An unmet need: tailoring extended adjuvant endocrine therapy

G Bianchini¹ and L Gianni^{*,1}

¹Department of Medical Oncology, Ospedale San Raffaele Scientific Institute, Via Olgettina 60, Milano 20132, Italy

Should every woman with a hormone-receptor-positive breast cancer receive endocrine adjuvant therapy for ≥ 10 years? The question is becoming very relevant in the light of the recently reported results of two large randomised trials demonstrating that 10 years of adjuvant tamoxifen produced a small but significant reduction of recurrences and deaths compared with the conventional duration of 5 years only (Davies *et al*, 2013; Gray *et al*, 2013). The results are in agreement with the well-characterised feature of hormone-receptor-positive tumours that carry long lasting risk of relapse persisting for more than a decade (Early Breast Cancer Trialists' Collaborative G, 2011; Dowsett *et al*, 2010). They also fit very well with the findings that extended endocrine treatment with aromatase inhibitors after 5 years of tamoxifen led to a significant reduction of risk of relapse (more than 40%) and death (Jakesz *et al*, 2007; Mamounas *et al*, 2008; Jin *et al*, 2012). However, no matter how large, the benefit of extended endocrine treatment is restricted to a fraction of the patients' population and must be weighted against the side effects of such prolonged chronic therapy (Muss *et al*, 2008; Amir *et al*, 2011; Davies *et al*, 2013). The identification of patients who will benefit from extended endocrine treatment is therefore very relevant to tailor the prescription of tamoxifen or aromatase inhibitors beyond 5 years and to avoid it in patients who will not derive additional benefit.

In their recent paper, Dubsky *et al* (2013) explored the prognostic value of the EndoPredict (EP) score for early (0–5 years) and late (> 5) distant recurrences in 1702 postmenopausal women with ER+/HER2– breast cancer treated with adjuvant endocrine treatment (tamoxifen for 5 years or tamoxifen for 2 years followed by anastrozole for 3 years). Their findings may be relevant to the need of tailoring extended endocrine therapy. EP is one of several multigene assays (i.e., Recurrence Score, 70-gene signature, PAM50, Breast Cancer Index) developed to identify among patients with estrogen receptor-positive, HER2-negative tumours treated with endocrine therapy those carrying a risk of relapse low enough to avoid chemotherapy (Paik *et al*, 2004; Buyse *et al*, 2006; Parker *et al*, 2009; Filipits *et al*, 2011; Jerevall *et al*, 2011). Because the purpose of these signatures was to define the

overall risk of recurrence at 10 years, until recently their potential time-varying prognostic value (i.e., the different prognostic value over time) has only occasionally been reported (Albain *et al*, 2010; Nielsen *et al*, 2010).

In their work, Dubsky *et al* (2013) analysed the time-varying value of EP in the same series of cases that they had already used to validate the assay (Filipits *et al*, 2011). They therefore report a secondary and unplanned analysis. In patients treated with 5 years of adjuvant tamoxifen, the high EP group had a higher risk of early (HR = 2.73, $P < 0.001$) as well as late relapse (HR = 2.87, $P = 0.013$). The EP score retained significance in multivariate analysis adjusted for clinico-pathological variables. In the group with low EP, the risk of distant event in the interval from 5 to 10 years was 3.71% (0.89–6.52%). However, extended endocrine treatment does not only reduce the risk of distant events but it is also capable of decreasing local, locoregional and contralateral events (Goss *et al*, 2003; Davies *et al*, 2013), all measures of benefit that must be taken into account when deciding about the opportunity of prescribing prolonged hormonal therapy.

The analysis performed by Dubsky *et al* (2013) was not limited to the multigene assay. They confirmed that tumour size and nodal status maintain their role of prognostic factors linked to the risk of early and late relapse independently from molecular markers (Bianchini *et al*, 2013; Dubsky *et al*, 2013; Sestak *et al*, 2013; Sgroi *et al*, 2013b). The combination of clinico-pathological variables and molecular assays should therefore improve the prognostic performance of either assessment alone (Pusztai, 2011). In keeping with such concept, Dubsky *et al* (2013) showed that a combined score, including EP, nodal status and tumour size (EPclin), performed very powerfully in defining a low-risk group associated with only 1.8% probability of distant metastasis from year 5 to 10. However, the group of patients defined by pathological variable in whom the assay is really informative, therapeutically relevant and clinically useful remains to be defined. For instance, in node-positive tumours the group with low EP may be at lower but still appreciable risk of relapse.

