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1 Drug description

Generic/Brand name/ATC code:

S-1, TS-1, Teysuno™/ L01BC53

Developer/Company:

Taiho Pharma Europe Ltd., Sanofi-Aventis

Description:

S-1 is an oral fluoropyrimidine

S-1 (Teysuno™) is a novel oral fluoropyrimidine derivative that contains three substances: tegafur, gimeracil and oteracil [1]. Tegafur, the main active substance in this pharmaceutical product, is a cytotoxic medicine that belongs to the anti-metabolites group. The prodrug tegafur is converted to 5-fluorouracil (5-FU) which is responsible for interfering with enzymes involved in producing new DNA. It thus inhibits the growth of cancer cells and eventually kills those cells. Gimeracil and oteracil support the administration of tegafur. Gimeracil inhibits the metabolism of 5-FU, resulting in high concentrations of 5-FU in the blood while oteracil reduces gastrointestinal toxicity [1].

S-1 is available in two different dosages (brown and white capsules). The white capsules consist of 20 mg tegafur, 5.8 mg gimeracil and 15.8 mg oteracil, whereas the brown capsules contain 15 mg tegafur, 4.35 mg gimeracil and 11.8 mg oteracil [1].

most commonly used dosage for NSCLC: 80mg/m² per day

The optimal dosage of S-1 for the treatment of non-small lung cancer (NSCLC) as well as the best chemotherapeutic agent it should be combined with cannot be determined yet, as the dosing regimens which were used in several clinical trials varied from 40mg/m^2 to 60mg/m^2 twice a day to 80mg/m^2 once daily. However, in the majority of trials and in the only phase III trial, 80mg/m^2 of S-1 daily were administered in combination with carboplatin.

For advanced gastric cancer, for which the EMA has granted market authorization, 25mg/m^2 of S-1 should be administered twice daily in combination with cisplatin [1].

Patients with kidney problems, severe leukopenia, neutropenia, thrombocytopenia or pregnant or breast feeding women should not receive S-1. Individuals suffering from severe and unexpected side effects, as well as patients with a deficiency of the enzyme dihydropyrimidine dehydrogenase (DPD) should not receive S-1 [1].

2 Indication

indicated in chemotherapy-naive patients with NSCLC

S-1 (Teysuno™) is indicated as 1st-line therapy for patients with advanced NSCLC in combination with a platinum-based chemotherapy.

3 Current regulatory status

not approved by EMA or FDA for NSCLC

The EMA has not yet approved S-1 (Teysuno™) for NSCLC, but granted market authorization for the treatment of advanced gastric cancer in combination with cisplatin in March 2011 [1].

Europe: market authorization for advanced gastric cancer

In the U.S., S-1 is not approved, but it has market authorization for gastric cancer in Japan, South Korea, China, Singapore and Taiwan. In Japan it is also licensed for six additional indications (colorectal, head and neck, non-small cell lung, metastatic breast, pancreatic and biliary tract cancers) [2].

4 Burden of disease

number one cause of cancer-related deaths worldwide

Lung cancer is the number one cause of cancer-related deaths worldwide [3]. The primary risk factor for lung cancer is smoking [4]. The number of cigarettes smoked per day and the number of years being a smoker has an influence on the risk of developing lung cancer, but also "second-hand smoke" is known to cause lung cancer [5]. Other, less frequent risk factors are the radioactive gas radon [6], asbestos [7], lung inflammation, lung scarring secondary to tuberculosis and a positive family history [8, 9]. Men are still more often affected by NSCLC than women, with the majority of patients being diagnosed at an age ≥ 65 years [10]. On average, patients are aged 71 years at the time of diagnosis of NSCLC.

