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Status and trends of chemotherapy for advanced NSCLC

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Abstract

With a response rate of 20%, cisplatin has been considered the key-drug in the treatment of NSCLC since 1980 and the combination of cisplatin-etoposide, cisplatin-vinblastine and cisplatin-vindesine have been considered standard regimens for NSCLC up to the mid 1990s. In the last 10 years, several new drugs have emerged; the most promising are vinorelbine, taxanes, gemcitabine and irinotecan which all have showed response rates of 20–30% among previously untreated patients. These agents have also been evaluated in combination with cisplatin, carboplatin or other drugs with encouraging results. There is not a single gold-standard doublet but cisplatin-based chemotherapy along with vinorelbine, taxanes or gemcitabine are the established standards in this setting. Carboplatin can replace cisplatin in selected patients but is not obviously as active in terms of survival impact. Triplets have not showed superiority over doublets in the vast majority of randomised studies. Genetic characteristics of the tumour are also important sources of prognostic information, and pharmacogenetic approaches, such as the tumoral detection of tumour specific mutations, that can predict chemoresistance to specific drugs, represent an area of great hope. Finally, the better understanding of the biology of lung cancer has led to the development of novel therapies directed at tumour-specific targets. Most of these targets are tumour growth factor signal pathways but tumour proliferation, angiogenesis or apoptosis may also be targeted. Several new agents have already demonstrated a promising activity. Nevertheless, most phase III studies have been disappointing and the combination of cytotoxic doublets and targeted agents have also failed to demonstrate any substantial improvement up to now.

1. Introduction

Lung cancer is a major cause of mortality worldwide, with an estimated annual incidence of over 1.2 million cases and overall mortality of over 1.1 million cases [1]. In Europe where the mortality rates are rising in women due to the increasing tobacco use, estimates of cancer incidence and mortality in 2000 predicted 375 000 new cases of lung cancer and 347 000 deaths due to this disease [2–4]. The overall 5-year survival rates of patients with lung cancer have only modestly increased over the last 25 years, remaining at approximately 14% [5]. This disappointing figure may have several reasons, including the age at diagnosis (median 69 years), the high frequency of co-morbidities, and the absence of significantly relevant improvement of the three major therapeutic modalities, i.e. surgery, radiotherapy and chemotherapy. Nevertheless, the emergence of some new drugs and concepts has broaden the perspectives of lung cancer management.

In the setting of lung cancer, non-small cell lung cancer (NSCLC) accounts for approximately 80% of all pulmonary tumours. Approximately half of these patients present with metastatic disease. In addition, a majority of patients with early stage/locally advanced disease at diagnosis will experience a later dissemination, so eventually more than 80% of patients with NSCLC require a systemic treatment during the course of their disease. The outcome of untreated patients with advanced NSCLC is predictable with a median survival time of 4 months, and a 1-year survival rate of 10–15%. In the individual data-based meta-analysis performed by the Medical Research Council and Institut Gustave-Roussy, a total of 1190 patients with advanced disease were included and the results suggest that cisplatin-based chemotherapy provide a reduction in the risk of death of 27% ($P < 0.0001$), an improvement of median survival of 6 weeks and an increase of survival of 10%

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at one year [6]. Furthermore, most studies that have evaluated the quality of life of patients reported an improvement of quality of life associated with the prolongation of life [7]. Even if the benefit is modest, most physicians and patients agree to consider chemotherapy as the standard treatment of patients with advanced NSCLC, at least for those with adequate performance status and age. In the present article, we will summarise the main recent advances of chemotherapy and the future directions of the medical treatment of patients with advanced NSCLC.

2. Main cytotoxic agents

With a response rate of 20%, cisplatin has been considered the key-drug in the treatment of NSCLC, since 1980 and the combination of cisplatin-etoposide, cisplatin-vinblastine and cisplatin-vindesine have been considered standard regimens for NSCLC up to the mid 1990s. In the last 10 years, several new cytotoxic agents have become available; these include the taxanes (paclitaxel and docetaxel), vinorelbine, gemcitabine and the topoisomerase 1 inhibitor irinotecan [8]. Table 1 summarises the response rate observed with these agents in a compilation of studies in which they were evaluated in chemonaive patients. Some of these new drugs were compared to the best supportive care or to older drugs in randomised studies [9,10]. They were also compared to old doublets and generally demonstrated an attractive activity/toxicity profile [11,12]. But all these recent agents have been mainly developed in combination with cisplatin.

