Adding Value to Clinical Data

IDDI's Experience
on Statistical Analyses of Biomarkers, and
Gene Expression Profiles
2003-2009

January, 2010

International Drug Development Institute
IDDI S.A.
30 Avenue Provinciale
1340 Louvain-la-Neuve
Belgium

IDDI Inc.
185 Alewife Brook Parkway, Suite 410
Cambridge, MA 02138
USA

Development of statistical methodology for the validation of surrogate endpoints and biomarkers

The methodology for the validation of surrogate endpoints and biomarkers has been the topic of intense research over the last years. IDDI played a key role in proposing new approaches for the validation of surrogate endpoints (Burzykowski, Molenberghs and Buyse, *The Evaluation of Surrogate Endpoints*, 2005). These approaches have been used, i.e, to study prostate specific antigen as a biomarker in patients with advanced prostate cancer (Buyse *et al*, *In: Biomarkers in Clinical Drug Development*, 2003).

Validation of a set of metagenes to predict distant metastases in women with node-positive breast cancer

Ten metagenes were identified by a biotechnology company that performed microarray analysis on samples from 601 patients with breast cancer in six different clinical studies. We fitted Cox models for previously identified 'metagenes' and tested the ability of these models to discriminate patients with a low risk of metastasis from patients with a high risk of metastasis. The available data was split into a 'training dataset' and a 'validation dataset'. The proposed final model was identified on the training dataset and validated in the validation dataset (Piette, Université Catholique de Louvain, Belgium).

Multi-center independent validation of a 70-gene signature for women with node-negative breast cancer

A 70-gene signature was shown in a single institution to have prognostic value in patients with node-negative breast cancer (van't Veer *et al*, ***Nature*** 2002;**415**:530-6). The purpose of this study was to validate this signature in independent patient samples (Buyse *et al*, ***J Natl Cancer Instit*** 2006;**98**: 1183-92).

Multi-center independent validation of a 76-gene signature for women with node-negative breast cancer

A 76-gene signature was shown in a single institution to have prognostic value in patients with node-negative breast cancer (Wang *et al*, ***Lancet*** 2005;**365**:671-9). The purpose of this study was to validate this gene

signature in independent patient samples (Desmedt *et al*, ***Clin Cancer Research*** 2007; 13:3207-14).

Multi-center independent validation of the genomic grade index (GGI) in node-negative breast cancer

The purpose of this study was to validate the genomic grade index developed at Institut Jules Bordet (Sotiriou *et al*, ***J Natl Cancer Instit*** 2006;**98**: 262-72).

Meta-analysis on the value of topo-II amplification to predict the benefit of anthracyclines

The purpose of this on-going meta-analysis is to validate the value of topo-II amplification to predict the clinical benefit of anthracyclines for the adjuvant treatment of women with early breast cancer (Di Leo *et al*, San Antonio Breast Cancer Symposium, December 2008).

Independent confirmation of the value of shed her2-neu to predict recurrence of early breast cancer

This study is being carried out in parallel with a randomized controlled trial, to confirm previously made observations that levels of shed her-2neu are strongly associated with disease recurrence after resection of a breast tumor.

Validation of biomarkers of bone quality as surrogate endpoints in osteoporosis

This on-going project will investigate biomarkers such as bone mineral density and bio-imaging parameters.

Independent Data Monitoring of clinical trial for new drug in osteoporosis

IDDI serves on the IDMC (Independent Data Monitoring Committee) of a large phase II clinical trial of a new drug for osteoporosis.

Validation of surrogate parameters in a study of cell therapy/ chondrocyte transplantation in cartilage defect patients

This on-going project will explore the predictive value of a chondrocyte score and other baseline parameters for clinical, radiological and/or health economic parameters.

Validation of Vera Tag, a proximity-based assay designed to detect and quantitate protein expression and dimerization in formalin-fixed paraffin-embedded (FFPE) tissue specimens to measure HER2 protein expression and HER2:HER2 dimer levels in early breast cancer.

