enzalutamide or abiraterone for castration-resistant prostate cancer: a multi-institution correlative biomarker study. Ann Oncol 2017; 28(7): 1508–1516.
16. Antonarakis ES, Lu C, Luber B et al. Clinical significance of androgen receptor splice variant-7 mRNA detection in circulating tumor cells of men with metastatic castration-resistant prostate cancer treated with first- and second-line abiraterone and enzalutamide. J Clin Oncol 2017; 35(19): 2149–2156.
17. Scher HI, Lu D, Schreiber NA et al. Association of ar-v7 on circulating tumor cells as a treatment-specific biomarker with outcomes and survival in castration-resistant prostate cancer. JAMA Oncol 2016; 2(11): 1441–1449.

doi:10.1093/annonc/mdx785
Published online 12 December 2017

Male breast cancer: pink ribbon blues

The pink ribbon is an internationally recognized symbol of breast cancer awareness. However, it has been argued that the colour pink may reinforce the misconception that breast cancer only affects women, potentially leading to delays in the diagnosis of male breast cancer, due to ignorance regarding the significance of male breast cancer signs and symptoms. The lifetime risk of developing breast cancer for men in the general population is 0.1%, and <1% of all breast cancer diagnoses occur in men [1]. Including a blue spot or a blue section in the pink ribbon has been advocated, to signify and acknowledge breast cancer also occurs in men.

Cardoso et al. are to be congratulated on initiating academic research dedicated to male breast cancer, the 'poor relation' of predominant female breast cancer [2]. This report has arisen from part I of the International Male Breast Cancer Program, a research collaboration conducted by groups from Europe and North America. It details the analysis of a large retrospective cohort of 1483 men diagnosed with breast cancer, with tumour available for central pathology assessment. The median age at diagnosis of 68 years is 7–10 years older than for female breast cancer. The study confirms that male breast cancers are predominantly ductal luminal HER2-negative grade 2 tumours that are androgen receptor positive. A smaller proportion of HER2-positive (8.7%) and triple negative (0.3%) male breast cancers were found, than observed in female breast cancer. Lobular carcinomas were also much less frequent in these male tumours.

In this cohort, for men diagnosed with non-metastatic disease, only 77% received adjuvant endocrine therapy, despite >95% having ER-positive tumours. Moreover, some men received adjuvant aromatase inhibitors, which might not be effective in the absence of concurrent gonadotropin-releasing hormone agonist (GnRHa). With a median follow-up of 7.1 years for overall survival, centrally assessed histologic grade was not significantly correlated with overall survival [3]. This program also recently reported that DCIS was the most commonly observed precursor lesions observed in male breast cancers, with very low rates of LCIS found [4].

Utilizing immunohistochemical (IHC) surrogates and study definitions of Ki67 ≥ 20% and/or Progesterone Receptor (PR) Allred score of <5 to distinguish luminal B-like from luminal A-like tumours, this cohort analysis classified 48.6% of the male breast tumours as luminal B-like/HER2-negative [2]. Given that high Ki67 ≥20% was reported in only one in four cases, it seems surprising that such a high proportion of cases were 'classified' as luminal B-like. Perhaps the use of the Allred score of <5 for PR, increased the proportion of tumours classified as luminal B-like, as compared with PR ≤20% cells positive which has been described as having utility [5]. Planned studies using RNA sequencing and the Nanostring platform may help to clarify the relative proportion of luminal B tumours in male breast cancer more accurately. A recent publication on the genomic landscape of 59 male breast cancers has noted less frequent *PIK3CA* mutations and *TP53* mutations than are seen in ER-positive HER2-negative female breast cancers, but more frequent somatic mutations in genes associated with DNA repair pathways [6].

Systemic treatment strategies for male breast cancer have mostly been determined by extrapolation from results of clinical trials conducted in women. Given the differences in the hormonal milieu and the importance of endocrine therapy in the management of luminal breast cancer, this is of concern. Published results in men treated for breast cancer are more limited; pooled analyses of men treated with hormonal therapies fulvestrant and aromatase inhibitors have been reported [7, 8].

