Harnessing new data on immunotherapies

Immunotherapies once again took center stage at the 2015 annual meeting of the American Society for Clinical Oncology in Chicago, though many other groundbreaking clinical advances were also presented. The meeting's theme, "Illumination and innovation: transforming data into learning," captured the current focus, by both researchers and practicing oncologists, on the importance of being able to draw on new and enticing data and use it as the basis for improving the care of and outcomes for cancer patients.

CheckMate 067: Two immunotherapies better than one for advanced melanoma

Key clinical point Nivolumab alone or combined with ipilimumab significantly improves progression-free survival (PFS) and objective response rates (ORRs), compared with ipilimumab alone in previously untreated metastatic melanoma. **Major finding** Median PFS was 11.5 months with nivolumab plus ipilimumab, 6.9 months with nivolumab, and 2.9 months with ipilimumab. **Data source** Phase 3, double-blind randomized trial in 945 patients with previously untreated metastatic melanoma. **Disclosures** Bristol-Myers Squibb funded the trial. Dr Wolchok reported financial relationships with several firms including research funding from and consulting or advising for Bristol-Myers Squibb.

Nivolumab and nivolumab plus ipilimumab are superior to ipilimumab alone in first-line metastatic melanoma, results from the phase 3 CheckMate 067 study suggest.

After a minimum of 9 months' follow-up, the risk of disease progression or death was reduced by 43% with nivolumab compared with ipilimumab alone (hazard ratio [HR], 0.57; $P < .001$) and by 58% with nivolumab plus ipilimumab compared with ipilimumab alone (HR, 0.42; $P < .001$).

The study was not powered to compare nivolumab plus ipilimumab with nivolumab.

Median PFS was 11.5 months with nivolumab plus ipilimumab, 6.9 months with nivolumab, and 2.9 months with ipilimumab alone, Dr Jedd Wolchok said at the meeting.

Overall, 43.7% of patients in the nivolumab arm, 57.6% in the combination arm, and 19% in the ipilimumab arm had objective responses assessed by RECIST version 1.1.

Complete responses were more common in the combination arm (11.5%) than in the nivolumab (9%) or ipilimumab (2.2%) arms, as were partial responses (46.2% vs 34.8% vs 16.8%, respectively).

The median duration of response has not been reached in any group, Dr Wolchok, chief of melanoma and immunotherapeutics at Memorial Sloan-Kettering Cancer Center, New York, reported.

Dr Michael B Atkins, deputy director of the Georgetown-Lombardi Comprehensive Cancer Center in Washington, who was invited to discuss CheckMate 067, said the principal take-home message is that, "Ipilimumab can no longer be considered as standard first-line immunotherapy for patients with advanced melanoma. This clearly has important implications for the field and for our patients."

Combination nivolumab and ipilimumab, however, is "expensive treatment" and raises legitimate concerns about cost and value, he added.

Judgment about whether the combination is worth it will need to be withheld until it's determined if it "can produce more long-term responses or cures, which may reduce the need for other therapies.

"Further, because of its early toxicity, in contrast to the long duration of monotherapy, the combination may actually involve less treatment and expense."

Ipilimumab, an anticytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) antibody, revolutionized the treatment of advanced melanoma just 5 years ago. But the landscape has changed with the 2014 approval of nivolumab and pembrolizumab, 2 antiprogrammed cell death-1 (PD-1) antibodies, and with recent phase 3 results reporting that pembrolizumab is superior to ipilimumab in advanced melanoma.

There are no clear-cut distinctions in efficacy or toxicity between nivolumab and pembrolizumab, so treatment decisions are largely based on other factors, such as dosing schedule, marketing cost, and experience, Dr Atkins said. Pembrolizumab is approved by the US Food and Drug Administration (FDA) at 2 mg/kg every 3 weeks, whereas nivolumab is approved at 3 mg/kg every 2 weeks.

CheckMate 067 randomly assigned 945 previously untreated patients with unresectable stage III or IV melanoma to nivolumab 3 mg/kg every 2 weeks or nivolumab

JCSO 2015;13:268-274. ©2015 Frontline Medical Communications. DOI 10.12788/jcso.0153.

