Economic Analyses in Clinical Trials

Nicole Mittmann (and Natasha Leighl)

Committee on Economic Analysis (formerly, Working Group on Economic Analysis, NCIC CTG)

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Financial Disclosures

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Learning Objectives

- Review concepts including:
  - Need for economic evaluations
  - Cost effectiveness analysis
  - Cost utility analysis
  - Cost minimization analysis
  - Incremental cost effectiveness ratio (ICER)

- Review criteria for inclusion of economic analysis alongside clinical trials

Why do we need Economic Evaluations?

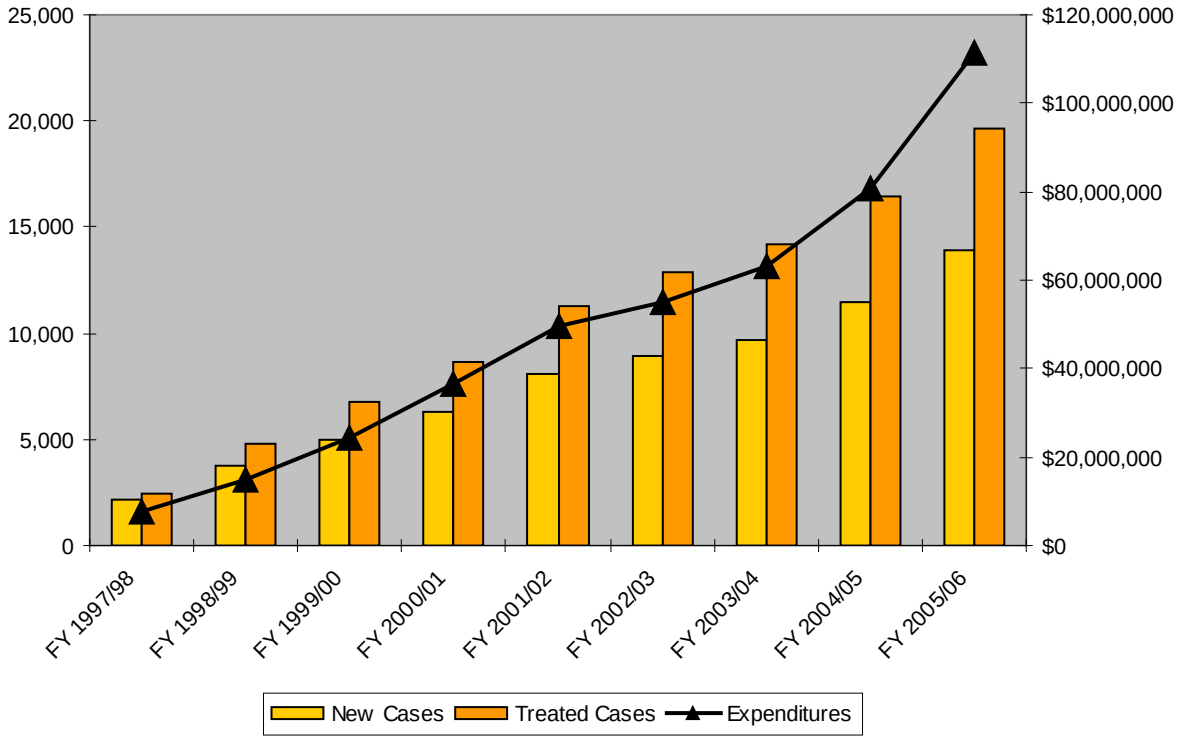
Drug Spending in Canada

- Drug spending estimated at $30 billion in 2008
- $900 per year per Canadian
- Prescription drugs estimated to account for 84% of total drug spending in 2008
- Amongst OECD countries, Canada has second-highest level of total per capita drug spending (including prescribed and non-prescribed drugs)
- United States (2006) has the highest level of per capita spending on drugs ($1,015), Canada ($770), Belgium ($703)

