

Accomplishments of NCIC CTG BR.10 8 January 2010

With our recently implemented annual process to review trials that can be closed to further follow-up, we have an opportunity to reflect on NCIC CTG trials that epitomize the role of an academic cooperative group in conceiving and conducting research that has extraordinary implications for health care delivery on an international level. BR.10 is an outstanding example of such a trial.

The BR.10 trial was activated on July 7, 1994 and compared adjuvant chemotherapy consisting of vinorelbine and cisplatin with observation in patients with completely resected Stage IB and II non-small cell lung cancer (NSCLC). Led by the NCIC CTG, the trial included collaboration with SWOG, ECOG and CALGB, resulting in the international branding of the trial as JBR.10. Between 1994 and 2001, 482 patients were accrued. The primary analysis demonstrated that four cycles of vinorelbine and cisplatin substantially improved overall survival (median 94 vs. 73 months; 5-year 69% vs. 54%).

Updated analyses confirm that with a median follow-up of nine years benefits persist. Secondary analyses demonstrated that adjuvant therapy was associated with transient and tolerable decrements in quality of life that resolved quickly and with ultimate benefits being seen. The treatment is exceptionally cost-effective; the BR.10 trial was NCIC CTG's first publication by our Working Group on Economic Analysis. This study has had a major influence in changing practice world-wide, and forms the basis of provincial, national and international (ASCO) guidelines for the adjuvant treatment of NSCLC. The development of a comprehensive bio-bank for this study, including snap frozen tissues, makes it unique. Numerous ancillary analyses have been conducted, including international meta-analyses (MRC UK, LACE), correlative studies, quality adjusted survival, as well as subset analyses in the elderly.

The publication list associated with BR.10 is extensive. Sixteen research papers have resulted from the BR.10 trial, including a recent updated survival analysis, and these have been published in high impact journals that include the New England Journal of Medicine and the Journal of Clinical Oncology. According to Google Scholar, the primary publication has been cited 543 times (January 7, 2010). Additionally, 32 abstracts have been presented or published; most recently, four were presented at the 2009 World Conference on Lung Cancer.

In closing BR.10, it is important that those responsible for this outstanding accomplishment be recognized. Frances Shepherd provided extraordinary leadership in developing this trial, formulating the collaborations that resulted in its successful conduct and overseeing the strategic implementation of database exploration. Without Dr. Shepherd's leadership, the trial would not have occurred. Special recognition also goes to the Study Chair, Timothy Winton, whose leadership exemplifies the collaboration with thoracic surgeons that was essential to this project. BR.10 was the first adjuvant lung cancer trial to collect a study-associated tumour bank prospectively and to stratify by an oncogene marker. Studies using BR.10 tumour samples have focused on many individual gene pathways as well as genome-wide microarray studies. The

exceptional capacity to perform correlative studies was a product of the efforts of Jean Viallet, Frances Shepherd and Ming Tsao; this work was possible because of support provided by Glaxo Wellcome. The contributions of our Intergroup partners at SWOG (led by Robert Livingston and Thomas Rice), ECOG (Russell Devore and Kenneth Kesler) and CALGB (James Rigas and Todd Demmy), and the support of CTEP are deeply appreciated.

A host of NCIC CTG Central Office faculty and staff made BR.10 happen; outstanding leadership, wisdom and long hours of toil were provided by Lesley Seymour and Keyue Ding. With the study now spanning the better part of two decades since a process to initiate the concept began, it is not surprising to know that other faculty played crucial roles including Keith James, Joe Pater, Benny Zee and Dongsheng Tu. A series of Study Coordinators provided exemplary support including Jon Ottaway, Barbara Graham and Nadine Magoski. Shakeel Virk greatly facilitated the ability to conduct the translational research. Our thanks and congratulations go to each of these trial leaders and the many investigators, clinical research associates, and Central Office staff who have contributed to this outstanding project.