Table 2 indicates the most frequently used doublets and the recommended doses and schedules. Randomised trials comparing new combination regimens with older platinum-containing doublets underline the greater possibilities that the new agents can offer [11,13–15]. The last generation of randomised studies was dedicated to the comparison of these new doublets between them. Several studies which all showed no significant or relevant differences among these doublets have been recently reported.. The 1594 ECOG study compared cisplatin-paclitaxel/24-hr with cisplatin-docetaxel, cisplatin-gemcitabine, or carboplatin-paclitaxel/3-h and no survival differences were showed among the four treatment arms [16]. This trial reported disappointingly low response rate (15.3%) for paclitaxel-carboplatin (with the highest median survival of 8.3 months) and only 21.3% and 21% for paclitaxel-cisplatin and gemcitabine-cisplatin, respectively. One-year survival rates in all arms were similar, ranging from 31% in the docetaxel-cisplatin arm to 36% in the gemcitabine-cisplatin arm. These regimens are all of approximately equal efficacy, and although they have different toxicity profiles and rates of toxicity, these differences may not necessarily have a significant impact on patient quality of life.

Table 1
Response rates observed with second-generation agents in a compilation of studies in chemonaive NSCLC patients

	n	% OR
Docetaxel	335	25
Paclitaxel	403	24
Vinorelbine	165	29
Gemcitabine	535	22

Table 2
The most frequently used modern doublets and the recommended doses and schedules

Gemcitabine*	1000 mg/m^2	day 1, 8, 15
Cisplatin	100 mg/m^2	d 2
Or		
Gemcitabine**	1250 mg/m^2	day 1, 8
Cisplatin	80 mg/m^2	day 1
Vinorelbine*	25 mg/m^2	day 1, 8, 15, 22
Cisplatin	100 mg/m^2	day 1
Docetaxel**	75 mg/m^2	day 1
Cisplatin	75 mg/m^2	day 1
Docetaxel**	75 mg/m^2	day 1
Carboplatin	AUC 6	day 1
Paclitaxel**	135 mg/m^2 (24 h)	day 1
Cisplatin	75 mg/m^2	day 2
Paclitaxel**	200 mg/m^2 (3 h)	day 1
Carboplatin	AUC 6	day 1

*q 3 weeks.
**q 4 weeks.

The South West Oncology Group (SWOG) conducted a randomised phase III trial comparing paclitaxel-carboplatin to the SWOG standard vinorelbine-cisplatin [17]. Both regimens gave comparable results to those observed in ECOG 1594, and within SWOG 9509 the two regimens were equally effective both in terms of survival (2 years: 16% for vinorelbine-cisplatin and 15% for paclitaxel-carboplatin) and quality of life.

The Italian Lung Cancer Study Group compared cisplatin-gemcitabine versus paclitaxel-carboplatin versus cisplatin-vinorelbine in untreated locally advanced or metastatic NSCLC [18]. Evaluation of toxicity data showed that all three regimens were well tolerated: There was more myelosuppression in the gemcitabine- and vinorelbine-containing arms (without clinical consequence) and it was noted that the extent of thrombocytopenia was lower when cisplatin-gemcitabine was given on a 21-day schedule rather than the historic 28-day regimen. This study failed to demonstrate a therapeutic advantage of any of these three regimens in terms of survival or response and this result is entirely

consistent with the results of the ECOG and SWOG trials, providing further evidence that all these regimens remain reasonable choices for patients with advanced NSCLC. Table 3 summarises the results of these studies.

