



Management of patients with should not use past or present history of solid cancer

Evidence-based Medicine

Official Recommendations

Expert opinion

Steps to be taken before initiation of abatacept therapy in patients with a history of cancer

No studies have been performed to evaluate the benefits or risks of abatacept treatment in patients with known cancer or with a diagnosis of solid cancer within the past 5 years. Given the absence of data, as with TNF antagonists, caution requires that physicians should not use abatacept in patients who have a history of cancer within the past 5 years (except localized basal-cell and epidermoid skin cancer with disease-free excision margins).

Course of action if cancer is diagnosed during abatacept therapy

Abatacept discontinuation should be discussed on a case-by-case basis, according to the nature of the cancer. The event should be reported to the pharmacovigilance center.

Current knowledge on the risk of solid cancer during abatacept therapy

- The risk of inducing malignant diseases is always a concern when a new immunomodulating agent is introduced, particularly one that affects the T cells, which play a central role against development of tumors. This risk was thoroughly assessed in the abatacept development program, as preclinical carcinogenicity studies in a murine model showed an increased incidence of mammary tumors related to loss of control of replication of the viruses associated with the development of these malignancies. Furthermore, during Phase III clinical trials, several cases of lung cancer occurred in the abatacept arm, compared to none in the placebo arm.
- However, safety data obtained during drug development programs may be limited, because the sample sizes are too small to capture rare events. Pooling clinical trials is useful to increase the sample size. During the clinical trials, the incidence rates of non-melanoma skin cancers were similar in the abatacept group and in the placebo group (abatacept, IR=0.69 [95%CI, 0.39-1.11]; placebo, IR=0.59 [0.19-1.37]) (Table 2) (4). However, 5 patients in the abatacept group were diagnosed with lung cancer versus none in the placebo group. No differences were noted between the two groups regarding the other types of cancer (Table 2) (4).
- An advantage of clinical trials is that they include an ideal control group, randomly assigned. However, the double-blind period is always fairly short, which does not allow the detection of events that may develop only after prolonged use of the drug. Open-label extension periods enable the detection of larger numbers of events over longer periods of exposition. They provide information on the time to occurrence of a specific event. In the double-blind period of the pivotal trials, the incidence of solid cancer (excluding non-melanoma skin cancer) was estimated at 0.59/100 patient-years (versus 0.63 in the placebo group). The incidence of solid cancer remained stable during the extension period of these trials, with up to 7 years of follow-up. The incidence of solid cancer was 0.71/100 patient-years in the cumulative period. Increase in the incidence of lung cancer was stable with increasing abatacept exposure (0.24 and 0.16 in the double-blind and cumulative period, respectively) (27).

However, during the extension period, we are missing the benefit of a control group. Two solutions are available. The incidence of the overall malignancies during the drug development program can be compared to the expected incidence in the general population. However, this approach does not take into account the increased risk related to the disease itself (e.g., the risk of lung cancer is higher in RA patients than in the general population). Alternatively, the incidence of malignancies can be compared in abatacept-treated patients and in several historical cohorts of established RA patients before the introduction of biotherapies.

- Comparisons of the rates of solid cancers in abatacept-treated patients to the expected rates in the general population based on information in the Surveillance Epidemiology and End Results (SEER) database from the US, which supplies age- and sex-specific incidence rates, showed no overall increase in the risk of cancer (standardized incidence ratio [SIR]= 0.82; 95%CI, 0.61-1.08). However, there was a trend toward an increase in the risk of lung cancer (SIR=1.51; 95%CI, 0.80-2.59). On the other hand, there were trends toward decreases in colorectal cancer (SIR=0.32; 95%CI, 0.04-1.16) and breast adenocarcinoma (SIR=0.41; 95%CI, 0.17-0.85). These findings are in line with data usually obtained in populations of RA patients, independently from the treatments used, and they probably reflect the characteristics of the disease rather than those of abatacept (13).
- Comparisons to data from RA cohorts are more informative. Five RA cohorts were used as comparison groups: the British Columbia Population-Based RA Cohort in Canada, Norfolk Arthritis Registry in the UK, National Data Bank for Rheumatic Diseases in the US, General Practice Research Database or GPRD in the UK, and Early RA Register in Sweden. Overall, these cohorts contain more than 94,000 RA patients treated without biologics.

During the clinical development program, 4150 patients with RA were exposed to abatacept. This program included two Phase IIb studies, five pivotal trials (AIM, ATTAIN, ASSURE, ARRIVE, ATTEST), and a study of the mechanism of action of abatacept.

The overall risk of cancer (excluding non-melanoma skin cancer) was not significantly higher in the abatacept-treated group than in the RA cohorts treated with non biologic DMARDs: SIR values ranged from 0.40 to 1.06 depending on the cohort. Table 3 shows the incidence ratios for the main malignancies. For none of these malignancies was the incidence outside the confidence interval of the incidence in the cohorts treated with non biologics DMARDs (Figures 1 and 2) (43).

These results do not suggest an increase in the risk of malignancies (particularly lung cancer) in abatacept-treated patients compared to RA cohorts treated with non biologics DMARDs.

