prIME LINES

December 2016

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YEAR IN REVIEW

As with recent years, 2016 was an active year for drug development and oncology research, with over 20 approvals for new agents or expansions of current indications from the United States Food and Drug Administration (FDA), including the approval of daratumumab for multiple myeloma on 21 November. Immunotherapy was once again the shining star of oncology, with head and neck cancer (H&N), renal cell carcinoma (RCC), and urothelial cancer joining melanoma and non-small cell lung cancer (NSCLC) as areas with approved immune checkpoint inhibitors. Several targeted therapies and combinations emerged as key players in NSCLC, melanoma, and sarcoma, and we learned a great deal about how to select and sequence treatment across a variety of cancers. Drug development continues apace, with several new agents making headlines in 2016, guaranteeing that next year will be just as full of major advancements in the treatment of cancer.

- **CDK4/6 Inhibitors Become Standard of Care in Hormone-Sensitive Metastatic Breast Cancer.** Development of cyclin-dependent kinase 4/6 (CDK4/6) inhibitors has led to important changes in the treatment of hormone receptor (HR)-positive, human epidermal growth factor 2 (HER2)-negative metastatic breast cancer (MBC). The first CDK4/6 inhibitor, palbociclib (Ibrance®, Pfizer), was approved by the FDA

in February 2015 for first-line therapy in combination with letrozole based on results from the randomized phase II PALOMA1 trial. In 2016 this approval was expanded to include second-line therapy in combination with fulvestrant in women who have progressed on first-line endocrine therapy (PALOMA3). In addition, results from the phase III PALOMA2 trial of the addition of palbociclib to letrozole with 10.3 months progression-free survival (PFS) benefit justified approval for previously untreated patients who are postmenopausal with HR-positive/HER2-negative breast cancer. A second CDK4/6 inhibitor, ribociclib (Novartis), also showed impressive benefit combined with letrozole for previously untreated metastatic ER-positive/HER2-negative disease in the phase III MONALEESA-2 trial; approval of this agent is expected soon. Based on the results from PALOMA trials, the updated American Society of Clinical Oncology (ASCO) guidelines on endocrine therapy for HR-positive MBC recommends including CDK4/6 inhibitor in combination with endocrine therapy in the standard of care for women with advanced HR-positive/HER2-negative breast cancer.

- **Primary Tumor Sidedness Impacts Treatment Selection in Colorectal Cancer.** In 2016 we learned that the location of the primary tumor in metastatic colorectal cancer (mCRC) has a major impact on patient outcomes and can predict response to epidermal growth factor receptor (EGFR) inhibitors in *KRAS*/*RAS*-wildtype mCRC. Retrospective analyses from six randomized clinical trials indicate that patients with left-sided tumors have better outcomes and benefit from anti-EGFR therapy. These data suggest anti–EGFR-based therapy should be the preferred treatment option for patients with left-sided tumors, while patients with right sided tumors seem to benefit more from chemotherapy and bevacizumab combinations. The jury is still out for use of anti-EGFR therapy in patients with right-sided tumors, particularly when rapid tumor shrinkage is needed.

- **Changing Treatment Paradigms in Genitourinary Malignancies.** In metastatic urothelial cancer, the approval of the programmed death receptor-1 ligand (PD-L1) atezolizumab (Tecentriq®, Genentech Oncology) in previously treated patients

represents the first new treatment for this malignancy in more than 30 years. Likewise, in renal cell carcinoma (RCC), the 2015 approval of the PD-1 inhibitor nivolumab (Opdivo®, Bristol-Myers Squibb) has resulted in significant changes in management of previously treated metastatic RCC. Adding to this, a novel VEGFR tyrosine kinase inhibitor (TKI), cabozantinib (Cometriq®, Exelixis), was approved for previously treated RCC early in 2016, and recent results from the CABOSUN trial suggest a role for cabozantinib in first-line RCC treatment based on its superiority to sunitinib in this setting. Finally, the combination of the VEGFR TKI lenvatinib (Lenvima®, Eisai) with everolimus (Afinitor®, Novartis) was approved as another treatment option for previously treated patients with RCC in 2016, replacing single-agent everolimus in this setting. The rapid expansion of treatment options in this field has led to important questions regarding optimal sequencing and potential for combinations, which will be a major focus of research in the coming years.