*Correspondence: Dr L Gianni; E-mail: gianni.luca@hsr.it

Published online 19 November 2013

© 2013 Cancer Research UK. All rights reserved 0007–0920/13

The absolute benefit from extended endocrine therapy is the result of the combination of the size of the risk of relapse and the extent of the relative treatment benefit. If a marker is purely prognostic, the relative treatment benefit is the same for each marker value and therefore the absolute benefit from a treatment is expected to increase proportionally with the increased risk of relapse. This is likely true for nodal status and tumour size. For markers that are both prognostic and predictive the absolute benefit is not necessarily correlated with the risk. This applies to many context-specific predictors, including the EP score, which was optimised to predict the risk of relapse in the context of patients treated with tamoxifen and is based on a combination of genes related to proliferation and ER signaling (Filipits *et al*, 2011). Even if the prognostic and predictive contribution to the prediction of risk by the EP score has not been formally characterised, the high-risk group defined by the assay is likely represented by patients with poorer prognosis (high proliferation) and deriving relatively low benefit from tamoxifen (low ER signaling). Indeed, there are several studies indicating the association between high ER protein and gene expression, and ER-related genes expression with benefit from tamoxifen and AIs (Bartlett *et al*, 2011; Early Breast Cancer Trialists' Collaborative G, 2011; Kim *et al*, 2011). The ambiguity of the EP score is in the fact that patients who should avoid extended adjuvant treatment are not only those at low risk of relapse (low EP category) but also those with low likelihood of benefit from the treatment, who are expected to fall particularly into the high-risk category of EP. In addition, patients with high ER signaling and low EP category could still derive major benefit from extended endocrine therapy in spite of the lower risk. All the above underscore the need for caution before the clinical implementation of molecular assays for decision making about extended endocrine therapy and call for in-depth investigation of their prognostic and predictive value.

Recently, other gene-expression signatures originally developed for tailoring administration of adjuvant chemotherapy to ER-positive/HER2-negative breast cancer patients treated with

endocrine therapy were assessed for their ability to predict early and late relapses (Table 1) (Sestak *et al*, 2013; Zhang *et al*, 2013; Sgroi *et al*, 2013a, b). Similar considerations as discussed above for EP also apply to these markers. Interestingly, some molecular markers (i.e., proliferation markers, Oncotype DX, IHC4) showed a significant time-varying prognostic value (Sestak *et al*, 2013; Sgroi *et al*, 2013b). Overall, these studies provided strong support to two key concepts. The first is that molecular features and corresponding biological functions associated with risk of early and late relapse are only partially overlapping. The second is that primary tumour samples collected at diagnosis can provide information on the clinical course of the disease that has prognostic value even at late intervals. In an effort to investigate how to use the molecular information of the initial diagnosis to define the time-varying risk of relapse, we investigated whether a different combination of proliferation markers and ER-related genes could improve the prediction of early and late relapses (Bianchini *et al*, 2013). A significant interaction between proliferation and ER-related gene was present in cases that relapsed late. In low proliferation tumours, a low expression of ER-related gene was associated with a higher risk of late relapse. The observation is in agreement with the findings of Dubsy *et al* (2013), given that low proliferation tumours (only 4% were high grade) were preferentially included in their study. Conversely, in high proliferation tumours, the group with high expression of ER-related genes was associated with low rates of relapse in the early period but with a high risk of relapse in the late period. Patients with tumours that follow within the category of high proliferation and high expression of ER genes could therefore be the ideal candidate to extended endocrine treatment, and the data warrant independent confirmation.

Meanwhile, it is appropriate not only to suggest caution in the application of molecular features and gene expression scores for tailoring extended endocrine therapy but also to encourage continuous research. The findings available so far, including the work of Dubsy *et al* (2013), suggest that the field is moving in the right direction.

