

Record of Recommendation

Re: Funding temsirolimus (Torisel[®]) in Advanced and Metastatic Renal Cell Carcinoma (RCC)

April 9, 2008

Discussion facilitated using the Decision Making Framework.

- All present will vote electronically when the vote is called by the chair. The voting process will be completed by 5 pm on November 28th. The decision will be made by a majority with dissenting voters given the opportunity to record their opinion. Dissenting opinions must be recorded within seven days of the result of the vote being announced.
- Core values and principles were reviewed and discussed along with competing obligations, constraints and relevant information.
- Options for a recommendation to the Deputy Minister were reviewed and each option was discussed. Two options were identified at this time:
 - 1) Approval of funding with restrictions
 - 2) Denial of funding
- An analysis of the projected benefits and burdens of each option was discussed.

Projected Benefits: as first line therapy in the treatment of advanced or metastatic renal cell carcinoma (RCC) in patients considered to have a poor prognosis.

- ✓ Like sunitinib and sorafenib, it is a targeted therapy that acts in the cell however differs from sunitinib and sorafenib by inhibiting the mTOR pathway rather than the VEGF and PDGF pathways.
- ✓ The results of the ARCC, a Phase III trial of temsirolimus versus IFN in Advanced RCC showed an improvement in overall survival and progression free survival in the temsirolimus arm compared to the IFN arm in chemotherapy naïve patients with histologically confirmed RCC of clear or non-clear histology,

Karnofsky PS \geq 60, measurable disease (RECIST) and at least 3 of 6 poor-risk features.

- ✓ Median overall survival was 10.9 months in the temsirolimus arm versus 7.3 months in the interferon arm.
- ✓ Median progression free survival (PFS) was 5.5 months in the temsirolimus arm versus 3.1 in the interferon arm.
- ✓ The objective response rate for temsirolimus was 8.6% compared to 3.1% for interferon.
- ✓ Clinical benefit (CR + PR + SD for \geq 24 weeks) was 32.1% for temsirolimus versus 15.5% for interferon.
- ✓ A subgroup analysis looked at the outcomes based on clear cell versus non-clear cell histology. The results showed efficacy in both. Overall survival in non-clear cell of 11.6 months versus 4.3 in the interferon arm and PFS of 7.9 months versus 1.8 for interferon.

Projected Burdens:

- ✓ Common toxicities with temsirolimus are fatigue, anorexia, rash, nausea, with very few grade 3-4 symptoms. Anemia can occur (20% grade 3-4) as well as hyperlipidemia, hyperglycemia, and hypercholesterolemia.
- ✓ The drug cost only per patient is approx. \$1250.00 per patient per week with the average length of therapy approximately 17 weeks (\$21,250/patient).
- ✓ Using IFN as the comparator the cost per life year gained is approx. \$151,500 with an estimated cost per quality adjusted life year of approx. \$150,100. However, a sensitivity analysis showed the best case scenario at approx. \$98,000/QALY (based on the proposed company pricing agreement and worst case scenario of \$164,800/QALY using lowest utility values).
- ✓ The budget impact calculated on an average length of therapy of 17 weeks is expected to be approximately \$425,000 to \$510,000 (20-24 patients).

Result of Vote:

The vote was conducted electronically. The question the Committee was asked to vote on is:

“Should the Committee support a recommendation to the Deputy Minister of Health to publicly fund Temsirolimus (Torisel[®]) as a single agent first line treatment in patients with documented evidence of histologically confirmed advanced or metastatic RCC, considered to be poor prognosis (based on a minimum of at least 3 of 6 poor risk features which include: LDH $>$ 1.5 x upper limit of normal; hemoglobin $<$ lower limit of normal; corrected calcium $>$ 2.5 mmol/L; time from diagnosis to first treatment $<$ 1 year; Karnofsky performance status (PS) 60-70; and multiple organ sites of metastasis), have PS of 60 or more and have received no previous systemic therapy. In any one patient, all of the following conditions must be met:

- 1) Temsirolimus may be a first line option regardless of histology.
 - 2) Temsirolimus may not be used after another tyrosine kinase inhibitor (i.e. sorafenib or sunitinib) or interferon as sequential therapy.
 - 3) In the event of severe toxicity (or intolerance) within the first 8 weeks of therapy (for clear cell histology only), a switch to another tyrosine kinase inhibitor (i.e. sorafenib or sunitinib) may be allowed.”
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- **The result of the vote was a majority in favor of recommending funding. There were no dissenting opinions recorded.**