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Investigation of TAS-102 in Colorectal Cancer Includes Findings on Neutropenia

Results of phase 1, 2, and 3 studies of TAS-102 in patients with colorectal cancer (CRC) were presented at a poster session at the 2016 annual meeting of the American Society of Clinical Oncology, Chicago. TAS-102 is an orally available combination of the antineoplastic thymidine-based nucleoside analogue trifluridine with a thymidine phosphorylase inhibitor, tipiracil. Trifluridine/tipiracil has been approved for patients with previously treated metastatic CRC (mCRC) in the United States,¹ Europe,² and Japan.³

Role of Neutropenia in Response to TAS-102

Atsushi Ohtsu, MD, PhD, National Cancer Center Hospital East, Kashiwa, Japan, and colleagues reported on the onset of neutropenia as an indicator of treatment

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Checkpoint Inhibitors Tolerable in Patients With Recurrent Glioblastoma

The prognosis for patients with glioblastoma (GBM) is poor; the disease often recurs after initial treatment, and there are no effective therapeutic options that prolong survival in patients with recurrent or progressive disease. Therefore, new therapeutic approaches are needed. During a poster session at ASCO, David A. Reardon, MD, Dana-Farber Cancer Institute and Harvard University School of Medicine, Boston, Massachusetts, presented updated results of a trial of checkpoint inhibitors in patients with recurrent GBM. The primary objective of this study, CheckMate-143

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Investigation of TAS-102 in Colorectal Cancer Includes Findings on Neutropenia

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response in the phase 3 RECURSE trial of TAS-102 versus placebo in patients with mCRC.⁴ The RECURSE trial (NCT01607957) enrolled patients with mCRC who had received 2 or more prior lines of therapy and randomly assigned them 2:1 to TAS-102 at 35 mg/m² twice daily or to placebo on days 1 to 5 and 8 to 12 of each 28-day cycle. All patients also received best supportive care. TAS-102 was associated with a significant improvement compared with placebo in overall survival (OS) (7.1 months vs 5.3 months; hazard ratio [HR], 0.68; *P* < .001) and progression-free survival (PFS) (2.0 months vs 1.7 months; HR, 0.48; *P* < .001).

Neutropenia occurs commonly in patients treated with TAS-102 and appears to be dose dependent. Greater-grade neutropenia appears to be associated with improved OS. The objectives of this post hoc analysis were to explore the association of neutropenia with the pharmacokinetics (PK) of and response to TAS-102 and the effect of treatment delay on outcome.

There were 138 patients treated with TAS-102 who had evaluable PK data of the 534 total TAS-102-treated population. Grade 3 or greater neutropenia was associated with significantly longer median OS and PFS regardless of the timing of onset (TABLE 1⁴). Any grade of neutropenia was also associated with better survival outcomes.

There was no correlation between PK parameters and onset of neutropenia. Treatment delays or dose reductions due to adverse events (AEs) were more likely to occur in patients receiving TAS-102 (54%) than placebo (14%) and were

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more likely to occur in patients with grade 3 or greater neutropenia. Patients in Japan were more likely than those in other regions to experience dose delays. Delays in TAS-102 treatment were associated with better OS and PFS and were attributed to the onset of grade 3 or greater neutropenia. Median OS was 10.1 to 17.3 months for TAS-102-treated patients with grade 3 or greater neutropenia and treatment delays, versus 4.9 months in treated patients with grade 3 or greater neu-

tropenia and no treatment delay; median OS was 5.3 months in placebo-treated patients. Median PFS was 3.7 to 5.8 months for TAS-102-treated patients with grade 3 or greater neutropenia and treatment delays, versus 1.8 months in treated patients with grade 3 or greater neutropenia and no treatment delay; median PFS was 1.7 months in placebo-treated patients.

The study authors concluded that prospective studies are needed to determine the correlation of TAS-102 PK parameters with the timing of neutropenia onset and treatment response.

The association of onset of neutropenia in Japanese patients with mCRC who were treated with TAS-102 (*n* = 112) versus placebo (*n* = 57) was also subjected to

TABLE 1. Earliest Onset of Grade ≥3 Neutropenia and Outcomes⁴

| Earliest Cycle of Grade ≥3 Neutropenia Onset in TAS-102 Arm | TAS-102/ Placebo Median PFS, mo | Hazard Ratio (95% CI) | TAS-102/ Placebo Median OS, mo | Hazard Ratio (95% CI) |
|---|---------------------------------------|--------------------------|--------------------------------------|--------------------------|
| 1 | 3.7/1.7 | 0.35 (0.25-0.48) | 9.7/5.3 | 0.45 (0.32-0.64) |
| 2 | 3.7/1.8 | 0.34 (0.25-0.46) | 8.7/6.3 | 0.56 (0.41-0.78) |
| ≥3 | 6.5/3.7 | 0.32 (0.18-0.56) | 13.8/10.2 | 0.36 (0.17-0.75) |
| None | 1.9/1.7 | 0.69 (0.58-0.82) | 5.5/5.3 | 0.97 (0.81-1.16) |

OS, overall survival; PFS, progression-free survival.

TABLE 2. Renal and Hepatic Function and Outcomes⁷

| | TAS-102 Versus Placebo: OS HR (95% CI) | Any TAS-102- Related Grade ≥3 AE, n (%) | Any TAS-102- Related SAE, n (%) | All TAS-102 Dose Reductions, n (%) |
|---|--|---|---------------------------------------|--|
| Hepatic | | | | |
| Normal | 0.63 (0.50-0.80) | 171/325 (52.6) | 25/325 (7.7) | 55/325 (16.9) |
| Mild G1 (total bilirubin ≤ULN and AST >ULN) | 0.71 (0.53-0.95) | 71/169 (42) | 20/169 (11.8) | 16/169 (9.5) |
| Mild G2 (total bilirubin >1 to 1.5 × ULN and any AST) | 0.44 (0.21-0.92) | 18/34 (52.9) | 5/34 (14.7) | 2/34 (5.9) |
| Renal | | | | |
| Normal (CrCL ≥90 mL/min) | 0.64 (0.51-0.81) | 138/306 (45.1) | 28/306 (9.2) | 33/306 (10.8) |
| Mild (CrCL 60-89 mL/min) | 0.71 (0.53-0.96) | 94/178 (52.8) | 16/178 (9.0) | 29/178 (16.3) |
| Moderate (CrCL 30-59 mL/min) | 0.85 (0.47-1.56) | 29/47 (61.7) | 6/47 (12.8) | 11/47 (23.4) |

AE, adverse event; AST, aspartate aminotransferase; CrCL, calculated creatinine clearance; G, grade impairment; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; SAE, serious adverse event; ULN, upper limit of normal.

a post hoc analysis of a phase 2 trial (Study J003-10040030; 090880) by Tomohiro Nishina, MD, PhD, National Hospital Organization Shikoku Cancer Center, Matsuyama, Japan, and colleagues.⁵ Results were similar to those reported for the RE-COURSE trial. Patients experiencing early-onset grade 3 or greater neutropenia had a longer median OS than did those treated with placebo. Patients who did not experience grade 3 or greater neutropenia did not have a survival benefit.

The authors concluded that grade 3 or greater neutropenia might become a predictive biomarker for response to TAS-102. Treatment with TAS-102 should not be discontinued permanently if grade 3 or greater neutropenia occurs.

Another abstract on the role of neutropenia in treatment with TAS-102 was accepted for publication only⁶; data were not presented at the meeting. In the abstract, Pashtoon M. Kasi, MD, Mayo School of Graduate Medical Education, Rochester, Minnesota, and colleagues discussed a cohort study of the association of chemotherapy-induced neutropenia at

1 month (CIN-1) and OS in patients receiving TAS-102 for refractory mCRC. The cohort included data from 3 centers in the United States and 1 in Japan on CIN, defined as a neutrophil count decrease of grade 2 or greater (absolute neutrophil count <1500/mm³).

Neutrophil assessments at 1 month were available for 149 patients. Patients who developed grade 2 or greater CIN-1 had a longer PFS (median, 3.0 months vs 2.4 months; *P* = .01) and OS (14.0 months vs 5.6 months, *P* <.0001). Only CIN-1 (adjusted HR, 0.21; 95% CI, 0.11-0.38) and higher baseline carcinoembryonic antigen levels (adjusted HR, 2.00; 95% CI, 1.22-3.35) were independent predictors of OS. Furthermore, CIN-1 was a statistically significant predictor of OS over a wide range of cut-offs.

The authors concluded that the occurrence of neutropenia after starting TAS-102 was associated with a better prognosis in patients with refractory mCRC. They also suggested that, to achieve better outcomes in patients not experiencing any

neutropenia, the dose of TAS-102 might be increased. Further investigation is needed in this area.

TAS-102 in Renal and Hepatic Impairment

Robert J. Mayer, MD, Dana-Farber Cancer Institute, Boston, Massachusetts, and colleagues presented a poster that included data on the efficacy and safety results in patients with impaired renal and hepatic function in the RECOURSE trial (NCT01607957).⁷ In this analysis, patients were classified by hepatic and renal function. Renal function was classified according to calculated creatinine clearance. OS and AE results are summarized in **TABLE 2**⁷.

OS and PFS benefits were seen for patients with normal and mild renal and hepatic impairment who were treated with TAS-102 compared with placebo. Patients with moderate renal impairment treated with TAS-102 did not have an OS benefit and had a higher rate of grade 3 or greater AEs compared with patients with normal or mild renal impairment, although these patients did have improved PFS and disease-control rates.

The authors attribute the lack of OS benefit to small numbers of patients or presence of comorbidities.

Ongoing Study of TAS-102 in Combination With Nintedanib

Yasutoshi Kuboki, MD, Department of Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan, presented a Trials in Progress poster⁸ on a multicenter phase 1/2 study of TAS-102 with nintedanib in patients with mCRC refractory to standard therapies (N-TASK FORCE; EPOC1410; 000017114).

Nintedanib is a triple angiokinase inhibitor of vascular endothelial growth factor receptors, platelet-derived growth factor A, beta receptors, and fibroblast growth factor receptors. It is being investigated as monotherapy versus placebo in a phase 3 study in mCRC refractory to standard therapies (LUME-Colon 1; NCT02149108). Based on encouraging safety and activity, the phase 1/2 study of TAS-102 plus nintedanib was initiated to assess the efficacy and safety of the combination. This study is an open-label, single-arm, multicenter trial. Part 1 will determine the recommended phase 2 dose of the combination. Phase 2 is expected to enroll 52 patients at this dose.