3. Is carboplatin as active as cisplatin?

Because cisplatin has significant toxicities including severe nausea and vomiting, renal toxicity requiring adequate hydration, ototoxicity and neuropathy, platin analogs have been developed. Among them, carboplatin, which was introduced in clinical trials in the early 1980s, is still the leading compound. Carboplatin has very limited nephrotoxicity and neurotoxicity, as well as a moderate ematogenic effect. In fact, myelosuppression and particularly thrombocytopenia is the dose limiting toxicity of carboplatin. Carboplatin-based chemotherapy in locally advanced and metastatic NSCLC has been widely used, particularly in the United States, as an alternative to cisplatin-based chemotherapy in order to minimise clinical toxicities [19]. Outside the United States, carboplatin has been increasingly used because it can be conveniently delivered as a short-time 1 h infusion and therefore on an outpatient basis. These practical considerations have contributed to the widespread use of this drug in replacement of cisplatin. Most previous studies suggest no clear difference and generally a better tolerance and comfort with carboplatin [16,17] Nevertheless a recent European study questions the equivalence of the two platinum compounds [20]. In this study, 618 patients were randomised to receive Paclitaxel 200 mg/m^2 in combination with either carboplatin at an AUC of 6 or cisplatin at 80 mg/m^2. Cycles were administered every three weeks in both arms. The two treatment arms were well-balanced with regard to gender (83% males), age (median 58 years), performance status (83% ECOG 0–1), stage (68% IV, 32% IIIB) and histology (38% squamous cell carcinoma). The response rate was 25% (70/279) in the paclitaxel/carboplatin arm and 28% (80/284) in the paclitaxel/cisplatin arm ($P = 0.45$). Responses were reviewed by an independent radiological committee. For all randomised patients, median survival was 8.5 months in the paclitaxel/carboplatin arm and 9.8 months in the paclitaxel/cisplatin arm (hazard ratio = 1.20, 90% CI: 1.03–1.40); the one-year survival rates were 33% and 38%, respectively. On the same dataset, a survival update after 22 months of additional follow-up yielded a median survival of 8.2 months in the paclitaxel/carboplatin arm and 9.8 months in the paclitaxel/cisplatin arm (hazard ratio = 1.22, 90% CI: 1.06–1.40; $P = 0.019$); the two-year survival rates were 9% and 15%, respectively. Excluding neutropenia and thrombocytopenia, which were more frequent in the paclitaxel/carboplatin arm, and nausea/vomiting and nephrotoxicity, which were more frequent in the paclitaxel/cisplatin arm, the rate of severe toxicities was generally low and comparable between the two arms. Overall quality of life (EORTC QLQ-C30 and LC-13) was also similar between the two arms. The preliminary results of TAX 326, in which docetaxel is combined with either cisplatin or carboplatin in the two investigational arms, go along the same lines [21]. In summary, carboplatin might not possess equivalent activity to cisplatin in the setting of lung cancer. That is also true for other platinum-sensitive tumours such as germ cell, head and neck, and oesophageal cancer [22–26]. On the other hand, cisplatin remains a cumbersome agent requiring heavy pretreatment hydration of patients and therefore a hospital stay of several hours or even overnight. Numerous patients with NSCLC requiring chemotherapy have contra-indications to the use of cisplatin such as inability to receive hyperhydration (cardiac dysfunction, superior venous cava syndrome) or previous neurological or hearing problems. In such cases, carboplatin is an appropriate alternative to cisplatin in 2003.

Table 3
Randomised phase III trials comparing different modern doublets

	n	OR	MS (m)	1 year S
Vinorelbine + Cisplatin	207	27%	8	33%
Paclitaxel + Carboplatin	201	27%	8	36%
Paclitaxel + Carboplatin	299	15%	8	34%
Gemcitabine + Cisplatin	301	21%	8	36%
Paclitaxel + Cisplatin	303	21%	8	31%
Docetaxel + Cisplatin	304	17%	7.5	31%
Paclitaxel + Carboplatin	201	32%	9	43%
Gemcitabine + Cisplatin	205	30%	9	37%
Vinorelbine + Cisplatin	201	30%	9	37%

4. Are platin-free regimens as active as those platin-based?

The recent cytotoxic agents have been combined and evaluated in several phase II studies. The activity of these new doublets was generally equivalent to that reported with cisplatin while the tolerance was often better. In a recently published article, Kosmidis and colleagues conducted a randomised study comparing the activity and toxicity of paclitaxel-gemcitabine (PG) and paclitaxel-carboplatin (PC) combinations for the treatment of advanced non-small-cell lung cancer [27]. A total of 509 chemonaive patients were randomised to paclitaxel 200 mg/m^2 on day 1 plus either carboplatin at AUC 6 on day 1 (group A) or gemcitabine 1000 mg/m^2 on days 1 and 8 (group B) every 3 weeks. The median survival time was 10.4 months (95% confidence interval [CI], 8.8 to 12 months) for group A and 9.8 months