Males are often excluded from pivotal phase III breast cancer clinical trials, perhaps without a valid scientific rationale. ASCO has recently introduced an initiative to broaden eligibility criteria to make clinical trials more representative, although male breast cancer is not a focus of their recent statement [9]. The randomized trials testing the addition of oral CDK4/6 inhibitors to endocrine therapy in hormone receptor-positive metastatic breast cancer have collectively enrolled a few thousand women. Some included premenopausal women receiving GnRHa therapy [10], but the trials did not allow men receiving concurrent GnRHa therapy to participate. In contrast numerically, a first case of male breast cancer responding to combined aromatase inhibitor plus palbociclib therapy was reported in 2016 [11].

There have been some opportunities for men with early breast cancer to participate in phase III adjuvant therapy trials in recent years. The APHINITY trial testing adjuvant pertuzumab with trastuzumab in HER2-positive breast cancer allowed men to participate. In total, 11 men were randomized (0.2% of trial population) [12]. The currently enrolling PALLAS trial testing the addition of a CDK4/6 inhibitor palbociclib to adjuvant endocrine therapy in hormone receptor-positive, HER2-negative breast cancer allows men to participate.

Of relevance to men with breast cancer, the adjuvant OLYMPIA trial testing the adjuvant PARP inhibitor olaparib in patients with a germline *BRCA* mutation, allows men to participate. It is estimated that men with a germline *BRCA2* mutation have a life-time risk of 7% of developing breast cancer, while those with a *BRCA1* mutation have a risk of 1% [13]. While the majority of male breast cancer is sporadic, a significant minority of men with breast cancer will have a *BRCA* mutation, underscoring the importance of considering genetic counselling and testing in this population. *BRCA2* mutations are the most common

germline mutation detected in men with breast cancer and this mutation also confers increased risks for prostate cancer.

The International Male Breast Cancer Program also includes a prospective study of new male breast cancer diagnoses with tumour collection, as well as prospective clinical studies testing the efficacy of breast cancer treatments in men. In the future such research will hopefully provide greater insights into the pathobiology and prognosis of male breast cancer, and enable evidence-based optimal management.

P. A. Francis
Department of Medical Oncology, PeterMacCallum Cancer Centre, Melbourne, Australia
(E-mail: prue.francis@petermac.org)

Funding

None declared.

Disclosure

The author received honoraria from AstraZeneca and gave an overseas lecture for Pfizer.

