Avastin® (bevacizumab) in lung cancer
SAiL study summary

Background

Two phase III clinical trials (E4599[1] and AVAiL[2,3]) have demonstrated that first-line bevacizumab (Avastin®) in combination with chemotherapy significantly improves outcomes for patients with advanced or recurrent non-squamous non-small cell lung cancer (NSCLC).

The SAiL (Safety of Avastin In Lung cancer) study was designed to extend this knowledge and experience by investigating the safety and efficacy of first line Avastin combined with standard chemotherapy regimens in a 'real-world' clinical population of patients with advanced NSCLC. The findings from SAiL therefore provide an important bridge between the relevance of data already demonstrated from randomised trials of first line Avastin, to the management of NSCLC in a clinical practice setting.

Study overview: Large 'real world' study

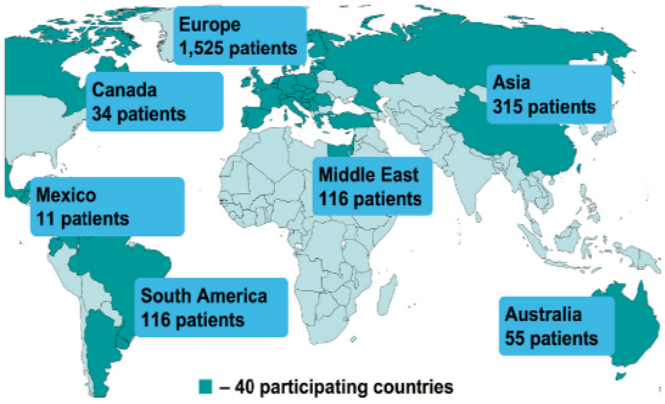

Figure 1 – SAiL: a global study with a safety population of 2,212 patients

- SAiL is a Phase IV international open-label, multicentre, single-arm study involving more than 2000 patients with untreated locally advanced, metastatic or recurrent non-squamous NSCLC.
- SAiL enrolled many patients who would not usually be included in randomised controlled Phase III trials, such as the elderly (those aged over 65 years) and those with poor performance status. SAiL also provided valuable information on the safety of Avastin-based therapy in patients who developed central nervous system (CNS) metastases during the study.
- The objective of SAiL was to confirm further safety and efficacy data for Avastin combined with a range of standard first line chemotherapy regimens, in a broad population of patients.
- Patients received Avastin (7.5 or 15mg/kg every 3 weeks) plus standard chemotherapy for up to 6 cycles, followed by single-agent Avastin maintenance until disease progression.

Efficacy: SAiL confirms consistent OS benefits with Avastin-based therapy over 1 year

- Patients in SAiL experienced an outstanding median overall survival (OS) of 14.6 months.
- Avastin was the first therapy to demonstrate a median OS for patients with lung cancer of over 1 year (E4599[1] and AVAiL[2]).
- The data from SAiL add to this consistent trend demonstrating the benefit of Avastin-based therapy in patients with advanced NSCLC.
- This represents an important advance since currently the prognosis for lung cancer patients with standard chemotherapy alone is 30% survival at 1 year and 10% survival at 2 years.[4]

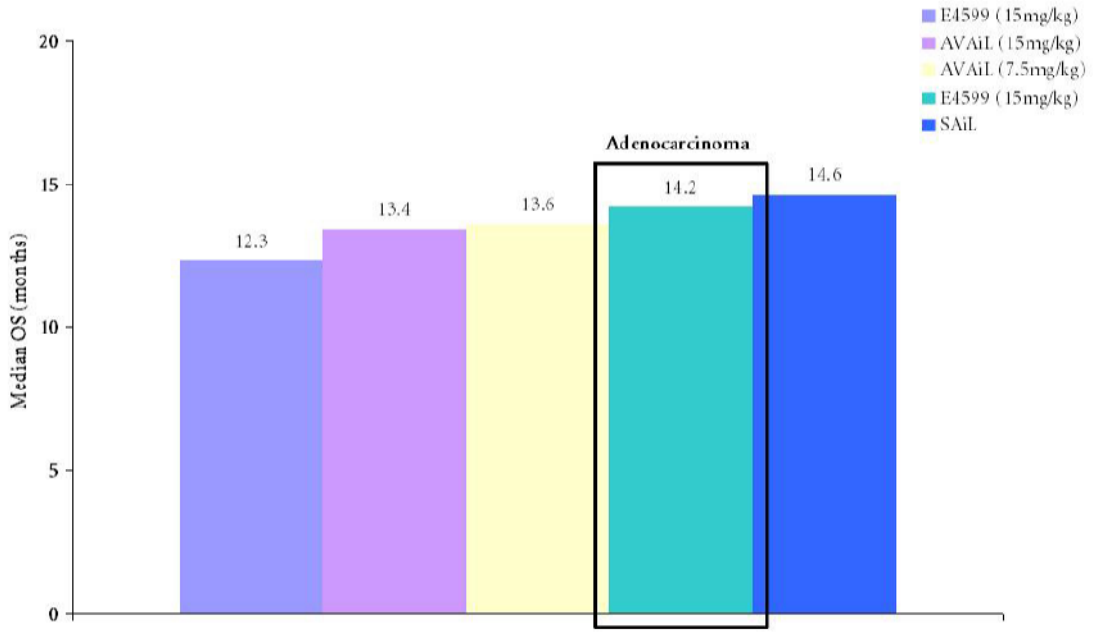

Figure 2 - SAiL confirms consistent OS benefits of Avastin-based therapy over 1 year and the longest OS in patients with adenocarcinoma NSCLC

Efficacy: in adenocarcinoma, the most common form of lung cancer

- The majority (86%) of patients in SAiL had a type of lung cancer called adenocarcinoma. This is the most common form of the disease.[5,6]
- Avastin-based therapy has previously demonstrated the longest survival time in first line treatment of adenocarcinoma of the lung[7]; the results of SAiL confirm this finding, with an unprecedented OS benefit in a broad patient population.

