Final Results of a Randomized Phase 2 Study of Palbociclib (PD 0332991), a Cyclin-Dependent Kinase (CDK) 4/6 Inhibitor, in Combination With Letrozole vs. Letrozole Alone for First-Line Treatment of ER+, HER2− Advanced Breast Cancer (PALOMA-1/TRIO-18)

Richard Finn, MD, Associate Professor of Medicine, University of California at Los Angeles

While breast cancer is known to be very diverse at the molecular level, clinically it falls into only three groups, Dr. Finn said. The estrogen receptor–positive (ER+) group, which represents about 60% of breast cancers, has anti-estrogens as the backbone of therapy. The human epidermal growth factor receptor 2 (HER2) amplified group, about 25% of breast cancers, is treated with anti-HER2 agents such as trastuzumab (herceptin), and the 15% of patients who are ER, progesterone (PR), and HER2 negative represent an unmet need.

Palbociclib is a first-in-class oral, selective cyclin-dependent kinase (CDK) 4/6 inhibitor that inhibits cell proliferation and cellular DNA synthesis by preventing cell-cycle progression from G1 to S phase. The human epidermal growth factor receptor 2 (HER2) amplified group, about 25% of breast cancers, is treated with anti-HER2 agents such as trastuzumab (herceptin), and the 15% of patients who are ER, progesterone (PR), and HER2 negative represent an unmet need.

Low nanomolar concentrations of palbociclib block retinoblastoma phosphorylation, inducing G1 arrest in sensitive cell lines. The retinoblastoma protein (Rb) is a tumor suppressor protein that is dysfunctional in some cancers. CDK 4/6 is dependent on another protein, cyclin B. Together, CDK 4/6 and cyclin B play a role in adding phosphates, hyperphosphorylating the Rb gene product. Rb is critical for regulating the transition from G1 to S phases of the cell cycle. Once Rb is hyperphosphorylated, it releases the brake from the G1/S transition. “So the idea is,” Dr. Finn said, “that by blocking this kinase, you block the hyperphosphorylation of Rb, and therefore block cell-cycle progression.”

In preclinical research, palbociclib preferentially inhibited proliferation of luminal ER+ human breast cancer cell lines. When palbociclib was combined with anti-estrogens, the cell growth-blocking effect was synergistic. In the phase 2 PALOMA-1/TRIO-18 study, investigators divided the patient population into two parts, the first including 66 postmenopausal women with ER+, HER2-negative breast cancer not previously treated for advanced disease (locally recurrent or metastatic), and the second meeting the same criteria but also having CCND1 amplification and/or loss of p16 (n = 99). CCND1 encodes for the cyclin D1 protein involved in G1/S cell-cycle transition.

Women in both parts were randomized 1:1 to palbociclib (125 mg daily) plus letrozole (2.5 mg daily) or to letrozole (2.5 mg) alone in a three-weeks-on, one-week-off schedule. The second part, looking at genomic changes in cyclin B1 or loss of p16, was testing whether or not biomarkers could be further refined.

Median age was 63 years in the palbociclib plus letrozole group and 64 years in the letrozole-alone group. Previously, in the adjuvant setting, about a third of patients had had prior hormonal therapy and approximately 43% had had prior chemotherapy.

Analysis of the part 1 and part 2 findings revealed similar dramatic improvements in the palbociclib plus letrozole arms, regardless of biomarkers. The control arms differed, however, with a longer PFS in the part 2 control arm (11.1 months vs. 5.7 months). “That might reflect how cyclin B1 or p16 selection affects responses to letrozole,” Dr. Finn speculated.

Secondary endpoint analysis revealed consistent benefits for the combination in objective response rate (43% vs. 33%) and in clinical benefit (complete response plus partial response and stable disease for at least 24 weeks, 81% vs. 58%).