primary risk factor: smoking

two types of lung cancer: NSCLC and SCLC

About 85 % of all lung cancers belong to NSCLC which can be differentiated further into 2 types: non-squamous carcinoma and squamous cell carcinoma [11]. About 3,600 people died of lung cancer and, overall, nearly 4,100 new cases of lung cancer were diagnosed in Austria in 2008 [12]. As NSCLC accounts for about 85% of all lung cancer cases [13, 14] of which up to 85% [16] can be expected to present with advanced disease, an estimated 2,900 persons present with advanced NSCLC per year in Austria.

classification according to TNM system

early stage disease, good performance status, female gender are associated with a good prognosis

The classification of NSCLC is done according to the tumour node metastases system (TNM) which takes into account primary tumour characteristics, the presence or absence of regional lymph node involvement and distant metastases. Four stages (I –IV) are distinguished; stage IIIB describes tumours which invade anatomical structures surrounding the lungs or with other tumour nodules in a different lobe of the same lung. In addition, lymph nodes other than those closest to the affected lung are involved. Stage IV refers to NSCLCs which have metastasized.

4 stages of NSCLC

The TNM system is used to guide treatment decisions [15]. In addition, patients' performance status, the histological type of the tumour and comorbidities are considered for the development of a treatment regimen [16].

K-ras and other biological markers like EGFR mutations are poor prognostic factors

Factors associated with a good prognosis are, besides early stage disease according to the TNM system, good performance status, female gender and no significant weight loss [17]. Poor prognostic factors, in contrast, include biologic prognostic factors like mutations of the tumour suppressor gene, the activation of proto-oncogene Kirsten-Rous sarcoma virus (K-ras) and other biological markers. For example, patients without EGFR mutations have a worse prognosis than those with mutations [18, 19]. Patients with stage IIIB and stage IV NSCLC have a median OS of 10 months and 6 months, respectively [16].

median OS for IIIB NSCLC: 10 months, for stage IV: 6 months

5 Current treatment

Treatment of patients with stage I to stage III NSCLC has a curative intent and comprises surgery, chemotherapy, radiation therapy or a combination of these treatment options. Patients with advanced tumours are treated with systemic therapy and/or palliative therapy. Appropriate treatment options for 1st –line therapy for patients with advanced disease (stage IV UICC7) are

combination chemotherapy

- Combination chemotherapy including either a
  - platinum compound (cisplatin or carboplatin) in addition to, for example, vinorelbine, paclitaxel, docetaxel, gemcitabine or pemetrexed
  - or, to avoid side-effects of platinum compounds, combinations of gemcitabine plus docetaxel or paclitaxel or vinorelbine, or paclitaxel plus vinorelbine

single agent chemotherapy

- Single-agent chemotherapy: several active agents are available including platinum compounds (cisplatin, carboplatin), taxanes (paclitaxel, docetaxel), vinorelbine, gemcitabine, pemetrexed, camptothecins (irinotecan, topotecan). However, single-agent chemotherapy is mainly used for elderly patients or for individuals with a compromised performance status and for none of the agents superiority was established.

monoclonal antibodies

- monoclonal antibodies (bevacizumab, cetuximab) in combination with chemotherapy or tyrosine kinase inhibitors (erlotinib, gefitinib) [20].

For patients without EGFR mutations or with unknown EGFR status, carboplatin or cisplatin based chemotherapy doublets either alone or in combination with a monoclonal antibody can be regarded as standard of care [20].

For patients with EGFR mutations, erlotinib or gefitinib are recommended instead of cytotoxic chemotherapy [20].

6 Evidence

one phase III trial

9 phase I/II trials

In addition to a free text search, a systematic literature search was conducted in Embase, Pubmed and the CRD Databases in May 2011. Overall, 85 references were identified, of which one phase III trial [21] and 9 phase II trials [22-30] were included in this report. The phase III trial evaluated S-1 in combination with carboplatin, whereas various combinations were used in the phase II trials. All studies were conducted in Japan.

