ORIGINAL ARTICLE

# Cytisine Therapy Improved Smoking Cessation in the Randomized Screening and Multiple Intervention on Lung Epidemics Lung Cancer Screening Trial

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## ABSTRACT

**Introduction:** Cytisine, a partial agonist-binding nicotine acetylcholine receptor, is a promising cessation intervention. We conducted a single-center, randomized, controlled trial (RCT) in Italy to assess the efficacy and tolerability of cytisine as a smoking cessation therapy among lung cancer screening participants.

**Methods:** From July 2019 to March 2020, the Screening and Multiple Intervention on Lung Epidemics RCT enrolled 869 current heavy tobacco users in a low-dose computed tomography screening program, with a randomized comparison of pharmacologic intervention with cytisine plus counseling (N = 470) versus counseling alone (N = 399). The primary outcome was continuous smoking abstinence at 12 months, biochemically verified through carbon monoxide measurement.

**Results:** At the 12-month follow-up, the quit rate was 32.1% (151 participants) in the intervention arm and 7.3% (29 participants) in the control arm. The adjusted OR of continuous abstinence was 7.2 (95% confidence interval: 4.6–11.2). Self-reported adverse events occurred more frequently in the intervention arm (399 events among 196 participants) than in the control arm (230 events among 133 participants, $p < 0.01$). The most common adverse

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events were gastrointestinal symptoms, comprising abdominal swelling, gastritis, and constipation.

**Conclusions:** The efficacy and safety observed in the Screening and Multiple Intervention on Lung Epidemics RCT indicate that cytisine, a very low-cost medication, is a useful treatment option for smoking cessation and a feasible strategy to improve low-dose computed tomography screening outcomes with a potential benefit for all-cause mortality.



*Keywords:* Cytisine; Smoking cessation; Lung cancer screening; Tobacco; Clinical trial

## Introduction

Lung cancer (LC) is the leading cause of cancer mortality in men and women, accounting for 28% of all cancer deaths in Europe.[1] Only 21% of patients with LC are still alive at five years, as approximately 70% of patients are diagnosed with having advanced disease.[2] Approximately 90% of LC cases are attributable to carcinogens contained in tobacco smoke.[3] The most effective intervention for LC prevention is smoking cessation therapy. At least two trials, the U.S. National Lung Screening Trial and the Dutch-Belgian LC screening trial (NELSON), revealed that early detection through low-dose computed tomography (LDCT) screening can achieve a 20% to 26% reduction in LC mortality,[4,5] and the Multicentre Italian Lung Detection trial revealed that extended screening beyond 5 years enhances the benefit to 39% reduction.[6]

Nonetheless, LC is just one determinant of smoking-related mortality, and mortality from cardiovascular and pulmonary diseases and other cancers limits the benefit of LDCT screening.[7] Indeed, the fact that a large proportion of screened individuals continue to smoke is a reason of the unclear LDCT benefit on overall mortality, because most of them die from smoking-related diseases other than LC.[5,8] In contrast, compared with permanent smoking, smoking cessation in older adulthood significantly improves life expectancy[9,10] even in patients with LC,[11] and we observed a statistically significant reduction in all-cause mortality in participants who stopped smoking during LDCT screening.[12]

Smoking cessation treatments are not systematically offered to LDCT screening participants, even though combined psychological and pharmacologic support could substantially increase quit rates.[13] The first-line medications are currently nicotine replacement therapies (NRTs), bupropion and varenicline.[14,15]

Cytisine, a plant-based alkaloid that is extracted from *Cytisus laburnum* and selective partial agonist at nicotinic acetylcholine receptors, has been licensed and used for smoking cessation in eastern Europe since the 1960s[15–18] and is currently manufactured as a generic agent by Sopharma a (Tabex) and Aflofarm Pharma (Desmoxan).[19,20] Cytisine is a promising cessation intervention that is highly effective and 10 times less expensive than NRT or varenicline.[15] Nevertheless, the level of evidence of its efficacy is limited by the few randomized trials available thus far.[15] In July 2021, varenicline was withdrawn from the market owing to unacceptable N-nitroso-varenicline levels.[21]

The Screening and Multiple Intervention on Lung Epidemics (SMILE) study was launched in 2019 to test the efficacy of LDCT screening in combination with a multifactorial preventive intervention, focused on smoking cessation therapy with cytisine and reduction of chronic inflammation with low-dose acetylsalicylic acid (cardioASA) in heavy tobacco users, with the aim of reducing all-cause mortality. The purpose of this analysis was to evaluate the efficacy and tolerability of cytisine for smoking cessation when administered in capsule form, with two different dosage schedules lasting 40 days and 84 days, respectively.

