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Submitted by
Eric First, MD.
Chief Medical Officer, Americas

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NCCN Colon/Rectal Cancers Panel

Re: Request for review of clinical data and recommendation for yttrium-90 resin microspheres in the NCCN Clinical Practice Guidelines in Oncology® - Colon/Rectal Cancers

On behalf of Sirtex Medical Ltd, I respectfully request the NCCN Colon/Rectal Cancers Panel to review the enclosed publication on the randomized phase III study[1] in support of the use of yttrium-90 resin microspheres in previously untreated patients with colorectal cancer with liver metastases plus or minus limited extrahepatic metastases.

Suggested Changes: We respectfully ask the NCCN Panel to consider the following:

Colon Cancer Guideline and Rectal Cancer Guideline:

- **"Principles of Radiation Therapy" COL-D, bullet 5 and REC-D, new bullet**: "Consider arterially directed embolization using yttrium-90 resin microspheres in select patients, with liver-only or liver predominant metastases. Addition of yttrium-90 resin microspheres to first-line FOLFOX or mFOLFOX with or without bevacizumab has been shown to improve liver-specific objective response and progression-free survival in a phase III randomized study.[1] Administration of yttrium-90 resin microspheres should be performed by trained medical staff at designated sites."

- **COL-7, new footnote** (beside "Systemic therapy") **and REC-E, 1 of 9, new footnote** (beside "FOLFOX" and "FOLFOX + bevacizumab"): "Consider arterially-directed embolization using yttrium-90 resin microspheres in addition to FOLFOX or mFOLFOX with or without bevacizumab. See Principles of Radiation Therapy (COL-D/REC-D)."

FDA Clearance: SIR-Spheres® Y-90 resin microspheres was approved by the FDA under a premarket approval application in 2002. SIR-Spheres® Y-90 resin microspheres is indicated for the treatment of unresectable metastatic liver tumors from primary colorectal cancer with adjuvant intra-hepatic artery chemotherapy (IHAC) of FUDR (Floxuridine).[2]

Rationale: SIRFLOX was the largest phase III, randomized, multicenter trial to date on first-line hepatic-directed therapies in metastatic colorectal cancer.[1] A total of 530 chemotherapy-naïve patients with liver metastases plus or minus limited extrahepatic metastases were randomly assigned to receive either FOLFOX or modified FOLFOX6 plus selective internal radiation therapy (SIRT) using yttrium-90 resin microspheres, plus or minus bevacizumab.

The addition of SIRT to FOLFOX-based first-line chemotherapy significantly improved objective response rate (78.7% vs. 68.8%; *P*=0.042) and delayed disease progression (20.5 vs. 12.6 mo; HR, 0.69; 95% CI, 0.55-0.90; *P*=0.002) in the liver.[1] There is no significant difference in objective response or progression-free survival in any site between the 2 groups. Grade ≥3 adverse events, including recognized SIRT-related effects, were reported in 73.4% and 85.4% of patients in control versus SIRT. The safety profile observed was as expected and was consistent with previous studies.

Sincerely,

Eric R. First., M.D.

References (**enclosed**):

1. van Hazel GA, et al. *J Clin Oncol*. 2016; 34:1723-1731.
2. SIR-Spheres® microspheres PI