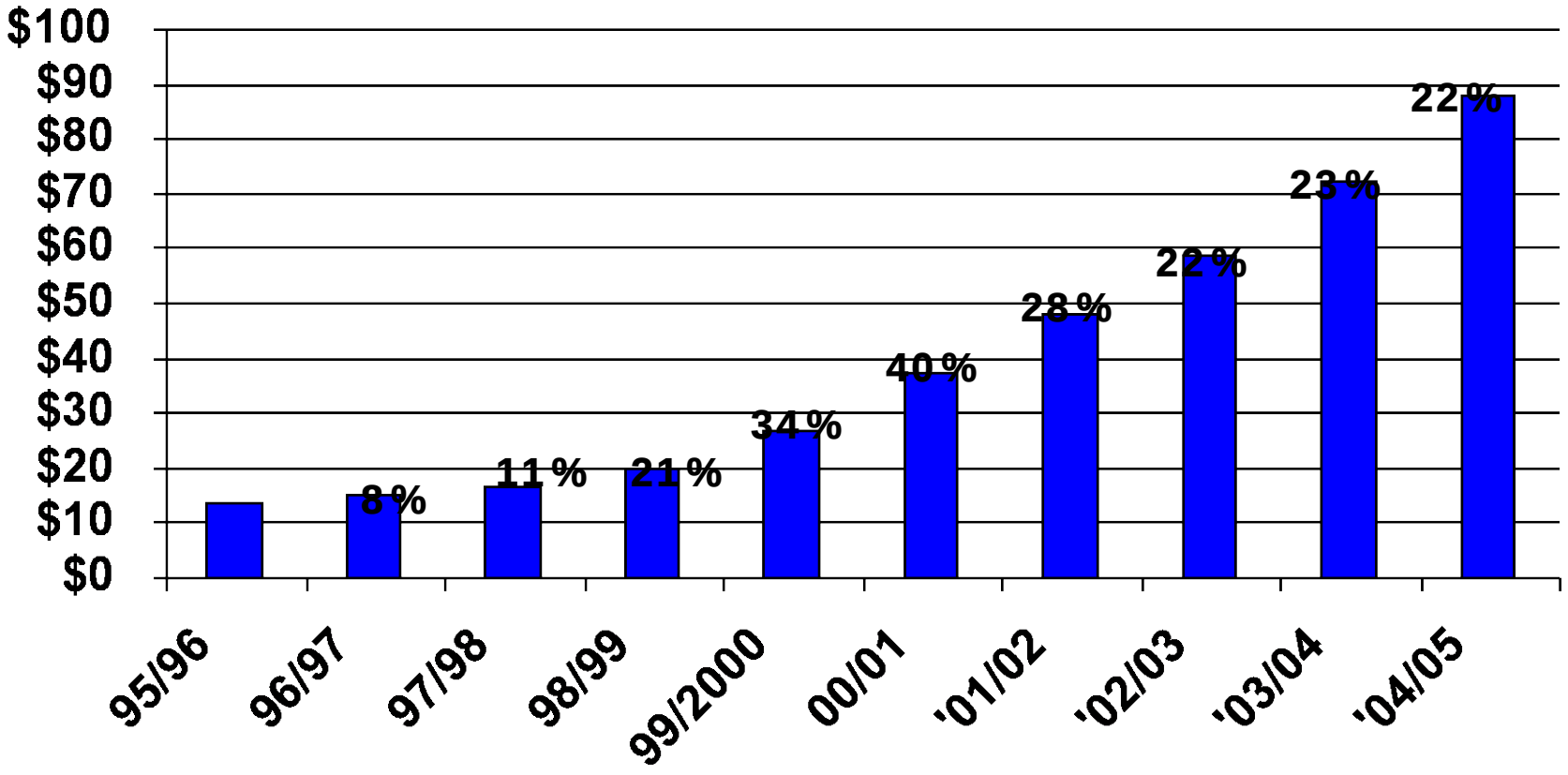
Economics and Cancer

- Cancer is growing problem – estimated cost of cancer care in US >$210 billion USD Meropol & Schulman, J Clin Oncol 2007;25(2):180-186
- New treatments that improve outcome should be adopted
- But with limited resources, economic constraints factor into resource allocation, in order to maximize population health
- 3 pillars of FDA approval of novel interventions:
  - Safety; Mechanism of action; Clinical efficacy
- 4th pillar - cost-effectiveness?
- Cost effectiveness – expression of an intervention's cost in relation to its benefit

NDFP Annual Expenditures and Cases

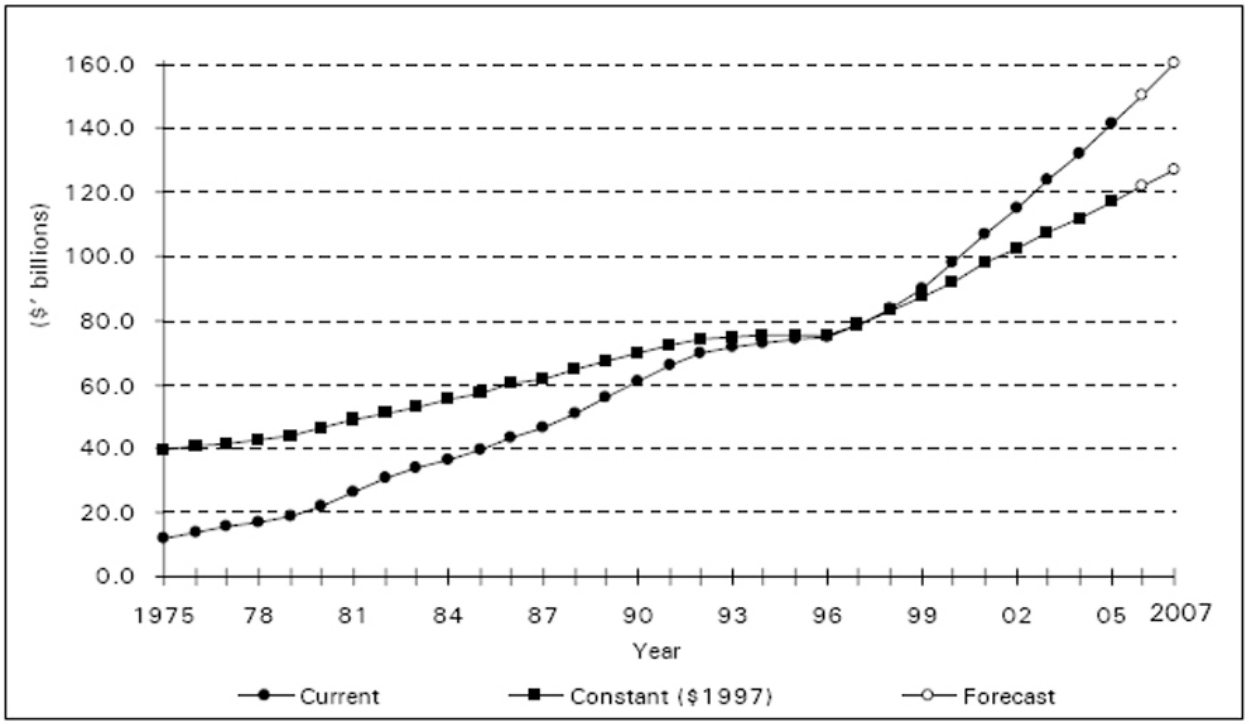


BCCA: Projected Growth in Provincial Drug Costs ($ Millions)