Table 1. Summary of studies investigating the risk of late relapse by molecular assays

References	Endocrine treatment	Patient population	Nodal status	Biomarker assessed	Group at high risk for late relapse
Dubsy <i>et al</i> , 2013	Tamoxifen or tamoxifen followed by anastrozole	ABCSG-06 ABCSG-08	Node negative and positive (96% G1 or G2)	EndoPredict (EP) EPclin (including tumour size and nodal status)	High EP High EPclin
Bianchini <i>et al</i> , 2013	Tamoxifen	Public data sets	Node negative and positive	Combination of proliferation (MKS, GGI) and estrogen-related genes (ERS) markers	High-proliferation/ high ERS Low-proliferation/low ERS
Zhang <i>et al</i> , 2013	Tamoxifen (2 or 5 years)	Stockholm TAM and institutional cohorts	Node negative	Breast Cancer Index (BCI) (linear combination model)	Intermediate/high BCI
Sgroi <i>et al</i> , 2013b	Tamoxifen or anastrozole	ATAC	Node negative	BCI (linear combination model) HOXB13/IL17BR (H/I) MGI IHC4 RS	Intermediate/high BCI High HOXB13/ IL17BR (H/I)
Sgroi <i>et al</i> , 2013a	Tamoxifene	MA.17	Node negative and positive	HOXB13/IL17BR (H/I)	High HOXB13/ IL17BR (H/I)
Sestak <i>et al</i> , 2013	Tamoxifen or anastrozole	ATAC	Node negative and positive	IHC4 RS ROR (from PAM50)	High ROR

Abbreviations: ERclin = combined EndoPredict and clinical variables; GGI = Genomic Grade Index (MapQuant Dx); HOXB13/IL17BR (H/I) = homeobox B13/interleukin 17 receptor B two-gene ratio; IHC4 = combination of four immunohistochemical markers; MGI = Molecular Grade Index; MKS = Mitotic Kinase Score; ROR = Risk Of Recurrence (Prosigna); RS = Recurrence Score (Oncotype DX).

