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Melanoma

PD-1 Checkpoint Inhibitor Opdivo First to Demonstrate Survival Benefit in Phase III

A study comparing Opdivo to dacarbazine chemotherapy in treatment naïve advanced melanoma patients marks first PD-1 immune checkpoint inhibitor to demonstrate a survival benefit in a phase III trial.

The trial, CheckMate-066, met its primary endpoint of overall survival, with median OS not reached in the Opdivo (nivolumab) arm, compared to 10.8 months in patients receiving dacarbazine chemotherapy.

The one-year survival rate was 73 percent for Opdivo vs. 42 percent for DTIC, and there was a 58 percent decrease in the risk of death for patients treated with Opdivo (HR: 0.42, $p < 0.0001$).

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Ovarian Cancer

Phase III Trebananib Trial Fails OS Endpoint In Recurrent Platinum-Resistant Ovarian Cancer

Top-line secondary endpoint results from the phase III TRINOVA-1 trial in women with recurrent platinum-resistant ovarian cancer did not demonstrate a statistically significant improvement in overall survival. The study evaluated trebananib plus paclitaxel versus placebo plus paclitaxel.

Median overall survival was 19.3 months in the trebananib arm versus 18.3 months in the control arm. The data will be submitted to a future medical conference and for publication according to Amgen, trebananib's sponsor.

In the previously reported primary endpoint analysis, the data demonstrated a statistically significant difference in progression-free survival for trebananib. In that analysis, patients treated with trebananib showed a 34 percent reduction in the risk of disease progression or death (HR = 0.66, 95 percent CI, 0.57, 0.77, $p < 0.001$). The median progression-free survival was 7.2 months in the trebananib arm versus 5.4 months in the control arm.

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Glioblastoma

Phase III Tumor Treating Fields Trial Halted Following Positive Results in Interim Analysis

A phase III trial of Tumor Treating Fields was terminated early following early success detailed in an interim analysis. The trial evaluated patients with newly diagnosed glioblastoma being treated with the NovoTTF-100A System, developed by Novocure, in combination with standard-of-care temozolomide.

The treatment extended both progression-free survival and overall survival compared to temozolomide alone. The trial's independent data monitoring committee recommended terminating the trial early and allowing all control patients to cross over to the treatment arm.

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Opdivo Increases Overall Survival In BRAF Wild-type Melanoma Trial

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The trial enrolled 418 patients with treatment naïve BRAF wild-type advanced melanoma, and the survival benefit was observed in both PD-L1 positive and PD-L1 negative patients treated with Opdivo.

The rate of objective response was significantly higher for Opdivo than dacarbazine, at 40 percent and 14 percent, respectively—and it included a higher percentage of complete responses, at 7.6 percent compared to 1 percent.

The data was published in *The New England Journal of Medicine* and presented during an oral session at the Society for Melanoma Research 2014 International Congress in Zurich, Switzerland.

The trial enrolled 418 patients who were randomized to receive either Opdivo 3 mg/kg every two weeks (n=210) or DTIC 1000 mg/m² every three weeks (n=208). Treatment continued until there was disease progression or an unacceptable level of toxicity. Thirty-eight percent of patients in the DTIC arm received Yervoy (ipilimumab) after stopping study treatment.

All randomized patients were followed for up to 16.7 months at the time of database lock. Secondary endpoints included progression free survival, objective response rate by RECIST v1.1 criteria and PD-L1 expression as a predictive biomarker of OS. PD-L1 positivity was defined as at least 5 percent of tumor cells showing cell-surface PD-L1 staining.

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The study, sponsored by Bristol-Myers Squibb, was designed in consultation with the Committee for Medicinal Products for Human Use, was primarily conducted in countries where DTIC is a commonly-used treatment in the first-line setting, including Canada, Europe and Australia, but not at U.S. trial sites.

Opdivo is a fully-human PD-1 immune checkpoint inhibitor that binds to the checkpoint receptor PD-1 expressed on activated T-cells.