Patients with mCRC refractory or intolerant to fluoropyrimidine, irinotecan, oxaliplatin, anti-angiogenesis inhibitor, and anti-epidermal growth factor receptor antibody (if wild-type Ras) and without prior regorafenib and TAS-102; at least 1 measurable lesion; and adequate performance status will be enrolled. The primary end point is PFS at 16 weeks; secondary end points include OS, PFS, response, safety, and PK parameters. The dose of nintedanib will be escalated from

150 mg twice daily to 200 mg twice daily with a fixed dose of TAS-102 (35 mg/m² twice daily on days 1 to 5 and 8 to 12 of each 28-day cycle). Enrollment is ongoing. •

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Checkpoint Inhibitors Tolerable in Patients With Recurrent Glioblastoma

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(NCT02017717), was to evaluate the safety and tolerability of nivolumab monotherapy and nivolumab in combination with ipilimumab in patients with recurrent GBM.

Checkpoint inhibition with the anti-programmed death-1 monoclonal antibody nivolumab and the anti-cytotoxic T-lymphocyte antigen-4 monoclonal antibody ipilimumab has shown activity in several tumor types, including brain metastases from melanoma in human patients, and in preclinical models of GBM.

Patients with a first recurrence of histologically confirmed grade 4 malignant glioma after prior treatment with radiotherapy and temozolomide, with no prior bevacizumab treatment, were eligible for CheckMate-143. Cohort 1 included patients randomly assigned to nivolumab monotherapy 3 mg/kg every 2 weeks (n = 10) or to nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks for 4 doses followed by nivolumab 3 mg/kg every 2 weeks (n = 10). In cohort 1b, which was non-randomized, patients received nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 3 weeks for 4 doses, then nivolumab 3 mg/kg every 2 weeks (n = 20).

Treatment continued until progressive disease occurred, or for as long as it was tolerated and the investigator determined there was benefit. Safety and tolerability were assessed after patients had completed 4 doses of study treatment. Adverse events (AEs) were assessed during treatment and for a minimum of 100 days after the last dose. The biomarker programmed death ligand-1 (PD-L1) was measured in pre-treatment tumor biopsy specimens by immunohistochemistry. Patients were followed for responses at the end of weeks 6 and 12 and every 8 weeks thereafter until disease progression or discontinuation. Overall survival (OS) was assessed every 3 months.

Cohorts were fairly well matched for baseline patient demographics and disease characteristics, given the small numbers in cohorts 1 and 1b. Most patients had quantifiable PD-L1 expression at baseline. The most common reason for study discontinuation was disease progression (75% in cohort 1, 50% in cohort 1b). As of the database lock in February 2016, 3 patients in the nivolumab monotherapy group were continuing on the study, and all 10 patients receiving nivolumab 1 mg/kg plus ipilimumab 3 mg/kg had died. Four patients in cohort 1b were continuing on the study, and 16 had died.

No new or unexpected safety signals were observed. There were no grade 3 or higher treatment-related AEs (TRAEs) in the nivolumab monotherapy arm. In the nivolumab 1 mg/kg plus ipilimumab 3 mg/kg arm, there were 7 treatment-related serious AEs (TRSAEs). In the nivolumab 3 mg/kg plus ipilimumab 1 mg/kg arm, there were 2 TRSAEs.

TRAEs with a potential immunologic cause occurred in each arm. In the nivolumab monotherapy arm there were 5 grade 2 or higher potentially immunologic TRAEs. In the nivolumab 1 mg/kg plus ipilimumab 3 mg/kg arm there were 10 potentially immunologic TRAEs, of which 6 were grade 3 or higher. In cohort 1b there were 14 potentially immunologic TRAEs, of which 3 were grade 3 or higher.

One patient in the nivolumab monotherapy arm had a partial response. Progression-free survival and OS are summarized in the **TABLE**. Median follow-up time was not specified.

The AEs seen in this study were consistent with those observed for nivolumab and ipilimumab in other studies, and no new safety signals were observed. The toxicity of nivolumab 3 mg/kg was lower than that of nivolumab combined with ipilimumab. The combination of nivolumab 3 mg/kg plus ipilimumab 1 mg/kg was more tolerable than nivolumab 1 mg/kg plus ipilimumab 3 mg/kg.

Nicholas A. Butowski, MD, Department of Neurological Surgery, University of California, San Francisco, who discussed this poster in the context of early-phase clinical trials, called the results encouraging.

Ongoing studies to further investigate nivolumab in GBM include the randomized phase 3 portion of CheckMate-143, evaluating the efficacy and safety of nivolumab versus bevacizumab in previously treated GBM, and a trial of nivolumab in combination with radiotherapy versus temozolomide plus radiotherapy in newly diagnosed GBM. •

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TABLE. Progression-Free Survival and Overall Survival

| | Cohort 1 | | Cohort 1b |
|---------------------------------|----------------------|------------------------------------|------------------------------------|
| | Nivo 3 mg/kg, n = 10 | Nivo 1 mg/kg + ipi 3 mg/kg, n = 10 | Nivo 3 mg/kg + ipi 1 mg/kg, n = 20 |
| PFS, median (95% CI), mo | 1.9 (1.3-6.5) | 2.1 (0.5-3.0) | 2.4 (1.4-4.7) |
| OS, median (95% CI), mo | 10.5 (4.1-NE) | 9.3 (4.0-12.7) | 7.3 (4.8-13.0) |
| OS, 1-y rate (95% CI) | 40% (12.3-67) | 30% (7.1-57.8) | 35% (15.7-55.2) |

ipi, ipilimumab; NE, not estimable; nivo, nivolumab; OS, overall survival; PFS, progression-free survival.

Ibrutinib Safe and Effective in CLL/SLL Regardless of Prior Lines of Therapy

Ibrutinib, a first-in-class oral inhibitor of Bruton’s tyrosine kinase, has been approved for the treatment of patients with chronic lymphocytic leukemia (CLL)/small lymphocytic leukemia (SLL), mantle cell lymphoma, and Waldenström macroglobulinemia.¹ Ibrutinib has been shown to be effective in phase 3 studies in previously treated and untreated CLL/SLL, although there have been suggestions that outcomes may be affected by prior lines of therapy.

During a poster session at ASCO, Susan M. O’Brien, MD, University of California Irvine, Irvine, California, presented an analysis of the outcomes of ibrutinib by line of therapy in patients with CLL from 2 phase 3 trials.² The objective of this analysis was to evaluate outcomes of ibrutinib treatment based on prior lines of therapy and following discontinuation in patients with CLL.

The phase 3 trials were RESONATE (PCYC-1112; NCT01578707) in previously treated CLL and RESONATE-2 (PCYC-1115/16; NCT01722487) in patients aged 65 years or older with treatment-naïve CLL. Patients with deletion 17p were excluded from the analysis. Subgroups were defined by the number of prior lines of therapy (0, 1, 2, and ≥3). End points included progression-free survival (PFS), overall survival (OS), OS from time of ibrutinib discontinuation, overall response rate (ORR), and adverse events (AEs).

In RESONATE (PCYC-1112), patients with CLL/SLL and 1 or more prior lines of therapy were randomly assigned to ibrutinib 420 mg orally once daily until progressive disease (PD) or unacceptable toxicity (n = 195) or to ofatumumab 300 mg intravenously followed by 11 doses of 2000 mg over 24 weeks (n = 196). Following PD, 131 patients in the ofatumumab arm crossed over to ibrutinib.

In RESONATE-2, patients with treatment-naïve CLL/SLL who were aged 65 years or older were randomly assigned to ibrutinib 420 mg orally once daily until PD or unacceptable toxicity (n = 136) or to chlorambucil 0.5 mg/kg to a maximum of 0.8 mg/kg on days 1 and 5 of a 28-day cycle for up to 12 cycles (n = 133). Following PD, 43 patients in the ofatumumab arm crossed over to ibrutinib.

Previously treated patients had a median of 3 prior lines of therapy; most patients had received prior anti-CD20 antibody (93%), purine analogue (87%), or alkylating agents (93%, including bendamustine, 41%). Median OS was not reached for either treatment-naïve or previously treated patients; median PFS was not reached except for those in the subgroup with 3 or more prior lines of therapy, for whom median PFS was 31.7 months. Median PFS was not reached for any patients with deletion 11q, regardless of the number of prior lines of therapy. Patient age, follow-up times, and efficacy by treatment subgroup are summarized in the [TABLE](#).² Median OS after ibrutinib discontinuation was not reached for those receiving ibrutinib as first- or second-line therapy; it was 7 to 9 months for those who received ibrutinib for higher lines of therapy. However, patient numbers are small in these subgroups. Survival after ibrutinib discontinuation for those with ibrutinib as the third or higher line was worse if discontinuation was due to PD than if it was due to AEs, but again, the numbers are small and follow-up times are relatively short.

Complete response (CR) rates increased over time for all subgroups. Most patients who had baseline anemia or thrombocytopenia experienced improvements in these parameters with treatment, independent of prior lines of therapy. Red blood cell and platelet transfusions, neutrophil growth factors, and intravenous immunoglobulin were used more commonly in the subgroups of patients receiving ibrutinib as the third or higher line of therapy.

The AE profile was similar in treatment-naïve and previously treated patients. AEs of interest that were grade 3 or higher included infections (21% and 34% in treatment-naïve and previously treated patients, respectively), major hemorrhage (4% and 5%, respectively), atrial fibrillation (2% and 6%, respectively), neutropenia (10% and 23%, respectively), and anemia (7% and 8%, respectively).

TABLE. Results by Prior Lines of Therapy²

| | Subgroups by Prior Lines of Therapy (N = 271), Lines (n) | | | |
|------------------------------|--|------------|------------|-------------|
| | 0 (n = 136) | 1 (n = 27) | 2 (n = 41) | ≥3 (n = 67) |
| Median age, y (range) | 73 (65-89) | 64 (30-85) | 66 (46-86) | 67 (44-83) |
| Median follow-up, mo | 22 | 30 | 31 | 30 |
| 2-y PFS rate | 92% | 89% | 80% | 69% |
| 30-mo OS rate | 97% | 93% | 83% | 82% |
| ORR (with PR-L) | 91% | 100% | 93% | 88% |

ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR-L, partial response with lymphocytosis.