Total Health Expenditure

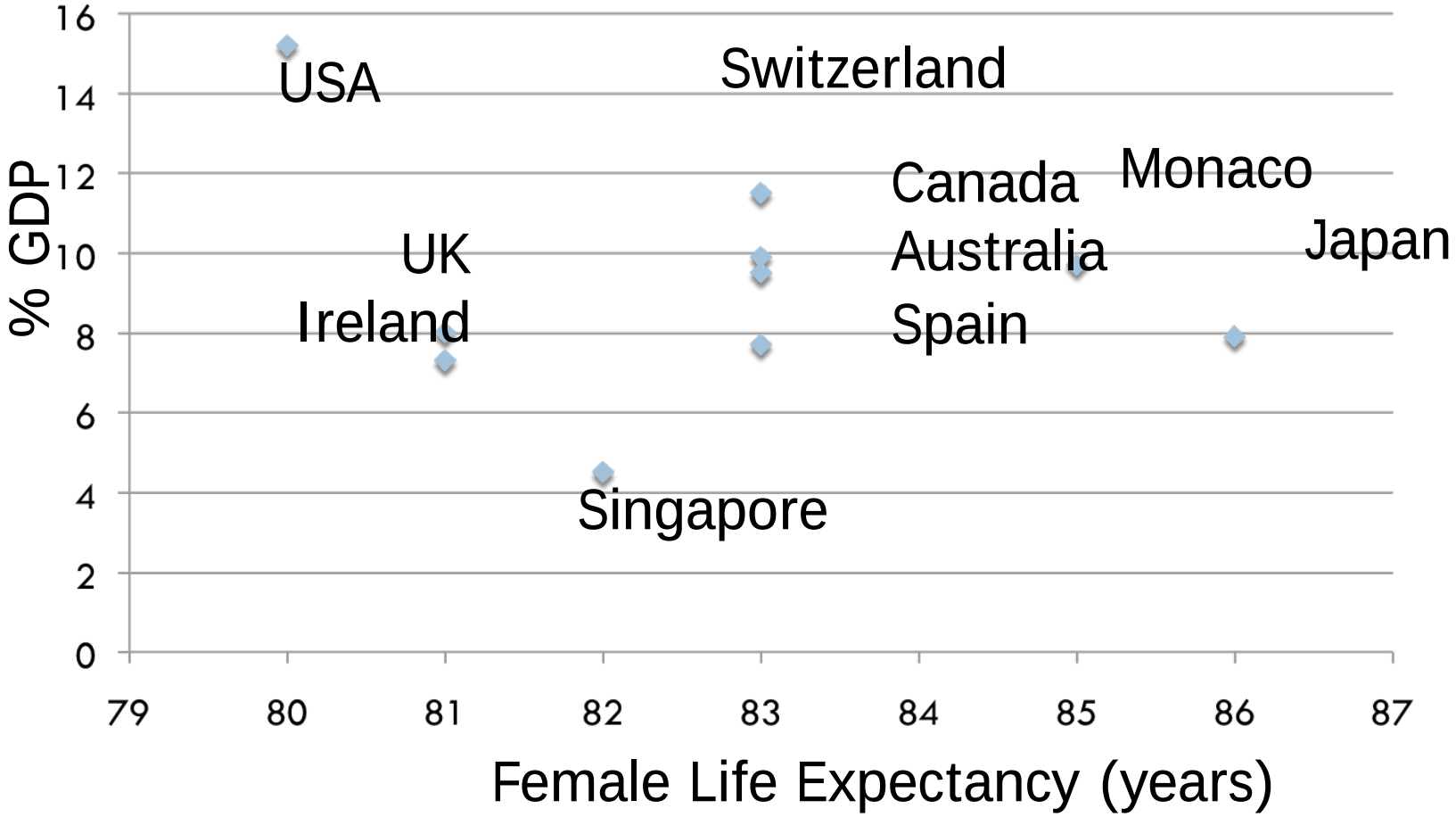
Figure 1. Total Health Expenditure, Canada, 1975 to 2007



Source: National Health Expenditure Database, CIHI.

From 1975-1991 average growth rate was 3.8%. Flattened growth in mid 1990s followed by strong growth since 1997

Cost of Health Care and Life Expectancy



Meropol & Schulman J Clin Oncol 2007

The Burden of the Disease will Increase

- Age
- Diseases
- Medications
- Home care
- Hospitals
- Devices/Technologies
- Screening

- **Need for "value for $" (hence Economic Analyses)**

Decision Making

- Efficacy
- Safety
- Cost-effectiveness

Committee on Economic Analysis

Formerly, Working Group on Economic Analysis

Mission

- Provide methodologic expertise and guidance to NCIC-CTG with respect to economic evaluations
- Contribute to national and international knowledge of economic evaluations in oncology

Goal

- Conduct economic evaluations based on NCIC-CTG trials
- Conduct methodologic studies using NCIC-CTG trial data

Membership List

- Co-Chairs – 1 economist, 1 oncologist
- Membership consists of
  - Disease site liaisons
  - Economists
  - Pharmacists
  - Administrator

- We are the only cooperative group with an economic analysis group!

CEA Liaisons

- In order to embed economic evaluations into NCIC CTG trials, need to increase profile of CEA members at level of disease site groups

- Leadership role in economic evaluation of oncology trials
- Liaise with payers and decision makers
- Active in targeting novel and expensive treatments
- Active in targeting non-drug studies
- Targeted economics
- Increase disease site participation
- Capacity Building Grants

Components of EA

- Outcomes
- Costs
- Quality of Life

Outcomes in a Clinical Trial

- Clinical Outcomes
  - OS, PFS, Tumour response
  - Adverse Events
- Others
  - Genotyping
  - "Patient Reported Outcomes"
  - Quality of Life
  - Resource Utilization
  - Health Preference
  - Economic outcomes
  - Complications

CEA Criteria for Determining if a Clinical Trial is Appropriate for an Economic Evaluation

- New intervention anticipated to have only a modest therapeutic benefit in a potentially large patient population
- Therapy potentially very costly
- High degree of uncertainty about economic impact of treatment
- Economic evaluation may yield important information in determining routine practice (e.g. equivalence trial)
- Economic data will assist future economic evaluations
- For intergroup trials, suitable number of Canadian patients (100)

Evans et al Chronic Dis Prev 2003

Incremental Cost Effectiveness Ratio

- ICER relates benefits of an intervention to its cost

- Incremental cost of Treatment A over B/

  Incremental benefit of Treatment A over B

- E.g. Cost of Treatment A $10,000; B $8,000 and improves survival by 1 year, quality-adjusted survival 0.8 years