Opdivo is being studied in multiple tumor types consisting of more than 50 trials – as monotherapy or in combination with other therapies – in which more than 7,000 patients have been enrolled worldwide. Among these are several potentially registrational trials in non-small cell lung cancer, melanoma, renal cell carcinoma, head and neck cancer, glioblastoma and non-Hodgkin lymphoma.

In 2012, the FDA granted Fast Track designation for Opdivo in NSCLC, melanoma and RCC, and a Breakthrough Therapy designation in May 2014 for the treatment of patients with Hodgkin lymphoma after failure of autologous stem cell transplant and brentuximab.

Study: Keytruda Improves PFS In Ipilimumab-Refractory Disease

A pre-specified analysis of a pivotal phase II study showed that Keytruda substantially improved the primary endpoint of progression-free survival compared to chemotherapy in patients with ipilimumab-refractory advanced melanoma.

At six months, the PFS rates for Keytruda (pembrolizumab) were 34 percent at the 2 mg/kg dose (95% CI, 27-41) (n=180) and 38 percent at the 10 mg/kg dose (95% CI, 31-45) (n=181), compared to 16 percent for chemotherapy (95% CI, 10-22) (n=179). The median duration of follow-up at the interim analysis was 10 months.

The study, named KEYNOTE-002, was presented at the Society of Melanoma Research 2014 International Congress in Zurich, Switzerland.

For the pre-specified analysis of PFS, no significant

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differences were observed between Keytruda doses (HR 0.91, range 0.71-1.16) ($P < 0.44$). An assessment of PFS by investigator review was shown to be consistent with the central review findings. In addition, the PFS effect in favor of Keytruda was consistent across all pre-specified sub-groups.

The objective of the pre-specified analysis was to evaluate the superiority of either dose of Keytruda over chemotherapy for PFS (conducted after ≥ 270 PFS events at a 0.25% significance level) (one-sided) (estimated HR, 0.66). The study was designed with co-primary endpoints of PFS and overall survival. An evaluation of overall survival is planned at the pre-specified final analysis in 2015.

Overall response rates (confirmed) for Keytruda were five to six times higher compared to chemotherapy. For Keytruda, ORR was 21 percent at 2 mg/kg dose (95% CI, 15-28) and 25 percent at 10 mg/kg dose (95% CI, 19-32), compared to 4 percent for chemotherapy (95% CI, 2-9) ($P < 0.0001$ for both comparisons).

At the time of pre-specified analysis, the median duration of response for Keytruda was not reached, and confirmed responses were ongoing in 92 percent of patients receiving 2 mg/kg dose (range 6+ to 50+) and 87 percent receiving 10 mg/kg dose (range 5+ to 48+), respectively.

The median duration of response was 37 weeks for chemotherapy arm and 63 percent of responses were ongoing (range 7+ to 41). There was no significant difference in ORR or duration of response between the doses of Keytruda ($P = 0.21$).

Keytruda, sponsored by Merck, is indicated in the U.S. at a dose of 2 mg/kg every three weeks for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

The indication is approved under accelerated approval based on tumor response rate and durability of response. An improvement in survival or disease-related symptoms has not yet been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

Keytruda is a humanized monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. By binding to the PD-1 receptor and blocking the interaction with the receptor ligands, Keytruda releases the PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response.

Addition of Immune Stimulant To Yervoy Therapy Increases Overall Survival, Study Says

Patients with metastatic melanoma who were treated with Yervoy survived 50 percent longer if they simultaneously received an immune stimulant, according to a study.

Patients in the phase II trial who received the combined therapies demonstrated a median overall survival of 17.5 months compared to 12.7 months with Yervoy (ipilimumab) alone, and also had fewer adverse side effects. The study was published in the *Journal of the American Medical Association*.

The group treated with both Yervoy and the immune stimulant sargramostim, had a one-year survival rate of 68.9 percent compared to 52.9 percent in the Yervoy -only arm. The median progression-free survival in both groups was 3.1 months.

Sargramostim is a form of granulocyte-macrophage colony-stimulating factor, which spurs the growth of white blood cells. It is used, among other things, to restore white blood cells following a stem cell transplant for cancer.