6.1 Efficacy and safety - Phase III studies

Table 1: Summary of efficacy

Study title Phase III Trial Comparing Oral S-1 Plus Carboplatin With Paclitaxel Plus Carboplatin in Chemotherapy-Naïve Patients With Advanced Non–Small-Cell Lung Cancer: Results of a West Japan Oncology Group Study [21]			
Study Identifier	UMIN000000503, LETS Study (Lung Cancer Evaluation of TS-1)		
Authors/Sponsor	Taiho Pharmaceutical Co Ldt.		
Design	Phase III, randomized (1:1 ratio), open-label, multicentre		
	Patient enrolment: August 2006 – May 2008		
Hypothesis	Non-inferiority to establish the non-inferiority of S-1 plus carboplatin compared with paclitaxel plus carboplatin as first-line therapy in terms of overall survival (OS) in patients with advanced NSCLC.		
Treatment groups	**I**(ntervention)	carboplatin (AUC, 5) on day 1 + oral S-1 (40 mg/m^2 twice per day) on days 1 to 14 every 3 weeks for a maximum of 6 cycles	
	C(ontrol)	carboplatin (AUC, 6) + paclitaxel (200 mg/m^2) on day 1 every 3 weeks for a maximum of 6 cycles	
Inclusion & Exclusion	Inclusion criteria	male and female patients between 20 to 75 years, confirmed NSCLC stage IIIB without any indications for radiotherapy or stage IV, no prior treatment, measurable disease, ECOG performance status of 0 or 1, estimated life expectancy of at least 12 weeks	
	Exclusion criteria	concomitant serious disease, symptomatic brain metastases, active concomitant malignancy, pleural effusion, cardiac effusion, or cardiac effusion necessitating treatment, uncontrolled diabetes	
Endpoint and definitions	Overall survival (primary endpoint)	OS	NA
	Progression-free survival	PFS	NA
	Quality-of-life	QoL	Functional Assessment of Cancer Therapy–Lung (FACT-L) Neurotoxicity subscale of the FACT/Gynecology Oncology Group-Neurotoxicity (GOG-Ntx) version 4.13 Alopecia score: single item "I have been bothered with hair loss"
	Disease control	DC	Best tumour response among complete response, partial response or stable disease that was confirmed and sustained for ≥6 weeks
Database lock	NA		

Results and analysis			
Analysis description	Planned interim analysis Non-inferiority of carboplatin and S-1 was to be concluded if the upper limit of the 95% CI of the HR was lower than 1.33; that is, the null hypothesis that the median OS of the carboplatin and S-1 group would be up to 3.48 months shorter than that of the carboplatin and paclitaxel group was analyzed.		
Patient Demographic and Clinical characteristics	Median age: I 64 years vs C 63 years Gender: Male: I 77.0% vs C 76.5% Female: I 23.0% vs C 23.5% Histology: Adenocarcinoma: I 69.1% vs C 69.4%; Non-adenocarcinoma: I 30.9% vs C 30.6% Clinical stage: IIIB I 24.1% vs C 24.2%, IV: I 75.9% vs C 75.8% Smoking status: Smokers: I 81.6% vs C 81.5%, Non-Smoker: I 18.4% vs C 18.5% ECOG PS: 0: I 31% vs C 32%, 1: I 69% vs C 68%		
Analysis Population (1)	Intent-to-treat population (ITT): all patient who underwent random assignment		
Analysis Population (2)	Per Protocol (PP): ITT population minus patients considered to have major violations of inclusion or exclusion criteria and those who did not receive any protocol treatment.		
Descriptive statistics and variability estimates	Treatment group (ITT)	I	C
	Number of subjects	n=282	n=281
	OS (months) median 95%CI	 15.2 12.4 – 17.1	 13.3 11.7 – 15.1
	1-year-survival rate	57.3 %	55.5 %
	PFS (months) median 95% CI	 4.1 3.7 – 4.7	 4.8 4.2 - 5.1
	FACT-L	p=0.602	
	FACT-GOG-Ntx at 6 weeks at 9 weeks	 41.2 41.0 p <0.001	 38.2 37.1
	Alopecia score at 6 weeks at 9 week	 3.8 3.7 p<0.001	 1.7 1.9
	DC rate (%)	71.7 p=0.635	73.5
Effect estimate per comparison	*Comparison groups (ITT)*		*I vs C*
	OS	HR	0.928
		95% CI	0.730 to 1.179
		p-value	-
	PFS	HR	0.998
		95% CI	0.837 to 1.190
		p-value	-
	Comparison groups (PP)		*I vs C*
	OS	HR	0.931
		95% CI	0.732 to 1.186
		p-value	-