Overall survival (OS) was not significantly longer for the combination (37.5 months vs. 33.3 months for letrozole; HR, 0.813; 95% CI, 0.492–1.345; P = 0.2105). However, Dr. Finn added, “Remember that survival events in ER-positive breast cancer take time to evolve. There’s only 30 events per arm
Antitumor Activity of the Anti-PD-1 Monoclonal Antibody MK-3475 in Melanoma: Correlation of Tumor PD-L1 Expression With Outcome

Adil I. Daud, MD, Co-Director of the University of California at San Francisco Melanoma Center

MK-3475, a humanized, monoclonal IgG4 antibody, is a very potent blocker of PD-1 ligands 1 and 2, both of which play some role in triggering the PD-1 pathway. “It is increasingly recognized that the immune system plays a major role in controlling cancer—and one of the ways that cancer cells evade the immune system,” Dr. Daud explained, “is by using the PD-1/PD-L1 pathway.” Cancer cells, he continued, co-opt this pathway and, in some models, they block T-lymphocyte action by expressing PD ligand. “One way to defeat this is by using a PD-1 antibody such as MK-3475.”

This phase 1B KEYNOTE-001 study analysis of advanced melanoma patients treated with MK-3475 aimed to test the relationship of tumor PD-L1 expression to outcomes and to assess the effects of MK-3475 on peripheral T-cell phenotype as a pharmacodynamics marker. In the complex trial, the tested population included five groups subdivided according to prior ipilimumab treatment (naïve, treated, or refractory), dosage (10 mg or 2 mg), and schedule (every two weeks or every three weeks). The primary response assessment was conducted according to rigorous RECIST (Response Evaluation Criteria in Solid Tumors) 1.1 criteria per independent central review (with a first assessment at 12 weeks). Within 60 days prior to the initiation of treatment, patients had a mandatory biopsy by a clinical trial immunohistochemical assay. Eighty-three patients were identified as having measurable PD-L1–positive tumors and 30 as having measurable PD-L1–negative tumors. PD-L1 positivity was defined as staining of at least 1% of tumor cells.

Among the 125 patients (mean age 63 years, 61% male) with evaluable PD-L1 expression, 89 (71%) were found to be PD-L1–positive, typical of melanoma trials, Dr. Daud said. He also noted that 76% of patients were BRAF wild type, and 57% had advanced disease (M1c) with visceral metastases. All patients had advanced, unresectable melanoma, measurable disease (per investigator assessment), and were Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.

Reductions in tumor size using MK-3475 were reported in 67% of patients. Tumor growth was more common among PD-L1–negative patients.

In the overall unselected population, the overall response rate (ORR), based on the optimally defined cut-point of at least one tumor cell with the protein present per 100 tumor cells stained, was 40% (95% CI, 31–50). “That’s high for immunotherapy,” Dr. Daud commented. For PD-L1–positive patients the ORR was 49% (95% CI, 40–65), as compared with 13% for PD-L1–negative patients (95% CI, 4–31; \( P = 0.0007 \)).

In the unselected population, the disease control rate (complete response plus partial response and stable disease) was 58%. It was 65% for the PD-L1–positive population and 37% for PD-L1–negative patients (PD-L1–positive vs. PD-L1–negative, \( P = 0.0070 \)).

PFS after 12 months was 45% in the PD-L1–positive group, significantly higher than the 18% found in the PD-L1–negative group (HR, 0.52; 95% CI, 0.32–0.86; \( P = 0.0051 \)).

Six-month OS estimates, however, were similar between groups, at 91% for PD-L1–positive patients and 79% for PD-L1–negative patients (HR, 0.83; 95% CI, 0.39–1.78; \( P = 0.3165 \)). Median OS was not reached for either group. While Dr. Daud attributed the lack of significant difference to the high activity of the drug and to the immaturity of the data with few survival events, he commented, “It’s still interesting that there’s no separation in the survival curves.”

An analysis of changes from baseline in the percentage of CD8–positive (“killer”) T-cells and in CD4–positive (“helper”) T cells showed significant median increases in both (14.6%; \( P < 0.001 \), and 15.7%; \( P < 0.001 \), respectively), but found no correlation between this T cell activation and response. Immune responses seemed to be improved similarly at all doses of MK-3475.

In patients whose tumors were PD-L1–negative, prior ipilimumab treatment did not affect outcomes.

“This is an extraordinarily active antibody in melanoma, with a durable objective response rate,” Dr. Daud said. He noted further that while fewer PD-L1–negative patients had responses, “their quality of responses was just as good.”

Studies with MK-3475, both as monotherapy and in combinations, are ongoing in patients with multiple solid tumors and hematological malignancies. They may provide more insight into the clinical utility of PD-L1 expression in patients treated with MK-3475, Dr. Daud said.