The randomized clinical trial was conducted by the Eastern Cooperative Oncology Group, enrolling 245 patients with stage 3 or stage 4 metastatic melanoma who had been treated with other drugs. The patients were followed for a median of 13.3 months.

The advantage in overall survival of nearly five months in the group receiving sargramostim was significant, as was the lower toxicity in that group. Why the drug combination did not prolong the time before the disease progress – as might be expected, because it did extend overall survival – is not clear, the researchers said.

“It could be that the treatment is causing inflammation that that looked like early disease progression, but we won’t know without further studies,” said F. Stephen Hodi, first author on the clinical trial report, and director of the Melanoma Treatment Center and Center for Immuno-Oncology at Dana-Farber Cancer Institute.

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Ovarian Cancer

Phase III Trebananib Trial Fails to Meet Primary Endpoint

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“While the overall survival results of the TRINOVA-1 study are disappointing, this study is the first of three phase III trials designed to evaluate the safety and efficacy of trebananib in patients with ovarian cancer,” said Sean Harper, executive vice president of Research and Development at Amgen. “We continue to explore the potential of trebananib’s novel anti-tumor mechanism of action in other cancer settings.”

TRINOVA-1 enrolled over 900 women with recurrent partially platinum-sensitive or -resistant (platinum-free interval of 12 months or less) epithelial ovarian, primary peritoneal or fallopian tube cancer. Patients were randomized 1:1 to receive either 15 mg/kg of intravenous trebananib weekly plus 80 mg/m² of intravenous paclitaxel weekly (three weeks on, one week off) or weekly intravenous placebo plus 80 mg/m² of intravenous paclitaxel weekly (three weeks on, one week off).

In the trebananib arm, the most frequently reported adverse events were localized edema, nausea and alopecia. The rate of discontinuation of investigational product due to adverse events was 20 percent in the trebananib arm versus seven percent in the control arm. No new safety signals were detected.

Trebananib is an investigational peptibody designed to inhibit the angiopoietin axis. Trebananib is designed to bind to both angiopoietin-1 and -2 (Ang1 and Ang2), and inhibit their interaction with the Tie2 receptor. The angiopoietins are also involved in lymphangiogenesis, the formation of new lymphatic vessels, which plays a key role in tumor metastasis.

Data from another trial in the recurrent platinum-resistant population (TRINOVA-2) is expected in Q4 2014. Data from a trial evaluating trebananib in combination with first-line chemotherapy treatment for patients with ovarian cancer (TRINOVA-3) is expected in 2015.

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Non-Small Cell Lung Cancer

Phase II Trial of BIND-014 Shows Anti-Tumor Activity in Q3W Arm

Positive results from an ongoing phase II study of BIND-014 in non-small cell lung cancer showed that it has met the primary objective in the once-every-three-weeks arm, as measured by overall response rate. The data demonstrate that BIND-014 is well-tolerated with clinically meaningful anti-tumor activity at a lower dose than conventional docetaxel in patients with advanced or metastatic NSCLC.

BIND-014, sponsored by BIND Therapeutics Inc., also demonstrates promising anti-tumor activity in patients with tumors expressing KRAS mutations. An additional signal was observed in patients with squamous cell carcinomas. The data were presented at the EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics in Barcelona, Spain.

“We believe the activity and tolerability of BIND-014 demonstrated in this study suggest meaningful differentiation from the historical docetaxel experience, in both the broader NSCLC patient population and in two important groups of patients with high unmet medical need,” said Hagop Youssoufian, chief medical officer of BIND Therapeutics. “Based on these positive results, we plan to conduct additional global, multicenter phase II studies to confirm and expand the dataset on BIND-014 and to define an expeditious regulatory path for BIND-014.”

The Q3W dosing arm of the open label, multicenter, phase II study enrolled 40 patients with advanced metastatic NSCLC who were treated with 60 mg/m² of BIND-014 on day 1 of a 21-day cycle.