- ICER – $2,000/LYG; $2,500/QALY

Components of EA

- Select type of analysis (CUA, CEA, CMA)
- Perspective – Societal; Payer (government), Patient
- Prospective or Retrospective Data Collection
- Resources and Costs – direct and indirect medical, lost productivity
- Time Horizon – lifetime; duration of clinical trial
  - What about after trial? Adjuvant – late effects, relapse and treatment
- Outcomes – OS in Phase III trial; (what about PFS in phase II?)
  - How do you value OS with cancer vs. cancer-free? Utilities, QALY
  - What about value of PFS, RR? Time with toxicity?
  - What comparator(s) should be used?
- Discounting – used for valuation of future costs, benefits
- Uncertainty – 95% confidence intervals, sensitivity analyses

Quality Adjusted Life Year (QALY)

- Integrates mortality and morbidity
- QALY= duration of health state * utility score during that health state
- 1 year with disease = fraction of a healthy year
- Considers impact on quality of life
- Considers impact of toxicity

Health Preference (Utility)

- Measure of health preference
  - 1-perfect health
  - 0-death
  - Average Canadian 0.92-0.96
  - Changes according to disease state
- Standardized tools available to measure
  - Direct-Time Trade Off, Standard Gamble
  - Indirect-HUI, EQ5D, VAS

Types of Economic Evaluation

- **Cost-effectiveness analysis (CEA)** – outcome measured units, e.g. life-years gained or clinical event avoided; sometimes used to refer to all economic evaluations

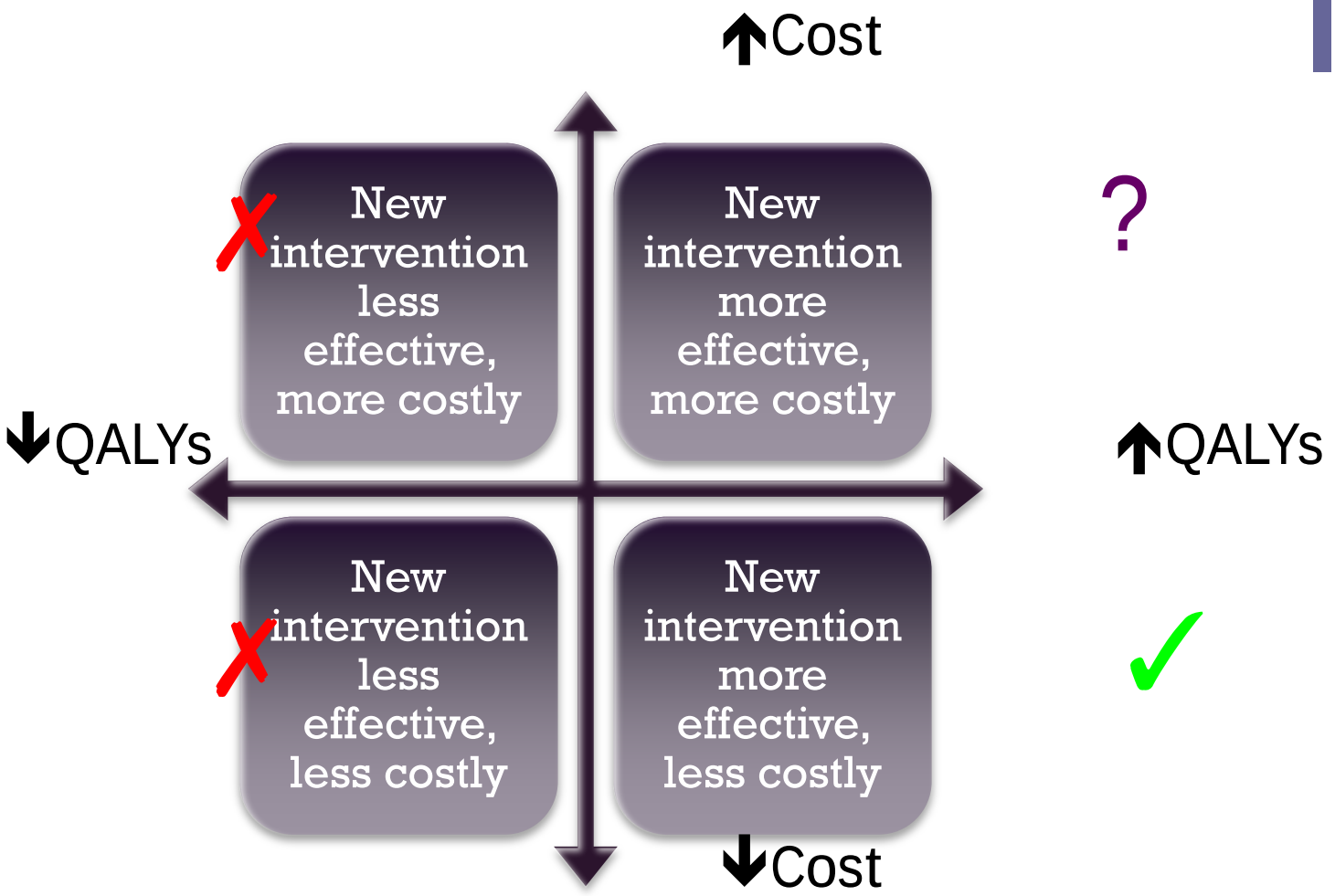
- **Cost-utility analysis (CUA)** – outcome measured in terms of health-related preference or value, e.g. quality-adjusted life-years (QALYs)

- **Cost-benefit analysis (CBA)** – values net benefits and opportunity costs in monetary terms

- **Cost-consequence analysis (CCA)** – costs and outcomes are listed separately in a disaggregated format, (no ICER)

