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Harnessing the Immune Power: A Uniquely Designed PD-1 Inhibitor for Esophageal Cancer

Announcer:
This is Project Oncology on ReachMD. This program, titled “Harnessing the Immune Power: A Uniquely Designed PD-1 Inhibitor for Esophageal Cancer,” is sponsored by BeOne Medicines. Dr. Jaffer A. Ajani received compensation from BeOne for their participation in this video.

Here’s your host, Dr. Charles Turck.

Dr. Turck:
Welcome to Project Oncology on ReachMD. I’m Dr. Charles Turck and joining me today to discuss the latest first-line immunotherapy treatment in esophageal squamous cell carcinoma, also known as ESCC, is Dr. Jaffer Ajani. He’s a GI medical oncologist working at the University of Texas’ MD Anderson Cancer Center in Houston. Dr. Ajani, welcome to the program.

Dr. Ajani:
Yeah. Thank you for having me here.

Dr. Turck:
So to start, Dr. Ajani, would you walk us through the unmet needs that patients with esophageal cancer face?

Dr. Ajani:
Absolutely. Esophageal cancer is the tenth most common cancer worldwide and sixth most prevalent cause of death due to cancer. More than two thirds patients with esophageal cancer are diagnosed with advanced or metastatic disease, and five-year survival rate is five percent for patients with metastatic disease.[1] So it’s clear that we need additional treatment options for these patients.

Dr. Turck:
Well, with that context in mind, what are the current immunotherapy treatment options?

Dr. Ajani:
Well, first, it’s important to note that there are two histologic types of esophageal cancer. One is called esophageal squamous cell carcinoma, or ESCC, and the other one is adenocarcinoma, also called EAC. ESCC comprises roughly 90 percent of esophageal cancers.[1] Currently, for unresectable locally advanced or metastatic ESCC, a PD-1 inhibitor in combination with chemotherapy is the standard of care for patients with tumor PD-L1 greater than or equal to one. For patients with tumor PD-L1 less than one, the standard of care would be chemotherapy alone. This aligns with the FDA approvals and the NCCN Guidelines.[2-5]

Dr. Turck:
And have there been any new FDA approvals in immunotherapy treatment for patients with unresectable locally advanced or metastatic ESCC recently?

Dr. Ajani:
Yes—tislelizumab plus platinum-based chemotherapy is the latest FDA approval for these patients. Tislelizumab is an anti-PD-1 antibody with three preclinical features that distinguish it from other PD-1 inhibitors being used in ESCC.

The first feature is the large coverage of the PD-1 receptor compared to nivolumab or pembrolizumab.[6]

In fact, preclinical data show that tislelizumab completely blocks PD-1 receptor, preventing PD-L1 or PD-L2 binding, compared to nivolumab or pembrolizumab, that showed partial inhibition of the PD-1 receptor.[6]

Second, the high binding affinity leads to slower dissociation from the PD-1 receptor. This potentially allows more time for T cells to proliferate and cause tumor cell killing. Compared to nivolumab and pembrolizumab, the dissociation rate for tislelizumab was 30- to 80-fold slower, respectively.[6]

Finally, the Fc portion of tislelizumab has been modified so that it has minimal binding to macrophages. This modification limits active T cell depletion in the tumor microenvironment and may avoid resistance to PD-1 inhibition.[7]

Dr. Turck:
Thanks for explaining those features, Dr. Ajani. And now, shifting gears a bit, would you walk us through the design of the trial that led to the FDA approval of tislelizumab in first-line ESCC?

Dr. Ajani:
Of course. The global study was called RATIONALE-306. It enrolled patients with unresectable locally advanced or metastatic ESCC who were not treated previously with systemic therapy for advanced disease. Patient needed to have ECOG performance of zero or one, with measurable or evaluable disease at the time of enrollment. The study was stratified by geographic region, use of prior definitive therapy, or chemotherapy.[1]

The experimental arm was tislelizumab 200 mg IV every three weeks plus chemotherapy, and the control arm was placebo plus chemotherapy. Treatment continued until unacceptable toxicity or disease progression.[1]

It's important to note that the chemotherapy options were physicians' choice of platinum plus fluoropyrimidine or platinum plus paclitaxel. Although FOLFOX is the most commonly used chemotherapy in the US, platinum plus paclitaxel can offer an alternative to patients who are unable to tolerate capecitabine just given orally or when there's no access to infusion pump.[1]

It was 1:1 randomization in this study with roughly 650 patients enrolled. The primary endpoint was overall survival, also called OS, in the intent to treat population. The key secondary endpoints included additional efficacy endpoints, and safety.[1]

Dr. Turck:
For those just tuning in, you're listening to Project Oncology on ReachMD. I'm Dr. Charles Turck, and today I'm speaking with Dr. Jaffer Ajani about an emerging PD-1 inhibitor for first-line esophageal squamous cell carcinoma, or ESCC.

