IJC
International Journal of Cancer

Personalised cancer medicine

Sarah E. Jackson and John D. Chester

Institute of Cancer and Genetics, School of Medicine, Cardiff University, Cardiff, United Kingdom

Mini Review

The evolving field of personalised medicine is playing an increasingly important role in cancer prevention, diagnosis, prognosis and therapeutics. Its importance in clinical management is demonstrated by the recent introduction into routine clinical practice of various individualised, molecularly targeted therapies with increased efficacy and/or reduced toxicity. The identification of cancer predisposition genes, such as the BRCA genes in breast cancer, permits screening programmes to identify patients "at-risk" of developing cancer and helps them make decisions on individual risk-modification behaviours. Personalised medicine also plays an increasingly important role in cancer treatment. It is increasingly clear that there are molecularly distinct subtypes of various common cancers, with different therapeutic approaches required for each subtype, for example, the use of the monoclonal antibodies (trastuzumab and cetuximab) in HER2-positive breast cancer and wild-type KRAS colorectal cancer; tyrosine kinase inhibitors (imatinib, gefitinib, erlotinib and crizotinib) in chronic myeloid leukaemia, gastrointestinal stromal tumours and non-small-cell lung cancer and intracellular agents (vemurafenib and olaparib) in metastatic malignant melanoma and ovarian, breast and prostate cancer. The efficacy of various targeted therapies in such disparate tumours suggests that we are entering an era in which treatment decisions will be based on tumour molecular abnormality profile or "signature," rather than tumour tissue type or anatomical site of origin, improving patient prognosis and quality of life. This mini review focuses on the role of personalised medicine in cancer prevention and treatment as well as its future direction in oncology.

Personalised medicine is an emerging approach to patient care in which an individual's characteristics, including their genetic profile, guide clinical decisions, aiming for the right treatment for the right patient at the right time. It is an evolving field in medicine with many resources dedicated to searching for diagnostic, prognostic and predictive biomarkers. Individualised medicine has diverse applications and is already used routinely in many specialities, such as measuring thiopurine methyltransferase before treatment with azathioprine in inflammatory bowel disease.[1]

Personalised medicine is particularly important in oncology, where there is an increased emphasis on prevention and where significant short-term toxicities and long-term functional implications are associated with surgical and chemoradiotherapy management strategies. Appropriate selection of patients for treatment, to maximise efficacy and minimise toxicity, has long been a fundamental part of routine clinical practice, but until recently clinicians have had limited tools with which to determine which patients will benefit and which may suffer avoidable toxicities. Exciting developments within personalised cancer medicine, including recognition of prognostic and predictive biomarkers that confer the ability to target treatments to those patients most likely to benefit, are improving survival outcomes, and are fast becoming an important part of routine clinical practice. In this review, we will focus on the application of personalised medicine in cancer, particularly in the prevention and treatment of cancer, and at how personalised medicine will influence clinical practice in the future.

Key words: stratified medicine, synthetic lethality, cancer predisposition genes, monoclonal antibody, tyrosine kinase inhibitor, PARP inhibitor

DOI: 10.1002/ijc.28940

History: Received 17 Feb 2014; Accepted 24 Apr 2014; Online 2 May 2014

Correspondence to: Sarah E. Jackson, Institute of Cancer and Genetics, School of Medicine, Cardiff University, Cardiff, United Kingdom, E-mail: s.e.jackson@doctors.org.uk or John D. Chester, Institute of Cancer and Genetics, School of Medicine, Cardiff University, Cardiff, United Kingdom, E-mail: chesterjd@cardiff.ac.uk

Personalised Medicine in Cancer Prevention

A cell with normal DNA develops into a cancerous cell through the accumulation of genetic changes. Some of these alterations are sporadically acquired and others are inherited in the form of cancer predisposition genes. The identification of cancer predisposition genes has led to the development of screening programmes to identify patients "at-risk" of developing cancer and helps them make decisions on individual risk-modification behaviours. However, an essential part of any screening programme is to have an appropriate accepted therapeutic intervention that can alter the natural history of the disease.[2]

