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Submitted by:

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NCCN Colon/Rectal/Anal Cancers Panel

Re: Yttrium-90 microspheres for right-sided primary colon cancer in the NCCN Clinical Practice Guidelines in Oncology® - Colon Cancers

On behalf of Sirtex Medical Ltd, I respectfully request the NCCN Colon/Rectal/Anal Cancers Panel to review the enclosed analysis on two randomized phase III studies[1] in support of the addition of yttrium-90 microspheres to standard first-line mFOLFOX6 chemotherapy ± bevacizumab in patients with **right-sided primary (RSP)** colorectal cancer with liver-only or liver-dominant metastases.

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

Colon Cancer Guideline:

- **COL-6, "Unresectable synchronous liver and/or lung metastases only", under "treatment", "Systemic therapy"**: Add "mFOLFOX6 ± bevacizumab + yttrium-90 microspheres [for right-sided colon and transverse colon only]*"

- **COL-C, 1 of 10, under "Initial therapy"**: Add "mFOLFOX6 ± bevacizumab + yttrium-90 microspheres (for right-sided colon and transverse colon only)*"

- **New Footnote ***: "Evidence strongly suggests that the addition of yttrium-90 microspheres to first-line mFOLFOX6 ± bevacizumab is associated with improved overall survival compared with mFOLFOX6 ± bevacizumab alone specifically for patients with right-sided colon (hepatic flexure through cecum) or transverse colon."

FDA Clearance:
SIR-Spheres® was approved by the FDA under a premarket approval application in 2002. SIR-Spheres® 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 Summary:
Patients with RSP colorectal cancers have worse prognosis for survival and fewer treatment options than patients with left-sided primary (LSP) tumors.[3] Recent data also demonstrated the predictive value of sidedness for therapies, such as cetuximab, in the first-line metastatic.[4,5] A recent analysis of 2 randomized phase III studies showed that addition of yttrium-90 microspheres to first-line mFOLFOX6 ± bevacizumab is associated with clinically meaningful (4.9 months) and statistically significant improvement in overall survival compared with mFOLFOX6 ± bevacizumab alone for patients with right-sided colon (hepatic flexure through cecum) or transverse colon.[2] This suggests that right-sidedness is an important predictive factor for selecting patients who may benefit from first-line addition of yttrium-90 microspheres.

Literature Support:
The SIRFLOX (n=530), FOXFIRE Global (n=209), and FOXFIRE (n=364) studies examined the addition of yttrium-90 microspheres to first-line mFOLFOX6 chemotherapy in liver-only or liver-dominant metastatic colorectal cancer.[6] While there was no survival improvement in the overall population,[6] a post-hoc analysis of data from SIRFLOX and FOXFIRE Global in which primary tumor location was prospectively captured, revealed an observed survival benefit specifically for RSP patients. In this analysis,[1] overall survival was significantly improved by the addition of yttrium-90 microspheres to first-line mFOLFOX6 chemotherapy (± bevacizumab) in patients with RSP defined as primary tumor proximal to the splenic flexure (median 22.0 vs. 17.1 months, with or without microspheres, respectively; HR, 0.64; 95% CI, 0.46–0.89; *P*=0.007). A standard statistical test of treatment interaction by location for overall survival also proved significant (Chi-square, 9.49; *P*=0.002; HR, 0.548; 95% CI, 0.37–0.80). No improvement in survival was seen from the addition of yttrium-90 microspheres to first-line chemotherapy for patients with LSP tumors (median 24.6 vs. 26.6 months, with or without microspheres, respectively; HR, 1.12; 95% CI, 0.92–1.36; *P*=0.279). For patients with RSP tumors, there was also a trend towards improved progression-free survival with the addition of yttrium-90 microspheres (median 10.8 vs. 8.7 months; HR, 0.73; 95% CI, 0.53–1.01; *P*=0.053).[1]

There were no significant differences in the rate of adverse events between patients with RSP and LSP.[1] Grade 3-5 adverse events were more common in patients receiving yttrium-90 microspheres (74.0% vs. 66.5%).[6] Most common adverse events associated with microsphere treatment include ascites (RSP: 4.5%; LSP: 4.9%), gastric ulcer (RSP: 4.0%; LSP: 1.7%), and duodenal ulcer (RSP: 0.6%; LSP: 1.3%).[6]

Yours faithfully,

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References (**enclosed**):

1. van Hazel G, et al. Impact of primary tumour location on survival in patients with metastatic colorectal cancer receiving selective internal radiation therapy and chemotherapy as first-line therapy. ESMO 19th World Congress on Gastrointestinal Cancer, Ann Oncol 2017; Abstract LBA-006.
2. SIR-Spheres® microspheres PI. Sirtex Medical Inc.
3. Petrelli F, et al. Prognostic survival associated with left-sided vs right-sided colon cancer: A systematic review and meta-analysis. JAMA Oncol 2017; 3: 211–9.
4. Venook AP, et al. Impact of primary tumor location on overall survival (OS) and progression-free survival (PFS) in patients (pts) with metastatic colorectal cancer (mCRC): Analysis of CALGB/SWOG 80405 (Alliance). 2016 ASCO Annual Meeting. J Clin Oncol 2016; 34 (Suppl): Abstract 3504.
5. Tejpar S, et al. Prognostic and predictive relevance of primary tumor location in patients with RAS wild-type metastatic colorectal cancer: retrospective analyses of the CRYSTAL and FIRE-3 trials. JAMA Oncol. 2017;3:194-201.
6. Wasan HS, et al. First-line selective internal radiotherapy plus chemotherapy versus chemotherapy alone in patients with liver metastases from colorectal cancer (FOXFIRE, SIRFLOX, and FOXFIRE-Global): a combined analysis of three multicentre, randomised, phase 3 trials. Lancet Oncol. August 3, 2017. [Epub ahead of print]