## Materials and Methods

### Study Oversight

The SMILE randomized controlled trial (RCT; ClinicalTrials.gov identifier: NCT03654105) is an ongoing single-center prospective study offering LDCT screening to all participants, together with factorial randomization to smoking cessation and anti-inflammatory intervention. The SMILE trial was conducted at the Fondazione IRCCS Istituto Nazionale dei Tumori of Milan after approval of the Institutional Review Board and Ethics Committee (code: INT 0021/11). All eligible volunteers provided written informed consent. The trial was designed to recruit 2000 individuals, with 80% expected current tobacco users, and an adequate sample size to detect a 30% reduction in C-reactive protein levels in the cardioASA arm and a 20% increase in the quitting rate in the cytisine arm, with an $\alpha$ value of 0.05 and a statistical power of 90%.

### Participants

A total of 1114 volunteers were recruited and randomized from July 2019 to March 2020, when enrolment was closed owing to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic. The statistical power of the study was re-estimated with the sample size that was reached, as described in the Supplementary Material. Eligible participants were

current heavy tobacco users aged 50 to 75 years with more than or equal to 30 pack-years (obtained multiplying the number of 20-cigarette packs smoked per day by the number of years the person has smoked), years, or former tobacco users with more than or equal to 30 pack-years who had stopped since 10 years or less. For the present analysis, we considered only current heavy tobacco user (excluding former tobacco user). Major details on recruitment and eligibility criteria are reported in the Supplementary Material. Of the 1114 randomized participants, 87 (7.8%) withdrew from the study before their scheduled first appointment, and 49 (4.4%) were lost owing to SARS-CoV-2 restrictions. For the present analysis, we excluded former tobacco users, including all current tobacco users randomized to the cytisine versus the control treatment (n = 869).

### Randomization

Eligible participants with signed informed consent were randomly allocated to four different groups, with stratification by smoking history, sex, and age at recruitment. Participants and the researchers who collected the outcome data were aware of the treatment allocation at the date of the first appointment. Current tobacco users were randomized into the following four different groups: (A) CardioASA, cytisine and smoking cessation counseling; (B) cytisine and counseling; (C) CardioASA and counseling; and (D) only counseling. Within the present analysis, we considered the combination of groups A and B (i.e., individuals who smoked tobacco receiving smoking cessation counseling plus cytisine) as the intervention arm and the combination of groups C and D (receiving smoking cessation counseling but not cytisine) as the control arm. The intervention arm was further randomized into the standard schedule of 40 days and a prolonged schedule of 84 days. Details on former tobacco users are reported in the Supplementary Materials. The randomization algorithm was implemented with 2000 participants, and the earlier cessation caused a slight imbalance among the four arms. The randomization algorithm had a factorial design which considered three different strata of population according to age ($\leq$65 versus $>$65 y), sex, and smoking status (current versus former). The algorithm was based on the recursive creation of an array of 100 binary values, on their shuffling within the array and the random extraction of one of these values. The algorithm started by evaluating the total population already randomized, and a corrective factor was recursively introduced on the basis of the number still missing to the achievement of the established 2000 volunteers. The complete balancing of the various arms was expected when the number of volunteers would have reached 2000 individuals. At the first level, the randomization stratified anti-inflammatory intervention or its control, and at the second-level treatment with cytisine or its control. For the first 45% of the population, the generation of the array happens in proportion, 45% for the largest arm and 55% for the smaller arm, whereas for the following 55% of the subjects, the proportion becomes 35% for the larger arm and 65% for the smaller arm, with further modularity in favor of the arm that was less numerous, to the exceeding of 10% of delta between the two values. Further details on the randomization algorithm and his later validation through simulations (Supplementary Table 1) are reported in the Supplementary Materials.

### Data Collection and Follow-Up

Each randomized volunteer was assigned a personal account on the SMILE website (https://www.programmasmile.it/) to complete online questionnaires. At baseline, sociodemographic characteristics and smoking history information were collected, together with pulmonary function tests, thoracic LDCT, carbon monoxide (CO) measurements, blood samples for the evaluation of the inflammatory, metabolic, and microRNA profiles, and anthropometric measurements were performed. Every 6 months, all participants were invited to complete online questionnaires on smoking and eating habits. Cytisine was offered as a free medication to all volunteers in the treatment arm, whereas the control arm received counseling and information on the available substances to help quitting, but no cost-free medications. Participants randomized to the intervention arm (i.e., the arm with cytisine medication) were offered additional telephone behavioral support. The protocol included three counseling calls for both arms: at 7/14/25 days from the start of cytisine therapy or baseline screening examination. In the intervention arm, the first phone call seven days after the start of therapy was used to verify the good tolerability of the drug and to give the tobacco user positive reinforcements and encouragement; the second phone call at 14 days was used to verify the smoking cessation and the 25 days counseling session to support the tobacco user and reduce the risk of relapses. In the control arm, the three phone calls were used to check the status of tobacco consumption, motivate, and collect information on the health status. In both arms, there was always the possibility for the participants to contact the counselor whenever needed. Adverse events (AEs) were recorded at each round and follow-up call, and participants were required to report any change in the state of health or hospitalization. Each AE was registered and classified by the investigators using the "Common