With future closure of NCIC CTG trials, we will continue to make note of those that have been associated with particularly outstanding research accomplishments. We are developing a user-friendly linkage on our website so that those interested can find primary publications associated with a specific closed trial. The special accomplishments of BR.10 exceed the capacity of that website! In the meantime, we will post this Bulletin item as a memo, with the listed citations on the "Permanent Trial Closure" website at <http://www.ctg.queensu.ca/trials/closure.html>.

Below we list the "curriculum vitae" of the BR.10 trial. Please take note of the large number of investigators, including "new investigators" who have contributed to the outstanding success of BR.10.

Article Publications

Primary Results and Follow-Up

Winton T, Livingston R, Johnson D, Rigas J, Johnston M, Butts C, Cormier Y, Goss G, Inculet R, Vallieres E, Fry W, Bethume D, Ayoub J, Ding K, Seymour L, Graham B, Tsao M-S, Gandara D, Kesler K, Demmy T, Shepherd F. Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. *N Engl J Med* 352: 2589-97, 2005.

Butts CA, Ding K, Seymour L, Twumasi-Ankrah P, Graham B, Gandara D, Johnson DH, Kesler KA, Green M, Vincent M, Cormier Y, Goss G, Findlay B, Johnston M, Tsao M-S, Shepherd FA. Randomized phase III trial of vinorelbine plus cisplatin compared with observation in completely resected stage IB and II non-small-cell lung cancer: updated survival analysis of JBR-10. *J Clin Oncol* 28: 29-34, 2010.

Secondary Endpoints

Jang RW, Le Maître A, Ding K, Winton T, Bezjak A, Seymour L, Shepherd FA, Leighl NB. Quality-adjusted time without symptoms or toxicity analysis of adjuvant chemotherapy in non-small-cell lung cancer: An analysis of the National Cancer Institute of Canada Clinical Trials Group JBR.10 trial. *J Clin Oncol* 27: 4268-73, 2009.

Bezjak A, Lee CW, Ding K, Brundage M, Winton T, Graham B, Whitehead M, Johnson DH, Livingston RB, Seymour L, Shepherd FA. Quality-of-life outcomes for adjuvant chemotherapy in early-stage non-small-cell lung cancer: results from a randomized trial, JBR.10. *J Clin Oncol* 26: 5052-9, 2008.

Ng R, Hasan B, Mittmann N, Florescu M, Shepherd FA, Ding K, Butts CA, Cormier Y, Darling G, Goss GD, Inculet R, Seymour L, Winton TL, Evans WK, Leighl NB. Economic analysis of NCIC CTG JBR.10: A randomized trial of adjuvant vinorelbine plus cisplatin compared with observation in early stage non-small-cell lung cancer - A report of the Working Group on Economic Analysis, and the Lung Disease Site Group, National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 25: 2256-61, 2007.

Subsets and Special Analyses

Hicks LK, Cheung MC, Ding K, Hasan B, Seymour L, Le Maître A, Leighl NB, Shepherd FA. Venous thromboembolism and nonsmall cell lung cancer: a pooled analysis of National Cancer Institute of Canada Clinical Trials Group trials. *Cancer* 115: 5516-25, 2009.

Asmis TR, Ding K, Seymour L, Shepherd FA, Leighl NB, Winton TL, Whitehead M, Spaans JN, Graham BC, Goss GD. Age and comorbidity as independent prognostic factors in the treatment of non-small-cell lung cancer: a review of National Cancer Institute of Canada Clinical Trials Group trials. *J Clin Oncol* 26: 54-9, 2008.

Gauthier I, Ding K, Winton T, Shepherd FA, Livingston R, Johnson DH, Rigas JR, Whitehead M, Graham B, Seymour L. Impact of hemoglobin levels on outcomes of adjuvant chemotherapy in resected non-small cell lung cancer: The JBR.10 trial experience. *Lung Cancer* 55: 357-63, 2007.

Pepe C, Hasan B, Winton TL, Seymour L, Graham B, Livingston RB, Johnson DH, Rigas JR, Ding K, Shepherd FA. Adjuvant vinorelbine and cisplatin in elderly patients: National Cancer Institute of Canada and Intergroup study JBR.10. *J Clin Oncol* 25: 1553-61, 2007.

