What's new in renal cell cancer research? Highlights of GU-ASCO 2014

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Abstract

One of the major areas of research presented at the 2014 Genitourinary Cancers Symposium (GU-ASCO 2014) pertained to the management of renal cell cancer (RCC). The following pages provide a summary of some of the most important presentations and posters presented during the 3-day symposium.

What is the best sequencing for sorafenib and sunitinib?

The Phase 3 Randomized Sequential Open-Label Study to Evaluate the Efficacy and Safety of Sorafenib Followed by Sunitinib Versus Sunitinib Followed by Sorafenib in the Treatment of First-Line Advanced/Metastatic Renal Cell Carcinoma (SWITCH) trial was the first study to prospectively evaluate whether there or not there is an advantage to the sequence of sorafenib followed by sunitinib (SO/SU) compared to sunitinib followed by sorafenib (SU/SO). The primary results of this study were presented at GU-ASCO 2014.[1]

The study, initiated in 2008, enrolled a total of 365 patients with metastatic RCC (mRCC) who had not previously received systemic therapy and were deemed to be unsuitable for cytokine therapy. Patients were randomized 1:1 to receive sunitinib or sorafenib. Patients were switched to the other therapy if they experienced disease progression or intolerable toxicity. The primary end point was the total progression-free survival (T-PFS) from the time of initial randomization to confirmed progression or death during second-line therapy. There were a number of secondary end points presented as well, including overall survival (OS), PFS in first-line treatment, PFS in second-line treatment and objective response rate. Safety and tolerability were also assessed.

At baseline, the 2 arms were well-balanced in terms of demographics and disease characteristics, with no statistically significant differences between treatment arms. At time of final T-PFS analysis, there was no statistically significant difference in T-PFS between treatment arms. The median T-PFS was 14.9 months for SU/SO and 12.5 months for SO/SU (hazard ratio [HR] 1.01, $p = 0.54$). There was also no significant difference between arms for OS (median 31.5 months for SO/SU and 30.2 months for SU/SO; HR 1.00, $p = 0.49$) (Fig. 1). However, more patients in the SO/SU arm reached second-line therapy compared to those in the SU/SO arm (57% vs. 42%, $p < 0.01$) and the second-line PFS was significantly longer for the SO/SU arm (median 5.4 months) compared to the SU/SO arm (2.8 months). The authors stressed that these results must be interpreted with caution, however, due to the imbalance between arms for patients initiating protocol-defined second-line therapy and the fact that there was no randomization immediately prior to the second line. There were also some differences in tolerability profiles, with diarrhea and hand-foot skin reaction being considerably higher in the SO/SU arm, while nausea and stomatitis were more common in the SU/SO arm.

This study concludes that both sequences achieved comparable PFS and OS with similar toxicity safety profiles, and further illustrates the ongoing need to determine the best sequencing strategies to optimize outcomes for mRCC patients.

Updated results from the International mRCC Database Consortium (IMDC)

There were 2 oral abstract presentations at GU-ASCO 2014 that provided up-to-date information from the Canadian-led IMDC. At the time of the GU-ASCO symposium, the registry included 3537 patients from 25 centres around the world, including 7 centres in Canada.[2]

Role of cytoreductive nephrectomy

Although cytoreductive nephrectomy (CN) had been proven to be advantageous in the interferon era, there have not been any randomized, controlled trials demonstrating its utility in the current era of targeted therapy. Researchers sought to use the IMDC database to help answer the question of whether or not CN still provides a survival benefit in patients with synchronous mRCC.[3] Included in the analysis were 982 patients with synchronous mRCC who underwent CN and 676 patients who did not. IMDC patients who underwent CN prior to metastases (n = 1587) were excluded from the analysis.

In terms of the patient characteristics, the group that had undergone CN included a higher proportion of patients with better prognosis (e.g., higher proportion of patients with favourable or intermediate IMDC prognostic criteria, better Karnofsky performance status [KPS], etc). The investigators therefore adjusted their results to account for these baseline differences.

