IMmotion151: A Randomized Phase 3 Study of Atezolizumab Plus Bevacizumab Versus Sunitinib In Untreated Metastatic Renal Cell Carcinoma

• Robert Motzer, MD, Memorial Sloan Kettering Cancer Center, New York, New York

In patients with untreated programmed death ligand-1–positive (PD-L1+) advanced renal cell carcinoma (RCC), progression-free survival (PFS) was improved with the combination of atezolizumab (Tecentriq, Genentech) and bevacizumab (Avastin, Genentech) compared with sunitinib (Sutent, Pfizer) in the IMmotion151 trial. Atezolizumab is a fully humanized monoclonal antibody of the immunoglobulin G1 isotype against PD-L1, Dr. Motzer said in a symposium press-cast.

The vascular endothelial growth factor (VEGF) inhibitor bevacizumab, which has some single-agent activity, is approved for first-line use in metastatic RCC (mRCC) in combination with interferon-alpha-2a. Atezolizumab has demonstrated antitumor activity and a tolerable safety profile in mRCC. A randomized phase 2 study indicated synergy and encouraging efficacy for the atezolizumab/bevacizumab combination versus sunitinib in PD-L1+ patients. Dr. Motzer speculated that atezolizumab’s T-cell–mediated cancer cell killing may be enhanced through bevacizumab’s reversal of VEGF-mediated immunosuppression.

IMmotion151 investigators randomized 915 patients in the phase 3 trial to either atezolizumab (1,200 mg intravenously [IV] once every three weeks) and bevacizumab (15 mg/kg IV once every three weeks) or sunitinib (50 mg orally once daily for four weeks on and then two weeks off). Patients were stratified by PD-L1 status: less than 1% or 1% or greater PD-L1 expression on tumor-infiltrating immune cells (IC).

The coprimary endpoints were PFS (based on RECIST v1.1 criteria) in PD-L1+ patients with 1% or greater IC and overall survival (OS) in intent-to-treat (ITT) patients. In the ITT population, 362 were PD-L1+. Median age was 62 years in the combination therapy group and 59 years in the sunitinib group. Sixty-seven percent were men. Nearly three-quarters of the patients were in the intermediate-risk category based on Memorial Sloan Kettering Cancer Center risk criteria.

PFS in the PD-L1+ group was a median of 11.2 months (95% confidence interval [CI], 8.9–15.0) compared with 7.7 months in the sunitinib group (hazard ratio [HR], 0.74; 95% CI, 6.8–9.7; P = 0.02). The secondary endpoint of OS in the ITT population was 11.2 months for the atezolizumab/bevacizumab arm and 8.4 months for the sunitinib arm (HR, 0.83; 95% CI, 0.70–0.97). Independent review committee assessment of PFS in the PD-L1+ arm showed a smaller benefit for the combination (8.9 months versus 7.2 months). All assessments were blinded to PD-L1 status.

Confirmed objective response rates were 43% and 35% in the combination and sunitinib arms, respectively, for PD-L1+ patients. In addition, median duration of response has not been reached in the atezolizumab/bevacizumab arm and was 12.9 months in the sunitinib arm. Sixty-five percent of combination arm patients have an ongoing response versus 53% in the sunitinib arm.

OS data, while immature, revealed a trend favoring the atezolizumab/bevacizumab combination in the ITT population (HR, 0.8; P = 0.09) and in the PD-L1+ population (not reached versus 23.3 months; HR, 0.68).

Safety results were similar in all treated patients and in those with PD-L1+ disease. Grade 3–4 adverse event rates were 40% and 54% in the combination and sunitinib populations, respectively. Sixteen percent of patients treated with atezolizumab/bevacizumab required systemic corticosteroid use within 30 days of an adverse event of special interest (rash, abnormal thyroid, adrenal insufficiency, liver function test abnormalities, colitis, pneumonitis). Time to symptom interference with activities of daily living in the ITT population was 11.3 months and 4.3 months for the combination and sunitinib groups, respectively.

“These study results support atezolizumab plus bevacizumab as a first-line treatment option for patients with PD-L1 advanced RCC,” Dr. Motzer concluded.

ASCO moderator Sumanta K. Pal, MD, of City of Hope in Duarte, California, commented that the results compared favorably with those for the nivolumab/ipilimumab (Opdivo/Yervoy, both Bristol-Myers Squibb) combination, but that with the latter combination, 60% of patients needed steroids.