So, Dr. Ajani, now that we've discussed the design of RATIONALE-306, let's move onto the results. What were some of the key findings?

Dr. Ajani:
Great question. For context, I will be focusing on patients with tumor PD-L1 greater than or equal to one percent, as that is aligned with the ODAC recommendation and the FDA approval.

The patient demographics showed that the median age was about 65 years, and more than 85 percent of patients were men, and roughly 80 percent of patients were either former or current smokers. 75 percent of patients enrolled in the study were from Asia, which was likely due the high incidence of ESCC in that region. Most of the patients had metastatic disease at the time of study enrollment.[8]

The primary analysis showed that tislelizumab plus chemotherapy resulted in a clinically meaningful improvement in OS compared to placebo plus chemotherapy. The median OS was 16.8 months for tislelizumab plus chemotherapy compared to 9.6 months of placebo and chemotherapy, resulting in a hazard ratio of 0.64. There was a 7.2-month difference in overall survival favoring tislelizumab plus chemotherapy. The survival improvement was maintained at three-year follow-up, and the tail end of the curves continued to separate with long-term follow-up.[8]

Dr. Turck:
And building off that, what did the analyses of the prespecified subgroups show?

Dr. Ajani:
So, when we look at the prespecified subgroup analyses for OS, a clinically meaningful improvement was observed across key subgroups, favoring tislelizumab plus chemotherapy.[8]

These included chemotherapy regimens, just platinum + fluoropyrimidine or platinum + paclitaxel, patients with metastatic

disease, patients with locally advanced, unresectable ESCC.[8]

At recent Congress, a post-hoc analysis of patients with locally advanced, unresectable ESCC demonstrated consistent OS benefit for tislelizumab plus chemotherapy. The primary analysis reported a stratified hazard ratio of 0.38, translating into 52 percent reduction in risk of death for these patients. The median overall survival was 25.6 months for tislelizumab plus chemotherapy arm compared to 11.5 months for placebo plus chemotherapy arm.[9]

Dr. Turck:
Interesting. And what can you tell us about the safety profile of tislelizumab plus chemotherapy?

Dr. Ajani:
So, in terms of the safety, we see that tislelizumab plus chemotherapy had generally a manageable safety profile. Nearly all patients experienced one or more treatment-related events, and comparable proportion of patients in each arm experienced at least one Grade 3 or higher treatment-related adverse event–67 percent of patients in tislelizumab plus chemotherapy, and 64 percent of patients in placebo plus chemotherapy. The most common Grade 3/4 side effects were related to decreased neutrophil count—31 percent in tislelizumab arm, 33 percent in the placebo arm—decreasing white blood cell count—11 percent in tislelizumab arm, 16 percent in the placebo arm—and anaemia—15 percent in tislelizumab arm and 13 percent in the placebo arm.[1]

Treatment-emergent events leading to death occurred in five percent of patients in both arms. 29 percent of patients in tislelizumab plus chemotherapy arm and 19 percent in the placebo and chemotherapy arm discontinued therapy due to treatment-related adverse event, and 70 percent of patients in tislelizumab arm and 63 percent in the placebo arm had treatment-related events that led to dose modification.[1]

So, since tislelizumab is a PD-1 inhibitor, patients may experience immune-related adverse event that you see with other anti-PD-1 inhibitors, so the healthcare providers should monitor patients closely for this toxicity.

Dr. Turck:
Thanks for that overview, Dr. Ajani. And now, before we wrap up our program, do you have any final thoughts you'd like our audience to take away from this discussion?

Dr. Ajani:
Yes. I'd like to summarize that tislelizumab is a uniquely designed PD-1 inhibitor with high binding affinity to PD-1 receptor. The modified Fc portion of the antibody minimizes the binding to macrophages, preventing them from clearing T cells in the tumor microenvironment—a process believed to contribute to anti-PD-1 resistance.[6,7]

In the global RATIONALE-306 trial, tislelizumab plus chemotherapy demonstrated a median OS of 16.8 months, an improvement of 7.2 months in OS versus placebo plus chemotherapy for patients with tumor PD-L1 greater than or equal to one percent. A post-hoc analysis of patients with locally advanced, unresectable ESCC demonstrated consistent overall survival benefit of tislelizumab plus chemotherapy arm, with a median overall survival of 25.6 months and a 14.1-month improvement over the placebo plus chemotherapy arm.[8]

Its safety profile was generally manageable, with no new safety signals identified. The most common treatment-related adverse event for all grades and Grade 3/4 in both groups were consistent with the adverse event profile for this type of treatment.[1]

In addition, tislelizumab offers flexible treatment options and can be combined with platinum plus fluoropyrimidine or platinum plus paclitaxel.