- **Immunotherapies Gain Ground in Head and Neck Cancer.** Patients with squamous cell carcinoma of the head and neck (SCCHN) who progress on first-line chemotherapy historically had no other treatment options beyond additional lines of chemotherapy. That changed this year with the approval of the first immunotherapies for SCCHN, PD-1 inhibitors pembrolizumab (Keytruda®, Merck) in August and nivolumab in November. Pembrolizumab was approved based on impressive overall response rate (ORR) in a phase Ib trial with phase III data expected in the near future. Nivolumab was approved based on impressive survival benefit, better tolerability, and better quality of life (QoL) compared to chemotherapy in a phase III trial. In both trials, efficacy was seen regardless of PD-L1 expression.

- **New Hope for Hepatocellular Carcinoma.** While no new agents were approved for hepatocellular carcinoma (HCC) in 2016, major developments have suggested important changes are on the horizon. In July 2016, results from the phase III RESOURCE trial showed that the multitarget TKI regorafenib (Stivarga®, Bayer HealthCare) significantly improves overall survival (OS) in previously treated, unresectable HCC. Approval of this agent is expected in 2017 and will likely have a

significant impact on the standard of care for this malignancy. Immunotherapy is another therapeutic strategy under rapid development in HCC cancer.

- **Targeted Therapy and Immunotherapy Continue to Raise the Bar in Lung Cancer.** Last year, immunotherapies made waves in NSCLC, with the approval of the PD-1 inhibitors nivolumab and pembrolizumab. That trend has continued this year with two important updates. Pembrolizumab is now approved for front-line treatment of metastatic NSCLC in patients whose tumors express high levels of PD-L1 (tumor proportion score ≥50%). Additionally, the PD-L1 inhibitor atezolizumab joined nivolumab and pembrolizumab as an option in the second-line space. Other immunotherapies are in development, as well as key immunotherapeutic combinations such as nivolumab with ipilimumab (Yervoy®, Bristol-Myers Squibb) and anti–PD-1/anti–PD-L1 with conventional therapy. Several targeted therapies gained prominence for NSCLC in 2016 as well. Early in the year, the approval of crizotinib (Xalkori®, Pfizer) was expanded to include patients with *ROS1*-rearranged NSCLC based on demonstrated benefit in this population. Crizotinib was previously approved to treat anaplastic lymphoma kinase (*ALK*)–mutation-positive NSCLC. A new blood-based companion diagnostic for the EGFR TKI, osimertinib (Tagrisso®, AstraZeneca Pharmaceuticals), designed to detect presence of T790M mutations in patients progressing on first-line EGFR TKI, was approved following on the 2015 approval of osimertinib for patients with T790M mutations. Finally, results from a phase III clinical trial suggest the second-generation ALK inhibitor alectinib (Alecensa®, Genentech) is more effective than crizotinib in previously untreated patients with *ALK*-mutated NSCLC, particularly in patients with central nervous system (CNS) metastases. Approval of alectinib is expected in 2017 and will likely result in major changes to the sequence of therapy in *ALK*-mutated NSCLC. Brigatinib is another promising next generation ALK inhibitor that may impact practice in the coming year.

- **A Focus on Combination Therapy in Melanoma.** Although no new agents were approved in the United States during 2016, melanoma remained an area of active

research. Several trials are ongoing, furthering the investigation of the role of targeted therapies and immunotherapeutic combinations in melanoma. For patients with BRAF mutations, the benefit of combining BRAF inhibitors with MEK inhibitors is well established. Recent results from the phase III COLUMBUS trial have highlighted the BRAF inhibitor encorafenib (Array BioPharma) and the MEK inhibitor binimetinib (Array BioPharma) as a potential new combination in this space. Compared to the single agent vemurafenib, combination of these agents significantly improved PFS, with a manageable toxicity profile. Approval of this combination is expected in 2017.

- **A New Treatment and Diagnostic Tool for Neuroendocrine Tumors.** The mammalian target of rapamycin (mTOR) inhibitor, everolimus (Afinitor®, Novartis), was approved for patients with progressive, well-differentiated, locally advanced or metastatic neuroendocrine tumors (NETs) of gastrointestinal or lung origin based on a seven month improvement in PFS compared to placebo and best-supportive care (RADIANT-4 trial). Also receiving approval this year was Netspot (Advanced Accelerator Applications), a diagnostic kit used for the preparation of the radioactive agent gallium-68 dotatate. Gallium-68 dotatate is a somatostatin analogue that binds to somatostatin receptors, indicating the location of somatostatin receptor-positive NETs.