Similarly reassuring data have been recorded in patients with juvenile idiopathic arthritis. During a mean follow-up of 21 months in 153 children (8-17 years) included in the extension period of the pivotal trial establishing the efficacy of abatacept in this indication, no cases of solid cancer were reported (44).

However, these data come from clinical studies where patients had no co-morbidities nor history of cancer within the 5 years preceding study initiation. In addition, in at least five studies, a mammogram was required before study inclusion of women, which selected patients at low risk for developing breast cancer. These facts underline the value of registry data. The reassuring results of therapeutic trials are supported by preliminary data from observational studies.

In a single-center retrospective study of 100 patients with established RA (>5 years in 75% of cases) treated with abatacept alone (40%) or in combination after failure of at least one TNF antagonist, after a median exposure time of 9 months there were two reports of cancer (1 case each of lung cancer and uterine cancer) (45). Furthermore, an interim analysis of data from 682 patients with established RA (12 years) in the French ORA registry treated with abatacept alone (33%) or in combination, usually after failure of TNF antagonist therapy (85%), showed no alarm symptoms of a potential cancer risk in this population with co-morbidities and 5.4% prevalence of previous cancer (46). These reassuring real-life data will have to be confirmed by longer follow-up periods.

Tables

- **Table 2 - Overall incidence rates of Malignancy in abatacept and placebo therapy in the clinical trials, and breakdowns of malignancies, lymphoma, lung cancer and non-melanoma skin cancer (44)**

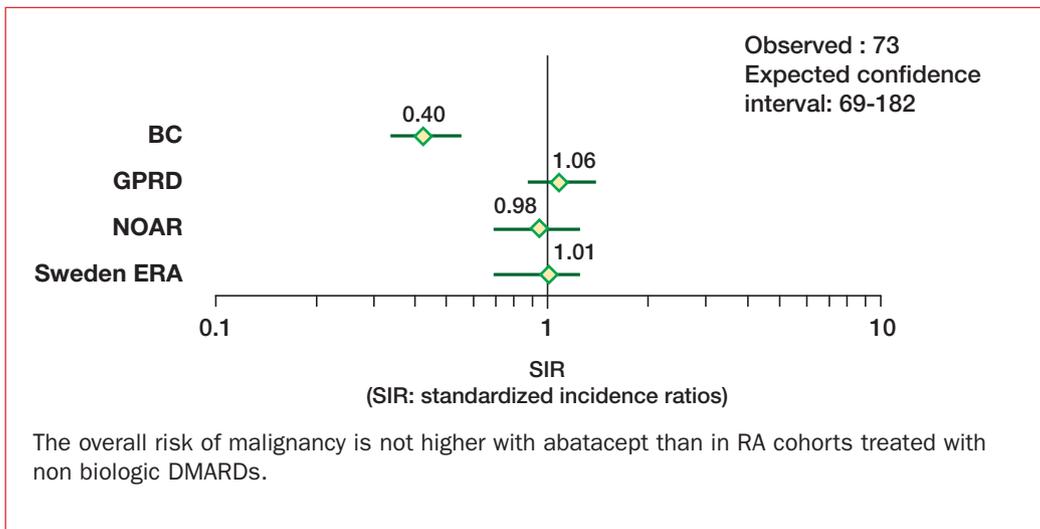
Tumors	n number of events rate per 100 patient-years [95%CI]	
	abatacept + MTX (N=3173)	placebo+ MTX (N=1099)
Malignant (other than non-melanoma skin cancer)	n=16 0.69 [0.39-1.11]	n=5 0.59 [0.19-1.37]
Solid cancer (any organ)	n=14 0.60 [0.33-1.01]	n=5 0.59 [0.19-1.37]
Lymphomas	n=1 0.04 [0.00-0.24]	n=0
Lung cancer	n=5 0.21 [0.07-0.50]	n=0
Non-melanoma skin cancer	n=19 0.82 [0.49-1.28]	n=7 0.82 [0.33-1.70]

● **Table 3 – Incidence rates of solid cancers during abatacept therapy, with break downs of malignancies (43)**

IR (95%CI) of malignancy*				
Malignancies	Double-blind placebo N=989	Double-blind abatacept N=1955	Five pivotal abatacept trials N=2689	Pooled abatacept N=4150
Patient-years	794	1688	8837	10365
All malignancies except non-melanoma skin cancer	0.63 (0.26-1.50)	0.59 (0.32-1.10)	0.74 (0.57-0.94)	0.71 (0.55-0.89)
Lung cancer	0	0.24 (0.09-0.64)	0.18 (0.10-0.29)	0.16 (0.10-0.26)
Colorectal cancer	0	0	0.02 (0.00-0.08)	0.02 (0.00-0.07)
Breast cancer	0.25 (0.06-1.01)	0.06 (0.01-0.43)	0.08 (0.03-0.16)	0.09 (0.04-0.16)

*events/100 patient-years; IR, incidence rate

● **Figure 1 – Overall incidence of malignancy during abatacept therapy compared to the incidence rate of malignancies in several RA cohorts treated with non biologic DMARDs (43)**



● **Figure 2 - Incidence of lung cancer during abatacept therapy compared to the incidence rate in several RA cohorts treated with non biologic DMARDs (43)**