	PFS	HR	0.992
		95% CI	0.832 to 1.184
		p-value	-
	Subgroup analysis: Male (n= 432)		*I vs C*
	OS	HR	0.854
		95% CI	0.657 to 1.111
	Subgroup analysis: Female (n= 131)		*I vs C*
	OS	HR	1.189
		95% CI	0.657 to 2.150
	Subgroup analysis: Stage IIIB (n= 136)		*I vs C*
	OS	HR	0.765
		95% CI	0.469 to 1.249
	Subgroup analysis: Stage IV (n=427)		*I vs C*
	OS	HR	0.977
		95% CI	0.742 to 1.286
	Subgroup analysis: Nonsmokers (n=104)		*I vs C*
	OS	HR	0.884
		95% CI	0.429 to 1.821
	Subgroup analysis: Smoker (n=459)		*I vs C*
	OS	HR	0.924
		95% CI	0.717 to 1.193

Abbreviations: AUC = area under the curve, ECOG = Eastern Cooperative Oncology Group, NA = not available, DC = disease control, HR = hazard ratio, CI = confidence interval

Table: most frequent adverse events

Common Toxicity Criteria version 3	Outcome (%)	I (n = 279)	C (n=279)	P-values
All Grades	Haematologic			(All)
	Leukopenia	55.4	86.0	<0.001
	Neutropenia	58.3	89.6	<0.001
	Anaemia	86.7	82.4	0.165
	Thrombocytopenia	87.4	63.1	<0.001
	Non-haematologic			(All)
	Nausea	62.4	49.1	0.002
	Vomiting	34.1	23.7	0.007
	Diarrhoea	32.6	20.8	0.002
	Neuropathy: sensory	15.8	81.0	<0.001
	Alopecia	9.3	76.7	<0.001
Grade 3	Haematologic			(Grade 3 or 4)
	Leukopenia	5.0	29.7	<0.001
	Neutropenia	18.3	31.9	<0.001
	Anaemia	15.5	14.3	0.680

	Thrombocytopenia	19.4	7.2	<0.001
	Non-haematologic			(Grade 3 or 4)
	Nausea	1.8	2.2	0.475
	Vomiting	1.8	1.1	0.837
	Diarrhoe	3.2	1.1	0.302
	Neuropathy: sensory	0.4	2.9	0.668
	Febrile neutropenia	1.1	6.8	<0.001
Grade 4	Haematologic			(Grade 3 or 4)
	Leukopenia	0.4	2.9	<0.001
	Neutropenia	2.9	44.8	<0.001
	Anaemia	3.6	2.5	0.680
	Thrombocytopenia	13.3	2.2	<0.001
	Non-haematologic			(Grade 3 or 4)
	Febrile neutropenia	0	0.4	<0.001
Grade 5	Death	0.4	0.4	

phase III trial showed non-inferiority in OS

In this phase III trial, 564 previously untreated patients with stage IIIB/IV NSCLC were randomised either to carboplatin + paclitaxel or to carboplatin + S-1. An interim analysis was performed to evaluate if carboplatin and S-1 was non-inferior to carboplatin and paclitaxel in terms of overall survival (OS). Median OS was in the carboplatin + S-1 arm 15.2 months compared to 13.3 months in the carboplatin + paclitaxel arm, resulting in a HR of 0.928, demonstrating the non-inferiority of S-1 therapy. Results consistent with these findings were also found in several subgroup analyses. The 1-year survival rate was 57.3 % and 55.5%.