Terminology Criteria for Adverse Events," version 5.0. All volunteers with negative or indeterminate baseline LDCT results were sent to a 12-month follow-up round, whereas those with suspicious LDCT results underwent a diagnostic workup within three months, according to the study protocol. At the 12-month round, the SARS-CoV-2 questionnaire, CO measurement, thoracic LDCT results, and blood samples were collected, and adherence to the interventions (cytisine and cardioASA) was assessed by the counselor. The standard cytisine schedule lasted 40 days, with a total of 165 tablets of 1.5 mg each. The prolonged schedule lasted 84 days with a reduced dosage after the first 40 days for a cumulative dose of 274 tablets. Supplementary Figure 1*A* to *C* reveals details on the timeline of the study procedures and on the different dosages of the standard and prolonged treatments. Current tobacco users assigned to the cardioASA treatment received 100-mg tablets per day for two years. Consideration regarding treatment with cardioASA is reported in the Supplementary Materials (Supplementary Tables 2 and 3).

### Study Objectives

The primary end point of the present analysis was continuous abstinence for 12 months from the baseline round in the two arms. Smoking cessation at 1 year was defined by a counselor with confirmation of a CO level of less than or equal to 9 parts per million (ppm). Expired CO was always tested with the same monitor (piCO, Bedfont Scientific Ltd.). We used the CO cutoff of 9 ppm because all participants were heavy tobacco users ($\geq$30 pack-years) with a high probability of chronic obstructive pulmonary disease.[22,23] All participants with a CO level greater than 9 ppm were defined by the counselor as current tobacco users, including those that claimed to have stopped. Participants who were lost at follow-up or withdrawn the study were considered as current tobacco users. The secondary end point was the point prevalence at 12 months, defined as abstinence for the 7 days before the 1-year visit, with confirmation of CO less than or equal to 9 ppm. Other end points were evaluated, including the reduction in the number of cigarettes smoked from the baseline round to 12 months, the difference between the standard and prolonged treatment, smoking relapses, self-reported treatment compliance, and AEs. The counselor reported the information obtained from each telephone counseling sessions and recorded the smoking cessation date. Relapsed were defined by the counselor's assessment as a person who resumed smoking (more than five cigarettes per d) after a continuous week of abstinence. The relapses were self-reported at each telephone counseling.

### Statistical Analysis

In this analysis, only randomized current tobacco users were included, and comparisons were made between the intervention and control arms. Descriptive statistics of the volunteers sociodemographic characteristics and smoking information were reported as numbers and percentages for categorical variables and as medians with interquartile ranges for continuous variables. Proportions were compared by the chi-square test or Fisher's exact test as appropriate. Continuous variables were compared by the Wilcoxon-Mann–Whitney test. Differences in smoking cessation in the intervention arm compared with the control arm were evaluated by quit rates and univariate and multivariate logistic regressions, estimating the OR with 95% confidence intervals (CIs). In the multivariate models, all selected baseline variables (age, sex, marital status, education, smoking, C-reactive protein, body mass index, CO level) were considered eligible, adding variables with a forward stepwise approach with a statistical significance level of 0.1. The first analysis was performed on all 869 randomized tobacco users, whereas sensitivity analyses were restricted to 750 participants with a completed baseline round and 633 participants with a completed 1-year round. Compliance was evaluated by reporting the frequency of those who stopped the cytisine treatment. The analyses were performed according to the intention-to-treat principle. All analyses were performed using the Statistical Analysis System Software (Release SAS: 9.04; SAS Institute, Cary, NC).

## Results

### Characteristics of the Participants

Of 4415 volunteers registered on the SMILE website, 1114 were randomized (Fig. 1), including 869 current tobacco users (78%). Of these, 470 (54%) were assigned to the intervention arm including cytisine and 399 (46%) were assigned to the control arm. Among tobacco users assigned to the intervention arm, 11% (52 of 470) withdrew for personal reasons or owing to the SARS-CoV-2 pandemic, whereas in the control arm, 17% (67 of 399) of the participants left the trial. The baseline round started in July 2019 and ended in March 2020 owing to coronavirus disease 2019 (COVID-19) restrictions. Screening resumed with the 1-year follow-up visits in October 2020 (Supplementary Fig. 1*A*). A total of 750 current tobacco users completed the baseline round: 418 in the intervention arm and 332 in the control arm. Loss to follow-up at 12 months was similar in the two groups, being 14.8% (62 of 418) and 16.5% (55 of 332), respectively. A total of 633 tobacco users completed the 1-year-round.