Alam N, Shepherd FA, Winton T, Graham B, Johnson D, Livingston R, Rigas J, Whitehead M, Ding K, Seymour L. Compliance with post-operative adjuvant chemotherapy in non-small cell lung cancer. An analysis of National Cancer Institute of Canada and intergroup trial JBR.10 and a review of the literature. *Lung Cancer* 47: 385-94, 2005.

Contributions to Pooling

Douillard J-Y, Tribodet H, Aubert D, Shepherd FA, Rosell R, Ding K, Veillard A-S, Seymour L, LeChevalier T, Spiro S, Stephens R, Pignon J-P, on behalf of the LACE Collaborative Group. Adjuvant cisplatin and vinorelbine for completely resected non-small cell lung cancer: Subgroup analysis of the Lung Adjuvant Cisplatin Evaluation (LACE). *J Thoracic Oncol*. 2009. (In Press)

Früh M, Rolland E, Pignon J-P, Seymour L, Ding K, Tribodet H, Winton T, LeChevalier T, Scagliotti GV, Douillard JY, Spiro S, Shepherd FA. Pooled analysis of the effect of age on adjuvant cisplatin-based chemotherapy for completely resected non-small-cell lung cancer. *J Clin Oncol* 26: 3573-81, 2008.

Pignon J-P, Tribodet H, Scagliotti GV, Douillard J-Y, Shepherd FA, Stephens RJ, Dunant A, Torri V, Rosell R, Seymour L, Spiro SG, Rolland E, Fossati R, Aubert D, Ding K, Waller D, LeChevalier T. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. *J Clin Oncol* 26: 3552-9, 2008.

Correlative Biology

Shedden K, Taylor JMG, Enkemann SA, Tsao M-S, Yeatman TJ, Gerald WL, Eschrich S, Jurisica I, Giordano TJ, Misek DE, Chang AC, Zhu CQ, Strumpf D, Hanash S, Shepherd FA, Ding K, Seymour L, Naoki K, Pennell N, Weir B, Verhaak R, Ladd-Acosta C, Golub T, Gruidl M, Sharma A, Szoke J, Zakowski M, Rusch V, Kris M, Viale A, Motoi N, Travis W, Conley B, Seshan VE, Meyerson M, Kuick R, Dobbin KK, Lively T, Jacobson JW, Beer DG. Gene expression-based survival prediction in lung adenocarcinoma: a multi-site, blinded validation study. *Nature Medicine* 14: 822-7, 2008.

Sève P, Lai R, Ding K, Winton T, Butts C, Mackey J, Dumontet C, Dabbagh L, Aviel-Ronen S, Seymour L, Whitehead M, Tsao M-S, Shepherd FA, Reiman T. Class III β -tubulin expression and benefit from adjuvant cisplatin/vinorelbine chemotherapy in operable non-small cell lung cancer: Analysis of NCIC JBR.10. *Clin Cancer Res* 13: 994-9, 2007.

Tsao M-S, Aviel-Ronen S, Ding K, Lau D, Liu N, Sakurada A, Whitehead M, Zhu C-Q, Livingston R, Johnson DH, Rigas J, Seymour L, Winton T, Shepherd FA. Prognostic and predictive importance of p53 and RAS for adjuvant chemotherapy in non-small-cell lung cancer. *J Clin Oncol* 25: 5240-7, 2007.

Abstract Publications

Primary Results and Follow-Up

Winton T, Livingston R, Johnson D, Rigas J, Cormier Y, Butts C, Ding K, Seymour L, Magoski N, Shepherd F. A prospective randomised trial of adjuvant vinorelbine and cisplatin in completely resected stage 1B and II non-small cell lung cancer. Intergroup JBR.10. *Proc Am Soc Clin Oncol* 23. 2004.

Vincent MD, Butts C, Seymour L, Ding K, Graham B, Twumasi-Ankrah P, Gandara D, Schiller J, Green M, Shepherd F. Updated survival analysis of JBR.10: A randomized phase III trial of vinorelbine/cisplatin versus observation in completely resected stage IB and II non-small cell lung cancer. *J Clin Oncol* 27[15s]. 2009.