AEs led to discontinuation at a similar rate across subgroups. No Richter transformation was observed in treatment-naïve patients; 8 previously treated patients discontinued treatment because of Richter transformation. Patients who received ibrutinib as an earlier line of therapy were less likely to discontinue as a result of PD. AEs leading to ibrutinib dose reductions in at least 3 patients included neutropenia, atrial fibrillation, and diarrhea.

The study authors concluded that ibrutinib treatment for CLL/SLLs is associated with favorable PFS, OS, and ORR regardless of prior lines of therapy. Patients receiving ibrutinib as first-line therapy had higher CR rates, less PD, less frequent AEs, and improved survival after discontinuation of ibrutinib

than did patients receiving ibrutinib after prior therapy. Further follow-up is needed to determine the effects of subsequent and salvage therapies after ibrutinib discontinuation. •

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Subcutaneous Administration of Daratumumab for Myeloma Under Investigation

Daratumumab is a first-in-class anti-CD38 monoclonal antibody that has been approved in the United States for the treatment of patients with multiple myeloma (MM) who have received at least 3 prior lines of therapy, including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD),¹ and in Europe for the treatment of relapsed and refractory MM previously treated with a PI and an IMiD that progressed on the last therapy.² Daratumumab is administered via intravenous (IV) infusion, which can take several hours. A more rapid method of administration might reduce administration costs and improve patient adherence and quality of life.

During a poster session at ASCO, Hareth Nahi, MD, PhD, Karolinska Institute and the Department of Medicine, Karolinska University Hospital, Huddinge, Sweden, described an open-label, dose-escalation phase 1b study of subcutaneous (SC) daratumumab with recombinant human hyaluronidase in patients with relapsed or refractory multiple myeloma (MMY1004; PAVO; NCT02519452).³

Efficacy and safety data for daratumumab have been determined based on IV administration. The approved recommended dose and schedule for daratumumab is 16 mg/kg IV

weekly for 8 weeks, then once every 2 weeks for 16 weeks, then every 4 weeks. Recombinant human hyaluronidase (rHuPh20) temporarily breaks down the hyaluronan barrier in SC tissue, increasing the dispersion of locally injected biologics via lymphatic and capillary vessels, allowing drugs to be delivered via SC injection. SC formulations of therapeutic antibodies in combination with rHuPh20 have been approved in Europe.

This phase 1b study was designed to evaluate the safety, pharmacokinetics (PK), and anti-MM activity of SC daratumumab in patients with relapsed or refractory MM who have received 2 or more prior therapies and who have not received prior anti-CD38 antibodies, including daratumumab.

This ongoing open-label, dose-escalation study consists of 2 parts. In part 1, sequential cohorts of patients will be enrolled to select the SC dose of daratumumab for part 2. Approximately 8 patients will enroll in each sequential cohort treated with doses of daratumumab 1200 mg and rHuPh20 30,000 U SC, then daratumumab 1800 mg and rHuPh20 45,000 U SC (subsequent doses to be determined), given weekly in 28-day cycles in cycles 1 and 2, every 2 weeks in cycles 3 to 6, and every 4

A more rapid method of administration might reduce administration costs and improve patient adherence and quality of life.

weeks thereafter. In the absence of dose-limiting toxicity in more than 2 patients in cycle 1, patients will be assigned to the next dose cohort; up to 5 additional dose cohorts may be evaluated. PK and safety data will be used by a safety evaluation team to determine dose escalation and the recommended part-2 dose.

In part 2, patients will be randomly assigned either to SC daratumumab and rHuPh20 at the recommended part-2 dose (n = 40) or to IV daratumumab 1200 mg (n = 40) to evaluate the PK, safety, and efficacy of SC daratumumab.

To prevent or manage infusion-related reactions, pre- and postinfusion medications (eg, steroids, paracetamol/acetaminophen, montelukast, and antihistamines similar to those administered with IV daratumumab) will be given.

The primary end points include determination of the serum trough concentrations of daratumumab just prior to day 1 of cycle 3 and the safety profile of SC versus IV daratumumab. Secondary end points include the immunogenicity of the SC formulation, overall response rate, duration of response, and time to response. Approximately 128 patients will be enrolled at 12 sites in 6 countries. The first patient was enrolled in October 2015; patients have already been enrolled in 5 countries.

Dr Nahi implied that the part-2 dose may already have been determined. However, the estimated primary completion date for the primary outcome measures is January 2017.⁴ •

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Practice-Changing Results Presented at Plenary Session

Late-breaking abstracts (LBAs) presented at the plenary session at ASCO were selected from more than 5000 abstracts for having the greatest potential to affect patient care, according to Julie M. Vose, MD, MBA, ASCO president. The presentations on prevention of breast cancer recurrence, treatment of elderly patients with glioblastoma, and double stem cell transplant for high-risk neuroblastoma are discussed here. Dr Vose noted that these studies show the power of collaboration between the United States and Canada.

Ten Years of Adjuvant Hormone Therapy Reduces the Risk of Breast Cancer Recurrence

Women with early-stage hormone-receptor-positive breast cancer face an indefinite risk of relapse, according to Paul E. Goss, MD, PhD, Massachusetts General Hospital, Boston, Massachusetts, who presented LBA1 on the randomized, phase 3, open-label clinical trial CCTG MA.17R, extending adjuvant le-

trozole for 5 years after completing an initial 5 years of aromatase inhibitor (AI) therapy, alone or preceded by tamoxifen, in postmenopausal women with early-stage breast cancer.

Adjuvant tamoxifen therapy for 5 years was shown to improve 15-year disease-free survival (DFS), but not overall survival (OS), compared with placebo in patients with hormone-receptor-positive, node-negative breast cancer.¹ In the precursor CCTG MA.17 trial, AI for 5 years after tamoxifen also improved DFS but not OS, with a 48% reduction in recurrences and a 39% reduction in mortality.^{2,3}

The CCTG MA.17R trial (NCT00754845) enrolled postmenopausal women who had hormone-receptor-positive breast cancer, had completed approximately 5 years of adjuvant AI therapy and any prior duration of tamoxifen, and had a minimum life expectancy of at least 5 years. The results of this trial were published in conjunction with the plenary presentation.⁴ Patients (n = 1918) were randomly

assigned to either letrozole 2.5 mg daily (n = 959) or placebo (n = 959) for 5 years. The trial aimed to determine whether extending AI from 5 to 10 years further improved patient outcomes. The primary objective was DFS from random assignment to time of recurrence or development of contralateral breast cancer (CBC). Secondary objectives included OS, all CBC, safety, and quality of life (QoL). Because the event rate was lower than expected, the trial was amended from an event-based to a time-based primary analysis.

Baseline characteristics between treatment groups were well balanced. At a median follow-up of 6.3 years, the 5-year DFS was 95% for the letrozole arm and 91% for the placebo arm (hazard ratio [HR], 0.66; $P = .01$), for a 34% reduction in recurrences. Most of the events were distant recurrences. There was a 58% reduction in CBC for the letrozole arm (HR, 0.42; $P = .007$). DFS by prespecified subgroups (including nodal status, prior chemotherapy, last dose of AI to randomization, years on tamoxifen, and duration of AI therapy) all favored the letrozole arm. As in previous AI trials, there was no significant difference in OS at a median follow-up of 6.3 years.

No new toxicities were reported. Bone pain, elevated alkaline phosphatase levels, and elevated alanine aminotransferase levels were significantly higher in the letrozole arm. Bone fractures were significantly higher in the letrozole arm (14%) than in the placebo arm (9%, $P = .001$), as was new-onset osteoporosis (11% vs 6%, $P < .0001$).

There were no differences in patient-reported QoL scores between the 2 groups except for a small difference in favor of placebo for the Short Form 36 Health Survey Role physical-function subscale, which measures difficulty accomplishing work or other physical activity. However, the difference was smaller than the minimum difference for clinical significance. The QoL findings were presented in greater detail in another session.⁵

Dr Goss concluded that this is the first study to show the benefit of extending AI beyond 5 years, with a 34% reduction in disease recurrence with no worsening of QoL, although bone health remains an important consideration. Unlike other cancer therapies, AIs are readily accessible, so the benefits shown in this trial should benefit women with breast cancer worldwide.

Ian E. Smith, MD, Royal Marsden Hospital and Institute of Cancer Research, London, England, discussed this presentation. He said that for a small but important subgroup of women, there is a continuing risk of relapse up to at least 15 years after diagnosis. A small (3.2%) but significant group of these

patients has improved DFS with 10 years of AI compared with 5 years, usually after tamoxifen. Although no major toxicities have emerged with prolonged AI treatment and the reduction in CBC contributes significantly to the DFS benefit, he does not believe the data sustain a novel adjuvant therapy because the difference in distant recurrence is only 1.1% so far.

Dr Smith concluded that an algorithm for the risk of late relapse is needed so that patients who do not need prolonged therapy can avoid it. The data do not support continuing letrozole beyond 10 years, although he suggested discussing the data with patients with high-risk disease who can tolerate AI therapy to help them make a choice.

Chemoradiation With Temozolomide Prolongs Survival in Glioblastoma

Glioblastoma is the most common primary brain tumor, with an average age at diagnosis of 64 years. The pivotal trial establishing the best-practice therapy of surgical resection followed by 6 weeks of radiation combined with oral temozolomide chemotherapy enrolled few patients age 65 and older. LBA2, a randomized phase 3 study of temozolomide and short-course radiation versus short-course radiation alone in the treatment of newly diagnosed glioblastoma in elderly patients (CCTG CE.6; EORTC 26062-22061; TROG 08.02), reported results of the first study to combine temozolomide and radiation therapy in older adults.

James R. Perry, MD, Odette Cancer and Sunnybrook Health Sciences Centres, Toronto, Canada, who presented the results, said treating older patients with glioblastoma presents a challenge because the disease tends to be more aggressive and patients are frailer, have comorbidities, and may have less access to care and caregivers. Older patients tend to receive less aggressive surgery, less radiotherapy, and less chemotherapy, even though up to 40% of tumors have MGMT promoter methylation, which is linked to better response to chemotherapy and longer survival.