- **Expanding Options for Patients With Ovarian Cancer.** Although bevacizumab was approved in Europe for high risk platinum-sensitive ovarian cancer in October 2012, in the United States this agent has been limited to platinum-resistant disease. However, on 6 December, the FDA extended the indication of bevacizumab to include platinum-sensitive disease based on the results from two trials, including a 5-month OS benefit in the GOG-0213 trial. Additional important data for platinum-sensitive ovarian cancer released this year are related to PARP inhibitors. PARP inhibitors are key players in the treatment milieu for patients with platinum-sensitive recurrent ovarian cancer who express mutations in BRCA-1 and BRCA-2. On 19 December, the FDA granted accelerated approval to rucaparib (Rubraca, Clovis

Oncology) for patients with advanced ovarian cancer who previously received ≥2 chemotherapies and whose tumors have the *BRCA* gene mutation identified with a next-generation sequencing-based companion diagnostic test (FoundationFocus CDx BRACA, Foundation Medicine). This approval is based on results from two single arm trials and pooled analysis that confirmed an objective response to rucaparib of 54%, with a median duration of response (DoR) of 9.2 months. However, recently reported results from a phase III trial of the PARP inhibitor niraparib (Tesaro) suggest that the utility of these agents may not be limited to patients with BRCA mutations. Niraparib maintenance improved PFS in patients, regardless of the presence or absence of BRCA mutations or defects in homologous recombination. This agent will definitely impact practice when approved in 2017.

- **Refined Adjuvant Treatment for Pancreatic Cancer.** This year, findings from the ESPAC-4 trial established the combination of capecitabine (Xeloda®, Genentech) plus gemcitabine (Gemzar®, Eli Lilly) as a new standard of care in the adjuvant setting for pancreatic cancer. In this trial, adding capecitabine to gemcitabine resulted in a 3-month survival improvement with minimal additional toxicity compared to gemcitabine monotherapy.

- **Improving Survival in Sarcoma.** Treatment of soft tissue sarcoma (STS) represents an area of significant unmet need; however, two new agents with demonstrated improvements in OS compared to current standards expanded the treatment armamentarium this year. On the basis of improved OS compared with doxorubicin, eribulin mesylate (Halaven®, Eisai) was approved in early 2016 for patients with progressive metastatic liposarcoma. This is the first time a novel agent has improved OS in liposarcoma. More recently, the addition of the platelet-derived growth factor receptor (PDGFR) alpha blocking antibody olaratumab to first-line doxorubicin was approved in patients with STS on the basis of a significant improvement in OS compared to single agent doxorubicin.

- **Several Key Developments in Hematologic Malignancies.** 2016 was also an active and exciting year in the field of hematologic malignancies, with new agents approved

in a variety of settings and further data supporting the use of currently approved standards.

- **Chronic Lymphocytic Leukemia (CLL).** This was another major year for approvals in CLL. Beginning in January, the CD20-targeted antibody ofatumumab (Arzerra®, GlaxoSmithKline) received expanded approval as maintenance therapy following a complete response (CR) or partial response (PR) to second-line or third-line therapy. In August this approval was again expanded to include treatment of relapsed CLL in combination with fludarabine and cyclophosphamide. In March the indication of the Bruton's tyrosine kinase (BTK) inhibitor ibrutinib (Imbruvica®, Pharmacyclics) was expanded to include first-line treatment following demonstration of an 84% reduction in the risk of progression or death compared to chlorambucil. Finally, 2016 saw the emergence of a new treatment option for patients with hard-to-treat 17p deletions. Venetoclax (Venclexta®, AbbVie), a B cell lymphoma 2 (BCL-2) targeting agent, was approved for patients with 17p deletions who have progressed on at least one prior therapy.
- **Follicular Lymphoma.** The indication of obinutuzumab (Gazyva®, Genentech), a next-generation anti-CD20 antibody used for the treatment of CLL, was expanded to include use in combination with bendamustine (Treanda®, Teva Oncology) (followed by obinutuzumab monotherapy) in patients with follicular lymphoma who have either relapsed after or are refractory to a rituximab-containing regimen. This approval was based on a significant clinically meaningful improvement in PFS over bendamustine monotherapy (29.2 months versus 14 months) in the phase III GADOLIN trial.
- **Hodgkin Lymphoma.** Five-year follow-up data from the pivotal trial of brentuximab vedotin (Adcentris®, Seattle Genetic, Inc.) in relapsed/refractory Hodgkin lymphoma demonstrated the durability of the

responses to this agent, with 38% of patients initially achieving CR still responding at 5 years. For patients who relapse on brentuximab vedotin, nivolumab is now approved. Nivolumab was approved, based on impressive overall response rates in two phase II trials, for use in patients with classic Hodgkin lymphoma who have relapsed or progressed following autologous stem cell transplant and post-transplant brentuximab vedotin-containing therapy.