Secondary Endpoints

Jang RW, Le Maître A, Ding K, Winton TL, Bezjak A, Seymour L, Shepherd FA, Leighl NB. A Q-TWiST analysis of adjuvant chemotherapy in non-small cell lung cancer in the NCIC CTG JBR.10 trial. *Proc Am Soc Clin Oncol* 26[15S Part I], 345s. 2008.

Ng R, Mittmann N, Florescu M, Shepherd FA, Salvarrey A, Seymour L, Winton T, Evans B, Leighl N, Canadian JBR.10 Investigators. An economic analysis of National Cancer Institute of Canada Clinical Trials Group JBR.10, a randomized trial of adjuvant vinorelbine plus cisplatin versus observation in early stage non-small cell lung cancer. *Proc Am Soc Clin Oncol* 24[18S Part 1], 402. 2006.

Shepherd F, Winton T, Livingston R, Johnson D, Rigas J, Cormier Y, Bezjak A, Ding K, Graham B, Seymour L. The impact of adjuvant vinorelbine and cisplatin on quality of life: Results from the National Cancer Institute of Canada Clinical Trials Group Trial BR.10 Randomised trial of VIN/CIS versus observation in stage IB and II non-small cell lung cancer. *Ann Oncol* 15[Suppl 3], iii165. 2004.

Bezjak A, Winton T, Ding K, Graham B, Seymour L, Ayoub J, Livingston R, Vallieres E, Rigas J, Demmy T, Devore R, Kessler K, Shepherd F. Quality of life in a trial of adjuvant chemotherapy for early stage completely resected non-small cell lung cancer (NCIC CTG BR.10). *Lung Cancer* 41[2], a0-58. 2003.

Bezjak A, Winton T, Ding K, Graham B, Seymour L, Ayoub J, Livingston R, Vallieres E, Rigas J, Demmy T, Devore R, Kessler K. Does adjuvant chemotherapy impair quality of life? Results of the NCIC CTG BR.10 trial of adjuvant navelbine/cisplatin for early stage completely resected non-small cell lung cancer. *International Society for Quality of Life Research*. 2003.

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Hicks L, Cheung M, Hasan B, Ding K, Seymour L, Leighl NB, Winton TL, Shepherd FA. Venous thromboembolism and non-small cell lung cancer: a pooled analysis of National Cancer Institute of Canada Clinical Trials Group. *Blood* 110[11]. 2007.

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review of prospectively randomized National Cancer Institute of Canada Clinical Trials Group trials. Proc Am Soc Clin Oncol 24[18S Part 1], 393. 2006.

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Asmis T, Ding K, Shepherd F, Leighl N, Seymour L. Are age and co morbidity independent prognostic factors in the treatment of metastatic non-small cell lung cancer. A review of a National Cancer Institute of Canada Clinical Trials Group randomized trial. Lung Cancer 49[Suppl 2], S85. 2005.

Gauthier I, Ding K, Winton T, Shepherd F, Livingston R, Johnson D, Rigas J, Whitehead M, Graham B, Seymour L. Do hemoglobin levels influence outcomes of adjuvant chemotherapy with cisplatin/vinorelbine in patients with completely resected non small cell lung cancer? The JBR.10 trial experience. Lung Cancer 49[Suppl 2], S280. 2005.

Gauthier I, Ding K, Winton T, Shepherd F, Livingston R, Johnson DH, Rigas JR, Whitehead M, Graham B, Seymour L. Impact of hemoglobin on outcomes of adjuvant chemotherapy with cisplatin/vinorelbine in patients with completely resected non small cell lung cancer in JBR.10. Proc Am Soc Clin Oncol 23[16S Part 1], 670s. 2005.

Alam N, Shepherd F, Winton T, Graham B, Johnson D, Livingston R, Rigas J, Whitehead M, Ding K, Seymour L. Compliance with adjuvant chemotherapy in non-small cell lung cancer: NCIC-CTG BR.10/JBR.10. Proc Am Soc Clin Oncol 22, 633. 2003.