Dr. Ajani:
The treatment data led to the approval of tislelizumab plus platinum-containing chemotherapy for first-line treatment of unresectable or metastatic ESCC with tumors that express PD-L1 greater than or equal to one. It's important to note that the FDA also approved tislelizumab for different dosing schedules. They include every two, every three, every four, or every six weeks, offering extra flexibility and convenience to prescribers and patients. Tislelizumab plus chemotherapy is listed as a preferred treatment option in the NCCN Guideline, providing an additional immunotherapy option for patients with untreated metastatic ESCC.

Dr. Turck:
That's a great summary as we come to the end of today's program. And I want to thank my guest, Dr. Jaffer Ajani, for sharing his insight into treating esophageal squamous cell carcinoma first-line with a PD-1 inhibitor. Dr. Ajani, it was great speaking with you today.

Dr. Ajani:
Yeah, it was great to participate in this program. Thank you.

Dr. Turck:
For ReachMD, I'm Dr. Charles Turck. Please stay tuned to hear some important safety information.

Announcer:

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Severe and Fatal Immune-Mediated Adverse Reactions

TEVIMBRA is a monoclonal antibody that belongs to a class of drugs that bind to either the programmed death receptor-1 (PD-1) or PD-ligand 1 (PD-L1), blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response, potentially breaking peripheral tolerance and inducing immune mediated adverse reactions.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. Immune-mediated adverse reactions can occur at any time after starting treatment with a PD-1/PDL1 blocking antibody. While immune-mediated adverse reactions usually manifest during treatment with PD-1/PD-L1 blocking antibodies, immune-mediated adverse reactions can also manifest after discontinuation of PD-1/PD-L1 blocking antibodies. Important immune-mediated adverse reactions listed here may not include all possible severe and fatal immune-mediated reactions.

Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue TEVIMBRA depending on severity. In general, if TEVIMBRA requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroids.

Immune-Mediated Pneumonitis
TEVIMBRA can cause immune-mediated pneumonitis, which can be fatal. In patients treated with other PD-1/PD-L1 blocking antibodies, the incidence of pneumonitis is higher in patients who have received prior thoracic radiation.

Immune-mediated pneumonitis occurred in 4.7% (113/2390) of patients receiving TEVIMBRA, including fatal (0.1%), Grade 4 (0.3%), Grade 3 (1.4%), and Grade 2 (1.9%) adverse reactions. Pneumonitis led to permanent discontinuation of TEVIMBRA in 44 (1.8%) patients and withholding of TEVIMBRA in 40 (1.7%) patients.

Eighty-one (71.7%) of the 113 patients received systemic corticosteroids. Seventy-four (65.5%) of the 113 patients received high-dose systemic corticosteroids. Immune-mediated pneumonitis resolved in 48.7% of the 113 patients. Of the 40 patients in whom TEVIMBRA was withheld for pneumonitis, 26 (65%) reinitiated TEVIMBRA after symptom improvement; of these, 5 (19%) patients had recurrence of pneumonitis.

Immune-Mediated Colitis
TEVIMBRA can cause immune-mediated colitis, which can be fatal. Cytomegalovirus infection/reactivation has been reported in patients with corticosteroid-refractory immunemediated colitis treated with PD-1/PD-L1 blocking antibodies. In cases of corticosteroidrefractory colitis, consider repeating infectious workup to exclude alternative etiologies.

Immune-mediated colitis occurred in 0.8% (19/2390) of patients receiving TEVIMBRA, including Grade 3 (0.3%) and Grade 2 (0.4%) adverse reactions. Colitis led to permanent discontinuation of TEVIMBRA in 5 (0.2%) patients and withholding of TEVIMBRA in 10 (0.4%) patients. Seventeen (89.5%) of the 19 patients received systemic corticosteroids. Twelve (63.2%) of the 19 patients received high-dose systemic corticosteroids. Two (10.5%) of the 19 patients received immunosuppressive treatment. Immune-mediated colitis resolved in 89.5% of the 19 patients. Of the 10 patients in whom TEVIMBRA was withheld for colitis, 9 (90%) reinitiated TEVIMBRA after symptom improvement; of these, 2 (22%) patients had recurrence of colitis.