Apalutamide Treatment and Metastasis-Free Survival in Prostate Cancer

• Eric J. Small, MD, Helen Diller Family Comprehensive Center, University of California, San Francisco, California

In the phase 3 SPARTAN trial among men with high-risk nonmetastatic castration-resistant prostate cancer (CRPC),
Apalutamide (Erleada, Janssen) decreased the risk of death and prolonged metastasis-free survival (MFS) compared with placebo, Dr. Small said in a press briefing.

He noted that metastatic CRPC is a uniformly fatal disease, with a median survival of approximately 2.5 years. It can develop from metastatic hormone-sensitive prostate cancer or from nonmetastatic prostate cancer that has developed resistance to androgen deprivation therapy.

Apalutamide is a next-generation oral competitive inhibitor of the androgen receptor developed for the treatment of patients with prostate cancer. It prevents binding of androgens to the androgen receptor and translocation of the androgen receptor to the nucleus, while impeding androgen receptor-mediated DNA transcription. The aim of the SPARTAN study was to see if the development of metastases and the transition from nonmetastatic to metastatic CRPC could be slowed with apalutamide.

SPARTAN investigators enrolled 1,207 men with nonmetastatic CRPC and prostate-specific antigen doubling time (PSADT) of 10 months or less, an indicator of high risk for metastatic disease and prostate cancer-specific death. Median age was 74 years, and PSADT was six months or less in 71% of patients. They were randomized double-blind: 2:1 to apalutamide (240 mg once daily) or placebo. The primary endpoint was MFS, defined as the time from randomization to first radiographic distant metastasis (per blinded central review) or death. Secondary endpoints included time to metastasis, progression-free survival, time to symptomatic progression, and overall survival. Patients were eligible to receive study-provided open-label abiraterone acetate (Zytiga, Janssen) plus prednisone after developing distant metastases.

Median MFS, the primary endpoint, was 40.5 months in the apalutamide group and 16.2 months in the placebo group, a 72% risk reduction (hazard ratio [HR], 0.28; 95% confidence interval, 0.23–0.35; P < 0.0001). The benefit was observed across all subgroups. The secondary endpoint of median time to metastasis was reduced by 73% in the apalutamide group (40.5 months versus 16.6 months; HR, 0.27; 95% CI, 0.22–0.34; P < 0.0001). Risk of local progression, distant progression, or death was reduced by 71% in the apalutamide group, and time to symptomatic progression was also reduced significantly (55%; P < 0.0001) in the apalutamide-treated patients. An immature overall survival analysis showed a 30% risk reduction for death (P = 0.07).

Dr. Small also noted a 94% risk reduction in time to PSA progression among patients receiving apalutamide (apalutamide not yet reached versus placebo 3.7 months; P < 0.0001).

Grade 3–4 adverse events were reported in 45% of patients receiving apalutamide and in 34% of those receiving placebo. Discontinuation rates for adverse events were 11% and 7% for apalutamide and placebo, respectively. Fatigue (30.4%) and rash (23.8%) were the most common adverse events in the apalutamide group. “The addition of apalutamide to androgen deprivation therapy was well tolerated, with maintained health-related quality of life,” Dr. Small said.

He concluded, “Overall, these data suggest that apalutamide should be considered as a new standard of care for men with high-risk nonmetastatic CRPC.”

Moderator Sumanta K. Pal, MD, of City of Hope in Duarte, California, commented, “Dr. Small’s dataset shows that apalutamide, a very potent hormonal therapy, delays the risk of metastasis or death by 72%—a very clinically meaningful finding. Moreover, the drug appeared to be very well tolerated.”

**PROSPER: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Enzalutamide in Men With Nonmetastatic Castration-Resistant Prostate Cancer**

- **Maha Hussain, MD, Northwestern University, Chicago, Illinois**

Among men with nonmetastatic castration-resistant prostate cancer (M0 CRPC) and rapidly rising prostate-specific antigen (PSA), treatment with enzalutamide (Xtandi, Astellas) led to clinically meaningful and statistically significant reductions in risk for developing prostate cancer metastases in the global, multicenter, phase 3 PROSPER trial.

Dr. Hussain said increasing baseline PSA and a PSA doubling time of less than 10 months predict development of metastases. Median bone metastasis-free survival (MFS) is 25–30 months. “Delaying time to all metastases is clinically relevant, with potential to delay cancer-related morbidity and prolong overall survival (OS),” she said.