CCTG CE.6 enrolled patients aged 65 years and older with newly diagnosed glioblastoma. Patients were randomly assigned to radiotherapy of 40 Gy in 15 fractions over 3 weeks (n = 281) or to radiotherapy plus temozolomide 75 mg/m² daily from the first to last day of radiotherapy plus temozolomide 150 to 200 mg/m² on days 1 to 5 of each 28-day cycle until disease progression or for a maximum of 12 cycles starting 4 weeks after the last radiotherapy dose (temozolomide maintenance, n = 281). The primary end point was

LBAs presented at the plenary session at ASCO were selected from more than 5000 abstracts for having the greatest potential to affect patient care.

TABLE 1. Responses in CCTG CE.6 Trial

| | Temozolomide Plus Radiotherapy | Radiotherapy | HR (95% CI) | P Value |
|---|--------------------------------|--------------|------------------|---------|
| Median OS | 9.3 mo | 7.6 mo | 0.67 (0.56-0.80) | <.0001 |
| Median PFS | 5.3 mo | 3.9 mo | 0.50 (0.41-0.60) | <.0001 |
| Median OS, unmethylated MGMT promoter | 10.0 mo | 7.9 mo | NA | NS |
| Median OS, methylated MGMT promoter | 13.5 mo | 7.7 mo | 0.53 (0.38-0.73) | <.0001 |
| Median PFS, unmethylated MGMT promoter | 4.8 mo | 4.4 mo | NA | NS |
| Median PFS, methylated MGMT promoter | 7.9 mo | 3.9 mo | 0.33 (0.23-0.47) | <.0001 |

HR, hazard ratio; NA, not applicable; NS, not significant; OS, overall survival; PFS, progression-free survival.

OS; secondary end points included progression-free survival (PFS), adverse events, QoL, and translational studies, including mandatory MGMT promoter status.

Toxicities were slightly milder than expected for temozolomide and were mostly grades 1 and 2. Baseline characteristics, including baseline QoL scores, were similar between treatment groups. Change scores between arms during treatment were similar for all functional QoL domains. In the combination group, change scores were significantly worse during the first week for nausea and vomiting and during all 3 weeks for constipation.

Responses are summarized in **TABLE 1**. Landmark analyses of OS at 12, 18, and 24 months all favor combination therapy.

Dr Perry concluded that the addition of temozolomide chemotherapy to standard short-course radiotherapy significantly improves PFS and OS in newly diagnosed elderly patients with glioblastoma. Nearly all patients were able to complete treatment, despite the potential for issues with mobility and access to treatment and caregivers. Patients with MGMT promoter methylation have the increased benefit of nearly doubled median survival. Dr Perry said he was surprised to see a clinical benefit in patients with unmethylated MGMT promoters as well, supporting the use of temozolomide plus radiotherapy as a new standard therapeutic option in nearly all elderly patients with glioblastoma.

Stuart A. Grossman, MD, Sidney Kimmel Cancer Center, Johns Hopkins, Baltimore, Maryland, discussed the glioblastoma trial. He pointed out that given the current average life span in the United States and Europe of about 80 years, the “elderly” subgroup of patients should probably not be defined with an age as young as 65 years. He suggested that the gold-standard treatment for glioblastoma is 60 Gy of radiotherapy plus temozolomide for 6 weeks followed by 6 months of temozolomide maintenance therapy. He also expressed con-

cern that the current study did not include a “best standard of care” arm and could have tested undertreatment. The current study did reinforce the importance of MGMT promoter methylation status for disease risk. Although Dr Grossman expressed concerns about late neurotoxicity with hypofractionated radiotherapy, this might not be a concern for patients with limited life expectancy.

Tandem Stem Cell Transplant Improves Outcomes for Children With High-Risk Neuroblastoma

Neuroblastoma is a tumor originating in the sympathetic neural crest, frequently in the adrenal gland, occurring in young children. Neuroblastoma accounts for more than 10% of childhood cancer mortality. Fewer than half of children with high-risk disease survive the current aggressive treatment modalities, which include induction with multi-agent chemotherapy, consolidation with autologous stem cell transplantation (ASCT), and postconsolidation immunotherapies. High-risk markers include age greater than 18 months and advanced-stage disease.

Julie R. Park, MD, Seattle Children’s Hospital, University of Washington, Seattle, Washington, presented LBA3, tandem myeloablative ASCT for high-risk neuroblastoma (Children’s Oncology Group ANBL0532). The rationale for the tandem transplant study was based on pilot studies showing tandem ASCT was tolerable and possibly effective and that early collection of stem cells in the neuroblastoma patient population was feasible.

The primary objective of ANBL0532 was to improve the 3-year survival of patients with high-risk neuroblastoma following treatment with tandem consolidation with thiopeta/cyclophosphamide followed by dose-modified carboplatin/etoposide/melphalan, compared with single consolidation with carboplatin/etoposide/melphalan.

The study enrolled patients with newly diagnosed, high-risk,

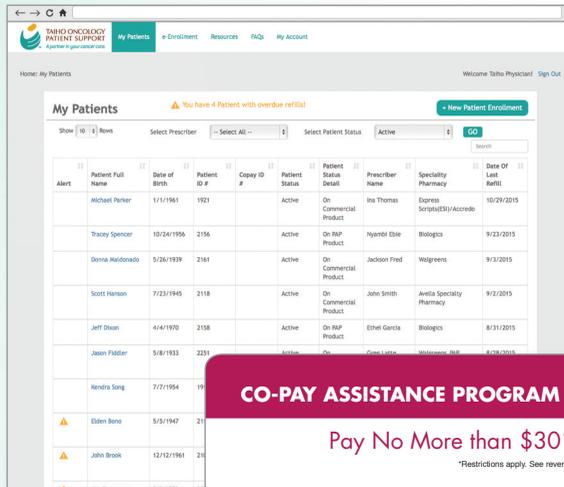


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Please see Important Safety Information and brief summary of Prescribing Information on the following pages.





Indication

LONSURF is indicated for the treatment of patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if *RAS* wild type, an anti-EGFR therapy.

Important Safety Information

WARNINGS AND PRECAUTIONS

Severe Myelosuppression: In Study 1, LONSURF caused severe and life-threatening myelosuppression (Grade 3-4) consisting of anemia (18%), neutropenia (38%), thrombocytopenia (5%), and febrile neutropenia (3.8%). One patient (0.2%) died due to neutropenic infection. In Study 1, 9.4% of LONSURF-treated patients received granulocyte-colony stimulating factors.

Obtain complete blood counts prior to and on day 15 of each cycle of LONSURF and more frequently as clinically indicated. Withhold LONSURF for febrile neutropenia, Grade 4 neutropenia, or platelets less than 50,000/mm³. Upon recovery, resume LONSURF at a reduced dose.

Embryo-Fetal Toxicity: LONSURF can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with LONSURF.

USE IN SPECIFIC POPULATIONS

Lactation: It is not known whether LONSURF or its metabolites are present in human milk. There are no data to assess the effects of LONSURF or its metabolites on the breast-fed infant or the effects on milk production. Because of the potential for serious adverse reactions in breast-fed infants, advise women not to breast-feed during treatment with LONSURF and for 1 day following the final dose.

Male Contraception: Advise males with female partners of reproductive potential to use condoms during treatment with LONSURF and for at least 3 months after the final dose.

Geriatric Use: Grade 3 or 4 neutropenia and thrombocytopenia and Grade 3 anemia occurred more commonly in patients 65 years or older who received LONSURF.

Renal Impairment: Patients with moderate renal impairment may require dose modifications for increased toxicity. No patients with severe renal impairment were enrolled in Study 1.

Hepatic Impairment: Patients with moderate or severe hepatic impairment were not enrolled in Study 1.

ADVERSE REACTIONS

Most Common Adverse Drug Reactions in Patients Treated With LONSURF (≥5%): The most common adverse drug reactions in LONSURF-treated patients vs placebo-treated patients with refractory mCRC, respectively, were asthenia/fatigue (52% vs 35%), nausea (48% vs 24%), decreased appetite (39% vs 29%), diarrhea (32% vs 12%), vomiting (28% vs 14%), abdominal pain (21% vs 18%), pyrexia (19% vs 14%), stomatitis (8% vs 6%), dysgeusia (7% vs 2%), and alopecia (7% vs 1%).

Additional Important Adverse Drug Reactions: The following occurred more frequently in LONSURF-treated patients compared to placebo: infections (27% vs 15%) and pulmonary emboli (2% vs 0%).

Interstitial lung disease (0.2%), including fatalities, has been reported in clinical studies and clinical practice settings in Asia.

Laboratory Test Abnormalities in Patients Treated With LONSURF: Laboratory test abnormalities in LONSURF-treated patients vs placebo-treated patients with refractory mCRC, respectively, were anemia (77% vs 33%), neutropenia (67% vs 1%), and thrombocytopenia (42% vs 8%).

Please see brief summary of Prescribing Information on the following pages.

Learn more at LONSURFhcp.com

LONSURF (trifluridine and tipiracil) tablets, for oral use
Initial U.S. Approval: 2015

Brief Summary of Prescribing Information

For complete Prescribing Information, consult official package insert.

1 INDICATIONS AND USAGE

LONSURF is indicated for the treatment of patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Severe Myelosuppression

In Study 1, LONSURF caused severe and life-threatening myelosuppression (Grade 3-4) consisting of anemia (18%), neutropenia (38%), thrombocytopenia (5%) and febrile neutropenia (3.8%). One patient (0.2%) died due to neutropenic infection. In Study 1, 9.4% of LONSURF-treated patients received granulocyte-colony stimulating factors.

Obtain complete blood counts prior to and on Day 15 of each cycle of LONSURF and more frequently as clinically indicated. Withhold LONSURF for febrile neutropenia, Grade 4 neutropenia, or platelets less than 50,000/mm³. Upon recovery resume LONSURF at a reduced dose. [see *Dosage and Administration (2.2) in the full Prescribing Information*]

5.2 Embryo-Fetal Toxicity

Based on animal studies and its mechanism of action, LONSURF can cause fetal harm when administered to a pregnant woman. Trifluridine/tipiracil caused embryo-fetal lethality and embryo-fetal toxicity in pregnant rats when orally administered during gestation at dose levels resulting in exposures lower than those achieved at the recommended dose of 35 mg/m² twice daily.

Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with LONSURF. [see *Use in Specific Populations (8.1, 8.3), Clinical Pharmacology (12.1) in the full Prescribing Information*]

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below are from Study 1, a randomized (2:1), double-blind, placebo-controlled trial in which 533 patients (median age 63 years; 61% men; 57% White, 35% Asian, 1% Black) with previously treated metastatic colorectal cancer received LONSURF as a single agent at a dose of 35 mg/m²/dose administered twice daily on Days 1 through 5 and Days 8 through 12 of each 28-day cycle. The mean duration of LONSURF therapy was 12.7 weeks.

The most common adverse drug reactions or laboratory abnormalities (all Grades and greater than or equal to 10% in incidence) in patients treated with LONSURF at a rate that exceeds the rate in patients receiving placebo were anemia, neutropenia, asthenia/fatigue, nausea, thrombocytopenia, decreased appetite, diarrhea, vomiting, abdominal pain, and pyrexia.

In Study 1, 3.6% of patients discontinued LONSURF for an adverse event and 13.7% of patients required a dose reduction. The most common adverse reactions leading to dose reduction were neutropenia, anemia, febrile neutropenia, fatigue, and diarrhea.

Table 1 Per Patient Incidence of Adverse Drug Reactions (≥5%) in Study 1 Occurring More Commonly (>2%) than in Patients Receiving Placebo.

| Adverse Reactions | LONSURF (N=533) | | Placebo (N=265) | |
|---|-----------------|-------------|-----------------|-------------|
| | All Grades | Grades 3-4* | All Grades | Grades 3-4* |
| Gastrointestinal disorders | | | | |
| Nausea | 48% | 2% | 24% | 1% |
| Diarrhea | 32% | 3% | 12% | <1% |
| Vomiting | 28% | 2% | 14% | <1% |
| Abdominal pain | 21% | 2% | 18% | 4% |
| Stomatitis | 8% | <1% | 6% | 0% |
| General disorders and administration site conditions | | | | |
| Asthenia/fatigue | 52% | 7% | 35% | 9% |
| Pyrexia | 19% | 1% | 14% | <1% |
| Metabolism and nutrition disorders | | | | |
| Decreased appetite | 39% | 4% | 29% | 5% |
| Nervous system disorders | | | | |
| Dysgeusia | 7% | 0% | 2% | 0% |
| Skin and subcutaneous tissue disorders | | | | |
| Alopecia | 7% | 0% | 1% | 0% |

*No Grade 4 definition for nausea, abdominal pain, or fatigue in National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03.

Table 2 Laboratory Test Abnormalities

| Laboratory Parameter | LONSURF (N=533*) | | | Placebo (N=265*) | | |
|---|------------------|-----|------|------------------|-----|-----|
| | Grade† | | | Grade† | | |
| | All % | 3 % | 4 % | All % | 3 % | 4 % |
| Blood and lymphatic system disorders | | | | | | |
| Anemia‡ | 77 | 18 | N/A# | 33 | 3 | N/A |
| Neutropenia | 67 | 27 | 11 | 1 | 0 | 0 |
| Thrombocytopenia | 42 | 5 | 1 | 8 | <1 | <1 |

*% based on number of patients with post-baseline samples, which may be less than 533 (LONSURF) or 265 (placebo)

† Common Terminology Criteria for Adverse Events (CTCAE), v4.03

‡ Anemia: No Grade 4 definition for these laboratory parameters in CTCAE, v4.03

One Grade 4 anemia adverse reaction based on clinical criteria was reported

In Study 1, infections occurred more frequently in LONSURF-treated patients (27%) compared to those receiving placebo (15%). The most commonly reported infections which occurred more frequently in LONSURF-treated patients were nasopharyngitis (4% versus 2%), and urinary tract infections (4% versus 2%).

In Study 1, pulmonary emboli occurred more frequently in LONSURF-treatment patients (2%) compared to no patients on placebo.

Additional Clinical Experience

Interstitial lung disease was reported in fifteen (0.2%) patients, three of which were fatal, among approximately 7,000 patients exposed to LONSURF in clinical studies and clinical practice settings in Asia.

7 DRUG INTERACTIONS

No pharmacokinetic drug-drug interaction studies have been conducted with LONSURF.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on animal data and its mechanism of action, LONSURF can cause fetal harm. LONSURF caused embryo-fetal lethality and embryo-fetal toxicity in pregnant rats when given during gestation at doses resulting in exposures lower than or similar to exposures at the recommended dose in humans. [see *Data*] There are no available data on LONSURF exposure in pregnant women. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Trifluridine/tipiracil was administered orally once daily to female rats during organogenesis at dose levels of 15, 50, and 150 mg/kg [trifluridine (FTD) equivalent]. Decreased fetal weight was observed at FTD doses greater than or equal to 50 mg/kg (approximately 0.33 times the exposure at the clinical dose of 35 mg/m² twice daily). At the FTD dose of 150 mg/kg (approximately 0.92 times the FTD exposure at the clinical dose of 35 mg/m² twice daily) embryolethality and structural anomalies (kinked tail, cleft palate, ectrodactyly, anasarca, alterations in great vessels, and skeletal anomalies) were observed.

8.2 Lactation

Risk Summary

It is not known whether LONSURF or its metabolites are present in human milk. In nursing rats, trifluridine and tipiracil or their metabolites were present in breast milk. There are no data to assess the effects of LONSURF or its metabolites on the breastfed infant or the effects on milk production. Because of the potential for serious adverse reactions in breastfeeding infants, advise women not to breastfeed during treatment with LONSURF and for one day following the final dose.

Data

Radioactivity was excreted in the milk of nursing rats dosed with trifluridine/tipiracil containing ¹⁴C-FTD or ¹⁴C-tipiracil (TPI). Levels of FTD-derived radioactivity were as high as approximately 50% of the exposure in maternal plasma an hour after dosing with trifluridine/tipiracil and were approximately the same as those in maternal plasma for up to 12 hours following dosing. Exposure to TPI-derived radioactivity was higher in milk than in maternal plasma beginning 2 hours after dosing and continuing for at least 12 hours following administration of trifluridine/tipiracil.

8.3 Females and Males of Reproductive Potential

Contraception

Females

LONSURF can cause fetal harm when administered to a pregnant woman. [see *Use in Specific Populations (8.1)*]

Advise females of reproductive potential to use effective contraception during treatment.

Males

Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use condoms during treatment with LONSURF and for at least 3 months after the final dose. [see *Nonclinical Toxicology (13.1) in the full Prescribing Information*]

8.4 Pediatric Use

Safety and effectiveness of LONSURF in pediatric patients have not been established.

Animal Data

Dental toxicity including whitening, breakage, and malocclusion (degeneration and disarrangement in the ameloblasts, papillary layer cells and odontoblasts) were observed in rats treated with trifluridine/tipiracil at doses greater than or equal to 50 mg/kg (approximately 0.33 times the exposure at the clinical dose of 35 mg/m² twice daily).

8.5 Geriatric Use

In Study 1, 533 patients received LONSURF; 44% were 65 years of age or over, while 7% were 75 and over. No overall differences in effectiveness were observed in patients 65 or older versus younger patients, and no adjustment is recommended for the starting dose of LONSURF based on age.

Patients 65 years of age or older who received LONSURF had a higher incidence of the following compared to patients younger than 65 years: Grade 3 or 4 neutropenia (48% vs 30%), Grade 3 anemia (26% vs 12%), and Grade 3 or 4 thrombocytopenia (9% vs 2%).

8.6 Hepatic Impairment

No dedicated clinical studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of LONSURF. No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin (TB) less than or equal to the upper limit of normal (ULN) and AST greater than ULN or TB less than 1 to 1.5 times ULN and any AST). Patients with moderate (TB greater than 1.5 to 3 times ULN and any AST) or severe (TB greater than 3 times ULN and any AST) hepatic impairment were not enrolled in Study 1. [see *Clinical Pharmacology (12.3) in the full Prescribing Information*]

8.7 Renal Impairment

No dedicated clinical studies have been conducted to evaluate the effect of renal impairment on the pharmacokinetics of LONSURF.

In Study 1, patients with moderate renal impairment (CL_{cr} = 30 to 59 mL/min, n = 47) had a higher incidence (difference of at least 5%) of ≥ Grade 3 adverse events, serious adverse events, and dose delays and reductions compared to patients with normal renal function (CL_{cr} ≥ 90 mL/min, n = 306) or patients with mild renal impairment (CL_{cr} = 60 to 89 mL/min, n = 178).

No dose adjustment to the starting dose of LONSURF is recommended in patients with mild or moderate renal impairment (CL_{cr} of 30 to 89 mL/min); however patients with moderate renal impairment may require dose modification for increased toxicity. No patients with severe renal impairment (CL_{cr} < 30 mL/min) were enrolled in Study 1. [see *Clinical Pharmacology (12.3) in the full Prescribing Information*]

8.8 Ethnicity

There were no clinically meaningful differences in Study 1 between Western and Asian subgroups with respect to overall incidence of adverse events or ≥ Grade 3 adverse events in either the LONSURF or placebo groups.

10 OVERDOSAGE

The highest dose of LONSURF administered in clinical studies was 180 mg/m² per day.

There is no known antidote for LONSURF overdose.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Severe Myelosuppression:

Advise the patient to immediately contact their healthcare provider if they experience signs or symptoms of infection and advise patients to keep all appointments for blood tests. [see *Warnings and Precautions (5.1)*]

Gastrointestinal toxicity:

Advise patients to contact their healthcare provider for severe or persistent nausea, vomiting, diarrhea, or abdominal pain. [see *Adverse Reactions (6.1)*]

Administration Instructions:

Advise the patient that LONSURF is available in two strengths and they may receive both strength tablets to provide the prescribed dose. Advise the patient of the importance of reading prescription labels carefully and taking the appropriate number of tablets.