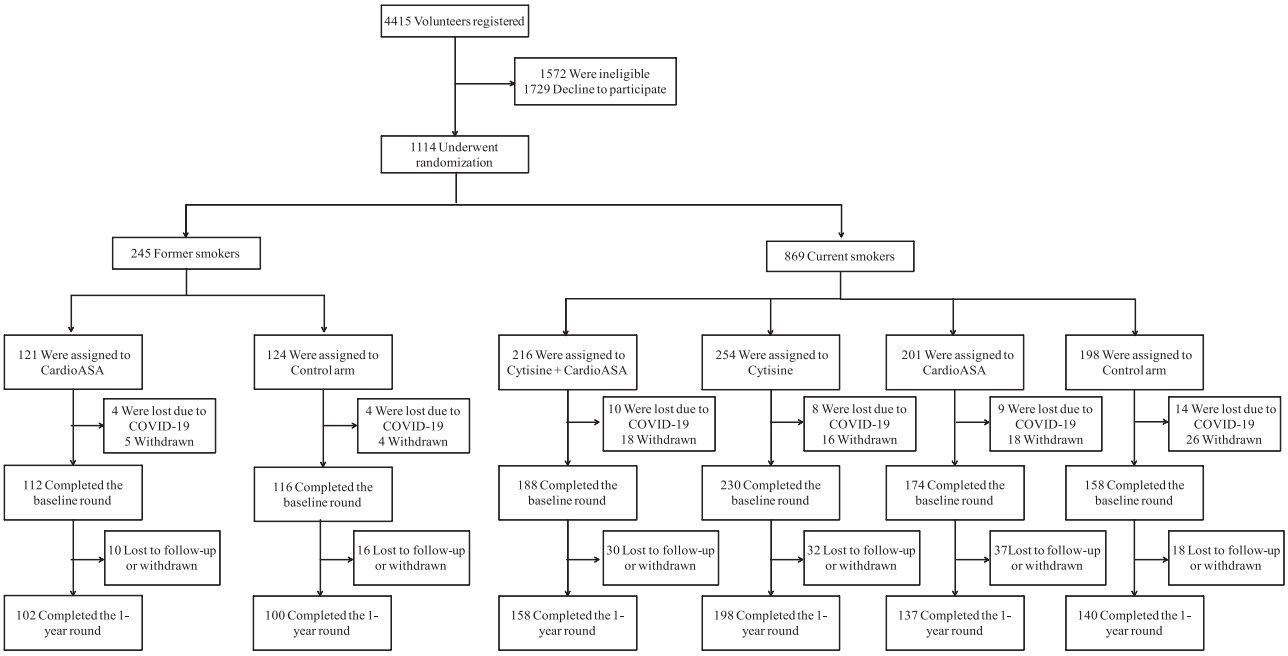


**Figure 1.** SMILE trial design: Consort diagram of the numbers of participants who were enrolled in the study stratified for all arms. CardioASA, chronic inflammation with low-dose acetylsalicylic acid; COVID-19, coronavirus disease 2019; SMILE, Screening and Multiple Intervention on Lung Epidemics.

Baseline characteristics were balanced between the two groups, except for the education level ($p = 0.016$) (Table 1 and Supplementary Tables 4 and 5).

## Outcomes

Table 2 illustrates the primary outcome results in terms of continuous abstinence for 12 months. The overall quit rate was significantly higher in the intervention arm than in the control arm (32.1% versus 7.3%), with a crude OR of 6.0 (95% CI: 4.0–9.2). The adjusted OR of continuous abstinence for 12 months was 7.2 (95% CI: 4.6–11.2). The 7-day point-prevalence abstinence was consistent with the primary end point, 37.5% (176 of 470) and 12.3% (49 of 399), respectively, with a corresponding OR of 4.3 (95% CI: 3.0–6.1). Sensitivity analysis revealed similar findings (Supplementary Table 6). Among 750 participants who attended the baseline round, the 12-month quit rate was

