Plenary Lecture #3: Global Cost of Cancer Care
Friday, December 9, 9:00 AM, Hall 3
Peter B. Bach, MD, MAPP
Memorial Sloan-Kettering Cancer Center, New York, NY

According to a 2014 IMS health report, cancer drugs represent 26% of specialty drug spending, more than $32B in the US in 2014, and specialty drug spending is growing faster than any other sector of healthcare. Unsurprisingly, cancer drugs are the largest sub-segment. These price rises are not just an economic curiosity. Because of the structure of many insurance products, the co-insurance on these expensive drugs is crippling, impacting access on a large scale. A recent study reported that more than 10% of Medicare beneficiaries with a cancer diagnosis face out of pocket expenses exceeding their incomes. In a nationally representative survey conducted in 2006, twenty-five percent of patients reported exhausting all or most of their savings. In a recent analysis of discontinuation rates among patients taking Gleevec and other highly effective drugs for Chronic Myeloid Leukemia, patients with high copayments were 42% more likely to be nonadherent.

Dr. Bach has researched this problem with a data-driven set of related projects that aim to achieve substantive change to pricing of and access to specialty drugs, beginning with cancer drugs because of established expertise, but expanding to other analogous areas rapidly.

In 2009, Dr. Bach’s team began tracking the launch prices of new cancer drugs, a project which has shown a 100-fold increase in introductory cancer drug prices, after adjusting for inflation. A follow-on study found that the increase in price is not accompanied in an increase in clinical value, with the cost of a year of life increasing by $8,500 a year.

In 2012, on behalf of Memorial Sloan Kettering Cancer Center, Dr. Bach publicly rejected the pricing of the cancer drug, Zaltrap, by announcing the hospital’s position in the New York Times. In response, the company lowered its price by 50%, proving that the price is not tied to any specific metric (i.e. R&D costs), but is rather determined by what the market can bear.

Dr. Bach launched a project in 2015 called the DrugAbacus (drugabacus.org), an interactive web based tool that allows users to manipulate various metrics to determine the ‘value’ of cancer drugs. DrugAbacus shifted the conversation of value-based pricing from one of theory to one more focused on implementation, and has been cited as a source of pricing for both CVS and Express Scripts.

The Zaltrap stance, the DrugAbacus, and much of his work has made MSKCC a leader in using evidence to shift the discussion on drug pricing, a consistent theme of which has been that the price a manufacturer sets is a product of the marketplace, not a product of the costs of their business or something else structural.
AACR Outstanding Investigator Award for Breast Cancer Research
funded by Susan G. Komen®

Decoding Breast Cancer Predisposition Genes
Fergus J. Couch, PhD
Mayo Clinic, Rochester, MN

Friday, December 9, 11:30 am, Hall 3

The AACR Outstanding Investigator Award for Breast Cancer Research, funded by Susan G. Komen®, recognizes an investigator of no more than 50 years of age whose novel and significant work has had or may have a far-reaching impact on the etiology, detection, diagnosis, treatment, or prevention of breast cancer. Such work may involve any discipline across the continuum of biomedical research, including basic, translational, clinical and epidemiological studies.

Dr. Fergus J. Couch is honored for his seminal work in identifying the inherited genes and mutations that predispose to breast cancer. Dr. Couch is a Professor and Chair of the Division of Experimental Pathology and Laboratory Medicine at the Mayo Clinic, with a joint appointment in the Departments of Health Sciences Research. Much of his research has focused on determining the clinical relevance of inherited variants of uncertain significance (VUS) in breast cancer predisposition genes using genetic epidemiology and molecular biology approaches, and as a founder and member of the Evidence based Network for the Interpretation of Germline Mutant Alleles (ENIGMA) consortium. Dr. Couch is also a leader in the BCRA Challenge and the Prospective Registry of Multiplex Testing (PROMPT) initiatives aimed at understanding alterations in cancer predisposition genes.

Dr. Couch is a distinguished national leader in cancer genetics. He is a co-founder of the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA), a Triple Negative Breast Cancer Consortium (TNBCC), and an effort to identify genetic factors that account for the missing heritability of breast cancer.

Hot Topic #1: Pathological Complete Responses in Anti-HER2 Therapies

Thursday morning, Dr. Alexei Prat presented the results of the PAMELA clinical trial, a non-randomized, open-label, multicentric, prospective translational research study in stage I-IIIA HER2+ BC. The PAM50 predictor was used to identify the intrinsic subtypes to predict pathological complete responses (pCR) in the breast (pCRB) following 18 weeks of neoadjuvant lapatinib (LAP) and trastuzumab (TRAS).

After analysis of the intrinsic subtype distribution at baseline vs. week 2 and comparison of Normal-like vs. non-Normal-like samples at week 2, at day 15, the majority of tumors became Normal-like (48.9%) or Luminal A (27.5%). Rates of pCRB were 46.9% in Normal-like tumors and 11.9% in non-Normal-like tumors.

The trial prospectively confirmed that the HER2-enriched (HER2-E) subtype is a strong predictor of sensitivity to dual HER2 blockade within HER2+ BC in the absence of chemotherapy. PAM50, at baseline and at week 2, provides independent information compared to HER2 status. Further studies on the validation of this research are ongoing.