Advise the patient to take LONSURF within 1 hour after eating their morning and evening meals. [see *Dosage and Administration (2.1) in the full Prescribing Information*]

Advise the patient that anyone else who handles their medication should wear gloves. [see *References (15) in the full Prescribing Information*]

Embryo-Fetal Toxicity:

Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with LONSURF. [see *Warnings and Precautions (5.2) and Use in Specific Populations (8.3)*]

Lactation:

Advise women not to breastfeed during treatment with LONSURF and for one day following the final dose. [see *Use in Specific Populations (8.2)*]

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TABLE 2. Event-Free Survival and Overall Survival Results After Single and Tandem ASCT

| | Single ASCT | Tandem ASCT | P Value |
|---|------------------|------------------|---------|
| 3-year EFS from randomization | 48.4% n = 179 | 61.4% n = 176 | .0081 |
| EFS for patients with INSS stage 4 disease who were older than 18 mo | 45.5% n = 136 | 59.1% n = 142 | .0083 |
| 3-year EFS for patients receiving immunotherapy | 56.0% n = 126 | 73.7% n = 120 | .0033 |
| 3-year OS for patients receiving immunotherapy | 74.4% n = 126 | 83.7% n = 120 | .0322 |

ASCT, autologous stem cell transplantation; EFS, event-free survival; INSS, International Neuroblastoma Staging System; OS, overall survival.

TABLE 3. Current Oncology Value Frameworks⁷⁻¹¹

| Value Framework | Core Question |
|---|---|
| ASCO Value Framework | What is the clinical benefit? Uses a scoring algorithm for clinical benefit, toxicity, tail of the survival curve, palliation, quality of life, and treatment-free interval, for a net health benefit score to be considered in relation to cost. |
| National Comprehensive Cancer Network (NCCN) Evidence Blocks | How do expert clinicians rate a treatment’s value? Takes into account efficacy, safety, the quality and quantity of evidence, consistency of evidence, and affordability. Currently available only for selected tumor types; in development for others. |
| Institute for Clinical and Economic Review (ICER) value assessment framework | What is the societal value of a therapeutic regimen? |
| DrugAbacus, developed at Memorial Sloan Kettering Cancer Center | What is the right price for a cancer drug? |
| European Society for Medical Oncology (ESMO) Magnitude of Clinical Benefit Scale | What is the clinical value in relation to cost? Includes evaluation forms for therapies that are potentially curative and those not likely to be. |

received isotretinoin or immunotherapy for postconsolidation; after additional trial results became available, all tandem transplant recipients received immunotherapy with isotretinoin plus the anti-GD2 antibody dinutuximab plus cytokines. The trial also included 27 patients with good-prognosis disease who were nonrandomly assigned to single ASCT.

There were no significant differences between treatment groups in baseline characteristics or grade 3 or higher nonhematologic toxicities. The 3-year OS was 71.5% for all randomly assigned patients, with a 3-year event-free survival of 54.8%. There was no significant difference in OS between treatment groups or for patients with International Neuroblastoma Staging System stage 4 disease who were older than 18 months, but the study was not powered to show a difference in OS. Other results are summarized in **TABLE 2**.

Dr Park concluded that tandem transplant consolidation improves outcome and does not increase toxicity or mortality in patients with high-risk neuroblastoma who survive induction without disease progression or severe induction-related toxicity. The benefit of tandem ASCT is maintained after anti-GD2-directed immunotherapy.

Using Oncology Value Frameworks

After the plenary abstract presentations, Deborah Schrag, MD, MPH, Harvard Medical School, Dana-Farber Cancer Institute, Boston, Massachusetts, discussed value frameworks in oncology and how they might help oncologists understand the plenary studies and quantify the value of the therapies presented.⁶ She noted that many studies presented at ASCO reveal small benefits at enormous costs. She called oncology drugs highly valued but unaffordable. The US average sales price for 1 month of chemotherapy for infused drugs was \$12,000 in 2015; the median annual household income is \$44,000 in the United States and \$1600 worldwide.

Dr Schrag asked, “How do we decide whether a cancer treatment is ‘worth it’ to a healthcare system given competing priorities on constrained resources? Value frameworks are intended to help with difficult decisions we wish we could avoid. The focus is on prioritization and policy setting, not individual decisions.”

Dr Schrag, who is a coauthor of the ASCO value framework, compared the core questions asked by 5 value frameworks that are currently available. These are summarized in **TABLE 3**.⁷⁻¹¹

Dr Schrag then evaluated the cancer regimens highlighted in the plenary session using 1 or more of these value frameworks. Tandem transplant for neuroblastoma scored very high for individual and health system values. She expected high-income countries would adopt this therapy and middle-income countries would seek to adopt it, although access to care will be a challenge. Temozolomide for glioblastoma in

metastatic neuroblastoma who were older than 18 months. Of 665 patients accrued, 13 were ineligible and 269 (40%) discontinued before randomization. After induction therapy, stem cell collection, and surgery, patients were randomly assigned to single (n = 179) or tandem (n = 176) ASCT, followed by postconsolidation with isotretinoin for patients receiving single transplant. Patients receiving tandem transplant initially

older patients has a moderate low health system value in the absence of MGMT promoter methylation. It will probably be adopted in high-income countries. The cost will be prohibitive for some middle-income countries. The individual value of extended AI for hormone-receptor-positive breast cancer is variable; the decision to adopt will be based on patient risk and tolerance. It has a low health system value. Dr Schrag suggested the priority should be to optimize adherence to the first 5 years of AI therapy.

Dr Schrag said that oncology value frameworks are not yet practical for clinical decision making at the bedside, in part because treatment costs vary enormously and exact figures are hard to obtain. She suggested that software tools may help, and ASCO is developing them. Nevertheless, she said that these types of deliberations cannot be ignored. The unaffordability of cancer treatment has adverse consequences, and there is a need to develop better policies to align care value with core values, including innovation, autonomy, compassion, and equity in healthcare.

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Biosimilars for Oncology Could Arrive in Near Future

Biologic agents are important in oncology and include cell therapies, cytokines, growth factors, and monoclonal antibodies. They are among the most expensive agents, driving the development of biosimilar drugs that are expected to cost less. Oncology biosimilars were first approved in Europe and India in 2007 and are now available in some parts of Europe, Australia, Asia, Russia, and India. Development and approval of biosimilars in the United States lags behind.¹

In the United States, biosimilars are biologic products that the FDA considers to be “highly similar” to a product that is already approved and licensed in the United States in terms of the safety, purity, and potency of the clinically active components. There can be minor differences in clinically inactive

components. This requires extensive characterization of the proposed biosimilar, including pharmacokinetic (PK) data in humans, and a confirmation that the safety, efficacy, and immunogenicity are similar to those of the reference product.²

There are currently no biosimilar oncology therapeutics available in the United States, and there is only 1 supportive agent, biosimilar filgrastim, approved in 2015. However, there are ongoing clinical trials of biosimilars, and these agents may be approved in the United States in the near future.

During ASCO, several presentations explored the use of biosimilars in oncology, including the education session “Biosimilars: Here and Now,” part of the Developmental Therapeutics and Translational Research Track,³ and a late-breaking presen-

tation⁴ and a poster⁵ on a proposed biosimilar to trastuzumab.

Steven J. Lemery, MD, MHS, session chair, associate acting-director, Division of Oncology Products, FDA, discussed regulatory approaches to biosimilar development. He noted that in addition to the filgrastim biosimilar approved last year, a biosimilar to infliximab, used in autoimmune diseases, was approved shortly thereafter; others are in development. A key feature of biosimilar development focuses on analytical similarity data. These include extensive physical characterization, including primary structure (that is, amino acid sequence), as well as higher-order structures, posttranslational modifications such as glycosylation, and functional characterization. Functional assays depend on the biologic agent and include binding assays and cell-based bioactivity assays. Also of interest are the presence of impurities and the stability of the biosimilar. These characterizations reflect the complexity of biologics and the fact that *biosimilar* does not mean *identical*.

Clinical data that can be required for approval include PK and pharmacodynamic (PD) comparisons in healthy volunteers, at least 1 clinical immunogenicity comparison, and a comparative clinical trial if residual uncertainties remain about the characterization, preclinical testing, or PK, PD, or immunogenicity data. The goal of a comparative clinical study would be to support equivalence (lack of clinically meaningful differences). Additional data are required for a biosimilar to be considered interchangeable in the United States—that is, be substitutable for another product by a pharmacist without the intervention of the healthcare provider.

The global view of biosimilars was presented by Martina Weise, MD, Federal Institute for Drugs and Medical Devices, Bonn, Germany, who discussed the European regulatory experience with biosimilars. Europe is ahead of the United States in biosimilar approval, with the first approval in 2006. There are now several supportive oncology drugs approved in Europe, and at least 1 anticancer agent Marketing Authorization Application under review for rituximab.

Comparability of a biosimilar to the reference product in Europe is based on characterizations similar to those required in the United States and can also be likened to the type of comparability required to ensure unchanged safety and efficacy for an approved biologic undergoing a manufacturing change process.

Francisco J. Esteva, MD, PhD, NYU Langone Medical Center, New York, New York, discussed the value and strategy for incorporating biosimilars into clinical practice. The proposed

biosimilars in development for oncology include those for trastuzumab (1 of which is discussed below), bevacizumab, rituximab, and cetuximab. Although the introduction of biosimilars is expected to result in healthcare savings, questions remain, including the level of acceptance by clinicians and patients

and coverage by payers. Lower costs could make these agents more readily available to more patients worldwide.

Dr Esteva noted that in addition to Myl-14010, a trastuzumab biosimilar already available in India, another trastuzumab biosimilar is available in South Korea, and others are in ongoing phase 3 trials. He suggested that although Myl-14010 is being tested in patients with HER2-positive metastatic breast cancer (MBC), the most “sensitive and homogeneous” population in whom to test biosimilar

monoclonal antibodies may be the neoadjuvant early-stage breast cancer population, in whom it may be easier to detect differences between the biosimilar and reference product. Some of the ongoing phase 3 trials of comparisons of trastuzumab biosimilars with trastuzumab are being conducted in early-stage breast cancer using pathologic complete response as a primary end point, which is acceptable for biosimilars.

However, although PK, PD, and immunogenicity are affected by prior treatment and the presence of metastatic disease, at least some of these data can be collected in healthy volunteers rather than patients. Because trastuzumab is used in different settings in combination therapy and as a single agent for maintenance therapy, biosimilar data may need to be collected in each type of clinical setting and disease stage. In addition, data from any breast cancer trial of a trastuzumab biosimilar may not be extrapolatable to gastric cancer.

Biosimilar Myl-14010 Is Comparable to Trastuzumab

The data presented at the meeting concerning the proposed trastuzumab biosimilar Myl-14010 illustrate the processes of preclinical and clinical analysis and testing that are essential for the development and approval of biosimilars.