Breast cancer

Breast cancer is hormonally driven and chemoprevention is an attractive, albeit nonselective, management strategy. The selective oestrogen receptor modulator tamoxifen has been

Table 1. Molecular targets for personalised cancer therapies

Cancer type	Cellular target	Targeted agent	Class of agent
Colorectal[16–18]	KRAS	Cetuximab	Monoclonal antibody against EGFR
Breast[19,20]	HER2	Trastuzumab	Monoclonal antibody against HER2/Neu (EGFR2)
Chronic myeloid leukaemia[21,22]	BCR-ABL fusion protein	Imatinib	Receptor tyrosine kinase inhibitor
Gastrointestinal stromal tumours[23,24]	c-KIT	Imatinib	Receptor tyrosine kinase inhibitor
Non-small-cell lung cancer[25–28]	EGFR	Erlotinib and gefitinib	Receptor tyrosine kinase inhibitor
Non-small-cell lung cancer[29,30]	EML4-ALK fusion protein	Crizotinib	Receptor tyrosine kinase inhibitor
Metastatic malignant melanoma[31,32]	BRAF V600E	Vemurafenib	B-raf/MEK/ERK pathway inhibitor
Ovarian, breast and prostate cancer (under investigation)[33,34]	BRCA1, BRCA2	Olaparib	Poly(ADP-ribose) polymerase (PARP) inhibitor

Abbreviations: APC: adenomatous polyposis coli; CML: chronic myeloid leukaemia; CRC: colorectal cancer; EGFR: epidermal growth factor receptor; EML4-ALK: echinoderm microtubule-associated protein-like 4—anaplastic lymphoma kinase fusion gene; FAP: familial adenomatous polyposis coli; GIST: gastrointestinal stromal tumour; NICE: National Institute for Health and Care Excellence; NSCLC: non-small cell lung cancer; PARP: poly(ADP-ribose) polymerase; TK: tyrosine kinase; TKI: tyrosine kinase inhibitor

shown in a number of phase III randomised controlled trials to reduce the incidence of breast cancer by 16–49% in high-risk females. However, it is unknown if this translates into a longevity benefit, and the significant side effects associated with tamoxifen preclude its long-term, unselected use.[3] A double-blind prospective randomised controlled trial of more than 19,000 postmenopausal women showed raloxifene, another selective oestrogen receptor modulator, to be an alternative, effective option, with fewer side effects in postmenopausal women at high risk of developing breast cancer.[3,4]

Selective preventative strategies can be used in female carriers of mutations in the BRCA1 or BRCA2 genes, which give a 45–65% chance of developing breast cancer by the age of 70.[5] These genes also increase the risk of ovarian, colon and prostate cancer.[6] Individualised genetic testing for the BRCA genes is available for individuals with a strong family history of breast cancer. Prophylactic options for individuals found to be carriers include removal of breast tissue, oophorectomy or chemical oestrogen deprivation. Although the BRCA genes are associated with a high penetrance, 30% of carriers will not develop breast cancer, prompting difficult, highly personal decisions.[5] Prophylactic mastectomy is a major operation with associated surgical risks and psychological harm. A Cochrane review found that worry over breast cancer was significantly reduced following a mastectomy, and that it was effective in reducing the incidence of deaths from breast cancer.[7] The decision is made more difficult by the twin uncertainties of cancer developing in the absence of surgery and of cancer not being completely avoided with surgery: the risk of breast cancer cannot be entirely eliminated, as some breast tissue remains. Motivations for acting to alleviate risk are influenced by family history and personal experiences of cancer.[8] This highlights the importance of individually counselling patients undergoing genetic testing.