untreated stage IIIB/IV of NSCLC

median OS was 15.2 months compared with 13.3 months, HR 0.928

OS: S-1+ carboplatin non-inferior in comparison to carboplatin +paclitaxel in interim-analysis

Quality-of-life (QoL) was evaluated using the FACT-L and the FACT/GOG-Ntx questionnaires. For the lung cancer subscale (FACT-L) no differences between the two treatment arms were found, but carboplatin + S-1 showed significant improvements in the FACT/GOG-Ntx (evaluation of chemotherapy-induced neuropathy) and the alopecia score.

Two deaths were reported as a result of toxicities. One patient died due to gastrointestinal haemorrhage in the carboplatin + S-1 arm and one death was associated with febrile neutropenia and pneumonia in the carboplatin + paclitaxel arm.

QoL evaluated by FACT-L and FACT/COG-Ntx

tolerable side effects of S-1

The treatment of S-1 + carboplatin was associated with more platelet transfusion and with higher rates of nausea, vomiting and diarrhoea of any grade. Other AEs of any grade (e.g. leukopenia, (febrile) neutropenia, neuropathy and alopecia) occurred more frequently in the carboplatin + paclitaxel arm [21]. Regarding side effects of higher grades, only thrombocytopenia was more often observed in the carboplatin + S-1 arm, whereas leukopenia, neutropenia and febrile neutropenia of grade 3/4 were observed more often in the carboplatin + paclitaxel arm, but dose delays, foremost due to haematological toxicity, were considerably more frequent in the S-1 arm (52%) than in the comparison group (10%).

56% patients in the carboplatin + paclitaxel arm and 61% patients in the carboplatin + S-1 arm discontinued treatment. Of those, 61% patients dis-

continued due to progressive disease in the carboplatin + S-1 group and 52% in the carboplatin + paclitaxel arm. Fewer patients, however, stopped treatment by reasons of toxicity in the S-1 group (I 11% vs C 14%).

6.2 Efficacy and safety - further studies

Studies with S-1 + platinum compound

4 phase II studies using S-1 + platinum compound all conducted in Japan

In this study 29 patients received oral S-1 (65mg/m^2 for 14 days) and **carboplatin** in a 4 week cycle [22]. No complete response (CR) occurred, but partial responses (PR) in 9 patients resulted in an overall response rate of 31.0%. The median survival was 16 months and the PFS was 4.5 months. Regarding toxicities, haematological adverse events of grade ≥3 were leukopenia (13.8%), neutropenia (10.3%), anaemia and thrombocytopenia (3.4% each). The only higher grade non-haematological adverse events were infections which were seen in 3.4% of all patients [22].

different dosages of S-1 used

55 patients were treated with oral S-1 (40 mg/m^2 twice daily) for 21 consecutive days. 60mg/m^2 of **cisplatin** was administered intravenously on day 8 [23]. Every 5 weeks this schedule was repeated. Out of the 55 eligible patients, 1 CR and 25 PR were observed, resulting in an overall response rate of 47%. The 1-year survival rate was 45 % and the 2-year survival rate was 17%. At a median follow-up of 28 months, median survival time was 11 months. Most common toxicities of grade 3 or 4 were neutropenia (29%), anaemia (22%) and leukopenia (6%). Anorexia of grade 3 or 4 was the most often observed non-haematological toxicity and occurred in 13% [23].

studies with cisplatin show similar results regarding OS (11 to 18 months)

no complete response observed

Another study investigated a combination therapy of S-1 with weekly **cisplatin** [24]. 26 previously untreated patients with stage IIIB/IV NSCLC were treated with oral S-1 (40mg/m^2 twice daily) for 21 days and three consecutive weekly low doses of cisplatin (25mg/m^2) followed by a 2-week rest period. 6 PR were observed but no CR, yielding an overall response rate of 23.1%. The median survival time was 13.4 months and the median PFS was 5.4 months. Haematological toxicities of grade 3 and 4 were observed in up to 15%. Most common non-haematological toxicities of grade ≥ 3 were diarrhoea and fatigue which occurred in 8% each. No treatment-related deaths were observed. [24].