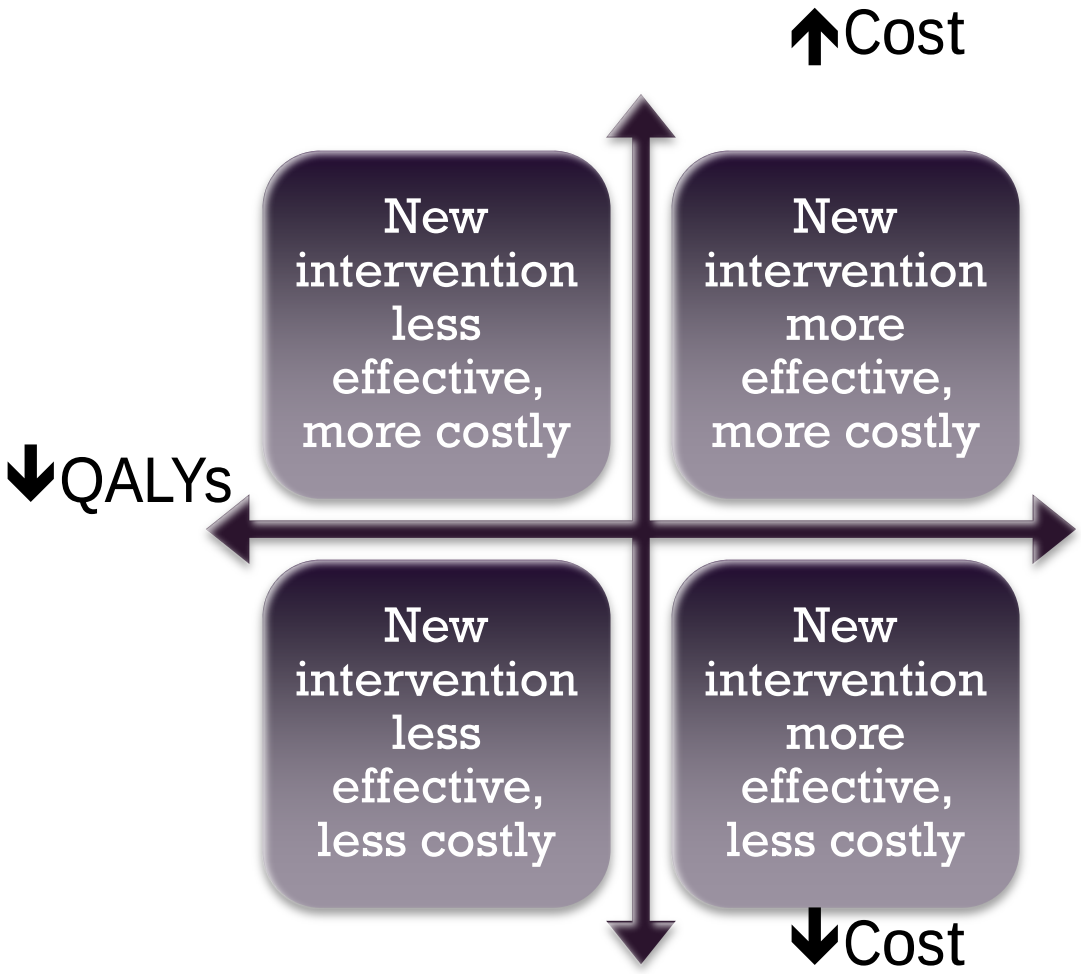
- **Cost-minimization analysis (CMA)** – Outcomes of intervention & alternatives are considered equivalent; alternative with lowest cost is selected