This study was funded by Merck. Dr. Daud has served on the advisory boards of Merck and GlaxoSmithKline.

A Phase I Study of IMCgp100: Durable Responses With a Novel First-in-Class Immunotherapy for Advanced Melanoma

Mark Middleton, MD, PhD, Professor of Experimental Cancer Medicine, University of Oxford, United Kingdom

Press briefing moderator Louis M. Weiner, MD, director of the Georgetown Lombardi Cancer Center, noted in introducing Dr. Middleton’s presentation: “Even with the best of our checkpoint inhibitor strategies to date, there still remains a reservoir of people whose cancers will not be responsive—because of the ways the cancers are defending themselves against the body’s immune system.”

IMCgp100, a first-in-class immunotherapy, is a bispecific biologic incorporating an engineered T-cell receptor with specificity for a peptide antigen derived from protein gp100, which is presented by HLA-A2. Expression of HLA-A2 antigen is important for tumor cell recognition by autologous T-lymphocytes. Expression of some HLA antigens may be selectively lost in several human tumors, including melanoma.
IMCgp100 binds tightly to tumor cells, activating adjacent killer T cells and stimulating a cascade of immune-activating molecules that recruit a further immune response. With the very tight binding of IMCgp100 to the cancer cell, T-cell receptor affinity is increased by 3,500,000. Cytotoxic T cells are recruited into proximity with the melanoma cells bearing HLA-A2 through binding to CD3 on the T cell. Then cytotoxic T cells are able to target the melanoma cells, leading to apoptosis.

HLA-A2, Dr. Middleton noted, is expressed in about 45% of melanoma patients. Existing immunotherapies target cell surface proteins, making only about 10% of potential targets within cancer recognizable to T cells. “By targeting HLA-presenting peptides, we bring many more targets (approximately 90%) into play. The results of this study offer proof of this concept.”

Thirty-one HLA-A2 patients (median age 61 years, 58% male) with stage IV or unresectable stage III melanoma with ECOG performance status of 1 or 0 and lymphocyte counts of at least 0.5 x 10^9/L were included in the study. Sixty percent had received systemic treatment (DTIC, 29%; ipilimumab, 6%; vemurafenib, 3%; or one or more experimental therapies, 22%) prior to the study.

IMCgp100 doses were escalated from 5 to 900 ng/kg until occurrence of dose-limiting toxicity. Rash was observed initially at 45 ng/kg. After two of four patients receiving IMCgp100 at 900 ng/kg developed grade 3 hypotension with edema, rash, and fever, the maximum tolerated dose (MTD) was defined at 600 ng/kg. Tumor flare was observed in patients with cutaneous or subcutaneous disease. “We generally see tumor flare as a good sign in immunotherapy. It’s a suggestion of an immune infiltrate, and it often precedes tumor shrinkage,” Dr. Middleton said.

Partial responses among the 16 patients receiving more than 135 ng/kg of IMCgp100 were reported in four, with three meeting RECIST criteria. “We see this as being extremely significant. It points to the potential of this drug for future therapy,” he said. Responses have lasted about a year in the first two patients, with further tumor shrinkage in one patient who remains asymptomatic.

“With IMCgp100, we have a first-in-class drug, a monoclonal T-cell receptor immunomodulator … that can be administered safely at biologically effective doses. It is associated with durable clinical responses in melanoma,” Dr. Middleton said.

For the ongoing study, a protocol amendment allowing daily dosing has been approved. “We feel that for pharmacokinetic reasons this may be more efficacious than once-weekly dosing,” Dr. Middleton said.

Dr. Weiner added, “This is an approach that essentially fills that gap in therapy … and I think that it, along with similar approaches, offers significant promise.”

Efficacy and Safety of Lurasidone in Bipolar I Depression: Pooled Results of Two Adjunctive Therapy Studies With Lithium or Valproate

• Joseph R. Calabrese, MD, Bipolar Disorders Research Chair at Case Western Reserve University, Cleveland, Ohio

The need to identify effective antidepressants for adjunctive use with mood stabilizers is clear. Lithium and valproate, while effective as mood stabilizers, are less effective for treating the depressive phase of bipolar disorder. Also, Dr. Calabrese said, few studies support the efficacy of standard tricyclic or serotoninergic antidepressants for the treatment of bipolar depression. Other studies of quetiapine and the olanzapine/fluoxetine combination, while showing efficacy in the depressed phase of bipolar disease, have side effects of sedation, somnolence, and metabolic burden.

