

# EVIDENCE WATCH

## A review and assessment of recent clinical trial data

*Oncology Exchange* provides overviews of important clinical trial data presented at the 41<sup>ST</sup> American Society of Clinical Oncology (ASCO) Annual Meeting, held May 13–17, 2005 in Orlando, Florida. Leading Canadian experts offer commentary and clinical interpretations.

### GI stromal tumour

#### PHASE 3, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF SU11248 IN PATIENTS (PTS) FOLLOWING FAILURE OF IMATINIB FOR METASTATIC GIST (ABSTRACT 4000).

**Investigators:** G.D. Demetri et al.

This double-blind, Phase III study was undertaken to explore therapeutic approaches for patients with metastatic gastrointestinal stromal tumour (GIST) whose tumours have become resistant to imatinib. Enrolled patients either had disease that progressed on imatinib therapy or did not tolerate the side effects of imatinib. They were randomized to receive placebo or 6-week cycles of single-agent SU11248 (50 mg once daily for 4 weeks, then 2 weeks with no therapy). Patients whose disease progressed during the

trial according to Response Evaluation Criteria In Solid Tumors (RECIST) were switched to unblinded therapy with SU11248, and were offered continued treatment for as long as they perceived clinical benefit.

At the first planned efficacy analysis on 312 patients, those receiving SU11248 had a median time to progression, the primary endpoint, of 6.3 months. This compared to 1.5 months for those on placebo, a more than 4-fold difference (hazard ratio 0.335 ( $p = 0.00001$ )). The trial was then

unblinded to enable all patients to receive the study drug. Overall survival also improved on SU11248, with a hazard ratio of 0.491 ( $p = 0.00674$ ). As patients who crossed over to SU11248 were recorded on the placebo survival curve, the difference between placebo and active drug was likely reduced. Patients receiving SU11248 experienced more adverse events, but very few were grade 3 and none were grade 4. Fatigue, diarrhea, oral mucositis, hand-foot syndrome, hypertension and hematologic events were reported.

#### COMMENTARY: A. Robert Turner MD, FRCPC, Professor of Medicine, University of Alberta, and Cross Cancer Institute, Edmonton, AB.

Gastrointestinal stromal tumour (GIST) was once unresponsive to any treatment that a medical oncologist could prescribe. Today, however, it is one of the most responsive tumours to the small molecule inhibitors that target tyrosine kinases, which are expressed on the cell surface as hematopoietic growth factor receptors and are involved in neoangiogenesis. Imatinib mesylate is remarkably effective in multiple phases of the treatment of GIST: it can be used in a neoadjuvant format, adjuvantly following surgery or in the treatment of recurrent, metastatic or inoperable disease. Most patients respond and tolerate it well. Some, however, cannot endure its side effects, particularly edema, and others have tumours resistant to imatinib mesylate. Resistant tumours can be treated by increasing the dose to a maximum of 800 mg/day,

but this often produces untoward side effects, for tumour control measured only in months.

The target of imatinib mesylate in GIST is the KIT kinase receptor. Related receptors include those of hematopoietic growth factors, FMS-related tyrosine kinase 3 (FLT3), vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF). SU11248 (sunitinib) inhibits the PDGF and VEGF receptors. While most clinical trials have been done on patients with metastatic GIST, and this malignancy appears to be the most sensitive, SU11248 has also shown activity in renal cell cancer, lung cancer and acute myelogenous leukemia.

It is gratifying to see the promise of anti-angiogenesis therapy finally being fulfilled. The extension of time to pro-

gression in these metastatic GIST patients resistant to imatinib mesylate is impressive — so hopefully further clinical trials will be done. Several other agents that target angiogenesis or the KIT mechanism are known whose relative benefits need to be explored. Further, there appears to be a new spectrum of side effects — hypertension, hand-foot syndrome and mouth pain — that we need to learn more about. Interestingly, SU11248 causes depigmentation of the hair while imatinib causes the opposite. Recently, a letter to the editor<sup>1</sup> from

researchers at the Institut Gustave Roussy reported that subungual splinter hemorrhages are a common finding in patients receiving anti-VEGF receptor agents such as SU11248 and BAY 43-9006. They suggest that splinter hemorrhages may be a surrogate marker of activity of these antiangiogenesis drugs.

#### References

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## Breast cancer

### DO STATINS REDUCE BREAST CANCER RISK? A CASE CONTROL STUDY IN US FEMALE VETERANS.

**Investigators: R. Kochhar et al.**

Animal research has shown that hydroxymethyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors, known as statins, may suppress tumour growth. Prior studies on the effect of statins on risk of breast cancer in humans have yielded conflicting results. This retrospective case control study presented by Kochhar et al used clinical and demo-

graphic information from the Veterans' Integrated Service Network (VISN) 16 database. Women who were taking statins prior to being diagnosed with breast cancer were classified as statin users; the analysis did not consider dose, duration or type of statin used. Out of 40,421 women with median age of 58 years (range 25–92 years), 4771 (11.8%)

were taking statins and 556 (1.38%) had breast cancer. The statin users were compared to those not taking statins. By multiple logistic regression analysis, after adjusting the data for age, smoking history, alcohol use and diabetes, 51% fewer of the women taking statins developed breast cancer (odds ratio 0.49, 95% CI 0.38–0.62,  $p \leq 0.0001$ ).