Preliminary median overall survival was 6.2 months for all patients treated, 9.6 months in patients with KRAS mutant tumors and 11.1 months in patients with squamous cell carcinoma.

Five patients achieved a partial response with a median duration of response of 5.2 months and median progression free survival of 2.7 months. There was one unconfirmed partial response that was not included in the analysis per RECIST v1.1.

Nine patients were enrolled with a confirmed KRAS mutation and two of those nine experienced an objective response; median PFS in patients with KRAS mutant tumors was 2.7 months.

In nine patients with squamous cell carcinoma there were no confirmed objective responses; however, median PFS in patients with squamous cell carcinoma

was 2.8 months. Prolonged (>4 cycles) disease control was also noted in six of nine patients with squamous histology.

The sponsor plans to initiate global, multicenter phase II studies of BIND-014 in patients with KRAS mutant NSCLC and in patients with NSCLC of squamous histology who have progressed on prior therapy. These studies aim to assess overall survival and additional endpoints to position BIND-014 for subsequent registration studies.

Based on the promising results of the Q3W arm presented today and the more patient-friendly once every three week dosing schedule, combined with the absence of a confirmed partial response in the first 22 patients enrolled on the Q1W schedule, the company will not continue enrollment on the weekly dosing schedule.

Opdivo Study Shows 41 Percent One-Year Survival In Patients With at Least Two Past Therapies

Results from CheckMate-063, a phase II single-arm, open-label study of Opdivo administered as a single agent in patients with advanced squamous cell non-small cell lung cancer who have progressed after at least two prior systemic treatments with 65 percent receiving three or more prior therapies, showed that 41 percent of Opdivo-treated patients were alive at one year.

The estimated one-year survival rate was 41 percent (95% CI = 31.6, 49.7) and median overall survival was 8.2 months (95% CI = 6.05, 10.91).

With approximately 11 months of minimum follow up, the study's primary endpoint of objective response rate was 15 percent (95% CI = 8.7, 22.2) as assessed by an independent review committee using RECIST 1.1 criteria and the median duration of response was not reached.

The data were presented at the 2014 Chicago Multidisciplinary Symposium on Thoracic Oncology.

"The phase II findings from CheckMate-063 are encouraging as there are no effective treatment options for patients with refractory squamous cell lung cancer after their disease has progressed through two prior therapies," said Suresh Ramalingam, professor and director of medical oncology at the Winship Cancer Institute of Emory University.

Checkmate-063, sponsored by Bristol-Myers Squibb, is a single arm, open-label study designed to assess advanced squamous cell NSCLC patients who progressed after both platinum-based therapy and at

least one additional systemic therapy with an ECOG Performance Status of 0 or 1 who were treated with Opdivo (nivolumab) as a single agent 3mg/kg by intravenous infusion every two weeks until disease progression or treatment discontinuation (n=117).

Secondary endpoints included investigator-assessed ORR. Overall survival, PFS and efficacy by PD-L1 expression status were exploratory endpoints. Seventy-six percent of patients were within three months of completion of their most recent therapy. The best response to the most recent prior systemic therapy was progressive disease in 61 percent of patients.

An additional 26 percent of patients had stable disease with a median duration of six months (95% CI, 4.73, 10.91) giving a disease control rate (defined as partial response + stable disease) of 41 percent. For patients with quantifiable PD-L1 expression, responses were observed independent of PD-L1 status.

Glioblastoma Tumor Treating Fields Trial Stopped Early after Analysis (Continued from page 1)

The trial data were presented at the annual meeting of the Society for Neuro-Oncology in Miami. The pre-specified, interim analysis of EF-14 trial data was conducted on the first 315 patients, representing approximately 50 percent of the targeted study population.

Patients treated with Tumor Treating Fields together with temozolomide demonstrated a median progression-free survival of 7.1 months compared to 4.0 months with temozolomide alone (HR=0.63, p=0.001). Median overall survival was 19.6 months compared to 16.6 months in the control arm (HR=0.75, p=0.034).