Adopting a New Technology



Laupacis et al. CMAJ 1992;146(4):473-81

Thresholds for Adopting Technology

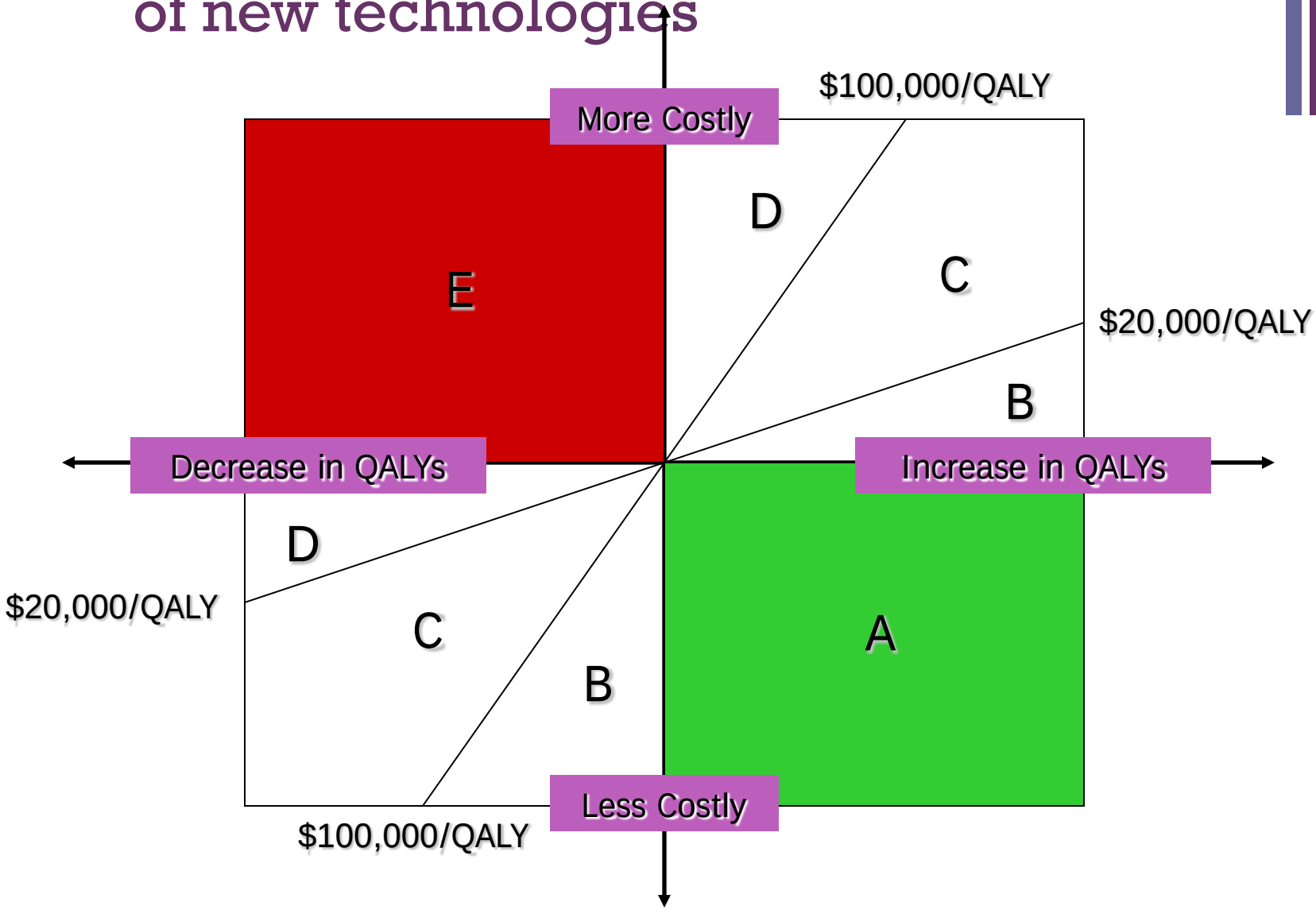


↑QALYs

$50K USD/QALY (1973) Hemodialysis

Laupacis et al. CMAJ 1992;146(4):473-81

Grades of recommendation for the adopti of new technologies



League Table of Values

INTERVENTION	COST/LY gained
bone marrow transplant	**$220,000**
inpatient hemodialysis	**$ 54,000**
neonatal ICU	**$ 30,900**
automobile airbags	**$ 20,000**
treatment of mild hypertension	**$ 19,100**
treatment of severe hypertension	**$ 9,400**
bypass surgery for left main	**$ 4,200**
mandatory smoke detectors	**$ 1,300**

Some Results from NCIC CTG trials

BR.10

- Adjuvant Chemotherapy in NSCLC
  - vinorelbine/cisplatin x 4 months vs. observation
  - HR OS 0.69 (p 0.04); 5y OS 69% v 54; 21m↑ MST
  - ICER $7,200/LYG (similar QALY) Ng et al. J Clin Oncol 2007

BR.21

- Palliative Erlotinib in NSCLC
  - HR OS 0.70 ($p<0.001$); 1y OS 31%v.21%;↑ QoL
  - ICER $96,000/LYG
  - Never smokers $39,500/LYG
  - EGFR FISH+ $33,350/LYG

Bradbury et al J Clin Oncol 2008

The NEW ENGLAND JOURNAL of MEDICINE

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Erlotinib in Previously Treated Non–Small-Cell Lung Cancer

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ABSTRACT

BACKGROUND

We conducted a randomized, placebo-controlled, double-blind trial to determine whether the epidermal growth factor receptor inhibitor erlotinib prolongs survival in non–small-cell lung cancer after the failure of first-line or second-line chemotherapy.

METHODS

Patients with stage IIIB or IV non–small-cell lung cancer, with performance status from 0 to 3, were eligible if they had received one or two prior chemotherapy regimens. The patients were stratified according to center, performance status, response to prior chemotherapy, number of prior regimens, and prior platinum-based therapy and were randomly assigned in a 2:1 ratio to receive oral erlotinib, at a dose of 150 mg daily, or placebo.

RESULTS

The median age of the 731 patients who underwent randomization was 61.4 years; 49 percent had received two prior chemotherapy regimens, and 93 percent had received platinum-based chemotherapy. The response rate was 8.9 percent in the erlotinib group and less than 1 percent in the placebo group ($P<0.001$); the median duration of the response was 7.9 months and 3.7 months, respectively. Progression-free survival was 2.2 months and 1.8 months, respectively (hazard ratio, 0.61, adjusted for stratification categories; $P<0.001$). Overall survival was 6.7 months and 4.7 months, respectively (hazard ratio, 0.70; $P<0.001$), in favor of erlotinib. Five percent of patients discontinued erlotinib because of toxic effects.

CONCLUSIONS

Erlotinib can prolong survival in patients with non–small-cell lung cancer after first-line or second-line chemotherapy.

From the Departments of Medical Oncology and Hematology (F.A.S.) and Radiation Oncology (A.B.), the University Health Network, Princess Margaret Hospital Site, and the University of Toronto (F.A.S., A.B.) — both in Toronto; the Instituto de Cancer Arnaldo Vieira de Carvalho, São Paulo (J.R.P.); the Oncological Institute Ion Chiricuta, Cluj-Napoca, Romania (T.C.); the Department of Medical Oncology, National Cancer Centre, Singapore (E.H.T.); the Department of Oncology, McGill University, Montreal (V.H.); the Faculty of Medicine, Chiangmai University, Chiangmai, Thailand (S.T.); the Confidence Medical Center, San Isidro, Argentina (D.C.); Pramongkutklao Hospital, Bangkok, Thailand (S.M.); Cross Cancer Institute, Edmonton, Alta., Canada (M.S.); the Instituto Nacional de Cancer, Praça da Cruz Vermelha, Rio de Janeiro, Brazil (R.M.); the Instituto Medico Alexander Fleming, Buenos Aires (M.K.); the Oncology Institute, Bucharest, Romania (M.D.); Hôtel Dieu Health Sciences Hospital, St. Catharines, Ont., Canada (B.F.); the National Cancer Institute of Canada Clinical Trials Group, Kingston, Ont., Canada (D.T., D.J., L.S.); and OSI Pharmaceuticals, Boulder, Colo. (G.C., P.S.).

*The investigators and centers participating in this National Cancer Institute of Canada Clinical Trials Group study are listed in the Appendix.

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ARTICLE

Economic Analysis: Randomized Placebo-Controlled Clinical Trial of Erlotinib in Advanced Non–Small Cell Lung Cancer

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Background The NCIC Clinical Trials Group conducted the BR.21 trial, a randomized placebo-controlled trial of erlotinib (an epidermal growth factor receptor tyrosine kinase inhibitor) in patients with previously treated advanced non–small cell lung cancer. This trial accrued patients between August 14, 2001, and January 31, 2003, and found that overall survival and quality of life were improved in the erlotinib arm than in the placebo arm. However, funding restrictions limit access to erlotinib in many countries. We undertook an economic analysis of erlotinib treatment in this trial and explored different molecular and clinical predictors of outcome to determine the cost-effectiveness of treating various populations with erlotinib.