Contributions to Pooling

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Douillard J, Tribodet H, Ha P, Shepherd F, Ding K, Winton T, LeChevalier T, Spiro S, Stephens R, Pignon JP. Lung adjuvant cisplatin evaluation (LACE vinorelbine project): Pooled analysis of adjuvant vinorelbine-cisplatin trials for completely resected non-small cell lung cancer. Ann Oncol 17[Suppl 9], 213. 2006.

Wheatley-Price P, Le Maître A, Ding K, Leighl NB, Hirsh V, Seymour L, Shepherd FA. The influence of sex on efficacy, toxicity and delivery of treatment in National Cancer Institute of

Canada Clinical Trials Group non-small cell lung cancer chemotherapy trials. Proc Am Soc Clin Oncol 26[15S Part I], 437s. 2008.

Correlative Biology

Craddock KJ, Buys TPH, Zhu CQ, Strumpf D, Pintillie M, Ding K, Seymour L, Jurisica I, Shepherd FA, Lam WL, Tsao M-S. High resolution genomic analysis of NSCLC reveals regions of DNA copy number gain that may be predictive of benefit from adjuvant chemotherapy. World Conference on Lung Cancer. 2009.

Ding K, Shepherd FA, Tsao MS, Le Maître A, Seymour L. P53 IHC protein expression and tumor size predict survival benefit from adjuvant chemotherapy in stage IB non small cell lung cancer patients. BIT's 2nd Annual World Cancer Congress. 2009.

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Strevel EL, Ding K, Seymour L, Tsao MS, Le Maître A, Shepherd FA, Burkes RL. Pathologic determinants of survival for adjuvant treatment of stage IB non-small cell lung cancer: An analysis of the National Cancer Institute of Canada and Intergroup Study JBR.10. World Conference on Lung Cancer. 2009.

Tsao M-S, Sakurada A, Aviel-Ronen S, Ding K, Liu N, Gandara DR, Johnson DH, Rigas JR, Seymour L, Shepherd FA. Impact of EGFR tyrosine kinase domain mutations on adjuvant chemotherapy in early stage non-small cell lung cancer. World Conference on Lung Cancer. 2009.

Twumasi-Ankrah P, Ding K, Seymour L, Shepherd FA, Tsao M-S. A *sparse* prognostic gene signature for stage IB and II patients with completely resected non-small cell lung cancer **(submitted)**. Proc Am Assoc Cancer Res. 2009.

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Tsao MS, Zhu C, Ding K, Strumpf D, Pintillie M, Meyerson M, Seymour L, Jurisica I, Shepherd FA. A 15-gene expression signature prognostic for survival and predictive for adjuvant chemotherapy benefit in JBR.10 patients. Proc Am Soc Clin Oncol 26[15S Part I], 399s. 2008.

Tsao MS, Aviel-Ronen S, Ding K, Lau D, Liu N, Whitehead M, Seymour L, Winton T, Shepherd FA. P53 protein over-expression but not *p53* gene mutation is a poor prognostic marker and a predictive marker for survival benefit from adjuvant chemotherapy in non-small cell lung cancer in the JBR.10 trial. Proc Am Soc Clin Oncol 25[18s Part 1]. 2007.

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Reiman T, Lai R, Ding K, Winton T, Butts C, Dabbagh L, Seymour L, Tsao M, Shepherd F, Sève P. Class III beta tubulin expression and benefit from adjuvant cisplatin/vinorelbine chemotherapy in operable non-small cell lung cancer: Analysis of the National Cancer Institute of Canada Clinical Trials Group study JBR.10. Proc Am Soc Clin Oncol 24[18S Part 1], 376. 2006.

Tsao MS, Zhu C-Q, Livingston R, Johnson DH, Gandara D, Viallet J, Ding K, Seymour L, Winton T, Shepherd F. The significance of K-ras mutations in the intergroup JBR.10 trial on adjuvant chemotherapy in completely resected early stage non-small cell lung cancer patients. Lung Cancer 49[Suppl 2], S41. 2005.