During an oral abstract session on breast cancer, Hope S. Rugo, MD, University of California San Francisco, San Francisco, California, presented late-breaking abstract LBA503 on the Heritage study, a randomized, double-blind, phase 3 safety and efficacy trial of Myl-14010 versus trastuzumab.⁴ She emphasized that although trastuzumab has revolutionized the treatment of women with HER2-positive breast cancer, there is a global need for more available alternatives.

Myl-14010 is a proposed trastuzumab biosimilar based on

Biosimilars in development for oncology include those for trastuzumab, bevacizumab, rituximab, and cetuximab.

TABLE 1. Summary of Dose-Normalized Pharmacokinetic Results⁵

| | AUC _{0-last} (mcg • h/mL) | AUC _{0-∞} (mcg • h/mL) | C _{max} (mcg/mL) |
|---|---------------------------------------|------------------------------------|------------------------------|
| Arithmetic Mean (% CV) | | | |
| Myl-14010, n = 42 | 48,055 (15.92) | 48,241 (16.19) | 200.4 (12.34) |
| EU trastuzumab, n = 41 | 49,823 (19.61) | 50,075 (19.81) | 192.6 (14.13) |
| US trastuzumab, n = 37 | 49,826 (13.98) | 50,181 (13.86) | 197.9 (16.25) |
| LSMEANS Ratio^a (90% CI)^b | | | |
| Myl-14010/EU trastuzumab | 0.97 (91.31%-103.05%) | 0.97 (91.17%-102.97%) | 1.04 (99.00%-109.82%) |
| Myl-14010/US trastuzumab | 0.96 (90.34%-102.29%) | 0.96 (89.96%-101.94%) | 1.02 (96.42%-107.26%) |
| ^a Ratio (A/B) = e(LSMEANS of [LNA - LNB]); Ratio (A/C) = e(LSMEANS of [LNA - LNC]), where A = Myl-14010, B = EU trastuzumab, and C = US trastuzumab ^b Using natural log-transformed parameter. | | | |
| <small>AUC_{0-∞}, area under the concentration versus time curve from time of dosing to infinity; (AUC_{0-last}), area under the concentration versus time curve from time of dosing to time of last quantifiable concentration; C_{max}, maximum concentration; CV, coefficient of variation; LN, natural logarithm; LSMEANS, least squares means.</small> | | | |

physicochemical analyses and nonclinical, PK, and PD studies. It has been tested for quality attributes, including the presence of impurities, glycosylation, primary amino acid sequence, higher-order structure, and function of the Fab and Fc antibody domains. Preclinical studies have included cardiotoxicity in cardiomyocytes in culture and PK and toxicity studies in cynomolgus monkeys.

Furthermore, Myl-14010 has been investigated in clinical PK and PD studies, including a PK bioequivalence trial versus trastuzumab available in the United States and European Union. Results were presented at this meeting by Cornelius F. Waller, MD, University of Freiburg Medical Center, Freiburg, Germany.⁵ This was a single-center, randomized, double-blind, 3-arm, parallel-group, phase 1 study (NCT02594761) conducted in healthy adult-male volunteers. The primary objective was to establish PK similarity of 3 agents: Myl-14010, US trastuzumab, and EU trastuzumab. For the primary end point, the bioequivalence criterion was that the 90% CIs of the mean ratios of the area under the concentration versus time curve (AUC) from time of dosing to infinity (AUC_{0-∞}) and from time of dosing to time of last quantifiable concentration (AUC_{0-last}) and maximum concentration (C_{max}) fell within 80% to 125% calculated using natural log-transformed data. Secondary end points included additional PK parameters, safety (including immunogenicity), left ventricular ejection fraction (LVEF), and local tolerance.

Patients (n = 132) were randomly assigned to receive 1 of the agents (n = 44 per group) at 8 mg/kg over 90 minutes as an intravenous infusion. Of these, 120 were included in the statistical analysis. Key PK results are summarized in **TABLE**

1.⁵ These results confirm the PK bioequivalence of Myl-14010 versus EU trastuzumab and US trastuzumab.

All infusions were well tolerated with minimal local reactions. No serious adverse events (SAEs) were reported. Adverse events (AEs) that were mild or moderate in intensity were reported in 83 patients (227 events: 91 for Myl-14010, 80 for EU trastuzumab, and 56 for US trastuzumab). The most frequently reported AE was headache, in 27.3%, 29.5%, and 22.7% of patients, respectively. There were no differences in cardiac parameters between groups. No treatment-induced or enhanced antidrug antibodies were detected. The authors concluded that, in addition to demonstrating that the proposed biosimilar Myl-14010 is bioequivalent to US and EU trastuzumab, no significant safety signals were seen.

The Heritage study is a confirmatory, double-blind, randomized clinical trial (2011-001965-42) designed to evaluate comparative efficacy and safety of Myl-14010 versus trastuzumab in patients with HER2-positive MBC.⁴

Patients with centrally confirmed, measurable HER2-positive MBC who had not received prior chemotherapy or trastuzumab for metastatic disease were eligible. They were randomly assigned to receive either Myl-14010 or trastuzumab with standard-of-care docetaxel or paclitaxel for a minimum of 8 cycles in part 1, followed by antibody monotherapy maintenance in part 2.

Primary objectives included overall response rate (ORR) at week 24 for part 1 and safety, tolerability, and immunogenicity for part 2. Secondary end points in part 1 included progression-free survival (PFS), overall survival (OS), PK parameters, and safety (including immunogenicity); those

TABLE 2. Ratio of Overall Response Rates and Differences Between Overall Response Rates⁴

| ITT Part I Population | | |
|---|-------------------------------|--|
| | Myl-14010 + taxane n = 230 | Trastuzumab + taxane n = 228 |
| ORR, n (%) (95% CI) | 160 (69.6) (63.62-75.51) | 146 (64.0) (57.81-70.26) |
| Ratio of ORR: Myl-14010/US trastuzumab (90% CI) (95% CI) | | 1.09 (0.974-1.211) (0.954-1.237) |
| Difference in ORR: Myl-14010/EU trastuzumab (90% CI) (95% CI) | | 5.53 (-1.70 to 12.69) (-3.08 to 14.04) |
| Per-Protocol Population | | |
| | Myl-14010 + taxane n = 222 | Trastuzumab + taxane n = 216 |
| ORR, n (%) (95% CI) | 158 (71.2) | 145 (67.1) |
| Ratio of ORR: Myl-14010/US trastuzumab (90% CI) (95% CI) | | 1.06 (0.954-1.178) (0.935-1.202) |
| Difference in ORR: Myl-14010/EU trastuzumab (95% CI) | | 4.0 (-4.59 to 12.61) |

ITT, intent to treat; ORR, overall response rate.

in part 2 included PFS, duration of response, and OS at week 48 and at 36 months or after 240 deaths from time of randomization.

Of 826 patients screened, 500 were randomly assigned, and 458 were included in the intent-to-treat (ITT) population after the protocol was amended to exclude patients who had received first-line therapy. Of patients assigned to Myl-14010, 173 completed part 1; 159 patients assigned to trastuzumab completed part 1. Disease progression was the most common reason for discontinuing treatment. Efficacy results for part 1 are summarized in [TABLE 2](#).⁴ The ratio of ORR for the test biosimilar to the reference biosimilar is required by the FDA. The difference in ORR between the test biosimilar and the reference biosimilar is required by the European Medicines Agency. Median PFS has not been reached. PFS at 48 weeks will be reported later this year. There was no significant difference in PFS at week 24 in the ITT part 1 patient population. These results confirm the efficacy equivalence based on both the ratio of ORR and difference between ORRs.

Safety was comparable between Myl-14010 and trastuzumab, with a similar number of SAEs, including neutropenia, febrile neutropenia, leukopenia, and pneumonia, in each arm. SAEs were as expected for the combination of trastuzumab plus taxanes in patients with MBC. There were 4 deaths in each arm, 1 in each “possibly” related to trastuzumab. There were no differences between arms in median LVEF. Dr Rugo said that although the Heritage study reported safety data for

24 weeks, there are a lot of safety data for Myl-14010 from its use in India, where it has been approved and used without adverse safety signals for the last 2 years. As a result of different regulatory requirements in that country, pharmacovigilance data have been collected outside clinical trials and submitted to global regulators.

Immunogenicity was low and similar between the biosimilar (2.4%) and reference trastuzumab (2.8%) and was consistent with previous results reported for trastuzumab. Trough minimum concentrations at cycle 6 were similar for both agents, and C_{max} and AUC were comparable and consistent with those reported in healthy volunteers.

Dr Rugo concluded that this study confirmed the efficacy equivalence between Myl-14010 and trastuzumab in combination with taxanes as first-line therapy for patients with HER2-positive MBC at 24 weeks. Myl-14010 and trastuzumab in this study have similar safety, immunogenicity, and PK profiles. Therefore, the proposed trastuzumab biosimilar Myl-14010 could be a new treatment option for patients with HER2-positive MBC, with the potential to meet the need for a more affordable treatment.

Don S. Dizon, MD, chair of the ASCO Cancer Communication Committee, said the results of this study were “incredibly exciting and may expand access to a potentially life-saving treatment.” Dr Rugo commented at a press briefing that she had no idea how pricing was determined, although she expects biosimilars will reduce the cost somewhat, worldwide. In the

United States, insurance covers trastuzumab, so there is less of an issue about access than in other countries. When asked if she herself would use a biosimilar to trastuzumab, she said that if it meets regulatory requirements and is approved, she would use a biosimilar. She said in response to a suggestion that others might be reluctant to use a biosimilar, “What people say and will do without evidence is independent of reality. If insurance companies [in the United States] say to use a biosimilar, it will be used.” Dr Rugo expects that Myl-14010 will change the treatment of patients with HER2-positive MBC worldwide.

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“Death With Dignity” Legislation and Care Discussed

During ASCO, an education session, “Death With Dignity or Physician-Assisted Suicide? A Thoughtful Discussion,” was presented as part of the Health Services Research and Quality of Care Track. The discussion included background on current death with dignity (DWD) legislation and a debate on the ethics and practical issues concerning this legislation in the context of the practice of oncology.