The NovoTTF-100A System creates a low intensity, alternating electric field within a tumor that exerts physical forces on electrically charged cellular components, preventing the normal mitotic process and causing cancer cell death.

The system is approved in the European Union and Switzerland for the treatment of glioblastoma. The device is intended for the treatment of adult patients with recurrent GBM who have progressed after surgery, radiotherapy and temozolomide treatment for their primary disease.

Prostate Cancer

Galeterone Shows Potential In CRPC AR Variants, Study Says

Updated interim results from the ongoing ARMOR2 phase II clinical trial of galeterone in castration-resistant prostate cancer patients demonstrated the potential of galeterone to treat CRPC expressing androgen receptor splice variants, including AR-V7, according to researchers.

The presence of AR C-terminal loss generally, and AR-V7 specifically, has been linked to poor responsiveness to hormonal agents commonly used to treat CRPC.

The data were presented at the EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics.

“Recent data have shown that the AR-V7 splice variant of the androgen receptor can be a predictor of resistance to treatment with enzalutamide and abiraterone,” said Mary-Ellen Taplin, associate professor of medicine, director of Genitourinary Clinical Research at the Dana-Farber Cancer Institute and Harvard Medical School. “We believe AR-V7 and other related variants are a mechanism of resistance in this disease and patients who have them may have a poorer prognosis.”

Consistent with a prior interim analysis, among 39 treatment naïve metastatic CRPC patients, 85 percent achieved a maximal reduction in PSA levels of at least 30 percent (PSA30) and 77 percent achieved a maximal reduction in PSA levels of at least 50 percent (PSA50). Among 60 combined non-metastatic and metastatic treatment naïve CRPC patients, 83 percent achieved a PSA30 and 70 percent achieved a PSA50.

In the second part of the ARMOR2 trial, circulating tumor cells were characterized for the presence of AR C-terminal loss. Seven treatment-naïve CRPC patients have been identified as having C-terminal loss in a retrospective subset analysis; six of these patients had maximal reductions in PSA levels of at least 50 percent.

The seventh patient, who did not show any PSA reduction, discontinued therapy due to an adverse event unrelated to galeterone after approximately six weeks in the trial and did not receive the full 12 week treatment regimen.

As of the data cutoff, the median time to PSA progression among the seven patients is 7.3 months, as defined by the Prostate Cancer Working Group 2 criteria.

Of the six responders with AR C-terminal loss, four elected to continue into an optional extension

phase of the trial following the initial 12 week treatment period. The time on treatment for these patients in the extension phase ranged from 155 days to more than 334 days as of the data cutoff.

“In the subset of seven patients who had circulating tumor cells with a higher ratio of N-terminal compared to C-terminal androgen receptors and so were likely to have the AR-V7 variant, six had favorable PSA responses to galeterone. This suggests that the presence of AR-V7 in circulating tumor cells does not preclude response to galeterone as has been shown to be the case for abiraterone and enzalutamide in independent clinical studies of those compounds,” Taplin said.

Based on the results demonstrated in ARMOR2 in patients with AR C-terminal loss and positive preclinical data in multiple AR-V7 models, Tokai Pharmaceuticals Inc., galeterone’s sponsor, expects to initiate ARMOR3-SV, an open-label phase III registrational trial in the first half of 2015.

In ARMOR3-SV, patients will be screened and those testing positive for AR-V7 will then be randomized to receive either galeterone or enzalutamide. The trial will have a primary endpoint of radiographic progression-free survival, with secondary endpoints that include overall survival, skeletal-related events and time to cytotoxic therapy.

Galeterone is an oral small molecule being developed for the treatment of CRPC that acts by actively disrupting AR signaling via multiple mechanisms of action.

Galeterone combines the mechanisms of action of CYP17 inhibition and androgen receptor antagonism with an additional mechanism of androgen receptor degradation.

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NCI CTEP-Approved Trials For the Month of November

The National Cancer Institute Cancer Therapy Evaluation Program approved the following clinical research studies last month. For further information, contact the principal investigator listed.