In the prior PREVAIL trial in men with chemotherapy-naïve metastatic CRPC, enzalutamide significantly improved OS and radiographic progression-free survival (rPFS). In the STRIVE trial, enzalutamide was superior to bicalutamide in improving rPFS in patients with chemotherapy-naïve M0 CRPC.

The PROSPER trial hypothesis, Dr. Hussain said, was that enzalutamide would delay metastasis development in men with M0 CRPC and rapidly rising PSA (doubling time of 10 months or less). Investigators randomized 1,401 men (mean age, approximately 74 years) with M0 CRPC, baseline PSA of 2 ng/mL or greater, and PSA doubling times of 10 months or less 2:1 to enzalutamide 160 mg per day or placebo. All patients received androgen deprivation therapy (ADT). The primary endpoint was MFS (defined as time from randomization to radiographic progression or death within 112 days of treatment discontinuation).

The median duration of therapy was 18.4 months in the enzalutamide arm and 11.1 months in the placebo arm. PSA doubling was less than six months in 77% of patients. Treatment discontinuation rates for adverse events were low (enzalutamide 9% versus placebo 6%). Grade 3 or higher adverse event rates were 31% in the enzalutamide group and 23% in the placebo group. The most frequently reported events were hypertension (5% enzalutamide versus 2% placebo) and fatigue (3% enzalutamide versus 1% placebo). Three percent of deaths in the enzalutamide arm were attributed to drug therapy compared with 1% in the placebo arm.

The primary endpoint of median MFS was 36.6 months in the enzalutamide plus ADT arm and 14.7 months in the placebo plus ADT arm (hazard ratio [HR], 0.29; 95% confidence interval, 0.24–0.35; P < 0.0001). “This was a 71% reduction in relative risk of radiographic progression or death,” Dr. Hussain said. The enzalutamide plus ADT benefit was consistent across all sub-
groups. Time to PSA progression also favored enzalutamide at 37.2 months versus 3.9 months for placebo (HR, 0.07; *P* < 0.0001).

The first interim analysis of OS revealed a nonsignificant 20% reduction in the relative risk of death with enzalutamide versus placebo. Median OS was not yet reached in either group.

Progression events (new bone metastases, new soft-tissue metastases, both, or death without documented radiographic progression) were reported in 23% and 49% of patients in the enzalutamide and placebo groups, respectively.

“The proportion of progression events in the enzalutamide arm was 50% less than that of the placebo arm,” Dr. Hussain observed.

She concluded, “In men with M0 CRPC and rapid PSA doubling time (median, 37 months), enzalutamide resulted in a clinically meaningful and statistically significant 71% reduction in the relative risk of developing M1 CRPC.”

### Integrative Healthcare Symposium

**The Integrative Healthcare Symposium Annual Conference, held February 22–24 in New York, hosted multidisciplinary practitioners of functional and integrative medicine. We review below key sessions on opioid addiction relapse prevention and on how extended understanding of healing indicates the use of integrative care as an expansion of conventional care.**

### Integrative Therapies for Relapse Prevention in Opioid Treatment

- Loretta Butehorn, PhD, CCH, Boston, Massachusetts

We need our natural 130-plus neurotransmitters, especially the dopamine, epinephrine, and serotonin varieties, to “feel like ourselves,” Dr. Butehorn said.

But head injury, mental health issues, and substance use disorders all impact these same neurotransmitters. Stress can either increase or decrease the supply. Dr. Butehorn observed that when she first started working in the field of addiction more than 30 years ago, heroin users, cocaine users, and alcoholics constituted discrete groups. “Today in drug treatment almost everybody uses multiple drugs, with only 2–3% coming in as single-drug users, usually an occasional alcoholic. So we think about a person with an addiction now as someone with a neurotransmitter vulnerability,” she said, “and any drug that can capture their neurotransmitters is going to keep them in trouble.” That capturing of the neurotransmitters impacts personality, behavior, memory, and multiple aspects of functioning. “Most likely they are not a very pleasant person to be around. The euphoria of drug use is a very short-lived phenomenon. As an addicted person, they are constantly withdrawing, looking for a drug, or being hungover in some way.”