Quantification of HER2 expression and HER2:HER2 proximity in formalin-fixed paraffin-embedded metastatic breast cancer specimens from a cohort of patients stringently pre-selected for HER2 gene amplification or HER2 over-expression identifies sub-populations with different probabilities of long term survival following treatment with trastuzumab. (Desmedt *et al*, Diagnostic Molecular Pathology, in press, 2008).

Determine the predictive value of topoisomerase alpha II gene aberrations for the efficacy of adjuvant anthracyclines-based chemotherapy in patients with early breast cancer.

Correlative study of (1) immunohistochemical versus Fluorescent In Situ Hybridization (FISH) detection of topoisomerase alpha II and (2) topoisomerase alpha II gene aberrations (FISH) with molecular subclasses of tumors.

Studies of prognostic factors in breast cancer

One study evaluated the impact of cyclinsE, neutrophil elastase and proteinase 3 expression levels on clinical outcome in primary breast cancer (Desmedt *et al*, **Int J Cancer 2006**; 119:2539-45) In another one, a range of potential markers (stathmin, cyclin D1, prolactin, PTEN, p53 protein, and PIK3CA mutation) were screened for their effect on survival and disease-free survival in primary breast cancer (Gardner et al, ASCO abstract).

Classification procedure for clinical diagnosis of breast cancer based on mass-spectrometry

Development of a classification rule based on mass-spectrometry data for breast cancer. This project was part of a competition in which several groups were asked to propose a classification rule based on the same dataset. The results were checked by using a validation dataset. (Valkenborg et al, ***Statistical Applications in Genetics and Molecular Biology 2008***; 7(2), article 12)

Performance of gene selection and classification method in a micro-array setting

A simulation study to investigate which classification approaches are most suitable for constructing classification rules based on cDNA micro arrays. (Van Sanden S, Lin D, Burzykowski T (2008). Performance of gene selection and classification methods in a microarray setting: A simulation study. *Communications in Statistics – Simulation and Computation*, 37, 409-424.)

Selection of genes with a potential for genomic biomarkers

Development of a procedure for selection of genes with expression levels exhibiting monotonic dose-response pattern. Such genes can be potentially useful as, e.g., markers of treatment response. (Lin et al, *Online Journal of Bioinformatics 2009*, 10(1), 67-73; Lin et al *The Open Applied Informatics Journal 2009 (accepted for publication)*)

Processing of mass–spectrometry data used to select peptides serving as biomarkers

Development of an algorithm for processing mass-spectrometry data, which can be used to select peptides that can serve as biomarkers. (Valkenborg et al, *Journal of Mass Spectrometry 2009*, 44, 516-529.)

Published references (2003-2009)

1. Buyse M, Vangeneugden T, Bijnens L, Geys H, Renard D, Burzykowski T, Molenberghs G. Validation of Biomarkers as Surrogates for Clinical Endpoints. **In**: *Biomarkers in Clinical Drug Development* (Bloom J.C. and Dean R.A, **eds**.: 149-168, Marcel Dekker, New York, 2003).

2. Buyse M, Vangeneugden T, Bijnens L, Geys H, Renard D, Burzykowski T, Molenberghs G. Validation of Biomarkers as Surrogates for Clinical Endpoints. (***Drugs and the Pharmaceutical Sciences*** **132**: 149-168, 2003).

3. Loi S, Buyse M, Sotiriou C, Cardoso F. Challenges in breast cancer trial design in the post-genomic era. (***Current Opinion Oncol*** **16**: 536-541, 2004).

4. Alonso A, Molenberghs G, Geys H, Buyse M, Vangeneugden T. A Unifying approach for surrogate marker validation based on Prentice's criteria. (***Statist in Med*** **25**: 205-221, 2006).