1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks for 4 doses, then nivolumab 3 mg/kg every 2 weeks, or ipilimumab 3 mg/kg every 3 weeks for 4 doses. Patients were stratified at baseline by PD-ligand 1 expression, BRAF status, and American Joint Commission on Cancer M stage.

The impact of PD-L1 expression

As seen in other studies, PD-L1 expression enriched response. ORRs in patients with tumors showing < 5% PD-L1 expression were 41.3% with nivolumab, 54% with nivolumab plus ipilimumab, and 17.8% with ipilimumab. This increased to 57.5%, 72.1%, and 21.3%, respectively, in patients with at least 5% PD-L1 expression in their tumors, Dr Wolchok said.

In patients with PD-L1-negative tumors, median PFS was 5.3 months with nivolumab, 11.2 months with nivolumab plus ipilimumab, and 2.8 months with ipilimumab. In patients with PD-L1-positive tumors, the median PFS was 14 months in both nivolumab groups and 3.9 months in the ipilimumab group.

The results suggest that nivolumab alone may have comparable efficacy to nivolumab plus ipilimumab in PD-L1-positive patients, Dr Atkins said, but added several caveats. Notably, that median PFS is not the optimal way to evaluate immunotherapy because it can be compounded by pseudo progression. Better measures include overall survival (OS) and response duration, but those data are immature. Furthermore, only 25%-28% of patients in the study were PD-L1 positive, and two-thirds of responders to nivolumab alone were PD-L1 negative. "PD-L1 expression is a weak biomarker," he said.

Greater efficacy, greater toxicity

Both Dr Wolchok and Dr Atkins agreed that combining the 2 immunotherapies increased treatment-related adverse events, but that most events were manageable. Moreover, treatment interruption did not prevent tumor response, with 67.5% of patients who discontinued the nivolumab-ipilimumab combination because of a treatment-related adverse event developing a response.

Grade 3-4 events were reported in 55% of the combination group, 16.3% of the nivolumab-alone group, and 27.3% of the ipilimumab-alone group. The most common of these events were diarrhea in 2.2% of patients in the nivolumab group, 9.3% of the combination group and 6.1% of the ipilimumab group; colitis (0.6%, 7.7%, 8.7%, repsectively); and increased alanine aminotransferase levels (1.3%, 8.3%, 1.6%).

"There is no signature adverse event for the combination," Dr Wolchok said. "With the use of immune-modulating agents, the majority of grade 3 and 4 select adverse events resolved in all of the groups with the use of established algorithms. However, as we observed in prior studies, most endocrine events did not."

There was 1 treatment-related death from neutropenia in the nivolumab group, 1 from cardiac arrest in the ipilimumab group, and none in the combination group.

An expanded access program is available for the combination of nivolumab and ipilimumab through the study sponsor, Bristol-Myers Squibb, Dr Wolchok noted.

— Patrice Wendling

Nivolumab transforms practice for advanced, refractory nonsquamous NSCLC

Key clinical point Nivolumab provided superior OS compared with docetaxel and should be considered the new standard of care for previously treated nonsquamous NSCLC.

Major finding The median OS was 12.2 months with nivolumab vs 9.4 months with docetaxel (HR, 0.73; P = .0015).

Data source A phase 3 randomized study in 582 patients with nonsquamous NSCLC that progressed after platinum chemotherapy.

Disclosures Bristol-Myers Squibb sponsored the study. Dr Paz-Ares reported honoraria from Bristol-Myers Squibb, Roche/Genentech, Lilly, Pfizer, Boehringer, and Clovis. Dr Herbst reported honoraria from Boehringer Ingelheim, Celgene, Lilly, Merck, NovaRx, and Pfizer; a consulting or advisory role with Biothera, DiaTech Oncology, Koltan Pharmaceuticals, N-of-One, and Quintiles; and research funding from Genentech/Roche and GlaxoSmithKline.

Nivolumab reduced the risk of death by nearly a third over docetaxel for patients with advanced, refractory nonsquamous non-small-cell lung cancer, results of CheckMate 057 showed.