no treatment related deaths

haematological grade 3 or 4 AEsin maximum of 29%

Another study [25] assessed S-1 (40mg/m^2 twice daily) in combination with **cisplatin** (60mg/m^2) in 40 previously untreated patients. Again, no CR response was observed, but due to a PR in 7 patients, the overall response rate was 17.5%. Median survival time was 17.9 months and PFS 4.3 months. .Grade 3 or 4 toxicities were anaemia (15%) and leucocytopenia (7.5%). No grade 4 non-haematological AE was observed [25].

Studies with S-1 only

2 other phase II studies

S-1 as mono-therapy

Two phase II studies investigated S-1 only [26, 27]. Patients received 50-75 mg/m^2 or 80 mg/m^2 daily. No CR was observed in either of the trials, but PR ranged between 12.5% [26]- 22.7% [27]. Median survival time was between 8.4 months [26] to 10.2 months [27]. Grade 4 toxicities were rare in both studies, because only fatigue and diarrhoea occurred in 1 patient each. Most frequent haematological grade ≥3 AEs were leucopenia, neutropenia and

anaemia in up to 6.8%; anorexia and diarrhoea were the most common non-haematological AEs of higher grades.

Studies with S-1 + other chemotherapeutic regimens

Three studies [28-30] comprising between 56 [28] and 80 patients [29] assessed S-1 at doses ranging from 40mg/m² to 80mg/m². It was combined with **doxetacel** [30], **irinotecan** [28] or **gemcitabine** [29]. Median OS was between 15 months [28, 30] and 19 months [29] and PFS ranged from about 4 months [29] to 5 months [28, 30]. No CR was observed in any of the trials and ORR were with 28% comparable. Regarding toxicities, the most frequent of grade ≥3 AE were neutropenia (25% [28] to 73% [30]), febrile neutropenia (6% [29] to 17% [30]) and thrombocytopenia 11% [29] to 14% [28].

3 other phase II studies:

combination with doxetacel, irinotecan or gemcitabine

7 Estimated costs

No cost estimates for S-1 (Teysuno™) are available yet in Austria.

costs for Teysuno™ unknown

might be higher than other treatment regimens

8 On-going research

No on-going phase III trials investigating S-1 (Teysuno™) in patients with NSCLC were found at ClinicalTrials.gov.

Nevertheless, a few on-going phase I/II trials are registered:

- NCT00874328: to determine the maximum-tolerated dose, the recommended dose, and to evaluate the response rate and toxicity of the S-1, irinotecan and cisplatin combination in patients with advanced or metastatic NSCLC. The estimated date for study completion is December 2012.
- NCT00227578: to evaluate the effect of administration S-1 together with cisplatin as a first-line therapy in the treatment of patients with stage III or IV NSCLC that cannot be removed by surgery. Start of this trial was in 2005, but there is no end date mentioned yet.
- NCT00227552: to investigate S-1 as second-line therapy in treating patients with un-resectable or recurrent stage III or stage IV NSCLC. The end of study date is unknown.

no on-going phase III trials

some on-going phase I/II studies were found

9 Commentary

At the moment, Teysuno™ (S-1) is not approved for the 1st-line therapy of advanced NSCLC, neither by the EMA nor by the FDA. However, the EMA approved, like several Asian countries, S-1 for gastric cancer in March 2011

not yet approved for NSCLC in Europe

[31]. In Japan, the drug is also licensed for other tumour entities including NSCLC [2].