Immune-Mediated Hepatitis

TEVIMBRA can cause immune-mediated hepatitis, which can be fatal. Immune-mediated hepatitis occurred in 1.3% (30/2390) of patients receiving TEVIMBRA, including Grade 4 (0.3%), Grade 3 (0.6%), and Grade 2 (0.3%) adverse reactions. Immunemediated hepatitis led to permanent discontinuation in 6 (0.3%) patients and withholding of TEVIMBRA in 19 (0.8%) patients. Twenty-five (83.3%) of the 30 patients received systemic corticosteroids. Twenty-four (80%) of the 30 patients received high-dose systemic corticosteroids. Two (6.7%) of the 30 patients received immunosuppressive treatment. Immunemediated hepatitis resolved in 66.7% of the 30 patients. Of the 19 patients in whom TEVIMBRA was withheld for hepatitis, 7 (37%) reinitiated TEVIMBRA after symptom improvement; of these, 1 (14%) patient had recurrence of hepatitis.

Immune-Mediated Endocrinopathies

Adrenal Insufficiency

TEVIMBRA can cause immune-mediated adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold TEVIMBRA depending on severity.

Immune-mediated adrenal insufficiency occurred in 0.5% (12/2390) of patients receiving TEVIMBRA, including Grade 4 (0.04%), Grade 3 (0.2%), and Grade 2 (0.3%) adverse reactions. Adrenal insufficiency did not lead to permanent discontinuation of TEVIMBRA. TEVIMBRA was withheld in 10 (0.4%) patients. All 12 patients received systemic corticosteroids. Three (25%) of the 12 patients received high-dose systemic corticosteroids. Adrenal insufficiency resolved in 25% of the 12 patients. Of the 10 patients in whom TEVIMBRA was withheld for adrenal insufficiency, 8 (80%) reinitiated TEVIMBRA after symptom improvement; of these, none of the patients had recurrence of adrenal insufficiency.

Hypophysitis

TEVIMBRA can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism. Initiate hormone replacement as clinically indicated. Withhold or permanently discontinue TEVIMBRA depending on severity.

Hypophysitis/hypopituitarism occurred in 0.3% (6/2390) of patients receiving TEVIMBRA; all were Grade 2 (0.3%). Hypophysitis did not lead to permanent discontinuation of TEVIMBRA. TEVIMBRA was withheld in 1 (0.04%) patient. Five (83.3%) of the 6 patients received systemic corticosteroids. One (17%) of the 6 patients received high-dose systemic corticosteroids. Hypophysitis/hypopituitarism resolved in 17% of the 6 patients. For the 1 patient where TEVIMBRA was withheld for hypophysitis/hypopituitarism, there was no recurrence of hypophysitis/hypopituitarism.

Thyroid Disorders

TEVIMBRA can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement for hypothyroidism or institute medical management of hyperthyroidism as clinically indicated. Withhold or permanently discontinue TEVIMBRA depending on severity.

Thyroiditis: Immune-mediated thyroiditis occurred in 1% (25/2390) of patients receiving TEVIMBRA, including Grade 2 (0.5%) adverse reactions. Thyroiditis did not lead to permanent discontinuation of TEVIMBRA. TEVIMBRA was withheld in 5 (0.2%) patients. Two (8%) of the 25 patients received systemic corticosteroids. Thyroiditis resolved in 36% of the 25 patients. All 5 patients in whom TEVIMBRA was withheld for thyroiditis reinitiated TEVIMBRA after symptom improvement; of these, 1 (20%) patient had recurrence of thyroiditis.

Hyperthyroidism: Immune-mediated hyperthyroidism occurred in 4.9% (118/2390) of patients receiving TEVIMBRA, including Grade 3 (0.04%) and Grade 2 (0.9%) adverse reactions. Hyperthyroidism led to the permanent discontinuation of TEVIMBRA in 1 (0.04%) patient and withholding of TEVIMBRA in 7 (0.3%) patients. Three (2.5%) of the 118 patients received systemic corticosteroids. Hyperthyroidism resolved in 76.3% of the 118 patients. Of the 7 patients in whom TEVIMBRA was withheld for hyperthyroidism, 5 (71.4%) reinitiated TEVIMBRA after symptom improvement; of these, none of the patients had recurrence of hyperthyroidism.