Methods Resource utilization was determined from individual patient data in the BR.21 trial database. The trial recruited 731 patients (488 in the erlotinib arm and 243 in the placebo arm). Costs arising from erlotinib treatment, diagnostic tests, outpatient visits, acute hospitalization, adverse events, lung cancer–related concomitant medications, transfusions, and radiation therapy were captured. The incremental cost-effectiveness ratio was calculated as the ratio of incremental cost (in 2007 Canadian dollars) to incremental effectiveness (life-years gained). In exploratory analyses, we evaluated the benefits of treatment in selected subgroups to determine the impact on the incremental cost-effectiveness ratio.

Results The incremental cost-effectiveness ratio for erlotinib treatment in the BR.21 trial population was $94 638 per life-year gained (95% confidence interval = $52 359 to $429 148). The major drivers of cost-effectiveness included the magnitude of survival benefit and erlotinib cost. Subgroup analyses revealed that erlotinib may be more cost-effective in never-smokers or patients with high *EGFR* gene copy number.

Conclusion With an incremental cost-effectiveness ratio of $94 638 per life-year gained, erlotinib treatment for patients with previously treated advanced non–small cell lung cancer is marginally cost-effective. The use of molecular predictors of benefit for targeted agents may help identify more or less cost-effective subgroups for treatment.

J Natl Cancer Inst 2010;102:1–9

Lung cancer is the leading cause of cancer-related death and imposes a considerable public health burden across the world (1). In Canada in 1998, it was estimated that the cost arising from lung cancer–related hospital care and mortality costs was $3.0 billion (Canadian dollars) (2). Estimates from the United States indicate that the cost of treating each lung cancer patient has increased by more than a factor of five from 1991 to 2002 (3). These costs may increase even more with the development of novel targeted therapies for lung cancer.

Non–small cell lung cancer (NSCLC) accounts for 85% of all primary lung cancers. The disease frequently presents in an advanced stage when cure is not possible, and treatment intent is palliative. First- and second-line chemotherapy is the standard of care for patients who have advanced NSCLC and a good performance status; such therapy has improved symptom control and survival benefits compared with best supportive care (4–6). After chemotherapy has failed, the only treatment shown to provide additional quality of life and survival benefit is the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, erlotinib (7,8).

The NCIC Clinical Trials Group undertook an international, randomized, placebo-controlled trial of erlotinib after the failure of first- or second-line chemotherapy, the BR.21 trial (NCT00036647, http://www.clinicaltrials.gov) (7). This landmark trial enrolled patients between August 14, 2001, and January 31, 2003, and was the first to demonstrate an advantage for an EGFR tyrosine kinase inhibitor in overall survival and in quality of life (7,8). Funding restrictions in many countries limit a patient's access to erlotinib; therefore, an accurate evaluation of the cost-effectiveness of erlotinib is important if patients are to have access to this therapy in publically funded health systems.

ICER of Subgroups based on clinical predictors of outcome

Characteristic	Number	ICER
Gender		
Female	256	$ 120,671.00
Male	475	$ 96,600.71
Histology		
Adenocarcinoma	365	$ 75,058.59
Non-adenocarcinoma	366	$ 239,978.38
Smoking Status		
Never Smoker	146	$ 39,486.54
Smoker (past/present)	545	$ 504,910.80
Ethnicity		
Asian	91	$ 83,181.17
Other	640	$ 109,380.43
Number of Prior Chemotherapy Regimens		
1	364	$ 67,843.85

ICER of Sub-groups Based on Molecular Predictors of Outcome

Characteristic	Number	ICER
EGFR Protein Expression		
Positive	184	$ 63,804.68
Negative	141	$ 469,002.59
EGFR gene mutation		
Exon 19 deletion and/or exon 21 L858R mutation	34	$ 138,168.32
Wildtype	170	$ 87,993.71
KRAS gene mutation		
Mutated	30	BSC dominant
Wildtype	176	$ 76,657.28
EGFR gene amplification		
Amplified	61	$ 33,353.01

CO.17

- OS of cetuximab + BSC vs. BSC was significantly longer
  - The trial demonstrated a significant survival advantage in the cetuximab arm, with an improved median overall survival of **6.1 months vs. 4.6 months** in the BSC group (HR 0.77, $p<0.005$) in patients with advanced colon cancer and patients intolerant to or progressing on prior irinotecan- and oxaliplatin-based regimens.
- KRAS wild type cohort had greater overall survival than the total population
  - In KRAS wildtype patients, the trial demonstrated a significant survival advantage in the cetuximab arm, with an improved median overall survival of **9.5 months vs. 4.8 months** in the BSC group (HR 0.55, $p<0.005$) in patients with advanced colon cancer and patients intolerant to or progressing on prior irinotecan- and oxaliplatin-based regimens.

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K-ras Mutations and Benefit from Cetuximab in Advanced Colorectal Cancer

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ABSTRACT

BACKGROUND

Treatment with cetuximab, a monoclonal antibody directed against the epidermal growth factor receptor, improves overall and progression-free survival and preserves the quality of life in patients with colorectal cancer that has not responded to chemotherapy. The mutation status of the *K-ras* gene in the tumor may affect the response to cetuximab and have treatment-independent prognostic value.

METHODS

We analyzed tumor samples, obtained from 394 of 572 patients (68.9%) with colorectal cancer who were randomly assigned to receive cetuximab plus best supportive care or best supportive care alone, to look for activating mutations in exon 2 of the *K-ras* gene. We assessed whether the mutation status of the *K-ras* gene was associated with survival in the cetuximab and supportive-care groups.

RESULTS

Of the tumors evaluated for *K-ras* mutations, 42.3% had at least one mutation in exon 2 of the gene. The effectiveness of cetuximab was significantly associated with *K-ras* mutation status ($P=0.01$ and $P<0.001$ for the interaction of *K-ras* mutation status with overall survival and progression-free survival, respectively). In patients with wild-type *K-ras* tumors, treatment with cetuximab as compared with supportive care alone significantly improved overall survival (median, 9.5 vs. 4.8 months; hazard ratio for death, 0.55; 95% confidence interval [CI], 0.41 to 0.74; $P<0.001$) and progression-free survival (median, 3.7 months vs. 1.9 months; hazard ratio for progression or death, 0.40; 95% CI, 0.30 to 0.54; $P<0.001$). Among patients with mutated *K-ras* tumors, there was no significant difference between those who were treated with cetuximab and those who received supportive care alone with respect to overall survival (hazard ratio, 0.98; $P=0.89$) or progression-free survival (hazard ratio, 0.99; $P=0.96$). In the group of patients receiving best supportive care alone, the mutation status of the *K-ras* gene was not significantly associated with overall survival (hazard ratio for death, 1.01; $P=0.97$).