The primary endpoint of median OS was 12.2 months for those receiving the PD-1 immune checkpoint inhibitor nivolumab and 9.4 months for those given docetaxel (HR, 0.73; P = .0015), study author Dr Luis Paz-Ares reported at the meeting.

At 1 year, 51% of the nivolumab group was alive, compared with 39% of the docetaxel group.

The survival advantage was seen across most subgroups, except never-smokers and those whose tumors were positive for epidermal growth factor receptor (EGFR) mutations.

The magnitude of the OS benefit in patients with PD-L1-positive tumors, however, was "unprecedented in this setting" and ranged from 17.2 months to 19.4 months, Dr Paz-Ares of the Hospital Universitario Virgen Del Rocio, Seville, Spain, said.

Treatment options for patients with nonsquamous histology who progress following platinum-based doublet chemotherapy are limited. Typical response rates in this context are about 10%, and median OS is about 8-10

months, he said.

Discussant Dr Roy Herbst, chief of medical oncology at Yale Comprehensive Cancer Center in New Haven, Conn, said, "This is a positive randomized phase 3 trial with a primary endpoint for all comers. The trial sets a new standard for the treatment of previously treated disease, and nivolumab is significantly less toxic than docetaxel."

CheckMate 057 randomly assigned 292 patients to nivolumab 3 mg/kg every 2 weeks and 290 patients to docetaxel 75 mg/kg every 3 weeks until disease progression or unacceptable toxicity occurred. Patients were stratified by prior maintenance therapy and line of therapy. PD-L1 expression was measured in pretreatment (archival or recent) tumor biopsies.

The ORR was significantly higher for patients receiving nivolumab than for those receiving docetaxel (19% vs 12%; $P = .0246$; odds ratio [OR], 1.72), Dr Paz-Ares said.

Most responses were partial (18% vs 12%), with only one complete response to nivolumab. The median duration of response was 17.2 months with nivolumab vs 5.6 months with docetaxel. PFS was similar between the nivolumab and docetaxel groups (2.3 months vs 4.2 months; HR, 0.92; $P = .39$), he said, explaining that progression was more rapid with nivolumab during the first 6 months before slowing to a 1-year PFS rate of 19% vs 8% for docetaxel.

PD-L1 expression emerged as a significant predictor of ORR, PFS, and OS, with ORRs as much as three times higher with nivolumab than docetaxel for patients with high PD-L1 expression, Dr Paz-Ares said.

Using 3 predefined cut points of 1%, 5%, 10% PD-L1 expression, OS was 17.2 months, 18.2 months, and 19.4 months with nivolumab vs 9.0 months, 8.1 months, and 8 months with docetaxel, respectively.

Dr Herbst described the PD-L1 biomarker as intriguing, but said for now it is only hypothesis generating and should not be used for patient selection. PD-L1 expression was not prospectively stratified in the study, and was not available for 22% of patients, and although it improves ORR, PFS, and OS, even patients with <1% expression seem to have at least equal activity to that of docetaxel with less toxicity, he noted.

Adverse events of any grade were reported in 69% of patients receiving nivolumab and 88% receiving docetaxel. More importantly, grade 3-4 events occurred in 10% vs 54%, Dr Paz-Ares said. The most common events with nivolumab were fatigue, nausea, and decreased appetite.

Notably, the dose intensity delivered was higher for nivolumab than for docetaxel (83% vs 66%), and 42% of nivolumab patients vs 50% of docetaxel patients received subsequent systemic therapy, suggesting little influence of further treatment on survival.

In a separate presentation at ASCO, nivolumab reduced the risk of death by 41%, compared with docetaxel, in previously treated advanced squamous NSCLC (HR, 0.59; $P = .00025$) in the phase 3 Check Mate 017 study.

Nivolumab received a second indication in March 2015 for use in metastatic squamous NSCLC following failure with platinum-based chemotherapy.