Hypothyroidism: Immune-mediated hypothyroidism occurred in 12.5% (299/2390) of patients receiving TEVIMBRA, including Grade 4 (0.04%), Grade 3 (0.04%), and Grade 2 (6.7%) adverse reactions. TEVIMBRA was permanently discontinued in 2 (0.1%) patients and treatment was withheld in 12 (0.5%) patients. Two (0.7%) of the 299 patients received systemic corticosteroids. One hundred ninety-five patients received hormone replacement therapy. Hypothyroidism resolved in 34.4% of the 299 patients. The majority (83.6%) of patients with hypothyroidism required long-term thyroid hormone replacement. Of the 12 patients in whom TEVIMBRA was withheld for hypothyroidism, 11 (91.7%) reinitiated TEVIMBRA after symptom improvement; of these, 2 (18.2%) patients had recurrence of hypothyroidism.

Type 1 Diabetes Mellitus, which can present with Diabetic Ketoacidosis

Diabetes mellitus has been reported with PD-1/PD-L1 blocking antibodies. Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold or permanently discontinue TEVIMBRA depending on severity.

Diabetes mellitus occurred in 0.7% (16/2390) of patients receiving TEVIMBRA, including Grade 4 (0.1%), Grade 3 (0.3%), and Grade 2 (0.3%) adverse reactions. TEVIMBRA was permanently discontinued in 4 (0.2%) patients, and TEVIMBRA treatment was withheld in 4 (0.2%) patients. Fourteen of the 16 patients received insulin therapy for diabetes mellitus. Diabetes mellitus resolved in 12.5% of the 16 patients. Of the 4 patients in whom TEVIMBRA was withheld for diabetes mellitus, 1 (25%) patient reinitiated TEVIMBRA after symptom improvement.

Immune-Mediated Nephritis with Renal Dysfunction
TEVIMBRA can cause immune-mediated nephritis, which can be fatal.

Immune-mediated nephritis with renal dysfunction occurred in 0.2% (5/2390) of patients receiving TEVIMBRA, including Grade 3 (0.04%) and Grade 2 (0.1%) adverse reactions. TEVIMBRA was permanently discontinued in 1 (0.04%) patient and treatment was withheld in 3 (0.1%) patients. Three (60%) out of 5 patients received systemic corticosteroids. Three (60%) of the 5 patients received high-dose systemic corticosteroids. Nephritis with renal dysfunction resolved in 40% of the 5 patients. Of the 3 patients in whom TEVIMBRA was withheld for nephritis, 2 (66.7%) reinitiated TEVIMBRA after symptom improvement and no patients had recurrence of nephritis.

Immune-Mediated Dermatologic Adverse Reactions
TEVIMBRA can cause immune-mediated rash or dermatitis. Cases of severe cutaneous adverse reactions (SCARs), including exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), have been reported, some with fatal outcome. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold or permanently discontinue TEVIMBRA depending on severity.

Immune-mediated dermatologic adverse reactions occurred in 13% (311/2390) of patients receiving TEVIMBRA, including Grade 4 (0.1%), Grade 3 (1.1%), and Grade 2 (3.4%) adverse reactions. Stevens-Johnson syndrome occurred in 1 (0.04%) patient. Dermatologic adverse reactions led to permanent discontinuation of TEVIMBRA in 3 (0.1%) patients and withholding of TEVIMBRA in 30 (1.3%) patients. Forty-four (14.1%) of the 311 patients received systemic corticosteroids. Nineteen (6.1%) of the 311 patients received high-dose systemic corticosteroids. Immune-mediated skin reactions resolved in 66.9% of the 311 patients. Of the 30 patients in whom TEVIMBRA was withheld for dermatologic adverse reactions, 26 (86.7%) reinitiated TEVIMBRA after symptom improvement; of these, 3 (12%) patients had recurrence of immune mediated dermatologic adverse reactions.

Other Immune-Mediated Adverse Reactions

The following clinically significant immune-mediated adverse reactions occurred at an incidence of less than 1% in 2390 patients who received TEVIMBRA or were reported with the use of other PD-1/PD-L1 blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions.

Cardiac/Vascular: Myocarditis, pericarditis, vasculitis.

Nervous System: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barre syndrome, nerve paresis, autoimmune neuropathy.

Ocular: Uveitis, iritis, and other ocular inflammatory toxicities. Some cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a VogtKoyanagi-Harada–like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss.

Gastrointestinal: Pancreatitis including increases in serum amylase and lipase levels, gastritis, duodenitis, stomatitis.

Musculoskeletal and Connective Tissue: Myositis/polymyositis/dermatomyositis, rhabdomyolysis and associated sequelae including renal failure, arthritis, polymyalgia rheumatica.

Endocrine: Hypoparathyroidism.

Other (Hematologic/Immune): Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenia, solid organ

transplant rejection, other transplant (including corneal graft) rejection.

This program was sponsored by BeOne Medicines. If you missed any part of this discussion, visit Project Oncology on ReachMD.com, where you can Be Part of the Knowledge.

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