References

1. Giordano S, Cohen D, Buzdar A et al. Breast carcinoma in men: a population-based study. Cancer 2004; 101(1): 51–57.
2. Cardoso F, Bartlett JMS, Slaets L et al. Characterization of male breast cancer: results of the EORTC 10085/TBCRC/BIG/NABCG International Male Breast Cancer Program. Ann Oncol 2018; 29(2): 405–417.
3. Vermeulen MA, Slaets L, Cardoso F et al. Pathological characterisation of male breast cancer: results of the EORTC 10085/TBCRC/BIG/NNABCG International Male Breast Cancer Program. Eur J Cancer 2017; 82: 219–227.
4. Doebar SC, Slaets L, Cardoso F et al. Male breast cancer precursor lesions: analysis of the EORTC 10085/TBCRC/BIG/NABCG International Male Breast Cancer Program. Mod Pathol 2017; 30(4): 509–518.
5. Prat A, Cheang MC, Martin M et al. Prognostic significance of progesterone receptor-positive tumour cells within IHC defined luminal A breast cancer. J Clin Oncol 2013; 31: 203–209.
6. Piscuoglio S, Ng CKY, Murray MP et al. The genomic landscape of male breast cancers. Clin Cancer Res 2016; 22(16): 15.
7. Zagouri F, Sergentanis TN, Chrysikos D et al. Fulvestrant and male breast cancer: a pooled analysis. Breast Cancer Res Treat 2015; 149(1): 269–275.
8. Zagouri F, Sergentanis TN, Azim HA et al. Aromatase inhibitors in male breast cancer: a pooled analysis. Breast Cancer Res Treat 2015; 151(1): 141–147.
9. Kim ES, Bruinooge SS, Roberts S, et al. Broadening eligibility criteria to make clinical trials more representative: American Society of Clinical Oncology and Friends of Cancer Research joint research statement. J Clin Oncol 2017; 35: 3737–3744.
10. Turner C, Ro J, Andre F et al. Palbociclib in hormone-receptor-positive advanced breast cancer. N Engl J Med 2015; 373(3): 209–219.
11. Sorscher S. A first case of male breast cancer responding to combined aromatase inhibitor/palbociclib therapy. Int J Cancer Clin Res 2016; 3(5): 069.
12. Von Minckwitz G, Procter M, de Azambuja E et al. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. N Engl J Med 2017; 377(2): 122–131.
13. Tai Y, Domchek S, Parmigiani G et al. Breast cancer risk among male BRCA1 and BRCA2 mutation carriers. J Natl Cancer Inst 2007; 99: 1811–1814.

doi:10.1093/annonc/mdx752
Published online 20 November 2017

Pharmacogenomics: time to rethink its role in precision medicine

The complex genetic landscape of human cancer is evident not only across cancers from different primary sites, but also amongst cancers of the same histopathologic subtype. Understanding the contribution of this genetic landscape to relevant clinical end points such as overall survival (OS), treatment response, and toxicity has helped facilitate the evolution and application of precision clinical oncology [1, 2]. Over the past several years, specific challenges posed by genetic heterogeneity have led to the implementation of novel biomarker-based clinical trial designs for drug development, which have led to improved survival for patients with a wide variety of tumor types [3]. However, whereas many of these successful biomarker-based clinical trials have utilized somatic mutation profiling, relatively fewer studies have harnessed the area of pharmacogenomics and germline variation.

For colorectal cancer (CRC), the role of germline variation in the efficacy and toxicity of cytotoxic chemotherapy has been the subject of widespread investigation [4]. Dihydropyrimidine dehydrogenase (*DPYD*) gene variation is a well-established example, whereby deleterious single-nucleotide polymorphisms in *DPYD* have been associated with severe toxicity to 5-fluorouracil (5-FU) therapy [5, 6]. However, despite multiple lines of evidence that specific *DPYD* variants can reliably predict 5-FU toxicity, a number of issues currently limit pre-treatment *DPYD* testing from standard clinical practice, namely: regional differences in population allele frequency, technical variation in genotyping methods, and a paucity of large-scale randomized studies [7]. Germline variation in UDP-glucuronosyltransferase 1A1 (*UGT1A1*) presents a similar example, in which the *UGT1A1*28* polymorphism is associated with an increased risk of irinotecan toxicity due to decreased drug metabolism [8–10]. As in the case for *DPYD*, widespread testing for *UGT1A1* polymorphisms in CRC patients remains controversial. It is noteworthy that neither the National Comprehensive Cancer Network (NCCN) [11] nor European Society of Medical Oncology (ESMO) [12] guidelines currently recommend routine clinical testing of *DPYD* and *UGT1A1* polymorphisms. This not only reflects the practical challenges of incorporating germline variability into therapeutic decision-making, but also signifies an opportunity to discover novel germline biomarkers through innovative approaches.

In this issue of *Annals of Oncology*, Abad and Martinez-Balibrea et al. describe the results of a rigorous multi-center study that examined the feasibility and clinical utility of using germline DNA biomarkers to select front-line chemotherapy for patients with metastatic CRC (mCRC) [13]. Using a randomized, phase II, open-label design, a total of 195 Spain-based patients with