— Patrice Wendling

Pembrolizumab active in head and neck cancer, regardless of HPV status

Key clinical point Immunotherapy with pembrolizumab is active in patients with recurrent or metastatic head and neck cancer. **Major finding** The ORR was 24.8% overall, 27.2% in human papillomavirus-negative patients, and 20.6% in HPV-positive patients. **Data source** Expansion cohort of 132 patients with recurrent or metastatic head and neck cancer from the phase 1b KEYNOTE-012 study. **Disclosures** Merck, Sharp & Dohme funded the study. Dr Seiwert reported honoraria from Novartis, Bayer/Onyx, and Merck and institutional research funding from Genentech/Roche and Boehringer Ingelheim. Several coauthors reported financial relationships including employment with MSD or its parent company, Merck. Dr Masters reported having no conflicts.

One in four patients with recurrent or metastatic head and neck cancer respond to anti-PD-1 immunotherapy with pembrolizumab, according to preliminary expanded cohort results from KEYNOTE-012.

Among 117 evaluable patients, the ORR with pembrolizumab was 24.8%, including 1 complete response and 28 partial responses.

Pembrolizumab was active in both HPV-negative and -positive tumors, with response rates of 27.2% and 20.6% respectively.

The efficacy is remarkable in this setting and when measured by response, pembrolizumab seems to be roughly twice as effective as cetuximab, our only targeted therapy, said study author Dr Tanguy Seiwert during a press briefing in advance of his presentation at the meeting.

In the pivotal EXTREME trial leading to cetuximab's approval, 36% of patients responded to cetuximab, when the EGFR inhibitor was added to platinum-based chemotherapy in recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN). Only 10%-13% of patients, however, respond to single-agent cetuximab. Also, several recent studies, with the exception of a retrospective EXTREME analysis, suggest cetuximab efficacy varies with HPV status, Dr Seiwert, from the University of Chicago, said in an interview.

Pembrolizumab was the first anti- PD-1 therapy to reach the market, after its approval by the FDA in September 2014 for use in metastatic melanoma.

The phase 1b, multi-cohort KEYNOTE-012 enrolled

patients with advanced solid tumors and previously reported a 20% response rate with pembrolizumab 10 mg/kg every 2 weeks in recurrent or metastatic SCCHN enriched for PD-L1-positive tumors.

For the expansion cohort, 132 patients with recurrent or metastatic SCCHN were enrolled, irrespective of PD-L1 expression or HPV status, and pembrolizumab was given at a fixed dose of 200 mg every 3 weeks. Mean age was 59 years and nearly 60% had received 2 or more previous lines of therapy. The primary endpoint was ORR per investigator assessment using RECIST v1.1.

Overall, 56% of patents had some tumor shrinkage. Median time to response was 9 weeks (range, 7.6-18 weeks).

Responses were durable, with 86% of responding patients remaining in response, Dr Seiwert said. Overall, 40 patients are still on therapy, Dr Seiwert said.

Data reported in a separate study at the meeting suggest that a novel interferon-gamma expression signature may be useful in predicting which patients are likely to benefit from therapy, with a negative predictive value of 95% and positive predictive value of 40%, he said.

Adverse events were reported in 60% of all 132 patients, most commonly fatigue, hypothyroidism, and decreased appetite. Serious grade 3-4 drug-related events were reported in 13 patients and included pneumonitis in 2 and facial swelling in 2.

Dr Gregory Masters of Christiana Care Health System in Newark, Del, commented in a statement that, "This is yet another example where PD-1 immunotherapy might work better and more reliably than existing drugs, and with fewer side effects. The diversity of patients who responded is greater than in any previous trials."

Dr Masters added that larger studies and longer follow-up are needed to assess the impact of treatment on survival.

Pembrolizumab is being evaluated against standard therapy in recurrent or metastatic head and neck cancer in two phase 3 trials, KEYNOTE-040 and KEYNOTE-048.

— Patrice Wendling

Adjuvant denosumab halves fracture risk for breast cancer patients on AIs

Key clinical point Denosumab reduces the risk of clinical fractures in postmenopausal women taking AIs for early breast cancer. **Major finding** The denosumab group was half as likely to have a first clinical fracture as the placebo group (HR, 0.50). **Data source** A randomized phase 3 trial in 3,425 postmenopausal women with early breast cancer taking AIs. **Disclosures** Amgen sponsored the trial. Dr Gnant disclosed employment of an immediate family member with Sandoz; receipt of honoraria from Amgen, AstraZeneca, GlaxoSmithKline, NanoString Technologies, Novartis, and Roche Pharma AG; a consulting or advisory role with Accelsiors, AstraZeneca, and Novartis; and receipt of research funding from GlaxoSmithKline, Novartis, Pfizer, Roche Pharma AG, Sanofi, and Smiths Medical.