Lurasidone, a new atypical antipsychotic agent, was tested in two six-week, double-blind, placebo-controlled studies at flexible doses of 20 mg to 120 mg a day given adjunctively with lithium or valproate. The primary endpoint was the score on the Montgomery–Asberg Depression Rating Scale (MADRS).

In an analysis of the pooled data, among 360 patients randomized to lurasidone plus either lithium or valproate, 19.2% discontinued therapy, compared with 17.4% in the placebo plus lithium or valproate group.

MADRS score reductions were significantly greater in the adjunctive lithium plus lurasidone group than in the placebo plus lithium group from weeks 2 to 6. For the valproate plus lurasidone group, reductions in MADRS total scores were significant in weeks 3 to 5, but marginal at week 6 ($P = 0.066$).

Responder criteria were met significantly more often in the adjunctive lurasidone patients than in placebo patients (48.2% vs. 36.7%, $P < 0.01$), as were remission criteria (42.3% vs. 31.8%, $P < 0.01$).

Lurasidone, as an adjunctive therapy with lithium or valproate, is an effective treatment for patients with bipolar depression, according to the pooled results from these two similarly designed studies, Dr. Calabrese concluded.

Efficacy and Safety of Memantine in a Global, Double-Blind, Placebo-Controlled, Randomized Withdrawal Study in Children With Autism Spectrum Disorder

• Antonio Y. Hardan, MD, Professor of Psychiatry and Behavioral Science at Stanford University, Palo Alto, California

Alterations of glutamatergic neurotransmission have been implicated in the pathogenesis of autism spectrum disorder (ASD). Preliminary evidence suggested that memantine, an antagonist of NMDA (N-methyl-D-aspartate) glutamate receptors, may provide benefits in communication and social behavior in pediatric ASD patients. Also, nonrandomized chart reviews and open-label studies have demonstrated some efficacy. Memantine is approved for treatment of moderate-to-severe Alzheimer’s disease.

Dr. Hardan led a multinational, double-blind, placebo-
controlled, randomized withdrawal trial of memantine in children with autism, testing for differences between active treatment and placebo in loss of therapeutic effect after treatment withdrawal. Investigators enrolled responders from an open-label lead-in study (MEM-MD-91), and randomized them to either full or reduced weight-based memantine doses or to placebo. Response in the lead-in open-label trial was defined as a 10-point or greater improvement in the Social Responsiveness Scale (SRS) total raw score compared with baseline after at least 12 weeks of memantine exposure. Clinical improvement on the SRS total score had been reported at similar rates (about 40 points) for memantine and placebo in the lead-in trials.

Loss of therapeutic response (LTR) was defined as a worsening by 10 or more points on the SRS from baseline. Those meeting LTR criteria were subsequently eligible for an open-label extension study (MEM-MD-69). Patients were stratified by ASD subtype (autism, Asperger disorder, or pervasive developmental disorder not otherwise specified).

The trial included boys and girls ages 6 to 12 years with SRS scores greater than 44 for girls and greater than 53 for boys. Out of 471 children in the intention-to-treat population, about two-thirds of patients in each treatment group met the LTR criterion after about two weeks (placebo, 69.0%; memantine reduced dose, 67.5%; memantine full dose, 66.7%). Time to LTR was similar between memantine and placebo groups (P = 0.63 for reduced memantine dose vs. placebo; P = 0.67 for the full memantine dose vs. placebo). No differences in results were observed according to autism subtype.

Adverse events were similar between groups, and most were mild to moderate in severity.

Dr. Hardan speculated that the negative outcome could be explained by an inherent lack of memantine effect, by too liberal an LTR criterion, by inadequate memantine doses, or by benefit in an unidentified subset of patients. “In an open-label study, usually the drug or intervention looks good, but then when you test the findings with a withdrawal phase you may learn otherwise,” he said.

He commented that a small trial with 40 to 50 subjects in a younger age group with more sensitive outcome measures could be useful to look for a signal of effect with memantine.