(95% CI, 8.0 to 11.7 months) for group B ($P=0.32$). Respective 1-year survival rates were 41.7% and 41.4%. The response rate for group A was 28.0% (2% complete responses [CR], 26% partial responses [PR] [95% CI, 22–34%]), and the response rate for group B was 35.0% (5% CR, 30% PR) [95% CI, 29–41%]) ($P=0.12$). Toxicity was mild. Grades 3/4 neutropenia, thrombocytopenia, and anemia for groups A and B were seen in 15% and 15%, 2% and 1%, and 5% and 2%, respectively. The mean total cost (outpatient clinic visits plus chemotherapy drug fee) for group A (€ 7612.64) versus group B (€ 7484.77) was not statistically different ($P<0.66$). The authors therefore concluded that the PG combination is as equally active and well tolerated as the PC combination in patients with advanced NSCLC.

The combination of gemcitabine and oxaliplatin has also showed an encouraging antitumour activity [28]. In a phase I/II trial, 44 patients, including 35 NSCLC (5 platinum-pretreated, 2 platinum-resistant) and 9 ovarian cancer patients (all platinum-pretreated, 2 platinum-resistant) were treated with this combination with the highest dose-level of 1500 mg/m^2 gemcitabine and 85 mg/m^2 oxaliplatin. Amongst 44 patients evaluable for activity, 12 NSCLC and 3 other patients experienced objective responses including 1 complete and 14 partial responses. This promising antitumour activity deserves further evaluation.

5. Are triplets more active than doublets?

There is a strong rationale to propose the combination of three cytotoxic agents in the treatment of solid malignancies. It is generally based on preclinical data suggesting a synergistic activity between drugs with different mechanism of action and the possibility of delivering lower doses of each drug without decreasing the antitumour effect or increasing the toxicity of the combination. Unfortunately, in spite of encouraging response rates in phase II studies, most triplets failed to demonstrate any superiority over standard doublets. Among the rare positive studies, Crino and colleagues [29] performed a comparative trial in 393 consecutive, previously untreated NSCLC patients, stages IIIB and IV, who were randomised to receive either cisplatin (120 mg/m^2 day 1) + etoposide (100 mg/m^2 days 1–3) every 3 weeks (PE) or cisplatin (120 mg/m^2 every 4 weeks) + mitomycin-C (8 mg/m^2 days 1–29–71) + vindesine (3 mg/m^2 days 1–8–15–22) (MVP) or cisplatin (120 mg/m^2 day 1) + mitomycin-C (6 mg/m^2 day 1) + ifosfamide (3 mg/m^2 day 2) every 3 weeks (MIC). Response rates were statistically higher for both MIC (40%) and MVP (36%) triplets than for the PE arm (23%). Survival estimates analysed by the log-rank test showed a significant benefit ($P<0.04$) for patients treated with the triplets (MVP; MIC) as compared to those in the PE arm.

Two recent randomised studies compared the gemcitabine-cisplatin standard doublet to the combination of gemcitabine-vinorelbine-cisplatin [30,31]. Results of these two trials were provocatively different as seen in Table 4. It can be concluded that the use of triplets remains investigational and of unproven benefit at the present time.

6. Second-line chemotherapy

With 1-year survival rates of approximately 40–50%, with current chemotherapy regimens, second-line treatment has become an important issue for patients whose disease progresses after receiving platinum combinations. First-line chemotherapy failure is predictive of the development of resistant clones [32] and the question of non-cross resistance between novel agents and cisplatin has not been fully answered. Response rates to single agents such as vindesine, etoposide, epirubicin and cisplatin have not exceeded 10% in second line. The new generation of cytotoxic agents seem more active with response rates ranging from 0 to 23% in several phase II studies. Among these drugs, docetaxel was the most promising with a response rate of approximately 20%. Phase II data led to two large phase III randomised trials where single agent docetaxel was compared to supportive care or ifosfamide or vinorelbine in patients having failed to cisplatin based first-line chemotherapy [33,34]. Both studies demonstrated the superiority of docetaxel over the comparator and a better quality of life with docetaxel given at 75mg/m^2 every three weeks.