- **Multiple Myeloma.** 2016 began and ended with important approvals in multiple myeloma. In January, the FDA expanded the approval of carfilzomib (Kyprolis®, Amgen) to include combination treatment with lenalidomide and dexamethasone for patients who have received 1 to 3 prior lines of therapy. This approval made carfilzomib the first agent to be approved as a single agent, doublet, or triplet in relapsed/refractory multiple myeloma. On 21 November, the FDA extended the indication of the anti-CD38 antibody daratumumab (Darzalex®, Janssen Biotech, Inc.) for use in combination with lenalidomide and dexamethasone or bortezomib and dexamethasone in patients with multiple myeloma who have received at least one prior therapy. This approval was based on the phase III POLLUX and CASTOR trials, which both showed impressive PFS benefits in this setting.

FROM THE LITERATURE

Osimertinib Better Than Platinum-Pemetrexed Chemotherapy in T790M-Mutated NSCLC

In the randomized, open-label, phase III AURA3 trial, a third generation EGFR TKI, osimertinib, significantly improved PFS compared to platinum-pemetrexed chemotherapy in 419 patients with T790M-positive NSCLC who had progressed on first-line EGFR-TKI therapy. In this trial, patients received either osimertinib 80 mg daily or 6 cycles of

pemetrexed in combination with either carboplatin or cisplatin with the potential for pemetrexed maintenance. Median PFS in patients receiving osimertinib was significantly longer than in patients receiving the platinum-pemetrexed chemotherapy (10.1 months vs 4.4 months; HR 0.3, *P*<.001). Benefit with osimertinib was seen across all predefined patient subgroups, including patients with CNS metastases (N = 144), where PFS with osimertinib was 8.2 months compared to 4.2 months with chemotherapy (HR 0.32). A greater percentage of patients responded to osimertinib (ORR 71% vs 31%) and had a longer DoR compared to those on chemotherapy (median DoR 9.7 months vs 4.1 months). Osimertinib was also better tolerated than chemotherapy, with lower rates of grade 3/4 adverse events (AEs) (23% vs 47%) and better patient-reported outcomes. Furthermore, findings from the AURA3 trial support previous evidence of the feasibility of detecting *EGFR* T790M from plasma cell-free tumor DNA (ctDNA) samples. There was no significant difference in osimertinib benefit for patients with T790M-positive status on both tumor and plasma analyses versus those in the intent-to-treat population. The authors concluded that these results are in line with the phase I and II trials of osimertinib, AURA1 and AURA2, supporting the use of osimertinib in second-line treatment of patients with T790M-mutated NSCLC. The results of the AURA3 study were presented at the Annual World Conference on Lung Cancer (WCLC) in Vienna on 6 December 2016 and were simultaneously published in *The New England Journal of Medicine.*

N Engl J Med. 2016 Dec 6. [Epub ahead of print].

For more information on this and other clinical trials presented during WCLC, please see prIME Clinical Updates in Lung Cancer: Critical Analysis and Practical Application of Key Data From the 2016 Annual Lung Cancer.

T-DM1 in First-Line Metastatic HER2-Positive Breast Cancer: Not Superior, but More Tolerable Than Taxane Plus Trastuzumab