5. Sotiriou C, Wirapati P, Loi S, Harris A, Fox S, Smeds J, Nordgren H, Farmer P, Praz V, Haibe-Kains B, Desmedt C, Larsimont D, Cardoso F, Peterse H, Nuyten D, Buyse M, Van de Vijver M, Bergh J, Piccart M, Delorenzi M. Gene expression profiling in breast cancer: understanding the molecular basis of histologic grade to improve prognosis. (***J Natl Cancer Instit*** **98**: 262-272, 2006).

6. Loi S, Sotiriou C, Buyse M, Rutgers EJT, Van't Veer LJ, Piccart MJ, Cardoso F. Molecular forecasting of breast cancer: time to move forward with clinical testing.(***J Clin Oncol*** **24**: 721-722, 2006).

7. Desmedt C, El Ouriaghli F, Durbecq V, Soree A, Colozza MA, Azambuja E, Paesmans M, Larsimont D, Buyse M, Harris A, Piccart M, Martiat P, Sotiriou C. Impact of cyclins E, neutrophil elastase and proteinase 3 expression levels on clinical outcome in primary breast cancer patients.(***Int J Cancer***: 2006).

8. Buyse M. Banques de tumeurs et recherche clinique – les nouveaux enjeux. (***Bull Cancer* 93**: S237-S240, 2006).

9. Buyse M, Loi S, van't Veer L, Viale G, Delorenzi M, Glas A, Saghatchian d'Assignies M, Bergh J, Lidereau R, Ellis P, Harris A, Bogaerts J, Therasse P, Amakrane M, Piette F, Rutgers E, Sotiriou C, Cardoso F, Piccart M. on behalf of the TRANSBIG Consortium. Independent validation and clinical utility of a 70-gene prognostic signature for patients with node-negative breast cancer. (***J Natl Cancer Instit*: 98**: 1183-1192, 2006).

10. Bogaerts J, Cardoso F, Buyse M, Braga S, Loi S, Harrison J, Bines J, Mook S, Decker N, Therasse P, Rutgers E, van't Veer L, Piccart M. on behalf of the TRANSBIG Consortium. Gene signature evaluation as a prognostic tool: challenges in the design of the MINDACT trial. (***Nature Clinical Practice Oncol* 3**: 540-551, 2006).

11. Loi S, Haibe-Kains B, Desmedt C, Lallemand F, Tutt A.M, Gillet C, Ellis P, Harris A.L, Bergh J, Foekens J.A, Klijn JGM, Larsimont D, Buyse M, Bontempi G, De Lorenzi M, Piccart MJ, Sotiriou CJ. Definition of clinically distinct molecular subtypes in estrogen receptor positive breast carcinomas through use of genomic grade. *(**J Clin Oncol* 24**: 2006).

12. Desmedt C, Piette F, Loi S, Wang Y, Lallemand F, Haibe-Kains B, Viale G, Delorenzi M, Zhang Y, Saghatchian d'Assignies M, Bergh J, Lidereau R, Ellis P, Harris A.L, Klijn J.G.M, Foekens J.A, Cardoso F, Piccart MJ, Buyse M, Sotiriou C. on behalf of the TRANSBIG Consortium. Strong time-dependency of the 76-gene prognostic signature for node-negative breast cancer patients in the TRANSBIG multi-centre independent validation series. (***J Clin Oncol* 24**: 2006).

13. Desmedt C, Piette F, Loi S, Wang Y, Lallemand F, Haibe-Kains B, Viale G, Delorenzi M, Zhang Y, Saghatchian d'Assignies M, Bergh J, Lidereau R, Ellis P, Harris A.L, Klijn J.G.M, Foekens J.A, Cardoso F, Piccart MJ, Buyse M, Sotiriou C. on behalf of the TRANSBIG Consortium. Strong time-dependency of the 76-gene prognostic signature for node-negative breast cancer patients in the TRANSBIG multi-centre independent validation series. (***Clin Cancer Research***, 2006).