Pemetrexed, a multitargeted antifolate, has recently shown activity both in first line [35,36] and second line chemotherapy [37]. A randomised study comparing pemetrexed to docetaxel in second line NSCLC patients has recently been completed and the results should be reported shortly.

Anyway, and in particular for second line therapy, the opinion and choice of each individual patient must be considered in priority [38].

7. Tailored CT

Existing therapies need to be optimised in order to improve the survival rate of patients with lung cancer. A

Table 4
Comparizon of gemcitabine-cisplatin (GC) and gemcitabine-vinorelbine-cisplatin (GVC)

	GC		GVC	
	Comella	Alberola	Comella	Alberola
n	120	137	120	136
OR	28%	41%	44%	40%
MS (w)	38	40.8	51	34.4

Table 5
Potential molecular markers of response in lung cancer

Biomarker	Drug
ERCC1 expression	Platinum compounds
XIAP	
GSTP1, XPD	
Ribonucleotide reductase	Gemcitabine
hENT1	
Ku	Irinotecan
Microtubule alterations	Taxanes, vinblastine, vinorelbine

rationale and treatment decision-making process based on the analysis of biomarkers of response and resistance to cytotoxic drugs appears to be a an important approach. At present, research on cancer survival is partly focused on translational pharmacogenomics, aimed at providing individualised chemotherapy based on genetic traits, such as polymorphisms, gene mutations, and overexpression of drug-targeted gene transcripts. Downregulation of crucial gene transcripts has also been found to be linked to enhanced response to chemotherapy. Cancer patients now require a reliable method able to determine which chemotherapy combinations are most likely to improve survival based on genetic markers [39,40]. The promise of personalised cancer treatment is one of the greatest expectations of patients and health-care professionals. Hereby we review some of the most promising biomarkers that could predict sensitivity to chemotherapy in the setting of NSCLC, as summarised in Table 5.

Cisplatin has long been the scaffolding of chemotherapy in lung cancer. Like many DNA alkylators, cisplatin acts as a cross-linker, inhibiting DNA replication, which is the critical target in cancer chemotherapy. Cross-links between guanine bases are induced by cisplatin, carboplatin and oxaliplatin. There are several major DNA repair pathways. Excision repair, including nucleotide excision repair (NER) has been strongly linked to cisplatin resistance. Excision repair cross complementation group-1 (ERCC1) is a key gene on the NER pathway. A growing list of reports link cisplatin, carboplatin and oxaliplatin resistance to ERCC1 mRNA expression. This relationship has been suggested for gastric cancer patients, ovarian cancer patients, colorectal cancer patients and more recently for non-small cell lung cancer patients [41–43].

Ribonucleotide reductase (RR) is the rate-limiting enzyme of the DNA synthesis pathway and converts ribonucleoside diphosphate to deoxyribonucleoside diphosphate, which is essential for DNA synthesis and repair. RR consists of two subunits, M1 and M2. The M1 subunit controls substrate specificity and global on/off enzyme activity, while the M2 subunit carries the catalytic domain responsible for substrate conversion. RRM1 also acts as a putative tumour suppressor and has been identified within the centromeric part of chromosome segment 11p15.5. This region, called LOH11A, is frequently lost in NSCLC; it has been completely mapped and sequenced, and loss of heterozygosity in this region has been shown to be highly predictive of poor survival in patients with resected NSCLC patients [44,45]. Along the same lines, overexpression of ribonucleotide reductase indicates resistance to gemcitabine in the human KB cancer cell line [46]. Recently, it has been shown that flavopiridol downregulates the ribonucleotide reductase M2 subunit, supporting the concept that this enzyme could become a relevant biomarker for gemcitabine response [47]. Gemcitabine is an hydrophobic compound and its cellular penetration is partly ensured by the transport membrane protein hENT1 (equilibrative nucleoside transporter). It has been demonstrated that deficiency in hENT1 confers high-level resistance to gemcitabine toxicity *in vitro* [48]. Interestingly, staining intensity of hENT1 varied markedly among human breast samples, suggesting that around one fourth of the tumours were hENT1 deficient.