Adjuvant denosumab is efficacious and safe for reducing fracture risk among women taking aromatase inhibitors (AIs) as part of their treatment for early breast cancer, finds the Austrian Breast & Colorectal Cancer Study Group's study 18 (ABCSG-18).

Compared with peers randomized to placebo in the phase 3 trial, women randomized to the antiresorptive monoclonal antibody at the dose typically used to treat osteoporosis were half as likely to experience a first clinical fracture, first author Dr Michael Gnant reported at the meeting. The benefit was similar whether women had normal bone mineral density at baseline or already had osteopenia.

Patients in the denosumab group did not have a significantly higher rate of adverse events, including the much-feared complication of osteonecrosis of the jaw.

"The actual fracture risk of postmenopausal breast cancer patients on AIs is substantial and may have been underestimated until today," commented Dr Gnant, professor of surgery at the Medical University of Vienna. "In these patients with only a modest risk of disease recurrence, adjuvant denosumab significantly reduced the bone side effects of AI treatment. We therefore believe that denosumab 60 mg every 6 months should be considered for clinical practice.

"Today, several clinical practice guidelines advocate the use of bisphosphonates for breast cancer patients receiving AIs, however, only if they are at high risk for fractures," he further noted. However, "patients with normal baseline bone mineral density showed a similar fracture risk but also similar benefit from denosumab as compared to patients with baseline T scores below -1, indicating that DEXA scans may be an insufficient way to assess the individual patient's fracture risk. In view of the benefits in this particular patient subgroup, we may have to rediscuss our current clinical practice guidelines."

Invited discussant Dr Robert E Coleman of the University of Sheffield and Weston Park Hospital in England, said, "It's very important to dissect out fractures related to subsequent recurrence from fractures due to poor bone health." Most of the reduction in fracture risk in ABCSG-18 appeared to be because of prevention of fractures before any recurrence, whereas most of that in the AZURE trial of an adjuvant bisphosphonate, another type of antiresorptive agent, appeared to be because of prevention of fractures from bone metastases. "So I think we are seeing something very different with denosumab to what we've seen to date with a bisphosphonate," he said.

"As oncologists, we are somewhat wedded to measuring bone mineral density as the reason for giving bone-targeted therapy to protect [against] bone loss, but there are

much better ways of predicting fracture with online algorithms such as FRAX [Fracture Risk Assessment Tool] and others," Dr Coleman said. "And bone mineral density is a pretty poor predictor of fracture, so it's perhaps not surprising that the risk reductions were fairly similar" across bone mineral density subgroups.

During a question and answer period, session attendee Dr Toru Watanabe, Hamamatsu (Japan) Oncology Center, said, "It is really clear that the osteoporosis-related fracture is prevented by denosumab at the dose usually used for the treatment of osteoporosis. That part is very clear. My question is, the same dose is being tested for modifying OS or PFS. Don't you think it's necessary to conduct some kind of dose-finding trial?"

Two studies are addressing the impact of denosumab on breast cancer outcomes, according to Dr Gnant: the investigators' ABCSG-18 study and the Study of Denosumab as Adjuvant Treatment for Women With High-Risk Early Breast Cancer Receiving Neoadjuvant or Adjuvant Therapy (D-CARE), which is using a higher initial dose and tapering after 1 year. "So we will have that indirect comparison at least. My personal expectation would be that there is a trade-off potentially between efficacy and tolerability," he commented.

The 3,425 postmenopausal breast cancer patients in ABCSG-18 were randomized evenly to receive 60 mg of denosumab or placebo every 6 months. Denosumab is approved by the FDA for the prevention and treatment of fractures due to bone metastases and osteoporosis after menopause , as well as other indications. The study used the dose for postmenopausal osteoporosis, which is much lower than that typically used for bone metastases (120 mg every 4 weeks), Dr Gnant noted.