She pointed out that four of five people addicted to opioids started off using prescribed painkillers. The highest-risk group for opioid addiction, according to a November 2017 Centers for Disease Control and Prevention report, is adults 45–54 years of age, with the largest increase from 2013 onward in non-Hispanic whites. Drug overdose death rate increases were also significantly greater in that age group (*P* < 0.005) versus other age groups.

Serotonin levels are disrupted by alcohol, nicotine, amphetamine, cocaine, phencyclidine (PCP), LSD, and MDMA (ecstasy), and dopamine levels are disrupted by cocaine, nicotine, PCP, amphetamine, caffeine, LSD, marijuana, alcohol, and opioids, she explained. Serotonin imbalances can lead to anxiety disorders (e.g., post-traumatic stress disorder, panic disorder, obsessive-compulsive disorder, generalized anxiety disorder) and mood disorders (e.g., bipolar disorder, major depressive disorder, depression). Dopamine imbalances can lead to psychotic disorders (e.g., schizophrenia, schizoaffective disorder) and Parkinson’s disease. A host of medications have been developed to rebalance neurotransmitters, including selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic and other antidepressants, and atypical antipsychotics. Dopamine antagonists and agonists have been developed for dopamine rebalance.

With substance addiction, addictive substances are “look-alikes” to natural neurotransmitters in the body. The natural neurotransmitter “pump”—because the body is receiving and using “foreign imports”—shuts down increasingly. So when people become addicted, they can’t “just stop” because they are no longer able to make the neurotransmitters that have kept them functioning in the past.

The typical detoxification program for addictive drug use, which used to be 21 days in length, is now three to five days, only long enough for some addictive drugs to leave the body; however, benzodiazepines, diazepam, alprazolam, and other antianxiety drugs stay in the system for up to two weeks, and marijuana stays longer. The major goal of medical detoxification with alcohol and benzodiazepines is to avoid seizures and delirium tremens, which, if untreated, can lead to death or disability. But beyond such acute risk, the body’s recovery of its ability to produce neurotransmitters is not rapid, and despite use of drugs to ease withdrawal (e.g., barbiturates, anticonvulsants, beta blockers/alpha adrenergic agonists, antipsychotics, buprenorphine, naltrexone), “protracted withdrawal syndrome” can last from six months to two years, Dr. Butehorn said. Withdrawal symptoms can include nausea, vomiting, diarrhea, shakes, body pain, spasms, seizures, hallucinations, multiple physical and emotional responses, and, especially, severe cravings.

The most vulnerable period for recidivism, she explained, is during postacute withdrawal. Postacute withdrawal syndrome (PAWS) is characterized by these severe cravings along with irritability, agitation, nausea, diarrhea, sleep disturbance, and memory disturbance. “But the main symptom is severe, severe craving.” Medications help for about 60% of the population, a rate typical for most ailments. “A protracted rollercoaster pattern of out-of-the-blue sudden-onset cravings can last up to two years.”

Single-photon emission computerized tomography brain scans of people with head trauma, depression, and schizophrenia, as well as those of long-term heroin and marijuana users, all reveal marked distortions of the cortex indicating lack of neurotransmitter activity, Dr. Butehorn said. Normalization of those distortions after cessation of addiction takes about 16 months in men and 19 months in women and occurs gradually. Beyond physical cravings, mental (obsessions/fixations), emotional (irritability, resentment, highs and lows), spiritual (disregard, cynicism, disdain) and consciousness (blankness, lack of awareness) symptoms may persist. “If the brain has been hijacked by drugs,
both mind and body are focused on the craving for relief. Without intervention, relapse is inevitable," she said.

Different integrative approaches are appropriate at various treatment stages. During detoxification, acupuncture and herbal and homeopathic remedies may be appropriate. At the PAWS stage, in addition to education, acupuncture, imagery, yoga, and tai chi are warranted, while in the rehabilitation and relapse phase, the full range of integrative approaches may be brought to bear.

While the first step in treatment is helping patients become more physically comfortable, the second most significant “alternative” strategy, according to Dr. Butehorn, is stimulating awareness and consciousness. The critical problem is that most patients expect to feel better soon, are not aware of PAWS or their own relapse history and patterns, and leave detox to go back to a very stressful life, with anxious family, probation, court dates, child protective issues, and health and job issues. In the past year, 65 patient interviews conducted by Dr. Butehorn revealed that 96% had multiple detoxes, relapses, and histories of multiple drug use. Three-quarters of them were unaware of PAWS, and 81% had never done a relapse history.