Colorectal cancer

The accumulation of germline mutations triggers colorectal cancer (CRC) development.[9] One percent of bowel cancers are caused by familial adenomatous polyposis coli (FAP), an autosomal dominant disorder with complete penetrance, where a mutation in the adenomatous polyposis coli (APC) gene causes truncation of the protein product and deregulation of the downstream Wnt signalling pathway. Formation of hundreds of polyps contributes to the frequent development of CRC by 40–50 years old.[9,10] Genetic screening identifies carriers and allows consideration of prophylactic bowel resection. This use of personalised medicine has led to a 55% reduction in CRC incidence and improved overall survival in patients with FAP, though, as in surgical prophylaxis for breast cancer above, surgery does not guarantee complete prevention of cancer development.[11,12]

A number of chemopreventative agents have been studied in CRC. An analysis of randomised controlled trials using aspirin for prevention of vascular events demonstrated that patients treated with aspirin developed fewer distant metastases and fewer fatal adenocarcinomas.[13] A randomised controlled trial in carriers of hereditary nonpolyposis CRC showed that daily aspirin therapy reduces the incidence of primary CRC.[14] Aspirin is a promising, but nonselective strategy. Stratified chemopreventive agents may be used in the future to delay or even prevent progression of polyps and reduce the need for drastic bowel surgery.[15]

Personalised Medicine in Cancer Treatment

Trastuzumab in breast cancer

An iconic and well-known example of personalised medicine is the use of trastuzumab, a humanised IgG1 monoclonal antibody in breast cancer patients whose tumours overexpress the oncogene HER2 (Table 1). HER2 regulates cell

proliferation and is overexpressed in 20–25% of patients with breast cancer. HER2-positive status confers a poor prognosis but is also a strong predictor of response to trastuzumab.[19] A Cochrane systematic review of eight randomised controlled trials involving 11,991 patients showed that breast cancer mortality was reduced by one-third when trastuzumab was added to standard chemotherapy regimens for longer than 6 months in the subset of patients who overexpress the HER2 growth factor. The rate of recurrent breast cancer in this cohort was also reduced by 40%.[20] Careful patient selection is important owing to the cardiotoxicity associated with the drug, which can negate any benefit, particularly in low-risk patients or those more susceptible to its side effects.

Cetuximab in CRC

The epidermal growth factor receptor (EGFR) is overexpressed in many epithelial cancers, resulting in dysregulated cell proliferation and an aggressive phenotype.[35] EGFR inhibition is therefore a promising therapeutic strategy in personalised medicine research. Cetuximab, a monoclonal antibody directed against EGFR, has proven utility in patients with CRC expressing wild-type KRAS, which encodes a downstream effector of EGFR involved in intracellular signalling. A randomised trial of 572 patients with CRC unresponsive to standard chemotherapy demonstrated that wild-type KRAS status predicted response to cetuximab, with improved quality of life and almost doubled overall and progression-free survival, when compared to patients with wild-type KRAS treated with supportive care only. Patients with mutated KRAS did not benefit from cetuximab treatment.[16] Cetuximab is therefore licensed for use in the 60%[17] of CRC tumours expressing the wild-type KRAS gene.[18] The use of KRAS status as a predictor of response to EGFR inhibitors in CRC is being extended to other cancers, such as non-small-cell lung cancer (NSCLC).

Predicting response to therapies based on gene mutation status allows individualised therapy and has potential health economic benefits by reducing prohibitive treatment costs.[16] Targeted therapies are expensive, and the cost of providing personalised medicine must not be underestimated, particularly in an era of public fiscal austerity. Personalised medicine provides the prospect of health-economic gains, on a population basis, by limiting expenditure to where it is most cost-effective—by ensuring drugs are targeted where they are going to be most effective and least toxic, costs of treatment and complications can be reduced.