Results from the phase III MARIANNE trial demonstrated the noninferiority, but not superiority, of the antibody-drug conjugate trastuzumab emtansine (T-DM1) with or without pertuzumab to trastuzumab plus taxane for first-line treatment of metastatic HER2-positive breast cancer. This large randomized trial compared two experimental arms—T-DM1 plus placebo and T-DM1 plus pertuzumab—to a control arm of trastuzumab plus taxane in 1095 women with metastatic HER2-positive breast cancer who had not received prior treatment for metastatic disease. Both experimental arms were found to be noninferior, but not superior, to the control arm in terms of PFS and ORR. PFS for trastuzumab plus taxane was 13.7 months compared to 14.1 months for T-DM1 alone (HR 0.91, *P* = .31), and 15.2 months for T-DM1 plus pertuzumab (HR 0.87, *P* = .14). A subgroup analysis showed a numerical trend toward increased treatment effect of T-DM1 in patients who had received HER2-directed therapy or taxanes during treatment for early breast cancer, consistent with previous observations. While ORR was not improved compared to control (58.7% and 64.2% vs 67.9%), DoR was longer in the two experimental arms compared to the control arm (T-DM1: 20.7 months; T-DM1 + pertuzumab: 21.2 months; trastuzumab + taxane: 12.5 months). Of note, patients in the experimental arms experienced lower rates of grade 3/4 AEs and fewer discontinuations due to AEs. Additionally, health-related QoL deteriorated more slowly in the experimental arms compared to the control arm (7.7 months and 9.0 months vs 3.6 months). The authors concluded that while T-DM1 with or without pertuzumab did not result in an improvement in PFS, it was more tolerable than trastuzumab plus taxane and remains an option for patients with first-line metastatic breast cancer who may not be able to tolerate the standard taxane plus trastuzumab/pertuzumab regimen. In the accompanying editorial, Komal Jhaveri, MD (Memorial Sloan Kettering Cancer Center, New York, United States), critically reviewed the data and noted that based on improved survival in CLEOPATRA trial, the preferred first-line regimen in HER-2 positive metastatic breast cancer is taxane with trastuzumab plus pertuzumab. However, based on

the benefit of T-DM1 in a group of patients who progressed within 12 months of adjuvant trastuzumab in the EMILIA trial and results from the MARIANNE trial, the National Comprehensive Cancer Network (NCCN) included T-DM1 as another first-line treatment option for patients not suitable for taxane plus trastuzumab/pertuzumab regimen.

***J Clin Oncol*. 2016 Nov 7. [Epub ahead of print].**

***J Clin Oncol*. 2016 Nov 7. [Epub ahead of print].**

Sustained Doubling of PFS With Sunitinib in Pancreatic Neuroendocrine Tumors

Final results from a phase III trial comparing sunitinib to placebo in 171 patients with advanced, well-differentiated, progressive pancreatic neuroendocrine tumors (PNETs) showed a confirmed more than doubling of PFS with sunitinib along with an almost 10-month OS benefit that did not reach statistical significance due to crossover. Initial results from this trial revealed that sunitinib improved PFS over placebo (11.4 months vs 5.5 months; HR 0.42, $P<.001$). This analysis included a retrospective blinded independent central review (BICR) of PFS and final OS results, including assessments highlighting the impact of crossover. Median PFS by BICR was 12.6 months with sunitinib compared to 5.8 months with placebo (HR 0.32, $P = .000015$), confirming earlier assessments. At five years following the close of the study, final OS results were 38.6 months with sunitinib versus 29.1 months with placebo (HR 0.73, $P = .094$). While these results did not reach statistical significance, they are likely confounded by the 69% of patients in the placebo arm who crossed over to sunitinib. A rank-preserving structural failure time (RPSFT) analysis used to adjust for crossover confirmed the OS benefit for sunitinib. The authors concluded that while the OS benefit of sunitinib did not reach statistical significance, the 9.5 month benefit without adjustment for crossover is highly clinically meaningful and, coupled with the more than doubled PFS, supports the use of sunitinib in this patient population with few treatment options.

***Ann Oncol*. 2016 Nov 10. [Epub ahead of print].**

ADDITIONAL PUBLICATIONS WORTH READING

Myocarditis Following Combination Immune Checkpoint Blockade. This interesting report details the cases of two patients with melanoma who experienced fatal myocarditis after treatment with the combination of nivolumab and ipilimumab. Fulminant myocarditis is a rare but serious side effect of immune checkpoint inhibitor therapy that occurs more frequently in patients receiving combination immunotherapy, but in less than 1% of patients. The authors provide details as to the development of myocarditis in these patients, along with suggested monitoring strategies for this potentially fatal complication.

N Engl J Med. 2016;375(18):1749-1755.