Main results showed that denosumab was highly efficacious in reducing the risk of first clinical fractures, meaning those that were clinically evident and causing symptoms (HR, 0.50; $P < .0001$), according to data presented at the meeting.

The estimated 6-year fracture rate was about 10% in the denosumab group and 20% in the placebo group. "Note that the frequency of clinical fractures reported in this trial is focusing on bone health is markedly higher than fracture rates reported in previous large AI trials. Obviously, we had a tendency to underreport them in those trials," Dr Gnant commented. "The true magnitude of the problem in clinical practice is likely reflected in the placebo group with about 1 of 5 patients experiencing a new clinical fracture within 5-6 years of adjuvant AI treatment."

Benefit was similar across numerous patient subgroups studied, including the subgroups of women who had a baseline bone mineral density T score of less than -1 and women who had a baseline bone mineral density T score of -1 or greater.

In addition, the denosumab group had improvements from baseline in bone mineral density of the lumbar spine, total hip, and femoral neck, whereas the placebo group had worsening at all sites ($P < .0001$ between groups for each site). And at 36 months, the denosumab group had significantly lower risks of both new vertebral fractures and new or worsening vertebral fractures.

"Adjuvant denosumab at this dose and schedule is safe," Dr Gnant maintained. The 2 groups had similar rates of various adverse events, with musculoskeletal disorders and vascular disorders (including hot flashes) predominating. "This means that we are in essence reporting the side effects of the underlying adjuvant AI treatment," he noted.

There were 31 cases of dental issues, but none met diagnostic criteria for osteonecrosis of the jaw. "We can safely say that at this dose of denosumab, 60 mg twice yearly, ONJ is not an issue," Dr Gnant commented. Additionally, none of the women experienced atypical fractures.

— Susan London

Aspirin, vitamin D levels protect against recurrent colorectal cancer

Key clinical point Aspirin and plasma vitamin D seem to offer survival advantages for patients with colorectal cancer. **Major finding** In a multivariable analysis, aspirin use after diagnosis was associated with improved OS (HR, 0.86) and colorectal cancer-specific survival (HR, .75). Highest vitamin D levels were associated with a 35% reduction in risk of death compared with lowest levels. **Data source** Retrospective cohort study of 25,644 patients (aspirin). Randomized controlled trial with 2,334 patients (vitamin D). **Disclosures** The Research Council of Norway sponsored the aspirin study. National Cancer Institute, Southwest Oncology Group, Bristol-Myers Squibb, and Aptuit Inc supported CALGB/SWOG 80405. Dr Bains reported no relevant disclosures. Dr Ng reported a consulting or advisory role with several companies, institutional research funding from Genentech/Roche and Pharmaville, and travel expenses from Gilead Sciences. Dr Chan reported a consulting/advisory role with Bayer Schering Pharma and Pfizer.

Both aspirin and higher plasma levels of vitamin D seem to be modestly effective in secondary prevention of colorectal cancer, investigators in a large cohort study and a randomized trial report.

Among more than 25,000 Norwegians with colorectal cancer, aspirin use was associated with a 14% improvement in OS, and a 25% improvement in colorectal cancer-specific survival, reported Dr Simer Bains from the Center for Molecular Medicine Norway at the University of Oslo.

A similar protective effect of plasma 25-hydroxy vitamin D (25[OH]D) was seen in a subanalysis of data from the CALGB/SWOG 80405 trial, which showed that patients

in the highest quintile had a significantly longer OS, compared with patients in the lowest quintile of 25(OH)D. Whether dietary vitamin D supplementation will have the same effect is unknown, however, said Dr Kimmie Ng of the Dana-Farber Cancer Institute, Boston, at the meeting.

"If confirmed, these are very important potential interventions as they are low cost, over-the-counter options that could have substantial implications for treatment of colon cancer patients, commented Dr Andrew T Chan of Massachusetts General Hospital, the invited discussant.

Aspirin study

The benefits of aspirin in primary prevention of colorectal and other cancers have been well documented, but the role of the "wonder drug" in secondary prevention is unclear, Dr Bains said.