REFERENCES

- Albain KS, Barlow WE, Shak S, Hortobagyi GN, Livingston RB, Yeh IT, Ravdin P, Bugarini R, Baehner FL, Davidson NE, Sledge GW, Winer EP, Hudis C, Ingle JN, Perez EA, Pritchard KI, Shepherd L, Gralow JR, Yoshizawa C, Allred DC, Osborne CK, Hayes DF (2010) Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial. *Lancet Oncol* **11**(1): 55–565.
- Amir E, Seruga B, Niraula S, Carlsson L, Ocana A (2011) Toxicity of adjuvant endocrine therapy in postmenopausal breast cancer patients: a systematic review and meta-analysis. *J Natl Cancer Inst* **103**(17): 1299–1309.
- Bartlett JM, Brookes CL, Robson T, van de Velde CJ, Billingham LJ, Campbell FM, Grant M, Hasenburg A, Hille ET, Kay C, Kieback DG, Putter H, Markopoulos C, Kranenbarg EM, Mallon EA, Dirix L, Seynaeve C, Rea D (2011) Estrogen receptor and progesterone receptor as predictive biomarkers of response to endocrine therapy: a prospectively powered pathology study in the Tamoxifen and Exemestane Adjuvant Multinational trial. *J Clin Oncol* **29**(12): 1531–1538.
- Bianchini G, Pusztai L, Karn T, Iwamoto T, Rody A, Kelly CM, Muller V, Schmidt M, Qi Y, Holtrich U, Becker S, Santarpia L, Fasolo A, Del Conte G, Zambetti M, Sotiriou C, Haibe-Kains B, Symmans WF, Gianni L (2013) Proliferation and estrogen signaling can distinguish patients at risk for early versus late relapse among estrogen receptor positive breast cancers. *Breast Cancer Res* **15**(5): R86.
- Buyse M, Loi S, van't Veer L, Viale G, Delorenzi M, Glas AM, d'Assignies MS, Bergh J, Lidereau R, Ellis P, Harris A, Bogaerts J, Therasse P, Floore A, Amakrane M, Piette F, Rutgers E, Sotiriou C, Cardoso F, Piccart MJ (2006) Validation and clinical utility of a 70-gene prognostic signature for women with node-negative breast cancer. *J Natl Cancer Inst* **98**(17): 1183–1192.
- Davies C, Pan H, Godwin J, Gray R, Arriagada R, Raina V, Abraham M, Alencar VHM, Badran A, Bonfill X, Bradbury J, Clarke M, Collins R, Davis SR, Delmestri A, Forbes JF, Haddad P, Hou M-F, Inbar M, Khaled H, Kielanowska J, Kwan W-H, Mathew BS, Mittra I, Müller B, Nicolucci A, Peralta O, Pernas F, Petruzelka L, Pienkowski T, Radhika R, Rajan B, Rubach MT, Tort S, Urrutia G, Valentini M, Wang Y, Peto R (2013) Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet* **381**(9869): 805–816.
- Dowsett M, Cuzick J, Ingle J, Coates A, Forbes J, Bliss J, Buyse M, Baum M, Buzdar A, Colleoni M, Coombes C, Snowdon C, Gnant M, Jakesz R, Kaufmann M, Boccardo F, Godwin J, Davies C, Peto R (2010) Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen. *J Clin Oncol* **28**(3): 509–518.
- Dubsky P, Brase J, Jakesz R, Rudas M (2013) The EndoPredict score provides prognostic information on late distant metastases in ER+/HER2- breast cancer patients. *Br J Cancer* **109**(12): 2959–2964.
- Early Breast Cancer Trialists' Collaborative G (2011) Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *Lancet* **378**(9793): 771–784.
- Filipits M, Rudas M, Jakesz R, Dubsky P, Fitzal F, Singer CF, Dietze O, Greil R, Jelen A, Sevela P, Freibauer C, Müller V, Jänicke F, Schmidt M, Kölbl H, Rody A, Kaufmann M, Schroth W, Brauch H, Schwab M, Fritz P, Weber KE, Feder IS, Hennig G, Kronenwett R, Gehrman M, Gnant M (2011) A new molecular predictor of distant recurrence in ER-positive, HER2-negative breast cancer adds independent information to conventional clinical risk factors. *Clin Cancer Res* **17**(18): 6012–6020.
- Goss PE, Ingle JN, Martino S, Robert NJ, Muss HB, Piccart MJ, Castiglione M, Tu D, Shepherd LE, Pritchard KI, Livingston RB, Davidson NE, Norton L, Perez EA, Abrams JS, Therasse P, Palmer MJ, Pater JL (2003) A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. *N Engl J Med* **349**(19): 1793–1802.
- Gray RG, Rea D, Handley K, Bowden SJ, Perry P, Earl HM, Poole CJ, Bates T, Chetiyawardana S, Dewar JA, Fernando IN, Grieve R, Nicoll J, Rayter Z, Robinson A, Salman A, Yarnold J, Bathers S, Marshall A, Lee M, on behalf of the aTTom Collaborative Group (2013) Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years in 6,953 women with early breast cancer. *ASCO Meeting Abstracts* **31**(18_suppl): 5.
- Jakesz R, Greil R, Gnant M, Schmid M, Kwasny W, Kubista E, Mlineritsch B, Tausch C, Stierer M, Hofbauer F, Renner K, Dadak C, Rucklinger E, Samonigg H (2007) Extended adjuvant therapy with anastrozole among postmenopausal breast cancer patients: results from the randomized Austrian Breast and Colorectal Cancer Study Group Trial 6a. *J Natl Cancer Inst* **99**(24): 1845–1853.