**Table 1.** Characteristics of the Participants

| Participants Characteristics | Total (N = 869) | Intervention (n = 470) | Control (n = 399) | *p* Value |
|---|---|---|---|---|
| Female sex, n (%) | 377 (43.4) | 211 (44.9) | 166 (41.6) | 0.33 |
| Age, median (IQR) | 60 (56-64) | 60 (56-64) | 60 (56-64) | 0.44 |
| Married, n (%) | 567 (65.2) | 297 (63.2) | 270 (67.7) | 0.14 |
| Level of education, n (%) | | | | |
| Primary, middle school | 121 (13.9) | 76 (16.2) | 45 (11.3) | 0.016[a] |
| Secondary school | 494 (56.8) | 273 (58.1) | 221 (55.4) | |
| Degree: master's, PhD | 254 (29.3) | 121 (25.7) | 133 (33.3) | |
| CRP, median (IQR)[b] | 1.3 (0.7-2.8) | 1.4 (0.7-2.8) | 1.2 (0.6-2.6) | 0.15 |
| BMI, median (IQR)[b] | 25.8 (23.1-28.9) | 26.1 (23.5-28.9) | 25.6 (22.8-28.8) | 0.26 |
| Carbon monoxide in exhaled breath, ppm, median (IQR)[b] | 19 (12-25) | 19 (13-26) | 18 (11-24) | 0.06 |
| Pack-years, median (IQR) | 43 (35-52) | 43 (35-52) | 43 (36-52) | 0.41 |
| Age at which the first cigarette was smoked, median (IQR) | 16 (15-18) | 17 (15-18) | 16 (15-18) | 0.23 |
| Previous attempt to stop smoking, n (%) | 703 (80.9) | 378 (80.4) | 325 (81.5) | 0.70 |

[a]Among participants who reported their level of education, the *p* value for the comparison of the two groups was less than 0.05.
[b]For these variables, the median was calculated considering the population at the baseline round.
BMI, body mass index; CRP, C-reactive protein; IQR, interquartile range.

**Table 2.** Smoking Cessation According to the Randomization Arm

| Smoking Cessation | Intervention (n = 470) | Control (n = 399) | OR (95% CI) | Adjusted OR[a] (95% CI) |
|---|---|---|---|---|
| Primary outcome: | | | | |
| Continuous abstinence for 12 mo, n (%) | 151 (32.1) | 29 (7.3) | 6.0 (4.0-9.2) | 7.2 (4.6-11.2) |
| Secondary outcome: | | | | |
| 7-d point-prevalence abstinence, n (%) | 176 (37.5) | 49 (12.3) | 4.3 (3.0-6.1) | 4.8 (3.3-6.9) |

*Note:* The primary end point was continuous abstinence for 12 months after the baseline round. The analysis is based on the intention-to-treat principle, and participants with a missing smoking status were classified as tobacco users. The secondary end point was the 7-day point-prevalence abstinence at the 1-year visit.

[a]Adjusted OR for sex, carbon monoxide levels, and pack-years at baseline.

36.1% in the intervention arm (151 of 418) and 8.7% in the control arm (29 of 332), with a crude OR of 6.0 (95% CI: 4.0–9.2) and an adjusted OR of 7.2 (95% CI: 4.6–11.2). Among the 633 participants who completed the 1-year round, the 12-month quit rate was 42.4% in the intervention arm (151 of 356) and 10.5% in the control arm (29 of 277), with a crude OR of 6.3 (95% CI: 4.1–9.8) and an adjusted OR of 7.8 (95% CI: 4.9–12.4). The adjusted OR of continuous abstinence for 12 months between standard and prolonged treatment was 1.5 (95% CI: 1.0–2.3). The crude OR was 1.4 (95% CI: 0.9–2.1) (Supplementary Table 7). Among those continuing smoking, the difference in the average number of cigarettes smoked between the baseline round and the 1-year round was higher in the intervention arm (7.3 versus 4.6, $p < 0.01$) (Supplementary Table 8). Consideration regarding treatment with cardioASA is reported in the Supplementary Tables 2 and 3.

## Trends Over Time

Smoking cessation and relapses over time in the intervention arm are described in Figure 2. In the intervention arm, 17.7% (83 of 470) of the participants had a relapse. Of these, 59.0% (49 of 83) relapsed during the SARS-CoV-2 restrictions (lockdown), and 14.5% (12 of 83) relapsed during the summer holiday (August). The time to first smoking cessation was 2 weeks in the standard and prolonged arms (Supplementary Table 9), whereas the time to relapse from baseline was shorter in the standard arm (19.4 versus 25.6 weeks, $p = 0.02$). The trend of smoking cessation and relapses over time in the two intervention arms and control arm is reported in Figure 3. The distribution of CO levels at 1-year round according to smoking status is illustrated in Supplementary Figure 2.