Tyrosine kinase inhibitors in chronic myeloid leukaemia, gastrointestinal stromal tumours and NSCLC

In chronic myeloid leukaemia (CML), a reciprocal translocation between the long arms of chromosome 9 and 22, termed the Philadelphia chromosome, results in expression of a BCR-ABL fusion oncoprotein with constitutive tyrosine kinase (TK) activity.[36] This promotes tumourigenesis but also provides an "Achilles' heel," ripe for exploitation by tumour-selective, molecularly targeted therapy. The TK inhibitor (TKI) imatinib produces a complete haematological response in most patients, transforming CML from a devastating diagnosis with a median survival of 5 years into a manageable, chronic disease requiring regular monitoring.[21,22]

Activating mutations of the tyrosine kinase oncogene c-KIT are found in 90% of primary gastrointestinal stromal tumours (GISTs), promoting tumour development. In an interesting, but molecularly distinct parallel to CML, imatinib induces a disease control rate of 80% in these tumours.[23,24] Although personalised medicine is designed to provide "precision therapies," targeted to specific molecular defects, this case of the same drug targeting two separate molecular defects is reminiscent of traditional, nonselective methods of drug design and use.

Similarly, in patients with advanced NSCLC and EGFR mutations, TKIs have been shown to be of clinical benefit. A phase III study demonstrated that 24.9% of patients treated with the TKI gefitinib plus standard chemotherapy had a 12-month progression-free survival, compared to 6.7% in patients treated with standard chemotherapy. In those patients with an EGFR mutation treated with gefitinib, progression-free survival was longer, whereas in EGFR mutation-negative patients progression-free survival was longer when treated with standard chemotherapy.[37] Improved progression-free survival in EGFR mutation patients treated with gefitinib was confirmed in another phase III study.[25] Similarly, the TKI erlotinib significantly increases survival and progression-free survival, and reduces symptoms compared to placebo.[26,27] The best responses were in female, nonsmoking, Asian patients. Currently, oral erlotinib is recommended as a first-line treatment for patients with advanced NSCLC who have appropriate mutations.[28]

Another TKI that has been demonstrated to be of value in a subset of NSCLC patients is crizotinib, which has been approved by the US Department of Food and Drug Administration for use in the 3–6% of NSCLC patients harbouring the echinoderm microtubule-associated protein-like 4, anaplastic lymphoma kinase (EML4-ALK) fusion oncogene, the prevalence of which increases to 10–20% in younger, nonsmoking patients with adenocarcinomas.[29] A phase III trial[30] of 347 EML4-ALK-positive patients with disease progression following treatment with platinum-based chemotherapy showed a dramatic improvement in progression-free survival in patients treated with crizotinib, 7.7 months, compared to 3.0 months in the patients treated with either pemetrexed or docetaxel; a 51% reduction in the risk of disease progression. The radiological response rate was also enhanced, with 65% of crizotinib-treated patients responding, compared to 20% not treated with crizotinib. Most toxicities associated with crizotinib were grade 1 or 2, although significant toxicities included lung fibrosis and elevated aminotransferase levels.

Vemurafenib in metastatic malignant melanoma

Stage IV malignant melanoma is a disease with very poor prognosis–median survival at diagnosis is only 18 months.[31]

However, recent advances in personalised therapy have resulted in a significant change in outlook for a large subset of metastatic malignant melanoma patients. Sixty-six percent of malignant melanomas have a BRAF oncogene mutations, resulting in a single amino acid substitution, V600E, which predicts increased disease severity and decreased response to existing cytotoxic chemotherapy.[32] Treatment with vemurafenib, a potent and selective Raf inhibitor, reduced the relative risk of mortality by 63% and the risk of death or disease progression by 74% in patients with unresectable, previously untreated stage IIIC/IV BRAF V600E mutation-positive malignant melanoma, compared to standard treatment.[31] Vemurafenib has consequently been approved in America and Europe as individualised therapy for treating patients with BRAF V600E mutation-positive unresectable or metastatic malignant melanoma.