To see whether the use of aspirin after a colorectal cancer diagnosis could make a difference, she and colleagues drew on Norway's birth-to-death national medical and prescription databases to identify a retrospective cohort of 25,644 patients with colorectal cancer diagnosed from 2004 to 2011. Of this group, 6,109 patients had documented aspirin exposure, defined as a prescription for more than 6 months of aspirin after a diagnosis of colorectal cancer, and 19,535 did not have documented aspirin exposure.

The aspirin user group had a higher mean age than did nonusers (74 vs 70 years), had slightly more men than women (56% vs 48% men among nonusers), had a higher proportion of well- or moderately differentiated tumors, and less advanced disease stage at diagnosis.

After 9 years of follow-up, there was no difference between the groups in OS on univariate analysis. Suspecting that the lack of effect might be attributable to the aspirin users being an older and potentially more fragile group with more comorbidities than nonusers, the authors performed a multivariate regression analysis controlling for age, gender, tumor stage, differentiation, and other drug use and found a hazard ratio for death with aspirin use of 0.86 ($P < .001$).

In both univariate and multivariate analysis, aspirin use was associated with improved colorectal cancer-specific survival, with HRs of 0.84 and 0.75, respectively ($P < .001$ for both).

Dr Bains acknowledged that the study was limited by the lack of randomization and inability to control for over-the-counter aspirin use.

Vitamin D

In a different study, Dr Ng and colleagues looked at the relationship between plasma 25(OH)D levels in patients with metastatic colorectal cancer enrolled in CALGB/SWOG 80405, which compared the FOLFIRI and FOLFOX regimens plus either cetuximab or bevacizumab, or both.

Plasma 25(OH)D levels were measured at baseline by radioimmunoassay before the start of therapy.

The investigators found that among patients in the highest quintile of plasma vitamin D levels, median OS was 32.6 months, compared with 24.5 months for patients in the lowest quintile ($P = .01$).

In a multivariate analysis adjusted for age, sex, race, performance status, chemotherapy backbone regimen, previous adjuvant therapy, RAS mutation status, season of blood draw, region of residency, body mass index and physical activity, the highest levels of 25(OH)D were associated with a 35% improvement in OS, compared with the lowest levels (HR, 0.65; P for trend = .001).

The investigators found that the association between vitamin D levels and survival persisted across all patient subgroups both before and after adjustment for prognostic factors.

A phase 2 randomized trial of vitamin D supplementation in patients undergoing adjuvant chemotherapy is currently underway, Dr Ng noted.

Dr Chan, the discussant, noted that "vitamin D and aspirin use are among the lifestyle factors most consistently associated with improved outcomes among patients with colorectal cancer in epidemiological studies," and that "the findings are supported by consistent evidence and biological plausibility."

— Neil Osterweil

Upfront chemo prolongs life in men with advanced, hormone-naive prostate cancer

Key clinical point Addition of chemotherapy to first-time hormone therapy improves survival in men with advanced prostate cancer. **Major finding** Adding docetaxel reduced the risk of treatment failure or death by 38% and the risk of death by 24%. **Data source** Randomized trial of 2,962 men with advanced, hormone-naive prostate cancer. **Disclosures** The trial receives funding and support in part from Sanofi-Aventis, Novartis, Pfizer, Janssen, and Astellas. Dr James has a consulting, advisory, or speakers bureau role with or receives honoraria or research funding (institutional) from Sanofi, Bayer, Merck, Astellas, Janssen, Pierre Fabre, Ferring, OncoGenex, and Pfizer.

Using chemotherapy earlier in the course of advanced prostate cancer improves outcomes, according to first survival results of the STAMPEDE trial.

Results showed that adding docetaxel to the standard of hormone therapy at the time of diagnosis reduced the risk of treatment failure or death by 38% and the risk of death by 24%, researchers reported in a press briefing held in advance of the meeting. The benefit was clear among men with metastatic disease but less so among those with nonmetastatic disease.

"Docetaxel improves survival in men with hormone-

naive prostate cancer starting hormone therapy for the first time," concluded lead researcher Dr Nicholas David James, director of the cancer research unit at the University of Warwick and consultant in clinical oncology at Queen Elizabeth Hospital Birmingham (England).