### The Efficacy of Vilazodone in Achieving Remission In Patients With Major Depressive Disorder: Post Hoc Analyses of a Phase IV Trial

- Leslie Citrome, MD, MPH, Clinical Professor of Psychiatry and Behavioral Sciences at New York Medical College in Valhalla, New York

While treatment response is the initial objective of therapy for major depressive disorder, symptom remission is generally considered the goal of depression management because it is associated with improved psychosocial functioning, lower risk of relapse and recurrence, and reduced health care utilization.

Vilazodone, a selective serotonin reuptake inhibitor and partial 5HT1A receptor agonist, produced clinically meaningful effects on remission of depression symptoms and/or depression-related anxiety in a randomized, double-blind, placebo-controlled trial in adults with major depressive disorder. The post-hoc analysis of phase 4 response and remission data comparing vilazodone (n = 253) to placebo (n = 252) also showed that clinically relevant single-digit numbers needed to treat (NNTs) for response and remission were achieved.

Participants had major depressive episodes ongoing for eight or more weeks but no more than 12 months with MADRS total scores of at least 26 at screening and baseline. Vilazodone was titrated from 10 mg/day in the first week to 40 mg/day in weeks 3 to 8. Among the criteria examined in the post-hoc analysis at the end of double-blind treatment were depression symptom remission (MADRS total score less than or equal to 10), depression symptom complete remission (MADRS total score of 5 or less), and anxiety symptom remission (Hamilton Anxiety Rating Scale [HAMA] of 7 or less).

MADRS response rates (MADRS 50% or more improvement) were reported at 51% for vilazodone and 33% for placebo (P < 0.001). The MADRS remission rates were 34% for vilazodone and 22% for placebo (P < 0.001). MADRS complete remissions were found in 18% and 8% of patients, respectively, for vilazodone and placebo, and HAMA remissions were reported at 49% for vilazodone and 35% for placebo (P < 0.001).

Vilazodone increased the chances for a MADRS response by a factor of 2.04, a MADRS remission by 1.82, a MADRS complete remission by 2.42, and a HAMA response by 1.82. The NNT at week 8 was five for a MADRS response and eight for a MADRS remission.

The most commonly experienced adverse event of nausea requires titration of vilazodone. “Vilazodone has reasonably low rates of sexual side effects and weight issues, making it an interesting option that may be found to be attractive,” Dr. Citrome concluded.

### Efficacy Comparison of TMS and Antidepressant Drugs in the Treatment of Major Depression; and Health Economics Comparison of TMS and Antidepressant Drugs in the Treatment of Major Depression

- Mark A. Demitrack, MD, chief medical officer of Neuronetics in Malvern, Pennsylvania

NeuroStar TMS (transcranial magnetic stimulation) Therapy is a Food and Drug Administration–approved noninvasive technology indicated for treatment of chronic or resistant unipolar nonpsychotic major depressive disorder. A comparison of TMS and next-choice pharmacotherapy demonstrated superior acute-phase improvements among patients using NeuroStar TMS Therapy, the Neuronetics TMS device.

NeuroStar TMS Therapy uses a small magnetic-resonance-strength magnet held adjacent to the surface of the head to induce an electrical current in the brain through a pulsed magnetic field. “You create an electric current of a strength that is above the depolarization threshold of neurons, causing local depolarization and regulating a neural network, reaching targets such as the anterior cingulate, the medial prefrontal cortex, the ventromedial prefrontal cortex, and deep areas of the limbic system. Done repeatedly, it has an enduring antidepressant effect in humans,” Dr. Demitrack said.
Data from the Neuronetics Outcome Study were used for a 1:1 propensity score matching with 305 patients in the STAR*D (Sequenced Treatment Alternative to Relieve Depression) population. Mean age was about 48 years (approximately 63% female). STAR*D was a National Institute of Mental Health–funded study of more than 4,000 outpatients with nonpsychotic depression treated sequentially with four treatment levels of pharmacotherapy (or cognitive behavioral therapy [CBT] as an option at level 2) until response or remission.

