukemia
2	Bendamustine	Treanda	Chronic lymphocytic leukemia & low grade non-Hodgkin lymphoma
3	Bexarotene	Targretin	Cutaneous T-cell lymphoma
4	Clofarabine	Clolar	Pediatric acute lymphocytic leukemia
5	Cytarabine liposomal	Depocyt	Leptomeningeal carcinomatosis
6	Decitabine	Dacogen	Myelodysplastic syndromes
7	Denileukin Diftiox	Ontak	Cutaneous T-cell lymphoma
8	Erwinase l-asparaginase	Erwinase	Acute lymphocytic leukemia
9	Everolimus	Afinitor	Renal cell cancer
10	Glucarpidase	Voraxane	Methotrexate toxicity
11	Ixabepilone	Ixempra	Metastatic breast cancer
12	Mafosfamide	N/A	Leptomeningeal carcinomatosis
13	Methoxsalen	(8-MOP)	Cutaneous T-cell lymphoma
14	Metyrosine	Demser	Pheochromocytoma
15	Nimotuzumab	Theracim	Head & neck cancer
16	Ofatumumab	Arzerra	Chronic lymphocytic leukemia
17	Pegaspargase	Oncaspar	Acute lymphocytic leukemia
18	Sargramostim	Leukine	Chemotherapy neutropenia
19	Thalidomide	Thalomid	Multiple myeloma
20	Thiotepa	N/A	Breast & ovarian cancer

Discussion

The number of new drug entities emerging from the large pipeline of cancer drugs is small but steadily increasing. The number of approved indications for existing drugs however is expanding faster. These include extending the approved drug to earlier lines of palliative treatment, to other patient groups or disease entities, to use in combinations with other therapeutic modalities, to use in combination with other drug(s), or to adjuvant therapy as emerging scientific studies prove them effective. At least one targeted therapy has been approved in the adjuvant setting (Gleevec for gastrointestinal stromal tumour).

Many drugs for rare or infrequent cancers are not commercially available in Canada but Health Canada has established a Special Access Program for such drugs. The drugs listed in Figure 6 indicate that these are usually for rare or infrequent cancers or conditions. This is an important mechanism for accessing cancer drugs not available or approved in Canada especially for uncommon cancers, which often are not studied to the extent of more common cancers.

The sheer number and complexity of new drugs and expanded indications provides a huge scientific and logistic challenge for Health Canada and pharmaceutical companies. Keeping abreast of the evolving evidence for new cancer drugs is vital for cancer specialists, and the provincial expert groups and public payers responsible for deciding whether to fund these new and usually expensive therapies. The timeliness of Health Canada approval has improved for cancer drugs over the past several years, and documentation on the Health Canada web site is improving. However further enhancements to the web site could make the information more coherent and useful for care providers and other interested parties.

The cost of cancer drugs may be partly contained by the imminent patent expiry of the originators' products, with potentially cheaper generic versions entering the market. However, many cancer drugs are forms of complex natural molecules that are difficult to manufacture identically. These have been called Subsequent Entry Biologics (SEBs) to differentiate them from generic drugs. There needs to be a process to ensure SEBs demonstrate similar therapeutic equivalence and safety to the existing reference product. (See article on "Subsequent Entry Biologics" in this publication. Canada is in the process of developing a regulatory approval process for SEBs.)

As these SEBs are complex to produce, it is uncertain if cost savings with SEBs or generic cancer drugs will be substantial. Also, brand name pharmaceutical manufacturers have a vested interest to protect and extend their patents beyond the usual 20 year patent

expiry period from initial filing. It is therefore difficult to predict with any certainty when, or at what price, generics or SEBs will arrive, even though several of the 42 cancer drugs studied will lose patent protection over the next few years.

Conclusion

With the expectation of upwards of 800 drugs in development, numerous indications for each, and the introduction of SEBs, Health Canada will be challenged to ensure patient safety and handle the volume in a timely fashion.

For public and private payers, the number of new drugs and indications represents potentially heavy new costs, especially if the expected price reductions from SEB or generic competition do not materialize.

Patients and oncologists welcome the growing range of treatment choices as a sign that research is bounding forward with important benefits for all. They fear the decisions by funders that only some patients will have access to some treatments, or that personal finances will be the final determinant of who benefits and who does not.