Poly(ADP-ribose) polymerase inhibitors

Synthetic lethality in cancer medicine describes a situation where inactivation of one of two alternative cellular pathways in a cancer cell is compatible with survival, but the additional inactivation of the other by a therapeutic drug leads to tumour cell death. Selective tumour toxicity can be achieved by using molecularly targeted drugs to inhibit pathways that would otherwise "rescue" a lethal defect caused by a tumour mutation. In principle, this approach is applicable across a wide variety of tumours and also spares normal cells, simultaneously improving the efficacy and reducing the toxicity of individualised therapies.[38]

A recent application of this approach has been in treating patients carrying the BRCA1 or BRCA2 mutations with poly(ADP-ribose) polymerase (PARP) inhibitors. Cells with BRCA mutations have nonfunctioning homologous recombination DNA repair mechanisms.[33] However, base-excision DNA repair mechanisms remain functional, "rescuing" a tumour cell from apoptotic death following DNA-damaging cancer therapy. PARP-1 inhibitors prevent base-excision repair occurring, producing tumour cell death in BRCA-deficient cells, but not in normal cells with functional homologous recombination pathways, thereby achieving selective cytotoxicity. Olaparib, a PARP inhibitor used in phase 1 trials, has encouraging selectivity and sensitivity in BRCA1 or BRCA2 mutation carriers with ovarian, breast and prostate cancer, with few associated adverse effects.[33] A phase 2 trial in women with advanced pretreated high-grade serous ovarian carcinoma confirmed the higher response rate in BRCA1 or BRCA2 mutation carriers.[34] Researchers are exploring the efficacy of PARP inhibitors and other synthetic lethal partners of PARP, such as PTEN, in many tumour types.[39]

The Future of Personalised Medicine

It is increasingly clear that there are molecularly distinct subtypes of various common cancers, with different therapeutic approaches required for each subtype. The importance of stratified medicine in the management of these patients is being recognised around the world, facilitating partnerships between hospitals and laboratories to incorporate molecular analysis into routine oncological practice. For example, the Stratified Medicine Programme in the UK[40] collects and analyses cancer samples as a part of routine cancer care, aiming to find molecular markers of prognostic and therapeutic significance. Many genes of potential significance are being investigated such as BRAF, KRAS and EGFR, discussed above, in six cancer types (breast, colorectal, lung, malignant melanoma, ovarian and prostate).

Current clinical trials are enlisting patients to test the efficacy of targeted medications. The BATTLE trial in stage IIIb/IV NSCLC patients is an exciting example of the potential benefit for patients of personalised therapy. It has been demonstrated that patients whose tumours have wild-type EGFR genes have significantly greater benefit from treatment with sorafenib, with a 1.5-month longer progression-free survival compared to EGFR-mutant tumours.[41] Similarly, breast cancer patients with and without the PIK3CA mutation are being recruited to compare treatment in combination with paclitaxel with the AKT inhibitor AZD5363 or with placebo,[42] and the TKI lapatinib is being studied as maintenance therapy in patients with advanced HER1/2-positive bladder cancer.[43]

As with other systemic agents for cancer therapy, the utility of new molecularly targeted agents is limited by primary or secondary resistance to therapy. Molecular defects in tumour cells, in addition to those targeted by the drugs, can result in either a failure to respond to drug from the outset or an early progression of disease, following initial response. This is likely due to both intrinsic and acquired resistance mechanisms. Acquired resistance develops following initial use of crizotinib in EML4-ALK NSCLC patients fuelling the development of second-generation EML4-ALK inhibitors. The use of EGFR inhibitors in NSCLC eventually leads to resistance, in some cases through secondary EGFR mutations or amplification of the MET oncogene. The use of MET inhibitors combined with EGFR inhibitors may allow multipathway inhibition and prolonged efficacy of therapy.[44] Similarly, in patients with BRAF V600E melanoma treated with vemurafenib, resistance and tumour recurrence commonly develops after 5–7 months. Acquired resistance mechanisms include the gain of additional mutations in BRAF as well as downstream effectors such as NRAS, MEK and ERK in subpopulations of tumour cells, with molecular evolution of the tumour resulting in tumour heterogeneity and consequent diminished efficacy of therapy in these subpopulations.[45] To combat this, future developments in rational therapeutic design will need to be directed at identifying, understanding and targeting these additional, disease-modifying molecular mutations to develop effective second-line or combination therapies in resistant subpopulations of tumours.