## Adverse Events

A total of 629 AEs were recorded (399 in the intervention arm and 230 in the control arm), which involved a total of 329 participants: 41.7% (196 of 470) in the intervention arm and 33.3% (133 of 399) in the control arm. The most common AEs were gastrointestinal symptoms or disorders, comprising abdominal swelling, gastritis, and constipation. A total of 50 events related to

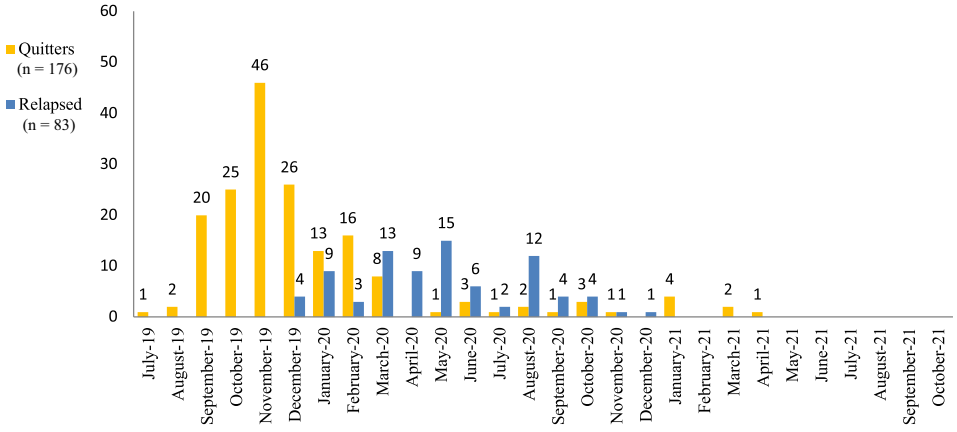


Figure includes current tobacco users randomized to the intervention arm.
Quitters were defined by the counselor as self-reported abstinence for at least a week. Relapsed were defined by the counselor as those who resumed smoking after a continuous week of abstinence. The relapses were self-reported at each telephone counseling, and biochemically confirmed by CO level > 9 ppm only at 12 months.

**Figure 2.** Time trends of tobacco cessation and relapses. CO, carbon monoxide; ppm, parts per million.

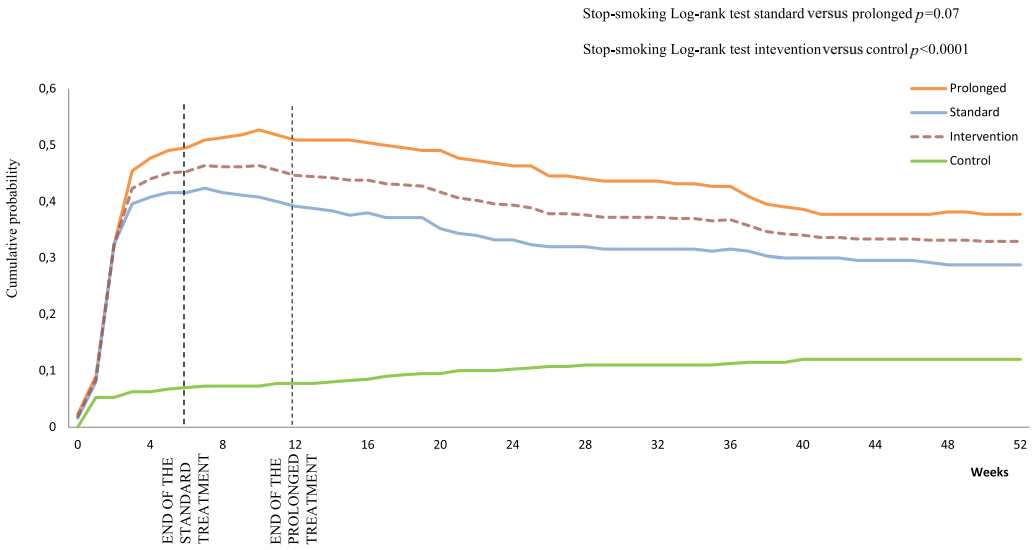


**Figure 3.** Cumulative probability and smoking cessation trend in the intervention and control arms.

SARS-CoV-2 were recorded: 6.4% (30 of 470) in the intervention arm and 5.0% (20 of 399) in the control arm (Table 3). Supplementary Table 10 lists the reported AEs related to the cytisine treatment observed in the intervention arm. The most frequent cytisine-related AEs were sleep disorders (57 of 470, 12.1%), nausea and vomiting (40 of 470, 8.5%), and increased appetite and weight gain (19 of 470, 4.0%). No differences in the AEs were observed between the standard and prolonged treatments (Supplementary Table 11).