one phase III trial with a large non-inferiority margin

S-1 + carboplatin is non-inferior to paclitaxel + carboplatin in terms of OS

some advantages: fewer higher grade AEs, some QoL outcomes improved

For NSCLC, several studies, mostly phase II, were found which investigated S-1 in different combinations and with different dosages. Only one phase III trial evaluated 1st-line therapy with oral S-1 + carboplatin in comparison to paclitaxel + carboplatin in previously untreated patients with advanced NSCLC. Within this trial, non-inferiority of S-1 for OS was demonstrated at a planned interim analysis (when final results can be expected remains unknown), but even the authors themselves mention that the selected non-inferiority margin of 1.33 (that is risk of death increased by 1/3 was tolerated) was large. Improved QoL results for S-1 were found for some scores, such as the alopecia score, but no difference was shown in the FACT-L score. Concerning AEs of higher grades, only thrombocytopenia was statistically significant more often observed in the S-1 group, whereas other AEs were more frequent in the comparison group, but dose delays due to haematological toxicity were necessary in 52% of carboplatin and S-1 courses and in 10% of the carboplatin and paclitaxel courses. These findings are consistent with those of the phase II studies, which assessed S-1 in combination with various different agents. Toxicity can thus be regarded as acceptable.

all trials conducted in Asian population, included young patients with excellent or good PS

unknown if differences between men and women

Nonetheless, it should be mentioned that all trials were conducted in Japan. In addition, patients in the phase III study were, with an average age of 63 years, younger than patients usually are at diagnosis and only patients in good condition were included. Estimating if S-1 is also non-inferior in frail and older Caucasian patients is therefore difficult. Furthermore, even though a subgroup analysis showed consistent results for several characteristics, these analyses were not sufficiently powered. It would be thus of interest to further investigate these variables as differences of efficacy of S-1 might exist between men and women.

comparator used does not reflect standard therapy

in addition, more targeted therapies increasingly used as 1st line therapy for patients with EGFR mutations, but no information on EGFR status for study population available

In addition, the comparator of the phase III study might not reflect standard therapy for patients which were included in the study (i.e. adenocarcinoma, good performance status), because monoclonal antibodies (e.g. bevacizumab or cetuximab) in addition to platinum-based chemotherapy doublets are recommended for these patients rather than chemotherapy alone [13, 16]. Moreover, EGFR testing prior to initial therapy is increasingly gaining importance to identify patients most likely to benefit from agents targeting the EGFR (e.g. gefitinib) [13], but the study did not provide information on the EGFR mutational status. Since superiority and not only non-inferiority in terms of prolonged PFS (but not for OS) was shown in phase III studies for gefitinib [32], it is unlikely that S-1 offers more distinct benefits to patients with EGFR mutations. Based on the available evidence, S-1 is an alternative to standard-chemotherapy only for patients not eligible for monoclonal antibodies and with unknown or negative EGFR mutation status.

oral application might offer advantages depending on therapy replaced but bears risk of adherence problems

Even though oral administration is usually an advantage of new therapies, this might not hold true in this case, since most chemotherapeutic regimens for NSCLC are administered intravenously every 3 weeks [16]. The S-1 regimen used in the phase III study also required patients to receive intravenous drugs every 3 weeks. Hence, the only advantage of a faster infusion time (by sparing the administration of a 2nd intravenous drug) might be outweighed by adherence problems when S-1 has to be taken autonomously and regularly at home. If S-1 replaces other intravenous agents which need to be administered more often, then oral administration offers an advantage.

costs unknown

An important question is how much S-1 will cost, but because of its oral application the price might be rather high. Since NSCLC is a very common type of cancer, the budget impact can thus be considerable. But even without market authorization for NSCLC, due to its licensing for gastric cancer, S-1 might be used off-label.

replacing well-established therapy might not be justified

In summary, the non-inferiority of S-1 was established in comparison to standard platinum-based doublet therapy and showed some advantages in terms of toxicities and QoL. However, the available evidence does currently not indicate that patients who qualify for more targeted treatment options will benefit from S-1, and the price is potentially higher than that for standard chemotherapeutics.

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