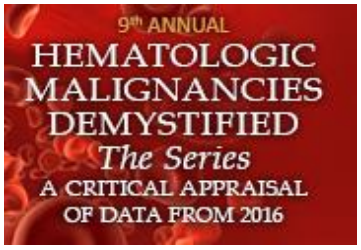
Vaginal Hormonal Interventions in Patients with Breast Cancer Receiving Aromatase Inhibitors. This randomized study sought to evaluate the safety of vaginal testosterone cream and an estradiol vaginal ring in postmenopausal patients with early breast cancer receiving aromatase inhibitors. Results indicate that persistent estradiol elevation is rare in patients using these interventions and use of these products is a reasonable consideration for patients experiencing urogenital atrophy. In an accompanying editorial, authors pointed out that evidence on risks of hormonal intravaginal interventions are rare, but they agreed that if nonhormonal approaches are unhelpful, the above interventions may have meaningful effects on QoL for these women.

JAMA Oncol. 2016 November 10. [Epub ahead of print].

JAMA Oncol. 2016 November 10. [Epub ahead of print].

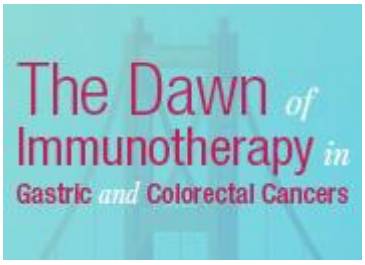
UPCOMING prIME EVENTS

prIME News Webcast—Looking Forward to 2017: Where Are We Going With NSCLC Immunotherapy?
10 January 2017 | New Haven, Connecticut, United States



[Hematologic Malignancies Demystified—The Series]
14 January 2017 | Chicago, Illinois, United States
21 January 2017 | New York, New York, United States
28 January 2017 | Houston, Texas, United States

[The Evolution of the Treatment Algorithm for Carcinoid Syndrome]
19January 2017 | San Francisco, California, United States



[The Dawn of Immunotherapy in Gastric and Colorectal Cancers]
20 January 2017 | San Francisco, California, United States

[2017 Progress and Controversies in Gynecologic Oncology Conference]
20 – 21 January 2017 | Barcelona, Spain

[One for All and All for One! The Expanding Role for PARP Inhibition in Ovarian Cancer]
21 January 2017 | Barcelona, Spain

Immunotherapy for Advanced Bladder Cancer: A Giant Step in the Right Direction?
16 February 2017 | Orlando, Florida, United States

Young Investigators Forum in Non-Small Cell Lung Cancer
9 March 2017 | Atlanta, Georgia, United States

Closing in on the End Game for HER2-Positive Breast Cancer
16 March 2017 | Vienna, Austria

OTHER prIME ACTIVITIES

Expert Review: Navigating the Expanding Treatment Landscape for Advanced Melanoma

Expert Practice℠ in Colorectal Cancer

[Expert Practice℠ in Head and Neck Cancer]

[Metronomic Chemotherapy for Metastatic Breast Cancer: Time for a Fresh Look at Dosing and Schedule]

[Frequently Asked Questions—Metronomic Chemotherapy for Metastatic Breast Cancer: Time for a Fresh Look at Dosing and Schedule]

[Virtual Poster Session: Practical Application of Key Data From the 2016 Annual Hematology Meeting in San Diego]

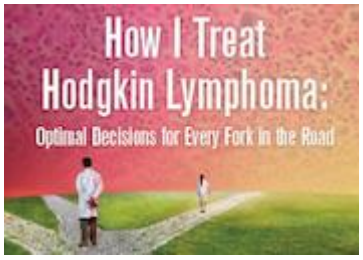
[Clinical Spotlight in Breast Cancer From the 2016 Annual Breast Cancer Meeting in San Antonio—Combination Strategies for ER-Positive, HER2-Negative Metastatic Breast Cancer]

[prIME Clinical Updates in Breast Cancer: Critical Analysis and Practical Application of Key Data From the 2016 Annual Breast Cancer Meeting in San Antonio]

[Downloadable Slides From Reaching New Heights in the Management of Non-Small Cell Lung Cancer: Focus on EGFR-Targeted Therapy]

[prIME Clinical Updates in Lung Cancer: Critical Analysis and Practical Application of Key Data From the 2016 Annual Lung Cancer Conference in Vienna]

[prIME Clinical Updates From the 2016 Annual Hematology Meeting in San Diego]



[Downloadable Slides From How I Treat Hodgkin Lymphoma: Optimal Decisions for Every Fork in the Road]

[Interactive Clinical Cases—Relapsed/Refractory Hodgkin Lymphoma: Nuances in Therapeutic Strategies to Improve Outcomes]