Working with individuals going through this process requires as many multisensory aids as possible to educate patients about what they can expect and what is occurring in their bodies. “Thinking changes grey matter, and inmaterial mental activity maps to material neural activity,” Dr. Butehorn stated. Temporary changes with detox include alterations in synchronized neuronal firing patterns with changes in oxygen and glucose use and neurochemical alterations. These changes lead to altered gene expression and strengthening of synapses, new synapses, and thickening brain cortex.

Before reviewing her 2015 study on homeopathic treatment with Nux vomica, Dr. Butehorn noted that the efficacy of homeopathy’s use of extreme dilute concentrations of substances is often challenged as being without research backing and as causing only placebo effects. She briefly cited seven studies that found significant benefits for homeopathic treatment in animals (pigs, rats, and mice) and children, groups for which placebo effects are implausible. In addition, she cited Luc Montangier, MD, who was awarded the 2008 Nobel Prize in Medicine for his discovery of the AIDS virus, who claimed in Science in December 2010 that the high dilutions used in homeopathy retain “water structures which mimic the original molecules.”

Dr. Butehorn’s trial included three cohorts of women (N = 901) with long-term addiction to multiple recreational and prescription drugs. Data had been collected previously at their postdetox residential clinic programs between 2006 and 2011. The women had been given the option of receiving Nux vomica (three pellets in 8 oz. of water as needed for cravings—typically one to three doses). In the first and second groups, the program completion rates were 66% and 64% among women receiving homeopathic treatment and 33% and 36% in those without. In the third program, relapse/program discontinuation rates were 24% among those receiving Nux vomica and 40% without.

Dr. Butehorn concluded, “Despite the sample being self-selected and the data from the first two cohorts being informally collected, as it was a clinical program and not focused on research, the trend of a similar percentage of successful treatment completion of those who used homeopathic treatment compared with those who did not warrants further study.”

She reiterated the need to help clients clearly understand PAWS, and restated, “Remember that consciousness is the most valuable item in the entire alternative/complementary/integrative toolkit.”

How Healing Works and What it Means for Health Care

• Wayne Jonas, MD, Professor of Family Medicine, Georgetown University, Washington, DC

What is now called “integrative health care” or “whole systems health” has evolved, Dr. Jonas said, from being previously designated “quackery” or “unconventional,” then as “alternative,” then “complementary,” and now—“integrative.” But where he now works in a mainstream hospital in Washington, DC, he sees many military patients. “They see it all as the same thing and don’t differentiate between integrative and conventional care.” But the public has embraced this wider definition in ways that formal systems of care and reimbursement have not. “If we don’t change how we deliver health care today, we are going to continue to go down the tubes of more poor outcomes, more and more dissatisfaction from everybody in the system, and unsustainable increases in costs,” Dr. Jonas warned. He added, “When the costs go up and resources go down, rationing occurs—and that’s what’s happening now.”

With the United States being first in health care spending but 37th in outcomes, and with health care soon to consume one-quarter of the national budget, the division between health care haves and have-nots is growing wider, and for the first time in 80 years, life expectancy is going down. “Health care is losing its value—it’s not worth the money,” he said.

The transition, Dr. Jonas said, one that is already occurring, is from a volume-based to a value-based system, with emphasis on reducing overuse of emergency departments and specialists. “This is where integrative health really shines,” he observed. In the area of pain management, there has been an awakening, and various guidelines from institutions such as the Food and Drug Administration, the Centers for Disease Control and Prevention, and the Veterans Administration now emphasize nonpharmacological approaches. In addition, the military has adopted battlefield acupuncture for pain management. Here, patients have already been making the transition over the last 30 years. “It is not an opioid problem,” Dr. Jonas commented. “It’s a chronic pain management problem.”

These are really problems of culture, he said, and the challenge of implementing what is already known has the difficult requirement that first you need to change people’s thinking. He cited examples of two patients, both with the “platinum” health care offered by the military, both coming from conventional mindsets, finding resolution of long-standing chronic problems through integrative health care. Integrative care, as Dr. Jonas indicated through a diagram (Figure 1), lies in the overlap of conventional care, self-care, and complementary and alternative medicine. A team approach was essential to both of the patients and their health issue resolutions, with physicians and pharmacologists as key members along with health coaches, behaviorial therapists, yoga therapists, family, and friends, and the support of their own mental and physical efforts. This team
approach to health emerges from a recognition that only 15% to 20% of health derives from medical treatment.