Kong Khoo is a Medical Oncologist based in Kelowna, BC and is Vice-Chair of the CACC.

Rosemary Colucci is a consultant to the health sector in strategic planning, stakeholder relations and advocacy strategy.

Daniel Gillespie is a consultant and research assistant to the CACC.

James D. Gowing is a Medical Oncologist and Hematologist at the Cambridge Memorial Hospital, Cambridge, ON, and co-Chair of the CACC.

Pierre Major is a Medical Oncologist based in Hamilton, ON and is Vice-Chair of the CACC.

Joseph Ragaz is a Medical Oncologist and Clinical Professor, School of Population and Public Health, Faculty of Medicine, University of British Columbia, Vancouver, BC; and Adjunct Professor, Medicine and Oncology, McGill University, Montreal QC.

David Saltman is a Medical Oncologist, Chair and Professor of the Discipline of Oncology, Faculty of Medicine, Memorial University, St. John's, NL

Colleen Savage is a public affairs and communications consultant who serves as CEO to the CACC.

References

- 1 Khoo K, Colucci R, Hryniuk W, Kamino R, Redina T, Savage C: The cost of cancer drugs in Canada Part 2: Who is bearing the cost? Report Card on Cancer in Canada 2008, 12: 23-32.
- 2 Health Canada Notice of Compliance database (<http://205.193.93.51/NocWeb/nocqrye.jsp>)
- 3 Health Canada Patent Registry (<http://www.patentregister.ca/>)

FIGURE 7

**APPROVED INDICATIONS FOR CANCER DRUGS
APPROVED BY HEALTH CANADA, 2000–2009**

1 Alemtuzumab (MabCampath)

1. NOC for relapsed refractory B-cell CLL treated with alkylators and fludarabine, 30-Nov-05
2. NOC for previously untreated progressive B-cell CLL, 27-Jan-09

2 Amifostine (Ethyol)

1. NOC as cytoprotective agent with radiation, 25-Apr-96
2. NOC to reduce incidence & severity of xerostomia of XRT in patients with SCC of Head & Neck, 08-May-01

3 Anagrelide (Agrylin)

1. NOC as platelet reducing agent, 19-Nov-97
2. NOC for thrombocytopenia related to MPD to reduce platelet count and risk for thrombo-hemorrhagic complications, 24-Jan-00

4 Anastrozole (Arimidex)

1. NOC for advanced breast cancer in postmenopausal women after previous hormone therapy, 01-Aug-96
2. NOC for hormonal treatment of advanced postmenopausal breast cancer, 29-May-00
3. NOC/c for adjuvant early HR+ breast cancer in postmenopausal women, 30-Jun-04
3. Final NOC for adjuvant early HR+ breast cancer in post menopausal women, 02-Dec-08

5 Aprepitant (Emend)

1. NOC for prevention of acute and delayed nausea & vomiting due to moderate & highly emetogenic cancer chemotherapy, 24-Aug-07

6 Azacitidine (Vidaza)

1. NOC for intermediate-2 and high risk myelodysplastic syndromes according to International Prognostic Scoring System, 23-Oct-09
2. NOC for AML with 20-30% blasts & multilineage dysplasia according to WHO classification, 23-Oct-09

7 Bevacizumab (Avastin)

1. NOC with chemo for metastatic colorectal cancer for first line therapy, 09-Sep-05
2. NOC/c with paclitaxel for Her2/Neu- metastatic breast cancer with ECOG PS 0-1, 06-Feb-09
3. NOC with carbo/paclitaxel for advanced unresectable, metastatic or recurrent nonsmall cell lung cancer, 27-Mar-09

8 Bortezomib (Velcade)

1. NOC/c for relapsed myeloma after front-line therapy and refractory to most recent therapy, 27-Jan-05
1. Final NOC relapsed myeloma after one prior therapy or not eligible for ASCT; Conditions met, 11-Sep-07

2. NOC for mantle cell NHL who have relapsed or refractory to at least one prior therapy, 09-Jun-08
3. NOC as part of combination therapy for previously untreated myeloma unsuitable for stem cell transplant, 02-Sep-08