"Docetaxel should be considered as routine practice in men with newly diagnosed metastatic disease," he asserted. "For nonmetastatic disease, there remains uncertainty as to whether there is a survival benefit or not, but it certainly improves failure-free survival by a substantial amount, so we would argue that it should be considered for selected men with high-risk nonmetastatic disease."

Clinicians should use an individualized approach to adding docetaxel in the subgroup with nonmetastatic disease. "What I am doing in my own clinic, for example, is having a discussion with the patients about the pros and cons. ¬ I think it will be something we discuss on a case-by-case basis," he said, adding that a planned meta-analysis should better clarify the survival benefit in this subgroup.

Dr Peter Paul Yu, ASCO president and a medical oncologist and hematologist, who is director of cancer research at the Palo Alto Medical Foundation, Sunnyvale, Calif, said that the STAMPEDE data contribute to an ongoing paradigm shift in treating advanced prostate cancer.

"The paradigm for years or even decades has been to treat this with hormone therapy because [it] is relatively less toxic. The advice has been to use hormone therapy until it's exhausted, until there is no response left, and then at the last moment use chemotherapy, which often is a potentially self-defeating strategy because you are using chemotherapy when the disease has evolved to a point where it's much more aggressive," he said.

Accumulating data, however, suggest that a strategy of combining chemotherapy with hormonal therapy upfront yields better outcomes than their sequential use. "This paradigm shift is continuing and should be highlighted," he maintained.

"The really interesting thing is the hint – and I would say a very strong hint as an editorial comment – that this strategy of bringing chemotherapy early on can have a benefit even in men who do not have evidence of metastases at the time they are starting hormone therapy – what we would traditionally call the adjuvant use of chemotherapy," Dr Yu added.

Men were eligible for STAMPEDE if they were starting long-term hormone therapy for the first time and had high-risk locally advanced disease, lymph node-positive disease, metastatic disease, or disease that had relapsed aggressively after surgery or radiation therapy. STAMPEDE has an innovative, adaptive design whereby novel agents can be incrementally added to those found to be efficacious in earlier arms, generating a new standard of care.

Dr James presented findings for 4 of the trial's 9 arms, in which 2,962 patients were randomized to standard of care (androgen-deprivation therapy with or without radiation therapy) alone, or with the addition of six cycles of docetaxel, 2 years of the bisphosphonate zoledronic acid, or both.

Docetaxel is approved by the FDA for treatment of metastatic hormone-refractory prostate cancer, and zoledronic acid is approved for the treatment of hypercalcemia due to cancer.

With a median follow-up of 42 months, compared with standard care alone, adding docetaxel significantly reduced the risks of failure-free survival events (HR, 0.62) and death (HR, 0.76). Median OS was 77 months with the drug and 67 months without it, and the difference was largely driven by prostate cancer deaths, according to Dr James.

About 60% of the men had metastases. In stratified analyses, adding docetaxel improved failure-free survival whether men had metastatic disease or not, but it improved OS only in those with metastatic disease (43 vs 65 months). However, the standard-care arm in the nonmetastatic subgroup performed better than expected, and there have been too few deaths in that subgroup overall to fully power the analysis, Dr James said.

Toxicity with the addition of docetaxel was manageable. Zoledronic acid did not improve either outcome relative to hormone therapy alone, and adding both zoledronic acid and docetaxel netted similar results to those seen with docetaxel alone.

Several other therapies, including next-generation hormone therapies and chemotherapy agents, also are showing promise in prostate cancer, and the optimal timing and sequencing of agents is unknown. STAMPEDE is the first to look at docetaxel and these hormone therapies at the time of diagnosis of advanced disease, he noted.

At present, the data support giving docetaxel before either abiraterone or enzalutamide in this treatment setting, as the drug's survival advantage persisted even though patients often went on to receive those hormone therapies; however, that strategy might change with future results from this and other trials. "To be honest, it would be a nice position to be in if we had two treatments that improved OS upfront. That just gives us a choice. It would be good news obviously," he concluded.

— Susan London