**COMMENTARY: Joseph Ragaz, MD, FRCPC, Director, Oncology Program at the McGill University Health Centre and Professor at McGill University Medical School.**

The issue of cancer prevention is an intensely studied area of breast cancer research. The most solid evidence for a significant reduction of cancer incidence due to intervention from a preventive agent comes from studies of antihormonal approaches. Ruby Kochhar et al's study brings statins to our attention as another class of potentially very effective and safe chemopreventive agents.

The first randomized trial of prevention, NSABP P-1, compared tamoxifen vs placebo and showed a significant 50% risk reduction (HR = 0.5). UK and Italian groups also demonstrated tamoxifen's impact, albeit lower in magnitude. Agents in 2 other antiestrogenic classes are currently being intensely tested for prevention: raloxifene and aromatase inhibitors (AIs). The NSABP P-2 prevention trial, which has already enrolled more than 17,000 women, is comparing tamoxifen to raloxifene, a refined selective estrogen response modifier (SERM) with a better risk-benefit ratio than tamoxifen. The UK intergroup IBIS 2 trial is comparing the AI anastrozole to placebo. Substantial reduction of breast cancer incidence is expected, as recent results of trials comparing AIs to tamoxifen have shown an almost 40% reduction of contralateral breast cancer. Interest in statins for breast cancer chemoprevention, another approach, is rising due to their direct impact on cholesterol and lipid levels, both associated with increased breast cancer risk.

#### PRECLINICAL STUDIES

Cholesterol is the main precursor for estrogens, and it is becoming evident that AIs profoundly reduce tissue estrogen levels. Statins inhibit HMG-CoA reductase, the rate-limiting enzyme in cholesterol synthesis, and hence may secondarily affect tissue estrogen metabolism. Laboratory studies confirm a profound antimitotic effect in many malignant cell lines, both cholesterol-mediated and through induction of growth factors, leading to either apoptosis or other types of cell death.<sup>1-4</sup> Cell culture and experimental animal studies show a strong association of statins and anti-breast cancer effect, explained by several plausible mechanisms including direct cell growth inhibition, interaction with negative growth factors, induction of apoptosis and intracellular cholesterol modulation.<sup>1-4</sup>

#### EARLIER EPIDEMIOLOGIC EVIDENCE

Human epidemiologic studies have not fully confirmed the strong preclinical evidence of statins' anti-breast cancer effect. Some studies have reported significant risk reduction, some no effect, and some an increased breast cancer incidence associated with statins. Boudreau et al<sup>5</sup> studied 975 women in 3 Washington state counties who were diagnosed with primary invasive breast carcinoma at ages 65–79, and

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## LANDMARKS

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compared them to 1007 matched controls randomly selected from a list of Social Security recipients. Statins neither increased nor decreased risk, with an odds ratio of 0.9 (95% CI 0.7–1.2). This provided reassurance that the increasing numbers of women who use statins — which are carcinogenic in rodents<sup>6</sup> — would not be subjected to higher risk of breast cancer. J.A. Cauley et al<sup>7</sup> conducted a multicentre prospective cohort study at 4 US community-based clinical centres. Among 7000 elderly women whose median age was 77 years, relative risk for the 576 (7.7%) who had received statins was reduced to 0.28 (95% CI 0.09–0.86). In women who used lipid-lowering drugs other than statins, relative risk was 0.37 (95% CI 0.14–0.99), suggesting that lowering lipids reduces the incidence of breast cancer.

On the other hand, Beck et al<sup>8</sup> found that among 13,592 statin users in Saskatchewan and 53,880 controls, statin use in women ≤ 55 years old was not associated with a statistically significant difference in breast cancer risk, with a relative rate of 0.81 (95% CI 0.53–1.24). In women > 55 years old, however, the higher relative rate of 1.15 (95% CI 0.97–1.37) in those taking statins indicated higher risk. J.A. Kaye et al<sup>3</sup> found that the breast cancer incidence among 50- to 79-year old women with untreated hyperlipidemia was substantially increased, with relative risk of 1.6 (95% CI 1.1–1.25). No evidence of risk reduction attributable to statins was found, with relative risk of 1.0 (95% CI 0.6–1.6). Importantly, a feature complicating the interpretation of these case-control epidemiologic studies is their non-randomized design and the fact that they examined women with underlying hyperlipidemia and high cholesterol levels — both very strong confounding breast cancer factors.

## NEXT: RANDOMIZED TRIALS

The present study is one of the largest ever reported. The significant 51% reduction of breast cancer incidence among statin users — after adjusting for age, smoking, alcohol use and diabetes — is in line with multiple preclinical studies investigating the impact of statins at a cellular level. To provide Level I evidence, however, randomized, prospective trials investigating the preventive potential of statins are required. These trials will need to restrict enrollment to a population of women at high risk for breast cancer and to exclude those with hyperlipidemia and hypercholesterolemia. As the adverse effects of statins are low (myositis, muscle problems and the need to monitor liver enzymes), some women at high risk of breast malignancy, even without hyperlipidemia, may consider taking statins, particularly as at the present time no large randomized controlled trials have been initiated. The definitive verdict of the impact of statins on breast cancer incidence, however, cannot be finalized until these studies are done. **CE**

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