Death With Dignity Legislation

Lynne P. Taylor, MD, session chair, University of Washington, Virginia Mason Medical Center, Seattle, Washington, discussed the implications of DWD legislation. “It all begins here with Karen Ann Quinlan,” she said. The 21-year-old became comatose after ingesting diazepam and alcohol in April 1975. In September 1975, her parents, who were devout Catholics, sued the hospital to disconnect her from the ventilator, citing “extraordinary means.” In March 31, 1976, the New Jersey Supreme Court allowed the ventilator to be removed. She died in 1985. This case is widely credited for the development of hospital ethics committees, where responsibilities of patients and families are compared with those of physicians and hospitals.

In the mid-20th century, the right to consent and to refuse medical care became much more prominent in Western

medical ethics and case law. The Quinlan decision made it permissible for a guardian to direct a physician or hospital to disconnect a ventilator to allow death. After Quinlan, the debate shifted to the use of intravenous lines, total parenteral nutrition, and percutaneous gastrostomy tubes. Gradually, “passive euthanasia,” or the concept of allowing someone to die, became acceptable. In 1996, 2 favorable decisions supported a right to limited physician-assisted suicide in the Ninth and Second US Circuit Courts, in Washington State and New York, respectively. These were taken, in 1997, to the US Supreme Court, which said there are no constitutional rights to physician aid in dying, but that each state may set its own policy. This decision allowed Oregon voters to reaffirm a 1994 vote for physician aid in dying. The US Supreme Court refused to hear an appeal, and physician aid in dying became legal in Oregon in 1997.

Dr Taylor said that the initiative passed in 2009 in Washington State, known as “death with dignity” to its proponents, is referred to as “physician-assisted suicide” by its detractors. The use of terminology reflecting the user’s opinion of physician aid in dying occurred throughout this session. The Washington law allows physicians to prescribe a lethal dose of secobarbital or other medications so that patients can self-administer the drug to end their life.

This law tries to ensure that all palliative care needs have been met. The patient has to have a terminal diagnosis, defined as death that is likely to occur in 6 months. A second opinion from a consulting physician has to concur. The patient has to have decisional capacity and the ability to self-medicate. The attending physician has to document 2 verbal requests for DWD from the patient, with a mandatory 15-day waiting period before accepting a written request. Physicians have to inform patients of their right to waive the request. “The distinction between the consulting and attending physician is important, particularly as we take care of patients, because it is the attending physician who writes the lethal prescription and the consulting physician who simply consults about the terminal nature of the illness. And so, in taking care of patients, the discussion about who is going to be the attending physician and who is going to be the consulting physician is part of the process,” Dr Taylor said.

She described the process of self-administration of secobarbital. “This is not an easy thing to do; patients think there will be a single pill. This is deliberately difficult; it is a horrible-tasting medication,” she said, noting that patients must open 100 of the 100-mg capsules to ingest the contents quickly in food, and that secobarbital, which is not covered by insurance, can cost \$4000, with prices rising.

In Washington State, the number of known deaths increased from 64 in 2009 to 170 in 2014. The number of deaths was small compared with the 7 million residents of Washington State. Those participants in the Death with Dignity Act who died tended to have cancer (nearly 80%) or neurodegenerative diseases, including amyotrophic lateral sclerosis (13%); this reflects what is occurring in other states. End-of-life concerns of those who died through the Death with Dignity Act predominantly consisted of losing autonomy, being less able to engage in activities making life enjoyable, and, to a lesser extent, being a burden on family, friends, and caregivers, and losing control of bodily functions. Inadequate pain control, or concern about it, was less common, and financial reasons were not very common. This was not surprising, Dr Taylor said, because most who take part are white, college-educated professionals. Physicians are well represented, she said.

The essential elements of the Washington State Death with Dignity Law have been published.¹ Safeguards include assessing informed consent on the basis of the patient’s awareness of the medical diagnosis and prognosis, the risks and the result of the medication (death), and the alternatives to DWD, including palliative care, hospice, and pain control. The physician has to deliver the prescription directly to the pharmacist, who in turn has to dispense the medication directly to the patient or identified agent.

Dr Taylor said that oncologists living in states where physician aid-in-dying laws are in effect will rarely be asked to par-

ticipate; however, they should contemplate their possible role. “You need to consider if you would agree to be an attending physician and write a prescription or a consulting physician to diagnose a terminal illness. If you cannot participate because of ethical, moral, or religious beliefs, you will need to consider if referring your patient to another colleague is your responsibility. Maximizing palliative care consultations, pain control, and relief of existential suffering remains a mainstay of oncology practice,” she concluded.

Experiences of a Palliative Care Physician

Physician-assisted death has been legalized in 5 states, including in Oregon and Washington by referendum, in Montana by constitutional challenge, in Vermont by legislative action, and in California by legislative action that is awaiting implementation; one-sixth of the US population now has access. The Canadian Supreme Court upheld the fundamental right to choose physician-assisted death this year.

Timothy E. Quill, MD, University of Rochester Medical Center, Rochester, New York, has been an advocate for legal access to physician-assisted death as a last-resort option in the United States. He concurred with Dr Taylor that many more people will ask about these options than will need them. Those who have witnessed a bad death may need reassurance. He said everyone in oncology has witnessed a bad death. Knowing there is a potential escape when suffering becomes unacceptable is important and reassuring to some people and allows them to focus on other things.

He noted that palliative care sometimes is inadequate. Correctable limitations of palliative care include limited access, inadequate physician training, barriers to pain management, reimbursement disincentives, being offered too late, and physicians’ lack of commitment. He noted that pain management is getting more complicated, especially for chronic illnesses. In addition, there are also uncorrectable limitations to palliative care, including the false expectation of relieving 100% of suffering, because people have seen that it is not true. Uncontrollable physical symptoms usually contain elements of psychosocial, existential, or spiritual suffering, and side effects of treatment may become unacceptable to patients over the long term. “Listen to the patient; they know what they want,” he said—for example, if they want to end life support. To do otherwise devalues patient choices.

Dr Quill encourages oncologists to commit to being a guide and partner for patients and to provide reassurance about the future when discussing their fears and hopes. He said that in Oregon, since passage of the Death with Dignity Act, 1 in 6 patients talk to their families about physician aid in dying, 1 in 50 talk with their doctor, and only 1 in 300 deaths occur by physician-assisted dying. He said physicians should explore the potential meaning and timing of asking about help in dy-

ing. There should be an effort to manage uncontrolled symptoms, psychosocial problems, and depression and anxiety.

Potential last-resort options for uncontrollable pain and intolerable suffering include accelerating opioids to sedation for pain, even if it might hasten death, and stopping life-sustaining therapy (eg, dialysis or ventilators or steroids for brain cancer). He noted, “These are probably legal but in a grayer area”; other options might be voluntarily stopping eating and drinking or palliative sedation, potentially to unconsciousness. Physician-assisted death should be the last of the last resorts.

Since passage of the law in Oregon, there have been improvements in end-of-life care, high rates of hospice referral before death, relatively strong opioid prescribing practices, statewide participation of physicians in Physician Orders for Life-Sustaining Treatment paradigm programs, and a strong commitment to palliative care.

Dr Quill affirmed the need for safeguards, including access to palliative care that must be proven to be ineffective before physician-assisted death can be considered, rigorous informed consent, a second opinion from a physician trained and certified in palliative care, and the ability of physicians to opt out. Nevertheless, he said, “In my opinion, you are not off the hook if you opt out. You need to think hard about other last-resort options you can provide, because referring to some stranger to provide aid in dying at the last moment is on shaky ground.”

He concluded that physician-assisted dying and last-resort options are sensible only in the context of excellent palliative care. Clarity about which options are available would reassure those who fear a bad death, increase responsiveness to extreme suffering, and provide more accountability when suffering persists.

Is Physician-Assisted Suicide Bad Medicine and Bad Public Policy?

Daniel Sulmasy, MD, PhD, The University of Chicago, Chicago, Illinois, argued that what he calls physician-assisted suicide is bad medicine and should not be medically necessary. He assumes that more can always be done for symptom control and that one option that is acceptable to him is to administer doses of drugs that render suffering patients unconscious.

One of his major concerns is that allowing physician-assisted suicide for any reason will result in a “slippery slope” of use in cases in which patients are quadriplegic or suffering from neurodegenerative disorders and cannot self-administer drugs, for children who cannot consent, and by mentally ill patients. He seemed to think that the availability of physician-assisted suicide will lead to worse end-of-life care or even replace it, in contrast to what Dr Quill has observed in Oregon, and that it will also lead to copycat suicides.

Final Words

During the panel discussion and question-and-answer period, Drs Quill and Sulmasy reiterated their positions and responded to each other’s presentations. Dr Sulmasy acknowledged that the desire for death is common in patients with cancer but “they are probably depressed, and that can be treated.” He conceded that some are not clinically depressed and rationally want suicide. Dr Sulmasy claimed that because countertransference is always operative in patient-physician relationships, the decision regarding aid in dying is about the physician’s desire to be rid of patient burden and makes patients think that is what they want. Dr Quill responded to this by acknowledging that countertransference is “something we work with all the time as we try to think about stopping treatment. The answer is, get really experienced people [in palliative care] to provide other perspectives.”

An attendee commented that in the nearly 20 years of the law in Oregon, there has been no slippery slope or physician-assisted deaths of mentally ill patients or children. His practice is nearly entirely physician-assisted death because his patients’ doctors will not participate. Another attendee commented that a major hospice provider in his area will not participate in physician-assisted dying. Dr Quill responded that this might prevent people who would benefit from hospice care from getting it, and the discussion will “go off-line because people need care, and people will make secret agreements with doctors and just won’t tell the hospice because they need the care.”

Harvey Cohen, MD, Duke University, Durham, North Carolina, suggested that whichever side of the argument people are on, “We need to have some humility about this discussion.” He referred to the words of neurosurgeon Paul Kalanithi, MD, whose book *When Breath Becomes Air* described his experience of dying with metastatic lung cancer. Dr Kalanithi wrote, “My relationship with statistics changed when I became one.” Dr Kalanithi’s book was discussed by his widow at the ASCO Book Club Session, also held during the annual meeting. Dr Cohen said, “No one in this room is one of the people we are talking about who are on this path. We are trying to empathize, but no empathy is perfect, and we have to be careful what kind of discussions we have in this situation.”

REFERENCE

1. Loggers ET, Starks H, Shannon-Dudley M, Back AL, Appelbaum FR, Stewart FM. Implementing a Death with Dignity program at a comprehensive cancer center. *N Engl J Med*. 2013;368(15):1417-1424. doi: 10.1056/NEJMsa1213398.