14. Lassere M, Johnson K, Boers M, Tugwell P, Brooks P, Simon L, Strand V, Conaghan P, Østergaard M, Maksymowych W.P, Landewé R, Bresnihan B, Tak P.P, Wakefield R, Mease P, Bingham CO III, Hughes M, Altman D, Buyse M, Galbraith S, Wells G. Definitions and validation criteria for biomarkers and surrogate endpoints: development and testing of a quantitative hierarchical levels of evidence schema. (***J Rheumatol* 34**: 607-615, 2007).

15. Buyse M. Towards the validation of statistically reliable biomarkers. (***Eur J Cancer Supplements 5:*** 89-95, 2007).

16. Buyse M. Signature dish. (***International Clinical Trials***, Summer 2007: 58-60, 2007).

17. Desmedt C, Sperinde J, Piette F, Huang W, Sotiriou C, Jin X, Tan Y, Durbecq V, Larsimont D, Giuliani R, Chappey C, Buyse M, Winslow J, Piccart M, Petropoulos C, Bates M. Quantitation of HER2 expression and HER2:HER2 proximity in formalin-fixed paraffin-embedded metastatic breast cancer specimens from a cohort of patients stringently pre-selected for HER2 gene amplification or HER2 over-expression identifies sub-populations with different probabilities of long-term survival following treatment with trastuzumab. (***Diagnostic Molecular Path,*** 2008)***.***

18. Desmedt C, Haibe-Kains B, Wirapati P, Buyse M, Bontempi G, Delorenzi M, Piccart M, Sotiriou C. Biological processes associated with breast cancer clinical outcome depend on the molecular subtypes. (***Clin Cancer Res***, 14: 16. 5158-5165, 2008)

19. Haibe-Kains B, Desmedt C, Piette F, Buyse M, Cardoso F, van't Veer L, Piccart M, Bontempi G, Sotiriou C. Comparison of prognostic gene expression signatures for breast cancer. (***BMC Genomics* 9**: 394, 2008).

20. Van Sanden S, Lin D, Burzykowski T Performance of gene selection and classification methods in a microarray setting: A simulation study. (***Communications in Statistics – Simulation and Computation*,** 37, 409-424, 2008).

21. Valkenborg D, Van Sanden S, Lin D; Kasim A, Zhu Qi, Haldermans P, Jansen I, Shkedy Z, Burzykowski T. (2008) A cross-validation study to select a classification procedure for clinical diagnosis based on proteomic mass spectromy. ***Statistical Applications in Genetics and Molecular Biology*** 7(2), article 12 (available at http://www.bepress.com/sagmb/vol7/iss2/art12).

22. Valkenborg D, Thomas G, Krols L, Kas K, Burzykowski T. A strategy for the prior processing of high-resolution mass spectral data obtained from high-dimensional combined fractional diagonal chromatography. (***Journal of Mass Spectrometry***, 44, 516-529, 2009).

23. Lin D, Shkedy Z,Yekutieli D, Dilba G, Burzykowski T, Goehlmann HWH, De Bondt A, Perera T, Geerts T, Bijnens L. Multiple contrast test for detecting monotonic dose-response relationship and FDR-adjusted confidence intervals for selected parameters in a microarray settting. (***Online Journal of Bioinformatics***, 10(1), 67-73, 2009).

24. Lin D, Shkedy Z, Burzykowski T, Aerts M, Goehlmann HWH, De Bondt A, Perera T, Geerts T, Talloen W, Bijnens L (2009) Classification of trends in dose-response microarray experiments using information theory selection methods. (*The* ***Open Applied Informatics Journal,*** *2009)*.

25. Gardner H, Burzykowski T, Nuciforo P, Liu W-H, Lee B, Rheinhardt J, Barrett C, Linnartz R, Dugan M, Hackl W, Eiermann W, Pienkowski T, Martin M, Robert N, Forbes J, Buyse M, Finn R, Lindsay M-A, Slamon D, Press M. PI3 Kinase Pathway Analysis in Tissue Microarrays Using Laser Capture Microdissection and Immunohistochemistry. (32nd San Antonio Breast Cancer Symposium, ***abstract 4043,*** *2009)*.