**Table 3.** Adverse Events and Serious Adverse Events

| Adverse Events and Serious Adverse Events | Intervention (n = 470) | Control (n = 399) |
|---|---|---|
| Adverse events | 399 | 230 |
| Participants with any adverse event, n (%) | 196 (41.7) | 133 (33.3)[a] |
| Any gastrointestinal event | 80 (17.0) | 59 (14.8) |
| Any psychiatric event | 77 (16.4) | 53 (13.3) |
| Any central nervous system event | 62 (13.2) | 39 (9.8) |
| Any cardiorespiratory event | 8 (1.7) | 5 (1.3) |
| Any other event | 22 (4.7) | 14 (3.5) |
| SARS-CoV-2 | 30 (6.4) | 20 (5.0) |
| Serious adverse events | 48 | 44 |
| Participants with a serious adverse event, n (%) | 39 (8.3) | 34 (8.5)[b] |
| Serious adverse events, n (%) | | |
| Death[c] | 2 (0.4) | 2 (0.5) |
| Cancer | 16 (3.4) | 13 (3.3) |
| CVD | 6 (1.3) | 8 (2.0) |
| Pneumonia | 3 (0.6) | 1 (0.3) |
| Other | 15 (3.2) | 13 (3.3) |
| SARS-CoV-2 | 1 (0.2) | 1 (0.3) |

*Note:* Participants who reported more than one event in the same category were counted only once.
[a] $p < 0.01$
[b] $p = 0.91$
[c] The two deaths that occurred in the intervention arm were from pulmonary neoplasm and from bowel cancer and the other two in the control arm were from multiple myeloma and from cardiocirculatory arrest owing to a probable heart attack.
CVD, cardiovascular disease; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

There were 92 serious AEs (SAEs): 48 in the intervention arm and 44 in the control group; 4 deaths were observed: two in the intervention arm and two in the control arm (Table 3). All the other SAEs are listed in Supplementary Table 12. There was no evidence of an interaction between cardioASA treatment and the development of AEs and SAEs (Supplementary Table 13). The detailed list of all AEs is illustrated in Supplementary Table 14.

Of the 470 participants randomized in the intervention arm, 13.8% (65 of 470) discontinued treatment, and among them, 63.1% (41 of 65) stopped cytisine owing to AEs. No SAEs were attributable to cytisine. Of volunteers who underwent the baseline screening round, 84% (633 of 750) completed the 1-year screening round with LDCT examination, CO measurement, blood sample collection, and counseling to assess the adherence to the interventions (cytisine and cardioASA) (Supplementary Table 15).

## Discussion

Cigarette smoking is the most widespread and serious addiction and a major cause of death from cancer and cardiovascular and pulmonary diseases, with more than 8 million people dying from a tobacco-related disease per year worldwide.[24] In Italy, more than 93,000 deaths are attributable to tobacco smoking (20.6% of the total deaths

in males and 7.9% in females), with direct and indirect costs of more than 26 billion euros.[25]

Nicotine is the main psychoactive component of tobacco and the reason for its strong addictiveness. Similar to varenicline, its synthetic derivative, cytisine, acts as a selective partial agonist at $\alpha_4\beta_2$ and binds to nicotinic acetylcholine receptors with an affinity that is higher than that of nicotine.[26,27]

Cytisine is the oldest medication licensed and used in central and eastern Europe for smoking cessation,[16,17] and products containing cytisine are available in central and eastern European countries, such as Russia and Poland, western Asia, and Canada.[28–32] Current Food and Drug Administration–approved drugs for smoking cessation in the United States are varenicline and bupropion. In 2018, the Food and Drug Administration approved an RCT in the United States to test the efficacy of cytisine at higher dosages (3 mg versus 1.5 mg), with promising results.[33] Cytisine was found to have an excellent efficacy and safety profile when randomly compared with placebo or NRT[20,34,35] and represents a valid alternative to varenicline, being well tolerated and substantially less expensive.[15,32] Varenicline has been used in most countries as a first-line antitobacco therapy since 2006, notwithstanding the higher market price than cytisine.[15,19] No differences in the reduction of craving and tobacco withdrawal symptoms between the two drugs have been reported.[26] In 2014, the National Institute for Health Research assessed the cost-effectiveness of cytisine compared with varenicline, revealing that cytisine had a more favorable cost-effectiveness profile.[36] Two recent randomized trials conducted in Australia and New Zealand revealed that cytisine had significantly fewer AEs than varenicline.[37,38] Moreover, in July 2021, the pharmaceutical producer recalled certain lots of varenicline owing to the presence of unacceptable N-nitroso-varenicline levels,[21] and varenicline is no longer available on the market.

The SMILE RCT has revealed that cytisine is very effective in promoting smoking cessation among LDCT screening volunteers, with a higher quit rate at 12 months than that in other studies with placebo comparison.[34,35] Cytisine was well tolerated by volunteers; no other AEs were observed besides those mentioned in previous cytisine studies,[20,34] whereas the SAEs were similar in the two arms. Of interest, only 4% of volunteers in the intervention arm reported weight gain. A more accurate evaluation of weight change will be assessed at 24 months for all participants. Moreover, in the cytisine arm, there was a significant ($p < 0.01$) reduction in the number of cigarettes smoked in those participants who had not stopped smoking. These results match favorably with those obtained with bupropion in a double-blind, placebo-controlled RCT conducted in Italy in 2004,[39] but cytisine is by far more cost-effective given its low price.