Healing is also strongly affected by the other 80% to 85%, which includes components of behavior, lifestyle, social, emotional, spiritual, and mental factors. This larger exploration of a patient’s personal determinants of health is embodied in what Dr. Jonas terms the “HOPE” (healing-oriented practices and environments), with the latter spiritual components asking the individual patient, “What really matters to you?” Lack of awareness of this component on the part of health care professionals may undermine the likelihood that a treatment plan will be adhered to. “It means asking a different set of questions,” Dr. Jonas said. “That’s part of the ‘patient-centered care’ that’s been officially recommended in National Academy of Medicine Institute of Medicine Guidelines for decades.”

The Pharmacist’s Role

The role of the pharmacist on the integrative team is a major one, and from one perspective, it has an inherent problem. The central job is to coordinate and organize medications for physicians and patients to avoid interactions and appropriately address quality and dosing issues. Because more than half of patients are using supplements of one kind or another, all patients must be asked about their current intake of them. Many patients are self-medicating for sleep, pain, or inflammatory conditions with vitamins, minerals, or herbs. Often, if they are not prompted, they do not tell their physicians, and the physicians usually do not ask.

Whether what the patients are already taking is potentially useful or not, the pharmacist’s input can be helpful. In an interview for P&T, Dr. Jonas gave an example from his practice of how he works with the pharmacist in his clinic around supplement use for sleep issues, which is very common. Conventional drugs often induce unfavorable side effects or have interactions with other medications. Properly delivered, supplements may offer safer and less-expensive treatments, but careful assessment of evidence, quality, and interactions is needed. “I’ll work with the pharmacist to ensure, number one, that the product has evidence and is of high quality, and that it will not interact adversely with other medications they are taking,” Dr. Jonas said. “Quality is important, also. The local health food store,” he added, “may not know anything about the quality of their products. Our pharmacists are educated about the common supplements and can provide guidance to both doctors and patients.” He emphasized, “This is a major role for pharmacists because there is a huge knowledge gap on both the provider and patient sides. Supplements are very commonly used and very rarely discussed. There are many examples of patients who’ve gotten into trouble because what they are taking alters the metabolism of the other drugs they are taking.”

Dr. Jonas specifically cited St. John’s wort (hypericum) because it upregulates p540 enzymes in the liver that also metabolize other medications, such as immunosuppressants and antiretroviral drugs used for human immunodeficiency virus infection. Patients with autoimmune diseases or organ transplants who are taking immunosuppressants are especially vulnerable, and there are instances of St. John’s wort inducing graft-versus-host disease when patients have started taking it on their own. Some supplements or herbs—notably vitamin K, but also garlic and ginko (often advertised to the elderly as helping with memory)—interfere with bleeding or platelet coagulation processes. Patients may already be taking conventional antiplatelet or anticoagulant agents, and the supplement will exacerbate bleeding risks, for example, before going into surgery. If neither patients nor physicians raise these issues, Dr. Jonas said, the pharmacist can sharpen the focus on them.

The Knowledge Gap

Is the currently extant research database on complementary agents sufficient given the potential for adverse interactions with conventional pharmaceuticals and the fact that they are being taken by a large portion of the public? “No, our database is not sufficient at all,” Dr. Jonas said. “There’s a paucity of research compared to what we know about pharmaceuticals. These substances are largely not patentable, so without commercial incentives, only the government can take up the research task.” He pointed out that the Office of Dietary Supplements budget is miniscule ($21.3 million in 2016), and that the part of the National Center for Complementary and Integrative Health’s $130 million total budget devoted to all complementary research (with some on supplements) is similarly insubstantial. “There is not nearly enough research being done to understand some of the complex interactions that are going on.” Calls to hold supplements to the standards of evidence-based medicine that conventional pharmaceuticals are held to without providing the needed research funding leave an uneasy status quo.

In the meantime, team care is essential, Dr. Jonas concluded, and team leaders can help integrate conventional, complementary, and lifestyle interventions. In particular, they can encourage self-care. “Evidence shows that patients managing their own care are healthier,” he said. “This is true integrative health and should be the goal of all of health care.”

REFERENCES