CONCLUSIONS

Patients with a colorectal tumor bearing mutated *K-ras* did not benefit from cetuximab, whereas patients with a tumor bearing wild-type *K-ras* did benefit from cetuximab. The mutation status of the *K-ras* gene had no influence on survival among patients treated with best supportive care alone. (ClinicalTrials.gov number, NCT00079066.)

From Flinders Medical Centre and Flinders University, Adelaide, Australia (C.S.K.); Bristol-Myers Squibb Research and Development, Princeton, NJ (S.K.-F.); Ottawa Hospital Research Institute, University of Ottawa, Ottawa (D.J.J.); National Cancer Institute of Canada Clinical Trials Group, Kingston, ON (C.J.O., D.T., S.R., L.S.); Austin Health, Melbourne, Australia (N.C.T.); National Health and Medical Research Council Clinical Trials Centre, University of Sydney, Sydney (R.J.S.); Allan Blair Cancer Centre, Regina, SK, Canada (H.C.); Cabrini Hospital and Alfred Hospital, Melbourne, Australia (J.D.S.); Queen Elizabeth Hospital and University of Adelaide, Adelaide, Australia (T.J.P.); Cross Cancer Institute, Edmonton, AB, Canada (H.-J.A.); Bristol-Myers Squibb, Wallingford, CT (C.L.); Princess Margaret Hospital, Toronto (M.J.M.); and Peter MacCallum Cancer Centre and University of Melbourne, Melbourne, Australia (J.R.Z.). Address reprint requests to Dr. Karapetis at the Department of Medical Oncology, Flinders Medical Centre, Flinders Dr., Bedford Park, SA 5042, Australia, or at c.karapetis@flinders.edu.au.

*Other participants in the CO.17 trial from the National Cancer Institute of Canada Clinical Trials Group and the Australasian Gastro-Intestinal Trials Group are listed in the Supplementary Appendix, available with the full text of this article at www.nejm.org.

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ARTICLE

Prospective Cost-Effectiveness Analysis of Cetuximab in Metastatic Colorectal Cancer: Evaluation of National Cancer Institute of Canada Clinical Trials Group CO.17 Trial

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Background The National Cancer Institute of Canada Clinical Trials Group CO.17 study showed that patients with advanced colorectal cancer had improved overall survival when cetuximab, an epidermal growth factor receptor–targeting antibody, was given in addition to best supportive care. We conducted a cost-effectiveness analysis using prospectively collected resource utilization and health utility data for patients in the CO.17 study who received cetuximab plus best supportive care (N = 283) or best supportive care alone (N = 274).

Methods Direct medical resource utilization data were collected, including medications, physician visits, toxicity management, blood products, emergency department visits, and hospitalizations. Mean survival times for the study arms were calculated for the entire population and for the subset of patients with wild-type *KRAS* tumors over an 18- to 19-month period. All costs were presented in 2007 Canadian dollars. One-way and probabilistic sensitivity analysis was used to determine the robustness of the results. Cost-effectiveness acceptability curves were determined. The 95% confidence intervals (CIs) for the incremental cost-effectiveness ratios and the incremental cost–utility ratios were estimated by use of a nonparametric bootstrapping method (with 1000 iterations).

Results For the entire study population, the mean improvement in overall and quality-adjusted survival with cetuximab was 0.12 years and 0.08 quality-adjusted life-years (QALYs), respectively. The incremental cost with cetuximab compared with best supportive care was $23 969. The incremental cost-effectiveness ratio was $199 742 per life-year gained (95% CI = $125 973 to $652 492 per life-year gained) and the incremental cost–utility ratio was $299 613 per QALY gained (95% CI = $187 440 to $898 201 per QALY gained). For patients with wild-type *KRAS* tumors, the incremental cost with cetuximab was $33 617 and mean gains in overall and quality-adjusted survival were 0.28 years and 0.18 QALYs, respectively. The incremental cost-effectiveness ratio was $120 061 per life-year gained (95% CI = $88 679 to $207 075 per life-year gained) and the incremental

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See "Funding" and "Notes" following "References."

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Results

Population	ICER	ICUR
Total Study Cohort	$200,000/LYG	$300,000/QALY
KRAS wildtype Cohort	$120,000/LYG	$187,000/QALY

HTA

Addendum to CADTH's Guidelines for the Economic Evaluation of Health Technologies: Specific Guidance for Oncology Products

DECEMBER 2009

NCIC CTG
NCIC GEC

Issues

- Ranking of importance of information
- Compliance with the completion of the "Other"
- Cost of embedding economic parameters
  - Time horizon/extrapolation
  - Compliance with completion
  - Workload
  - Electronic Data Collection
- Methods of collection
  - Prospective / retrospective

Economic Analyses in Clinical Trials

- Important addition to strengthen, complement results of ongoing clinical trials
- Helps clinicians, patients and policy-makers interpret value of novel interventions
- Timely economic evaluation of CTG interventions may facilitate uptake of novel therapies

Final Lessons

- There will be opportunities to reduce costs (e.g., an inexpensive blood test can replace the need for repeated endomyocardial biopsy), but there may be MORE opportunities to increase costs.
- The key issue will be considering the increased costs in relation to the increased benefit.
- Other "soft" factors (e.g., Social, Legal, Ethical & Equitable, Environmental, Political) will be important to consider.

Learnings

- Resources
- Different areas of oncology
- Health preference (longitudinal)
- Sample size


SIGH!
BETWEEN YOU AND ME, THEY'RE MUCH MORE EXPENSIVE THAN THE GENERIC, AND NOWHERE NEAR AS GOOD!
A DOCTOR
SAMPLES
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