Phase II

9598: A Phase II Therapeutic Trial of the Use of Dabrafenib and Trametinib in Patients with BRAF V600E Mutation Positive Lesions in Erdheim Chester Disease. National Institutes of Health; Estrada-Veras, Juvianee Ibrahim. (301) 594-2952

9653: Phase II Trial of Gemcitabine-Eribulin (GE) in Cisplatin Ineligible Patients with Advanced or Unresectable Urothelial Carcinoma of the Bladder. University of California Davis Comprehensive Cancer Center P2C; Sadeghi, Sarmad. (323) 865-0553

9880: Haploidentical Donor Natural Killer (NK) Cell Infusion with Subcutaneous Recombinant Human IL-15 (rhIL-15) in Adults with Refractory or Relapsed Acute Myelogenous Leukemia. University of Minnesota Medical Center-Fairview; Miller, Jeffrey Steven (612) 624-0123

NRG-BN001: Randomized Phase II Trial of Hypofractionated Dose-Escalated Photon IMRT or Proton Beam Therapy Versus Conventional Photon Irradiation with Concomitant and Adjuvant Temozolomide in Patients with Newly Diagnosed Glioblastoma. NRG Oncology; Mehta, Minesh P. (410) 328-9629

NRG-HN002: A Randomized Phase II Trial for Patients with p16 Positive, Non-Smoking Associated, Locoregionally Advanced Oropharyngeal Cancer. NRG Oncology; Yom, Sue Sun (415) 353-7410

Other Phases

A151315: An Analysis of Baseline Serum NTx and BAP as Independent Predictors of Overall Survival and Risk of SREs. Alliance for Clinical Trials in Oncology; Saylor, Philip James. (617) 643-1763

ECOG-E2197F-ECOG-ICSC: Tumor MicroEnvironment of Metastasis (TMEM) and MenaCalc: Validation as Prognostic and Predictive Markers. ECOG-ACRIN Cancer Research Group; Sparano, Joseph Anthony (718) 904-2555

FDA News

Cyramza Combination Approved In Advanced Gastric Cancer

FDA approved Cyramza (ramucirumab) in combination with paclitaxel as a treatment for advanced or metastatic stomach or gastroesophageal junction adenocarcinoma whose cancer has progressed on or after prior fluoropyrimidine- or platinum-containing chemotherapy.

Cyramza now has two FDA approvals for these patients, following an approval in April of Cyramza as a single agent, and was previously granted an Orphan Drug Designation. The latest approval was based on the phase III RAINBOW trial, which compared Cyramza plus paclitaxel to placebo plus paclitaxel. Efficacy endpoints in the trial included overall survival, progression-free survival and objective response rate.

Cyramza is an anti-angiogenic therapy. It is a vascular endothelial growth factor receptor 2 antagonist that blocks the binding of VEGF receptor ligands VEGF-A, VEGF-C, and VEGF-D. Cyramza inhibited angiogenesis in an in vivo animal model.

RAINBOW was a multinational clinical trial initiated in 2010, which randomized 665 patients. Cyramza plus paclitaxel significantly extended median overall survival compared with placebo plus paclitaxel (9.6 months (95% CI: 8.5, 10.8) compared to 7.4 months (95% CI: 6.3, 8.4), respectively (HR=0.81 [95% CI: 0.68, 0.96]; P=0.017).

FDA approved the expanded use of Lymphoseek (technetium Tc 99m tilmanocept) injection for lymphatic mapping in solid tumors, and adding sentinel lymph node detection for breast cancer and melanoma to the approved indications.

The FDA also allowed expanded utilization of Lymphoseek with or without scintigraphic imaging, known as lymphoscintigraphy, to enable pre-operative imaging and mapping of lymph nodes to facilitate node localization during surgical procedures. Lymphoseek is developed by Navidea Biopharmaceuticals Inc.

Lymphoseek is the first and only FDA-approved radiopharmaceutical agent for sentinel lymph node detection, is the only FDA-approved agent for lymphatic mapping of solid tumors, and will be immediately available using existing reimbursement codes for this expanded population of cancer patients.