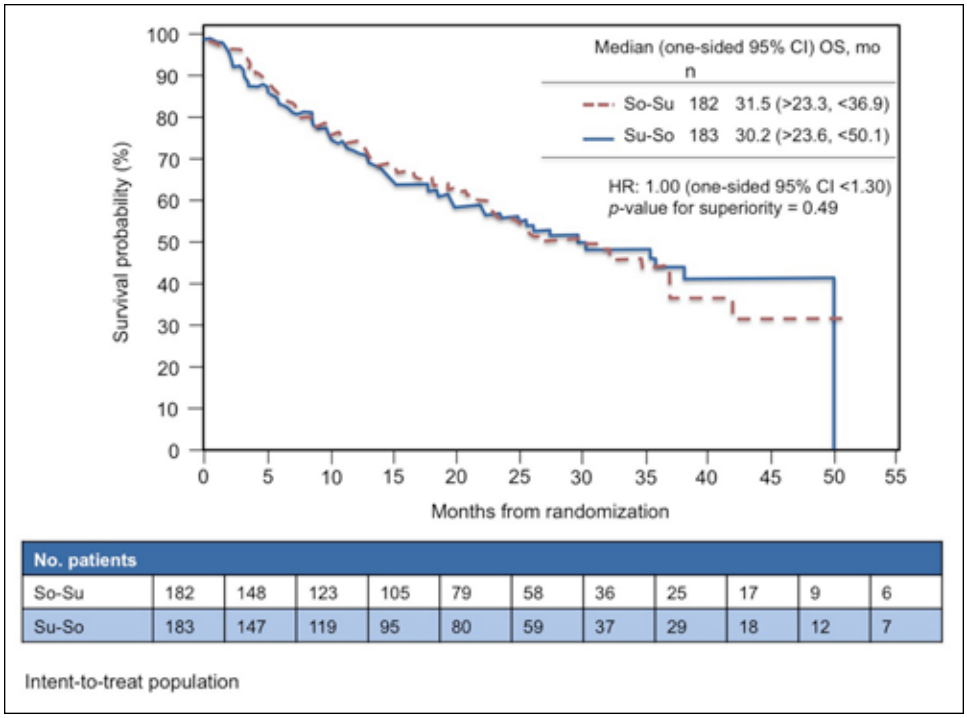


Fig. 1. SWITCH Study: Total progression-free survival by sequence of sorafenib and sunitinib.

The median overall survival was found to be 20.6 months for patients who underwent CN and 9.5 months for those who did not (HR adjusted for IMDC prognostic criteria: 0.60, 95% confidence interval [CI] 0.52 to 0.69, $p < 0.0001$) (Fig. 2). The investigators then stratified the patients within each group by life expectancy and found that the incremental benefit associated with CN was larger among those with a longer predicted life expectancy. They also stratified their results by the number of IMDC prognostic criteria, and found that CN was associated with significant benefit only in those patients meeting three or fewer IMDC criteria.

The authors conclude that patients with synchronous mRCC with a life expectancy of greater than 1 year appear to have a survival benefit with cytoreductive nephrectomy and targeted therapy.

The authors concluded that CN may extend overall survival in patients with mRCC, but that patients with 4 or more IMDC factors and limited life expectancy should probably not receive CN.