Efficacy: in disease control

- SAiL demonstrated efficacy as measured by disease control rate (DCR) and time to disease progression (TTP), endpoints that give a more detailed picture of the valuable clinical benefits of a therapy in terms of a patient's symptom improvement.
- Patients in SAiL experienced a DCR of 88.7%, a figure considerably higher than that previously reported in clinical trials of NSCLC.[1,2]
- SAiL also demonstrated a TTP of 7.8 months, a measure reflecting the time from the beginning of treatment until a patient's lung cancer is documented to progresses.

Efficacy: in diverse patient groups

- The OS of 14.6 months was observed in the overall broad study population, including those with the following baseline characteristics:
  - 6% of patients had poor performance status. These patients are normally not included in randomised controlled Phase III trials.
  - 73.4% of patients were receiving concomitant medications (e.g., anticoagulants).

Safety: low incidence of bleeding

- Twenty-six percent of patients in SAiL had central tumour location. These patients were previously perceived to be ineligible for Avastin-based
- A low incidence of clinically significant[i] side effects was observed; the overall rate of bleeding was low (3.6%) and pulmonary haemorrhage was a rare

[i] Clinically significant is defined as grade 3 or higher.

therapy because of the risk of bleeding.

event (0.7%).[8]

- Physicians treating patients in SAiL reported that very few side effects[ii] required interruption or discontinuation of Avastin therapy and that the majority of side effects resolved or improved.[8]
- The overall rate of bleeding in SAiL was low (3.6%) and pulmonary haemorrhage was a rare event (0.7%). In addition, only two (0.1%) patients experienced clinically significant CNS bleeding among the more than 200 patients who developed CNS metastases during the study.[8] These findings concur with those reported by a recent retrospective exploratory analysis of over 13,000 patients from 13 phase II/III trials of Avastin-based therapy across multiple cancer types, which recommended that patients with CNS metastases should not be generally excluded from Avastin therapy or clinical trials.[9]

4. Flexibility: with multiple chemotherapies

- Biologic therapies such as Avastin are typically prescribed together with chemotherapy. The combinability of Avastin with different chemotherapies is important as some patients tolerate and/or respond better to some chemotherapy agents than others.
- A broad range of chemotherapy regimens were used in the study, the main ones were: carboplatin doublets (49%) and cisplatin doublets (38%).
- SAiL demonstrates the consistent efficacy of Avastin across a wide range of regimens commonly used in clinical practice.[10]

Efficacy & safety- summary

- SAiL demonstrates an outstanding overall survival benefit of 14.6 months in a broad range of patients with NSCLC, including those patients with adenocarcinoma of the lung.
- SAiL provides important confirmation of the favourable and manageable safety profile of Avastin.
- Results were consistent across chemotherapy regimens and across patient types.

-0-

References

1 Sandler A, et al. Paclitaxel-Carboplatin Alone or with Bevacizumab for Non-Small-Cell Lung Cancer. N Engl J Med 355: 2542-50, 2006.
2 Reck M, et al. Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for non squamous non–small-cell lung cancer: AVAiL. J Clin Oncol 27:1227–34, 2009.
3 Reck M, et al. Overall survival with cisplatin/gemcitabine and bevacizumab or placebo as first-line therapy for non-squamous non-small cell lung cancer: results from a randomised phase III trial (AVAiL). Ann Oncol 2010; in press.
4 Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med; 346:92-8, 2002.
5 Alberg AJ, et al. Epidemiology of lung cancer. Chest 123:21S-49S, 2003.
6 Govindan R, et al. Changing epidemiology of small cell lung cancer in the United States over the last 30 years: Analysis of the Surveillance, Epidemiology, and End Results database. J Clin Oncol 24: 4539-44, 2006.
7 Sandler A, et al. Treatment outcomes by tumor histology in Eastern Cooperative Group (ECOG) study E4599 of bevacizumab (BV) with paclitaxel/carboplatin (PC) for advanced non-small cell lung cancer (NSCLC). J Thorac Oncol 2008; 3:11(Suppl. 4):S283 (Abstract 133).
8 Dansin E, et al. Safety and efficacy of first-line bevacizumab-based therapy in advanced non-small cell lung cancer (NSCLC): results of the SAiL study (MO19390). Poster discussion 219 on 23 September 2009, ECCO 15 and ESMO 34.
9 Besse et al. Bevacizumab Safety in Patients with Central Nervous System Metastases. Clin Cancer Res 16: 269-78.
10 Crino, L et al. Safety and efficacy of first-line bevacizumab-based therapy in advanced non-squamous non-small cell lung cancer (SAiL; MO19390): a multicentre, single-arm phase 4 study. Lancet Oncol; early online, July 2010.

[ii] Side effects included bleeding, hypertension and proteinuria.