The SMILE RCT aimed to compare a 40-day schedule with a prolonged treatment of 84 days (more similar to varenicline), but the study failed to reach the adequate sample size to prove a significant benefit associated with prolonged schedule. Nonetheless, the adjusted OR of continuous abstinence for 12 months between standard and prolonged treatment reveals encouraging results in favor of the scheme that provided a prolonged treatment: OR 1.5 (95% CI: 1.0–2.3; Fig. 3).

The LDCT screening period represents a recognized opportunity window to offer heavy tobacco users intense and prolonged smoking cessation counseling. The implementation of a smoking cessation therapy is still under debate, and until now, most of the LDCT screening studies did not routinely offer a cost-free pharmacologic therapy in addition to intensive counseling.[4–6] A recent systematic review identified five randomized control trials that evaluated smoking cessation interventions during LDCT screening: none of these interventions provided a zero-cost pharmacologic therapy in combination with counseling.[40] In these trials, the used strategy was insufficient to determine a significant change in smoking habits, whereas it is now well-established that the combination of pharmacologic therapies and systematic counseling increases the long-term smoking cessation rate.[13] In the SMILE RCT, the use of cytisine together with intensive behavioral support by the counselor resulted in a very high CO-confirmed quitting rate at 12 months, with an OR of 6.0.

Because of the COVID-19 pandemic and consequent restrictions, the SMILE RCT enrolment had to be closed in March 2020, well before reaching the target of 2000 participants. Nonetheless, thanks to the implementation of rapid antigenic swabs, the screening activity was resumed in October 2020, having applied a SARS-CoV-2–specific prevention algorithm approved by the ethics committee.[41] As a consequence, during the Italian second wave of SARS-CoV-2 (October 2020–May 2021), SMILE participants had the possibility of safely adhering to their 1-year–round LDCT screening and prevention schedule (Supplementary Fig. 1*A*).

The SMILE trial was the first program revealing that LDCT screening could be combined with pharmacologic therapy to improve smoking cessation. The strengths of this study were the evaluation of the continuous smoking abstinence for 12 months and the confirmation of abstinence by direct interview and CO level measurement at the 1-year follow-up. The SMILE program proved to be feasible and safe even during the COVID-19 pandemic, with no risk of infection for screened volunteers and hospital personnel.[41]

A study limitation was the researchers' and volunteers' awareness of the allocation arm, which could have caused a reporting bias of AEs and differences in the compliance to the screening program after the randomization.

In conclusion, the well-revealed efficacy and availability at low cost make cytisine a useful treatment option for smoking cessation and a valid alternative to varenicline, with substantial benefits for the health care system budget in all countries where varenicline is no longer available and a better cost-effectiveness profile than bupropion. Furthermore, according to some surveys, current heavy tobacco users have a greater propensity to use medicines of natural origin. Finally, introducing antismoking therapy with a favorable cost-effectiveness ratio in LDCT screening programs satisfies an ethical need and could improve the global outcome of preventive strategies against LC and other smoking-related diseases.

## CRediT Authorship Contribution Statement

**Ugo Pastorino:** Study design, Patient recruitment and management, Data collection, Data analysis, Data interpretation, Writing.

**Vito Ladisa**: Study design, Data collection, Data interpretation, Writing.

**Sara Trussardo**: Patient recruitment and management, Data collection, Data analysis, Writing.

**Federica Sabia**: Study design, Data collection, Data analysis, Data interpretation, Writing.

**Luigi Rolli**: Patient recruitment and management, Data collection, Data analysis, Writing.

**Camilla Valsecchi**: Data collection, Data analysis, Data interpretation, Writing.

**Roberta E. Ledda**: Study design, Patient recruitment and management, Data collection, Data analysis, Writing.

**Gianluca Milanese**: Study design, Patient recruitment and management, Data collection, Data analysis, Writing.

**Paola Suatoni**: Patient recruitment and management, Data collection, Writing.

**Mattia Boeri**: Study design, Data collection, Data analysis, Writing.

**Gabriella Sozzi**: Study design, Data collection, Data analysis, Writing.

**Alfonso Marchianò**: Study design, Patient recruitment and management, Data collection, Data analysis, Writing.

**Elena Munarini**: Study design, Data collection, Data analysis, Data interpretation, Writing.

**Roberto Boffi**: Study design, Data collection, Data analysis, Writing.

**Silvano Gallus**: Study design, Data collection, Data analysis, Data interpretation, Writing.

**Giovanni Apolone**: Study design, Data analysis, Data interpretation, Writing.

## Ethical Approval

This study was approved by the Institutional Review Board and Ethics Committee (code: INT 0021/11).

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## Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2022.07.007.

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