Microtubules are cytoskeletal protein polymers that present a large protein surface in the cell. In interphase, there is about 1000 μm^2 of microtubule surface [49]. Microtubules are polymers built by the self-association of α/β-tubulin dimers and are critical for cell growth and division, motility and signaling. Recently, beta-tubulin (HM40) mutations have been described in vincristine-resistant acute leukemia [50]. Previously, beta-tubulin mutations had been identified in ovarian and lung cancer patients who were resistant either to paclitaxel or epithilone [51]. Further research is warranted to identify the precise frequency of beta-tubulin mutations in the clinical setting and their relationship to chemoresistance to anti-microtubule drugs [52]. Indeed false positive mutations have been described and were related to pseudo-gene amplification [53]. However, it seems that multiple microtubule alterations could be involved in the mechanisms of this resistance, including up- or down-regulation of several transcripts. The level of class III beta-tubulin (Hβ4) isotype in a cell can affect its response to paclitaxel. Antisense oligonucleotides targeting class III β-tubulin led to a 39% increase in sensitivity to paclitaxel in resistant lung cancer cells A549-T24 [50,51]. Quantitative PCR showed a significant correlation between increased expression of class III β-tubulin isotype and paclitaxel resistance in human ovarian carcinoma xenografts [54].

Nevertheless, while ERCC1 expression or β-tubulin or RRM1 mutations might predict response to individual drugs, there has been little exploration of associations between these and others factors, nor is there functional evidence that these changes are responsible for resistance. There is often a stronger association with survival than response in these studies, which may

simply reflect that these changes are one of many abnormalities in these cells and reflect the severity of the malignant phenotype rather than a direct functional relationship with the particular factor. Similarly LOH at one site is more likely to be part of a pattern of multiple LOH (in itself a phenotypic change) and outcome may be related to the chance of LOH at any site within a particular cell rather than LOH at a specific site with functional implications. These studies are still awaited.

Nucleotide polymorphisms are one of the most frequent changes that can be found in gene sequences. In many instances, they are neutral polymorphisms but they can have functional consequences. Polymorphisms can disclose the underlying host factors that explain inter-individual differences in treatment efficacy. The glutathione S-transferases are key conjugation enzymes in this response, and GSTM1- and GSTT1-null genotypes have been associated with better survival in breast cancer patients treated with a combination of cyclophosphamide, adriamycin and 5-fluorouracil [55]. XPD (excision repair cross complementing group 2) is involved in the nucleotide excision repair pathway, like ERCC1. XPD polymorphisms can modulate the effect of the DNA repair capacity. In this respect, the variant Lys 751Gln and Asp312Asn homozygous alleles show a suboptimal DNA repair capacity in lung cancer patients in comparison with controls with wild-type genotypes. This raises the hypothesis that variants of these polymorphisms could be sensors of cisplatin chemosensitivity [56]. XRCC1 plays a central role in the base excision repair process. Recently, a polymorphism in exon 10 (Arg-Gln, codon 399) has been detected. Colorectal cancer patients who responded to oxaliplatin had an Arg/Arg genotype, while non-responders were homozygous for the variant Gln/Gln or heterozygous for Gln/Arg [57]. It is also well known that human thymidylate synthase (TS) gene polymorphism is a discriminant of response to 5-fluorouracil chemotherapy. The TS gene promoter is polymorphic, having either double or triple tandem repeats of a 28 base-pair sequence. Recently, it has been documented that the sequences in the TS promoter may predict response to pre-operative 5-fluorouracil-based chemoradiation in rectal cancer [58].

8. Conclusion

Chemotherapy has become the main treatment of advanced non-small cell lung cancer in the last decade. Several new cytotoxic agents have been proven superior to older agents even if the statistically significant benefit observed remains modest in terms of survival impact. The new combinations are generally more active and better tolerated than the old one. The next is a biological approach of the disease management and, collectively, there is a vast body of information on gene transcripts and on gene polymorphisms that could be useful for the design of customised chemotherapy for cancer patients. Gene transcripts can be examined in RNA isolated from good quality paraffin-embedded tumour tissues, and the corresponding protein can be analysed by immunohistochemical techniques. As there are solid pre-clinical data for some of these genetic markers, their validation and implementation in clinical practice should be encouraged with the integration of the best biomarkers in prospective trials and the implementation of pharmacogenomic-based clinical trials, as achieved in an ongoing Spanish trial.

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