Continuing on the topic of HER2 therapy, Dr. Grazia Arpino presented the results of PERTAIN, a randomized, two-arm, open-label, multicenter phase II trial assessing the efficacy and safety of pertuzumab (PER) given in combination with trastuzumab (TRAS) plus an aromatase inhibitor (AI) in first-line patients with HER2+ and HR+ metastatic or locally advanced BC (LA/MBC). Stemming from the research that HER2-ER bidirectional cross-talk may contribute to resistance to single and anti-HER2 therapies, PERTAIN hypothesized that PER + TRAS + AI (Arm A) could offer additional benefits.

258 postmenopausal patients with HER2+ and HR+ LA/MBC who had not been treated previously with systemic therapy (except endocrine therapy), were randomized to Arm A or Arm B (TRAS + AI). The primary endpoint was progression-free survival (PFS).

The trial successfully met its primary objective: Arm A was superior to Arm B in postmenopausal women with HER2+/ER+ LA/MBC. The 27-month duration of response for Arm A compares to the 15.1 months for Arm B in patients who did not receive induction chemotherapy, with a 0.018 p-value. Arm A was also well tolerated and no new safety issues were identified. Overall survival will be further studied after a minimum follow-up of 60 months for all patients.

Dr. Maki Tanioka then discussed predictors of pCR in CALGB 40601, a randomized phase III trial looking at women with HER2+ BC. Dr. Tanioka’s group looked at 161 samples of women who received paclitaxel and TRAS with and without LAP. They built a logistic
regression model for pCR using the elastic net method to test various data combinations of gene signature, DNA copy number, and mutations to better understand TRAS-based regimen responsiveness.

In a DawnRank analysis, chromosome 6 was highly ranked among pCR samples (low among non-pCR samples), and was thus predictive of increased sensitivity to TRAS-paclitaxel regimens. Among non-pCR samples, deletions at chromosomes 22q and 11q were highly ranked, predicting increased resistance. On further computational analysis, 15 overlap genes were identified, but only MAPK14 at chromosome 6p and CBL at chromosome 11q correlated with DNA copy number and mRNA gene expression values.

Dr. Tanioka concluded that gene expression signatures and DNA copy number changes were most predictive of pCR in CALGB 40601, and experimental validation of these predictors of sensitivity and resistance are underway.

Next, Mothaffar Rimawi presented data from NSABP B52, a phase III trial that evaluated pCR in estrogen receptor-positive (ER+), HER2+ BC treated with neoadjuvant docetaxel, carboplatin, TRAS, and PER, with and without estrogen deprivation. His team hypothesized that concurrent inhibition of ER and HER2 plus chemotherapy will not be antagonistic, and will overcome resistance to treatment, thus improving pCR rates in patients with ER+/HER2+ BC.

Data showed that the addition of estrogen deprivation was not antagonistic and did not significantly increase gastrointestinal toxicity or incidence of anemia, hypokalemia, or febrile neutropenia. The overall pCR rate was 41% in the control group and 46% in the experimental group that received estrogen deprivation. This improvement was not statistically significant.

“Given the toxicity of standard chemotherapy, findings from NSABP B52 argue for a tailored de-escalation approach where toxic treatments are omitted and replaced with less toxic ones without compromising outcomes,” Dr. Rimawi concluded.

Dr. Carmine De Angelis introduced a study of GS-6510, a new inhibitor of the epigenetic regulator BRD4. GS-6510 was assessed in ER+ BC models as monotherapy or in combination with fulvestrant (FUL), and was found to enhance the efficacy of endocrine therapies in parental cells, particularly with estrogen deprivation and tamoxifen. In combination with FUL in vivo, it induced tumor regression in the HBCx34 PDX model. Furthermore, in the endocrine-resistant models MCF7 EDR and TAMR, GS-6510 in combination with FUL was associated with a significantly greater cell growth inhibition and a better suppression of ER, c-MYC, and phospho-RB protein levels compared to single agents.

In conclusion, BRD4 is a suitable target for therapeutic intervention in ER+ BC. The growth inhibitory effects observed in some of the ER-independent endocrine-resistant models suggest that additional genes and pathways involved in endocrine resistance could be affected by GS-6510.

Dr. John J. Flanagan discussed proteolysis targeting chimera (PROTAC) molecules that consist of an ER ligand and E3 ligase binding domain to bring ER and E3 ligase together for ER degradation. According to his data, PROTACs and fulvestrant significantly reduced ERα levels, compared to controls, while many clinical selective ER downregulators (SERDs) alone appeared to behave more as potent antagonists than degraders. An exception was seen in MCF-7 cells, where SERDs GDC810 and AZD9496 showed ≈50% reduction in ER. Further studies showed that PROTACs could reduce receptor levels in the nucleus, while SERDs such as AZD9496 could only cause reductions in cytosol. Dr. Flanagan closed with data about an oral form of PROTAC that demonstrated promising in vitro target engagement and ER degradation.

Hot Topic #2: ER Degradation

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