The evolving field of personalised medicine is an exciting area of cancer sciences with a diversity of applications, including real improvements in clinical outcomes for appropriately selected subsets of patients. Its importance in clinical

management is demonstrated by the recent, rapid integration of various individualised, molecularly targeted therapies into routine clinical practice. The efficacy of various target therapies in such disparate tumours suggests that we are approaching an era in which treatment decisions will be based on tumour molecular abnormality profile or "signature," rather than tumour tissue type or anatomical site of origin, improving patient prognosis and quality of life.

References

1. Zhou Z. Clinical pharmacogenomics of thiopurine S-methyltransferase. *Curr Clin Pharmacol* 2006;1:119–28.
2. Wilson JMG, Jungner G. Principles and practice of screening for disease. World Health Organization Public Health Papers No. 34, 1968.
3. Martino S, Costantino J, McNabb M, et al. The role of selective oestrogen receptor modulators in the prevention of breast cancer: comparison of the trials. *Oncologist* 2004;9:116–25.
4. Vogel VG, Costantino JP, Wickerham DL, et al. Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 Trial. *JAMA* 2006; 295:2727–41.
5. Rhaman N, Stratton MR. The genetics of breast cancer susceptibility. *Annu Rev Genet* 1998;32: 95–121.
6. Chen S, Parmigiani G. Meta-analysis of *BRCA1* and *BRCA2* penetrance. *J Clin Oncol* 2007;25: 1329–33.
7. Lostumbo L, Carbine NE, Wallace J. Prophylactic mastectomy for the prevention of breast cancer. *Cochrane Database Syst Rev* 2010;11:CD002748.
8. Singh K, Lester J, Karlan B, et al. Impact of family history on choosing risk-reducing surgery among BRCA mutation carriers. *Am J Obstet Gynecol* 2013;208:329.e1–6.
9. Pineda M, González S, Lázaro C, et al. Detection of genetic alterations in hereditary colorectal cancer screening. *Mutat Res* 2010;693:19–31.
10. Half E, Bercovich D, Rozen P. Familial adenomatous polyposis. *Orphanet J Rare Dis* 2009;4:22.
11. Kartheuser A, Stangherlin P, Brandt D, et al. Restorative proctocolectomy and ileal pouch-anal anastomosis for familial adenomatous polyposis revisited. *Fam Cancer* 2006;5:241–60; discussion 261-2.
12. Galiatsatos P, Foulkes WD. Familial adenomatous polyposis. *Nature* 2006;101:385–98.
13. Rothwell PM, Wilson M, Price JF, et al. Effect of daily aspirin on risk of cancer metastasis: a study of incident cancers during randomised controlled trials. *Lancet* 2012;379:1591–601.
14. Burn J, Gerdes AM, Macrae F, et al. Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial. *Lancet* 2011; 378:2081–7.
15. Arber N, Levin B. Chemoprevention of colorectal neoplasia: the potential for personalized medicine. *Gastroenterology* 2008;134:1224–37.
16. Karapetis CS, Khambata-Ford S, Jonker DJ, et al. *K-ras* mutations and benefit from cetuximab in advanced colorectal cancer. *N Engl J Med* 2008; 359:1757–65.
17. Fearon ER. Molecular genetics of colorectal cancer. *Annu Rev Pathol* 2011;6:479–507.
18. European Medicines Agency. Committee for Medicinal Products for Human Use Post-Authorisation Summary of Positive Opinion for Erbitux. Doc.Ref. EMEA/CHMP/280402/2008. London 2008. Available at: http://www.emea.europa.eu/docs/en_GB/document_library/Summary_of_opinion/human/000558/WC500059827.pdf.
19. Goldenberg MM. Trastuzumab, a recombinant DNA-derived humanized monoclonal antibody, a novel agent for the treatment of metastatic breast cancer. *Clin Ther* 1999;21:309–18.