9 Cetuximab (Erbix)

1. NOC for metastatic relapsed colorectal cancer with irinotecan or as monotherapy intolerant of irinotecan, 09-Sep-05
2. NOC with radiation for locally advanced squamous cell H&N cancer, 11-Sep-08

10 Cabergoline (Dostinex)

1. NOC for treatment of hyperprolactinemic disorders either idiopathic or pituitary adenoma (prolactinoma) or inhibition of physiologic lactation, 30-Jun-00

11 Capecitabine (Xeloda)

1. NOC for refractory metastatic breast cancer, 31-Aug-98
2. NOC for first line treatment of metastatic colorectal cancer, 17-Jul-00
3. NOC with docetaxel for advanced or metastatic breast cancer after failure of prior anthracycline chemo, 28-Dec-01
4. NOC for adjuvant treatment of Duke C colon cancer, 07-Dec-05
5. NOC with oxaliplatin for metastatic colorectal cancer after irinotecan containing combination chemotherapy, 03-Dec-09

12 Dasatinib (Sprycel)

1. NOC/c for chronic, accelerated or blast phase adult Ph+ CML resistant or intolerant to prior Rx including imatinib, 26-Mar-07
2. NOC for adult Ph+ ALL resistant or intolerant of other therapies, 17-Jul-07
1. Full NOC for CML resistant or intolerant to prior therapy, 19-Nov-09

13 Docetaxel (Taxotere)

1. NOC for advanced or metastatic nonsmall cell lung cancer, 21-Jul-95
2. NOC for advanced or metastatic breast cancer, 21-Jul-95
3. NOC for advanced ovarian cancer, 06-May-99
4. NOC for locally advanced or metastatic breast cancer, 03-Mar-01
5. NOC for monotherapy for recurrent or metastatic SCC of H&N after a previous chemo regimen, 19-Feb-02
6. NOC with capecitabine for metastatic breast cancer after prior anthracycline chemotherapy, 27-Aug-02
7. NOC with prednisone or prednisolone for hormone refractory prostate cancer, 22-Apr-05
8. NOC/c with doxorubicin & cyclophosphamide for adjuvant node+ breast cancer (TAC), 14-Dec-06

14 Erlotinib (Tarceva)

1. NOC for nonsmall cell lung cancer after failure of at least one prior chemotherapy regimen, 07-Jul-05

FIGURE 7 CONTINUED

**APPROVED INDICATIONS FOR CANCER DRUGS
APPROVED BY HEALTH CANADA, 2000–2009**

15 Exemestane (Aromasin)

1. NOC for advanced or metastatic postmenopausal breast cancer, 17-Aug-00
2. NOC for adjuvant treatment of early postmenopausal breast cancer, 17-May-06

16 Fludarabine (Fludara)

1. NOC for CLL and low grade NHL failed other conventional treatment, 30-Oct-01

17 Fulvestrant (Faslodex)

1. NOC for post menopausal advanced breast cancer failed prior endocrine therapy, 17-Feb-04

18 Gefitinib (Iressa)

1. NOC/c for relapsed nonsmall cell lung cancer who have failed 2 or more chemotherapy regimens, 17-Dec-03
2. NOC for first line treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) not amenable to curative therapy who have activating mutations of the EGFR-TK, 18-Dec-09

19 Gemcitabine (Gemzar)

1. NOC for advanced or metastatic pancreas cancer after prior therapy, 25-Oct-96
2. NOC for first line treatment of advanced/ metastatic pancreas cancer, 19-Feb-98
3. NOC in combination with cisplatin for advanced or metastatic NSCLC, 19-Aug-99
4. NOC in combination with cisplatin for advanced or metastatic TCC of bladder, 21-Jan-02
5. NOC with paclitaxel for relapsed metastatic breast cancer after adjuvant anthracyclines, 30-Sep-05