- Jerevall PL, Ma XJ, Li H, Salunga R, Kesty NC, Erlander MG, Sgroi DC, Holmlund B, Skoog L, Fornander T, Nordenskjöld B, Stal O (2011) Prognostic utility of HOXB13:IL17BR and molecular grade index in early-stage breast cancer patients from the Stockholm trial. *Br J Cancer* **104**(11): 1762–1769.
- Jin H, Tu D, Zhao N, Shepherd LE, Goss PE (2012) Longer-term outcomes of letrozole versus placebo after 5 years of tamoxifen in the NCIC CTG MA.17 trial: analyses adjusting for treatment crossover. *J Clin Oncol* **30**(7): 718–721.
- Kim C, Tang G, Pogue-Geile KL, Costantino JP, Baehner FL, Baker J, Cronin MT, Watson D, Shak S, Bohn OL, Fumagalli D, Taniyama Y, Lee A, Reilly ML, Vogel VG, McCaskill-Stevens W, Ford LG, Geyer Jr. CE, Wickerham DL, Wolmark N, Paik S (2011) Estrogen receptor (ESR1) mRNA expression and benefit from tamoxifen in the treatment and prevention of estrogen receptor-positive breast cancer. *J Clin Oncol* **29**(31): 4160–4167.
- Mamounas EP, Jeong JH, Wickerham DL, Smith RE, Ganz PA, Land SR, Eisen A, Fehrenbacher L, Farrar WB, Atkins JN, Pajon ER, Vogel VG, Kroener JF, Hutchins LF, Robidoux A, Hoehn JL, Ingle JN, Geyer Jr. CE, Costantino JP, Wolmark N (2008) Benefit from exemestane as extended adjuvant therapy after 5 years of adjuvant tamoxifen: intention-to-treat analysis of the National Surgical Adjuvant Breast And Bowel Project B-33 trial. *J Clin Oncol* **26**(12): 1965–1971.
- Muss HB, Tu D, Ingle JN, Martino S, Robert NJ, Pater JL, Whelan TJ, Palmer MJ, Piccart MJ, Shepherd LE, Pritchard KI, He Z, Goss PE (2008) Efficacy, toxicity, and quality of life in older women with early-stage breast cancer treated with letrozole or placebo after 5 years of tamoxifen: NCIC CTG intergroup trial MA.17. *J Clin Oncol* **26**(12): 1956–1964.
- Nielsen TO, Parker JS, Leung S, Voduc D, Ebbert M, Vickery T, Davies SR, Snider J, Stijleman IJ, Reed J, Cheang MCU, Mardis ER, Perou CM, Bernard PS, Ellis MJ (2010) A comparison of PAM50 intrinsic subtyping with immunohistochemistry and clinical prognostic factors in tamoxifen-treated estrogen receptor-positive breast cancer. *Clin Cancer Res* **16**(21): 5222–5232.
- Paik S, Shak S, Tang G, Kim C, Baker J, Cronin M, Baehner FL, Walker MG, Watson D, Park T, Hiller W, Fisher ER, Wickerham DL, Bryant J, Wolmark N (2004) A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med* **351**(27): 2817–2826.
- Parker JS, Mullins M, Cheang MC, Leung S, Voduc D, Vickery T, Davies S, Fauron C, He X, Hu Z, Quackenbush JF, Stijleman IJ, Palazzo J, Marron JS, Nobel AB, Mardis E, Nielsen TO, Ellis MJ, Perou CM, Bernard PS (2009) Supervised risk predictor of breast cancer based on intrinsic subtypes. *J Clin Oncol* **27**(8): 1160–1167.
- Pusztai L (2011) Anatomy and biology: two complementary sides of breast cancer prognostication. *J Clin Oncol* **29**(33): 4347–4348.
- Sestak I, Dowsett M, Zabaglo L, Lopez-Knowles E, Ferree S, Cowens JW, Cuzick J (2013) Factors predicting late recurrence for estrogen receptor-positive breast cancer. *J Natl Cancer Inst* **105**(19): 1504–1511.
- Sgroi DC, Carney E, Zarrella E, Steffel L, Binns SN, Finkelstein DM, Szymonifka J, Bhan AK, Shepherd LE, Zhang Y, Schnabel CA, Erlander MG, Ingle JN, Porter P, Muss HB, Pritchard KI, Tu D, Rimm DL, Goss PE (2013a) Prediction of late disease recurrence and extended adjuvant Letrozole benefit by the HOXB13/IL17BR biomarker. *J Natl Cancer Inst* **105**(14): 1036–1042.
- Sgroi DC, Sestak I, Cuzick J, Zhang Y, Schnabel CA, Schroeder B, Erlander MG, Dunbier A, Sidhu K, Lopez-Knowles E, Goss PE, Dowsett M (2013b) Prediction of late distant recurrence in patients with oestrogen-receptor-positive breast cancer: a prospective comparison of the breast-cancer index (BCI) assay, 21-gene recurrence score, and IHC4 in the TransATAC study population. *Lancet Oncol* **14**(11): 1067–1076.
- Zhang Y, Schnabel CA, Schroeder BE, Jerevall P-L, Jankowitz RC, Fornander T, Stål O, Brufsky AM, Sgroi D, Erlander MG (2013) Breast Cancer Index identifies early-stage estrogen receptor-positive breast cancer patients at risk for early- and late-distant recurrence. *Clin Cancer Res* **19**(15): 4196–4205.

This work is licensed under the Creative Commons Attribution-NonCommercial-Share Alike 3.0 Unported License. To view a copy of this license, visit <http://creativecommons.org/licenses/by-nc-sa/3.0/>