The expanded approval is supported by data from Navidea's combined analysis of Lymphoseek's

prospective phase III data in melanoma, breast cancer, and certain head and neck cancers from more than 500 subjects. Findings indicated that Lymphoseek accurately identified lymph nodes for assessment in the trial subjects, and is likely to be predictive of overall node pathology status.

FDA granted a Fast Track designation to MM-398 (nanoliposomal irinotecan injection) for the treatment of patients with metastatic adenocarcinoma of the pancreas who have been previously treated with gemcitabine-based therapy.

Fast Track is designed by the FDA to facilitate and expedite the development and review of drugs that treat serious conditions and fill an unmet medical need.

Merrimack is currently preparing a New Drug Application for the indication. Fast Track designation allows sections of the NDA to be submitted to the FDA as they are completed.

According to Merrimack, the company expects to initiate the NDA submission in 2014 with the goal of completing the NDA submission late in the first quarter or early in the second quarter of 2015.

FDA and the European Medicines Agency have granted MM-398 orphan drug designation in metastatic pancreatic cancer.

MM-398 is a nanoliposomal encapsulation of the chemotherapeutic irinotecan. MM-398 has demonstrated extended circulation in comparison to free irinotecan in the clinical setting. The activated form of irinotecan is SN-38, which functions by inhibiting topoisomerase I and promoting cell death.

FDA granted Orphan Drug Designation to the JCAR015 chimeric antigen receptor product candidate, developed by Juno Therapeutics Inc., for the treatment of acute lymphoblastic leukemia. Phase I trials are currently underway at Memorial Sloan Kettering Cancer Center, Juno's collaboration partner.

All three of Juno's CAR T cell product candidates currently in trial, including JCAR015, are based on chimeric antigen receptor technology that employs the body's immune system to attack cancer cells.

JCAR017, in phase I/II trials at Seattle Children's Hospital, is being tested for pediatric and young adult relapsed/refractory CD19 positive leukemia.

JCAR014, currently in phase I/II trials at the Fred Hutchinson Cancer Research Center, is being tested for relapsed or refractory chronic lymphocytic leukemia, non-Hodgkin's lymphoma, and acute lymphoblastic leukemia.

FDA has opened a public docket and is requesting comments on proposed criteria for "first generic" abbreviated new drug application submissions.

The purpose is to facilitate FDA's establishment of review prioritization under the Generic Drug User Fee Amendments of 2012.

Establishing clear criteria for this review prioritization category will allow the agency to appropriately prioritize and track ANDA submissions.

Clear criteria for this category will also lead to less industry confusion and more consistent identification of first generic submissions, the agency said.

FDA is requesting comments and supporting information on the following criteria—a first generic application is any received ANDA:

(1) That is a first-to-file ANDA eligible for 180-day exclusivity, or for which there are no blocking patents or exclusivities; and

(2) for which there is no previously-approved ANDA for the drug product.

FDA believes that these proposed criteria appropriately focus FDA's resources on approving as quickly as possible, new safe and effective generic drug products for patient use.

The agency said these criteria enable it to prioritize review of a pending ANDA when the date on which the ANDA can be approved alters due to changes in the patent or exclusivity landscape.

Under these proposed criteria, first generic status is predicated largely on circumstances outside agency control, and ones that may change while the ANDA is pending, for example, developments related to the disposition of related patent litigation.

FDA also is seeking comments and supporting information on mechanisms the agency could put in place to facilitate ANDA sponsor submission of such relevant information in a timely manner, in addition to that already required under the regulations.

As a result of such developments, ANDA submissions that originally met the criteria for a first generic submission may no longer meet those criteria, the agency said. For example, the validity of a patent may be upheld in litigation, thereby blocking approval until patent expiration.

The agency is therefore seeking comment on whether it should change the review prioritization for an ANDA that no longer meets the first generic criteria during its review.

Comments must be submitted by Dec. 19. Electronic comments can be submitted to the federal eRulemaking Portal: <http://www.regulations.gov>.