20 Goserelin (Zoladex)

1. NOC for advanced/metastatic hormone dependent prostate cancer, 14-Feb-96
2. NOC for endometrial thinning agent prior to endometrial ablation, 20-Mar-97
3. NOC for palliative treatment of peri- & pre-menopausal advanced breast cancer who are ER/PR+, 08-Apr-98
4. NOC for adjuvant therapy with radiation for locally advanced prostate cancer T3-T4, 18-Aug-99
5. NOC with nonsteroidal antiandrogen for locally advanced bulky T2B, T2C, T3, T4 prostate cancer, 18-Aug-99
6. NOC for hormonal therapy of endometriosis for pain relief & reduction of endometriotic lesions, 15-Mar-00
7. NOC for adjuvant therapy for peri & premenopausal early breast cancer who are ER/PR+, 19-Mar-03

21 Y-90 ibritumomab tiuxetan (Zevalin)

1. NOC for relapsed or refractory low grade or follicular CD20+ NHL, 10-May-05

22 Imatinib (Gleevec)

1. NOC/c for adult Ph+ CML in chronic, accelerated or blast phase after failure of interferon therapy, 20-Sep-01
2. NOC/c for adult patients with advanced unresectable or metastatic GIST, 07-Aug-02
3. NOC/c for newly diagnosed adult CML, 08-Oct-03
4. NOC for adult Ph+ ALL for primary Rx as induction therapy, 08-Mar-07
5. NOC for relapsed or refractory Ph+ ALL as monotherapy, 08-Mar-07
6. NOC/c for pediatric newly diagnosed chronic phase Ph+ CML, 24-May-07
7. NOC for MDS/MPD with PDGFR gene rearrangements, 10-Jan-08
8. NOC for aggressive subtypes of systemic mastocytosis (ASM & SM-AHNMD) without D816V c-kit mutation, 10-Jan-08
9. NOC for hypereosinophilia syndrome/ chronic eosinophilic leukemia with FIP1L1 PDGFR-alpha rearrangement, 10-Jan-08
10. NOC for adults with unresectable, recurrent or metastatic dermatofibrosarcoma protuberans, 10-Jan-08
11. NOC/c for adjuvant treatment of adult patients who are at intermediate to high risk of relapse following complete resection of c-kit (CD 117) positive GIST, 22-Dec-09

23 Lapatinib (Tykerb)

1. NOC in combination with capecitabine for Her2/Neu+ advanced or metastatic breast cancer previously treated with anthracyclines, taxanes and trastuzumab, 15-May-09

24 Lenalidomide (Revlimid)

1. NOC/c for low & intermediate risk myelodysplastic syndrome with 5q-, 17-Jan-08
2. NOC in combination with dexamethasone for multiple myeloma patients who have received one prior Rx, 02-Oct-08

25 Letrozole (Femara)

1. NOC for advanced metastatic ER/PR+ breast cancer who have progression after antiestrogen therapy, 21-May-97
2. NOC for first line therapy for advanced or metastatic ER/PR+ post menopausal breast cancer, 11-May-01
3. NOC/c for extended adjuvant therapy of ER/PR+ post-menopausal breast cancer after standard adjuvant tamoxifen, 01-Apr-05
4. NOC/c for adjuvant front line therapy for postmenopausal ER/PR+ early breast cancer, 06-Oct-06