20. Moja L, Tagliabue L, Balduzzi S, et al. Trastuzumab containing regimens for early breast cancer. *Cochrane Database Syst Rev* 2012;4:CD006243.
21. Smith BD. Imatinib for chronic myeloid leukemia: the impact of its effectiveness and long-term side effects. *J Natl Cancer Inst* 2011;103:527–9.
22. Goldman JM, Marin D. Is imatinib still and acceptable first-line treatment for CML in chronic phase? *Oncology* 2012;26:901–7.
23. Heinrich MC, Corless CL, Demetri GD, et al. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. *J Clin Oncol* 2003;21:4342–9.
24. Hornick JL, Fletcher CDM. The role of KIT in the management of patients with gastrointestinal stromal tumors. *Hum Pathol* 2007;38:679–87.
25. Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. *Lancet Oncol* 2010;11:121–8.
26. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med* 2005;353:123–32.
27. Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol* 2012;13:239–46.
28. Wang Y, Schmid-Bindert G, Zhou C. Erlotinib in the treatment of advanced non-small cell lung cancer: an update for clinicians. *Ther Adv Med Oncol* 2012;4:19–29.
29. Shaw AT, Yeap BY, Mino-Kenudson M, et al. Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-ALK. *J Clin Oncol* 2009;27:4247–53.
30. Shaw AT, Kim DW, Nakagawa K, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. *N Engl J Med* 2013;368: 2385–94.
31. Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med* 2011;364:2507–16.
32. Tsai J, Lee JT, Wang W, et al. Discovery of a selective inhibitor of oncogenic B-Raf kinase with potent antimelanoma activity. *Proc Natl Acad Sci USA* 2008;105:3041–6.
33. Fong PC, Boss DS, Yap TA, et al. Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. *N Engl J Med* 2009;361: 123–34.
34. Gelmon KA, Tischkowitz M, Mackay H, et al. Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: a phase 2, multicentre, open-label, non-randomised study. *Lancet Oncol* 2011;12:852–61.
35. Wheeler DL, Dunn EF, Harari PM. Understanding resistance to EGFR inhibitors-impact on future treatment strategies. *Nat Rev Clin Oncol* 2010;7:493–507.
36. Druker BJ, Talpaz M, Resta DJ, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. *N Engl J Med* 2001;344:1031–7.
37. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009;361:947–57.
38. Kaelin WG. The concept of synthetic lethality in the context of anticancer therapy. *Nat Rev Cancer* 2005;5:689–98.
39. Nijman SMB. Synthetic lethality: general principles, utility and detection using genetic screens in human cells. *FEBS Lett* 2011;585:1–6.
40. Shaw E, Tuff A, Sharpe R, et al. Emerging findings in the Cancer Research UK Stratified Medicine Programme. *J Clin Oncol* 2012;(Suppl): abstr TPS10633.
41. Kim ES, Herbst RS, Wistuba II, et al. The BATTLE trial: personalizing therapy for lung cancer. *Cancer Discov* 2011;1:44–53.
42. Clinical Trials.gov. Investigating safety, tolerability and efficacy of AZD5363 when combined with paclitaxel in breast cancer patients (BEECH). Available at: http://clinicaltrials.gov/show/NCT01625286.
43. Clinical Trials.gov. A double blind randomised study of lapatinib and placebo in metastatic TCC of the urothelium (LaMB). Available at: http://clinicaltrials.gov/show/NCT00949455.
44. Pao W, Chmielecki J. Rational, biologically based treatment of EGFR-mutant non-small-cell lung cancer. *Nat Rev Cancer* 2010;10:760–74.
45. Sullivan RJ, Flaherty KT. Resistance to BRAF-targeted therapy in melanoma. *Eur J Cancer* 2013;49:1297–304.