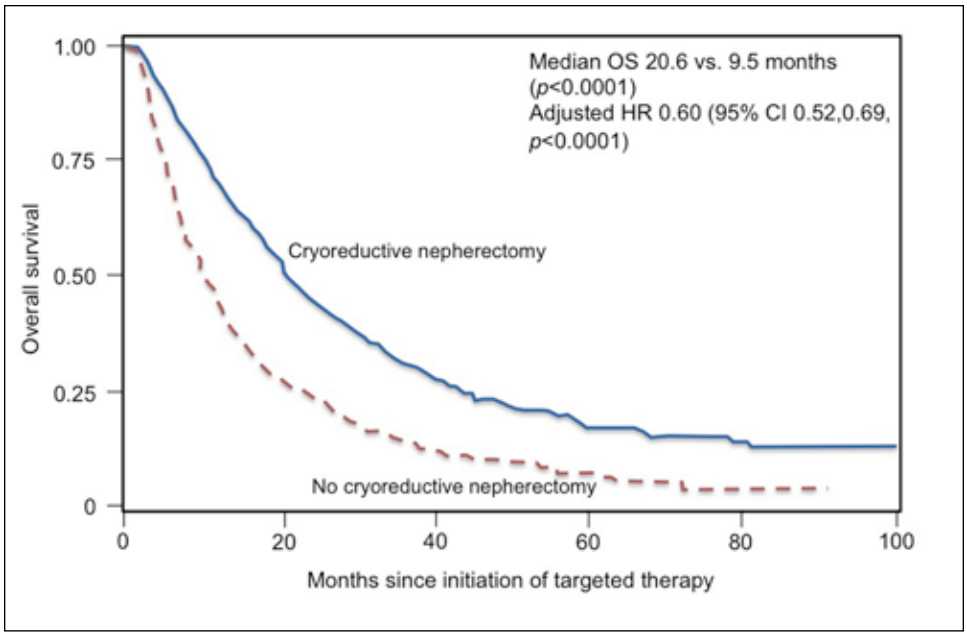


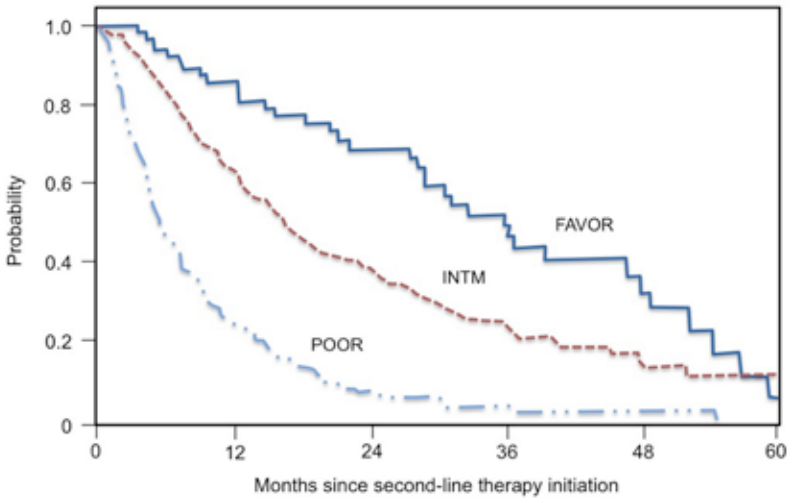
Fig. 2. International mRCC Database Consortium (IMDC): Overall survival: Cytoreductive nephrectomy versus no cytoreductive nephrectomy among patients with renal cell carcinoma and synchronous metastases.

Prognostic factors in second-line targeted therapy

Another analysis from the IMDC presented at GU-ASCO 2014 sought to validate the IMDC prognostic model in patients with mRCC receiving next-line targeted therapy after progression on first-line targeted therapy, and to compare the IMDC model to the 3-item Memorial Sloan Kettering Cancer Center (MSKCC) second-line prognostic model.[4]

The 6 IMDC prognostic factors are KPS <80%, diagnosis-to-treatment interval of less than 1 year, anemia, hypercalcemia, neutrophilia and thrombocytosis. If a patient has none of these prognostic factors, he or she is considered to have a favourable prognosis; 1 to 2 factors indicates an intermediate prognosis and 3 to 6 factors indicates a poor prognosis. The MSKCC model includes only 3 factors: KPS <80%, hypercalcemia and anemia. It was validated in the interferon era.

The population for this analysis consisted of 1021 patients from the IMDC who received a second-line targeted therapy after discontinuing a first-line targeted therapy. Of these patients, 22% had received immunotherapy prior to the first-line targeted therapy. Sunitinib was the most common first-line targeted therapy (66.5%), followed by sorafenib (19.8%). The most common second-line targeted therapies were sorafenib (29%), sunitinib (22%), everolimus (22%) and temsirolimus (12%).



No. of patients at risk						
FAVOR	76	52	31	19	8	1
INTM	529	257	97	37	9	4
POOR	261	49	9	3	1	0

Fig. 3. International mRCC Database Consortium (IMDC) prognostic Group: Overall survival with second-line targeted therapy.

In the univariate analysis, all 6 IMDC prognostic factors correlated with OS. In the multivariate analysis, 5 of the criteria remained statistically significant; only hypercalcemia did not. When the cohort was separated into favourable (n = 76), intermediate (n = 529) and poor prognosis (n = 261) by the IMDC criteria, the curves clearly separated (Fig. 3). The median OS for favourable, intermediate and poor prognosis were 35.3, 16.6 and 5.4 months, respectively. Statistical analysis suggested that the 6-item IMDC model enhances the predictive performance relative to the 3-item MSKCC model.

Other prognostic indicators in RCC

At GU-ASCO 2014, there were 2 other oral abstract presentations dealing with prognostic indicators in specific populations of patients with RCC. In clear cell RCC, American investigators validated the earlier observation that the presence of the single nucleotide variant rs11762213 located in the MET oncogene is an independent predictor of adverse cancer specific survival and time to recurrence.[5]

Another American group presented their findings showing that, in papillary RCC, lymphopenia is an independent risk factor for lower OS.[6] They concluded that the absolute lymphocyte count can significantly increase the accuracy of already established prognostic factors in this population.

References

NB: In addition to the published citations below, information for this article was also taken from the posters and lectures presented at the 2014 GU-ASCO meeting.

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