26 Nelarabine (Atriance)

1. NOC/c for adult or pediatric T-cell ALL or T-cell lymphoblastic NHL after at least 2 prior therapies, 22-Sep-07

- 27 **Nilotinib (Tasigna)**
1. NOC/c for accelerated phase Ph+ adult CML resistant to or intolerant of at least one prior therapy including imatinib, 09-Sep-08
- 28 **Oxaliplatin (Eloxatin)**
1. NOC with infusional 5-FU/ leucovorin for advanced and metastatic colorectal cancer, 12-Sep-07
 2. NOC with infusional 5-FU/ leucovorin for adjuvant treatment for resected Duke C colon cancer, 18-Dec-07
- 29 **Paclitaxel-nab (Abraxane)**
1. NOC for treatment of metastatic breast cancer, 07-Jun-06
- 30 **Panitumumab (Vectibix)**
1. NOC/c for monotherapy of metastatic refractory k-ras wild type colorectal cancer, 03-Apr-08
- 31 **Pegylated liposomal doxorubicin (Caelyx)**
1. NOC for AIDS related Kaposi sarcoma not responding to prior therapy, 20-Jul-98
 2. NOC for treatment of advanced ovarian cancer following failure of standard first-line therapy, 20-Jan-01
 3. NOC for monotherapy for metastatic breast cancer where there is an increased cardiac risk for conventional doxorubicin, 09-Jun-03
- 32 **Pemetrexed (Alimta)**
1. NOC for mesothelioma first line Rx, 21-May-04
 2. NOC for locally advanced or metastatic nonsmall cell lung cancer after prior therapy, 11-Jan-07
 3. NOC in combination with cisplatin therapy for initial treatment of good performance status patients with locally advanced or metastatic NSCLC other than predominantly squamous cell histology, 02-Sep-08
- 33 **Porfimer (Photofrin)**
1. NOC for PDT for recurrent superficial papillary bladder cancer who have failed standard intra-vesicular therapy, 1993?
 2. NOC for PDT to reduce obstruction & palliation of dysphagia in patients with obstructing esophageal cancer, 13-Jul-95
 3. NOC for PDT to reduce obstruction & palliation of obstructing endobronchial NSCLC, 16-Jul-99
 4. NOC for PDT of superficial endobronchial NSCLC ineligible for surgery or radiation, 16-Jul-99
 5. NOC for PDT for high grade dysplasia associated with Barrett's esophagus ineligible for surgery, 14-Mar-03
- 34 **Rituximab (Rituxan)**
1. NOC for relapsed or refractory follicular or low grade B-cell NHL, 17-Mar-00
 2. NOC with CHOP for DLB CD20+ NHL, 06-Nov-02
 3. NOC with CVP for previously untreated stage 3 or 4 follicular NHL, 20-Dec-05
4. NOC in combination with MTX for adult patients with moderate to severely active rheumatoid arthritis, 16-Jun-06
 5. NOC for maintenance therapy of follicular NHL who have responded to CHOP or CHOP-R, 28-Jul-06
 6. NOC for previously untreated B-cell CLL (stage B or C) in combination with Fludarabine and Cyclophosphamide, 07-Aug-09
- 35 **Sorafenib (Nexavar)**
1. NOC/c for advanced renal cancer of clear cell histology who have failed or unsuitable for cytokine therapy, 28-Jul-06
 2. NOC for advanced unresectable liver cancer, 28-Jan-08
1. Full NOC for advanced renal cancer of clear cell histology; conditions met on this date, 12-Jun-09
- 36 **Sunitinib (Sutent)**
1. NOC for relapsed GIST resistant or intolerant of imatinib, 16-May-06
 2. NOC/c for metastatic renal cell cancer of clear cell histology after failure of or unsuitable for cytokine therapy, 17-Aug-06
 3. NOC/c for metastatic renal cell cancer of clear cell histology (first line), 01-May-08
- 37 **Temozolomide (Temodal)**
1. NOC for GBM or anaplastic astrocytoma recurring or progressing after standard therapy, 25-Oct-99
 2. NOC for newly diagnosed glioblastoma multiforme concomitantly with radiotherapy and then maintenance treatment, 31-Jan-06
- 38 **Temsirolimus (Torisel)**
1. NOC for metastatic renal cell cancers, 21-Dec-07
- 39 **Thyrotropin-alfa (Thyrogen)**
1. NOC as adjunct diagnostic tool for serum thyroglobulin testing with or without radioiodine imaging of well differentiated thyroid cancer to avoid hypothyroid state, 31-May-02
 2. NOC as adjunct to radioactive iodine for remnant ablation to avoid hypothyroidism, 28-Aug-09
- 40 **I-131 tositumomab (Bexxar)**
1. NOC for CD20+ relapsed or refractory low grade, follicular or transformed NHL, 18-Aug-05
- 41 **Trastuzumab (Herceptin)**
1. NOC for Her2/Neu+ metastatic breast cancer, 13-Aug-99
 2. NOC for adjuvant treatment of Her2/Neu+ early breast cancer after surgery and conventional chemo, 18-Oct-06
- 42 **Zoledronic acid (Zometa)**
1. NOC for hypercalcemia of malignancy, 21-Aug-00
 2. NOC for bone metastasis from prostate cancer with standard antineoplastic therapy, 07-Aug-02
 3. NOC for bone metastasis from solid tumours and myeloma to prevent or delay bone complications, 04-Feb-03