Dr. Demitrack reported that responses (Quick Inventory of Depressive Symptomatology-Self Report [QIDS-SR] less than 11) were found in 53.7% of NeuroStar patients and in 29.0% of STAR*D patients receiving next-choice medication. Remission (QIDS-SR less than 6) was reported in 27.0% of the NeuroStar population and in 5.2% of the STAR*D population. A more conservative analysis (reverse propensity matching) placed the STAR*D response and remission rates at 39.0% and 18.0%, respectively. Within-group differences (baseline to six weeks) and between-group comparisons were significant (P < 0.0001).

“The bottom line,” Dr. Demitrack said, “is that this analysis is showing you that TMS is doing much better in its acute outcomes compared to drug of next choice in a matched pharmaco-resistant population.”

Although the demonstrated short-term benefits of TMS were considerable, the larger benefit of TMR, Dr. Demitrack continued, is in its durability of effect and tolerability. “The dropout rate over time tends to be better for TMS than for pharmacotherapy, so costs are better, as well.”

A further analysis assessing costs for TMS versus STAR*D revealed an incremental cost-effectiveness ratio (ICER) ranging from $36,383 per quality of life year to $59,028 in the more conservative forward-matched model. The usual standard for “willingness to pay” is $50,000. The mean annual cost for TMS was estimated at $11,886, compared with $10,888 for STAR*D patients (a difference of $998). For an average insurer, Dr. Demitrack emphasized, the cost of achieving the higher remission rate cited in the first poster (27% as compared with 5.2% to 18.0%, depending on the model) would be an additional $0.25 per month per member. “They are getting a statistically significant better remission rate at that low cost,” Dr. Demitrack said.

Electroconvulsive Therapy (ECT) Improves Major Depression More Than Pharmacological Therapy Alone: A Naturalistic Approach

Neusa S. da Rocha, MD, PhD, Universidade Federal do Rio Grande do Sul in Porto Alegre, Brazil

While several meta-analyses have proven the efficacy of electroconvulsive therapy (ECT) for depressive disorders, transferring the results to real-life patients with medical and psychiatric comorbidities has remained a challenge. “There is a prejudice against electroconvulsive therapy. But it is a very good therapy for severely depressed patients,” Dr. da Rocha said. Her naturalistic study of ECT showed larger improvements in depression (Hamilton Rating Scale for Depression [HAM-D]) than with pharmacological therapy alone.

The goal of Dr. da Rocha’s study was to evaluate outcomes in a cohort of severely depressed psychiatric inpatients. All 147 had been admitted to a psychiatric unit using the Mini International Neuropsychiatry Interview (MINI). Cohorts were divided into those treated via ECT (n = 43) and those not treated with ECT (n = 104). The main outcomes were improvement in depression on the 17-item HAM-D, response (at least 50% on HAM-D), remission (7 or less on HAM-D), and time of hospitalization.

The ECT patients were older (51.12 years ± 14.85 vs. 43.07 years ± 13.88, P = 0.002), and had fewer prior hospitalizations (2.9 ± 3.13 vs. 5.51 ± 1.6, P = 0.51) and more prior ECT (32.5% vs. 10.5%, P = 0.002).

Even though mean HAM-D scores at admission were higher in the ECT group (25.05 vs. 21.61 for non-ECT, P = 0.001), they were similar at discharge (7.7 vs. 7.5, P = 0.75), with greater mean improvement in the ECT group (18.24 vs. 14.2, P = 0.004). Also, response to therapy was reported in 84.3% of ECT patients and in 75.5% of non-ECT patients. Remission was reported similarly in both groups, in 58.1% of ECT patients and in 58.7% of non-ECT patients.

After correction for baseline confounders, mean duration of hospitalization was similar between groups at 27.66 days for ECT and 24.57 days for non-ECT (P = 0.25), but longer in raw measures (35.48 vs. 24.57 days, P < 0.001).

Dr. da Rocha said that similarity in HAM-D scores at discharge, despite the higher baseline scores in the ECT group, along with higher response rates for ECT, reinforce the efficacy and effectiveness of ECT for severely depressed patients. Longer uncorrected mean duration of hospitalization for the ECT patients, she said, points to the need to know clinical predictors of ECT response in advance.

Dr. da Rocha’s overall comment on ECT: “I think it’s old but it’s good and should be used more than it is used nowadays. If we had some predictors of the effectiveness of ECT we could use it earlier during an admission.” Further studies are planned.