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Immune Checkpoint Inhibitors in Early-Stage Non-Small Cell Lung Cancer: New standard of Care?

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Abstract: Worldwide, lung cancer is the first cancer in incidence and mortality. The most common histological type is non-small cell lung cancer (NSCLC). At an early stage, resection is the standard curative treatment, but relapse is high, which could be explained by micrometastatic disease. Adjuvant and neoadjuvant chemotherapy have little benefits in disease-free survival and overall survival, which is why new strategies have been studied. Immune checkpoint inhibitors (ICI) act by increasing the surveillance of the immune system. They have been used for years in advanced stage NSCLC, however, new schemes in earlier stages, be it as adjuvant therapy, neoadjuvant therapy or both, have demonstrated an important benefit in the endpoints studied. This review aims to describe the biologic rationale of ICIs in early-stage NSCLC and discuss the selected trials and endpoints.

Key words: non-small cell lung cancer (NSCLC); immunotherapy; immune checkpoint inhibitor

1. Introduction

Lung cancer is the leading cancer in incidence and mortality worldwide according to GLOBOCAN by 2022, accounting for 12.4% of new cancer cases and 18.7% of cancer deaths in the world, i.e. more than 1.8 million deaths [1]. In Chile, lung cancer is a public health problem [2] and, according to GLOBOCAN, is the leading cause of cancer deaths in the country [3]. Measures focused on prevention and screening have made it possible to reduce cancer incidence and mortality in some regions and to achieve earlier diagnosis [4]. The most frequent histological type is non-small cell lung cancer (NSCLC), accounting for 80% of the cases [5]. Between 25-30% are candidates for surgical resection with curative intent [6], a figure that is increasing thanks to screening programs [7]. In these patients, surgical approach is the standard treatment with curative intent. However, recurrence is high, being between 30-55% depending on the stage at diagnosis. This is partly due to micrometastatic disease, which is not evaluable on imaging [8]. Both adjuvant chemotherapy (CT) and neoadjuvant chemotherapy (NA CT) are intended to control micrometastatic disease, improve disease-free survival (DFS), defined as the time from randomization to disease recurrence or death, and overall survival (OS), defined as the time from randomization to death. However, the benefit of both strategies is limited, with an OS benefit of 5% at 5 years [9, 10]. The recent introduction of immune checkpoint inhibitors (ICI) in early stage NSCLC has shown benefit in the different schemes studied in phase III trials and some have already been approved by regulatory agencies. The aim of this review is

to describe the biological rationale for using immunotherapy, particularly ICI, in early stage NSCLC and to discuss the various selected schemes, trials and outcomes.

2. Chemotherapy in Early Stage NSCLC

Adjuvant chemotherapy (CT), consisting of 4 cycles of CT with two agents, mainly based on cisplatin. It has been studied in resectable stage I-III patients and, compared to placebo, has demonstrated a 5-year DFS benefit of 5.8% (HR 0.84 [0.78-0.91; p<0.001]) and a 5-year OS benefit of 5.4% (HR 0.89 [0.82-0.96; p=0.005]). Grade 3-4 adverse events (AEs) (severe and life-threatening, respectively) were frequent, present in 66% of patients, preventing completion of CT cycles in 34%. The most frequent grade 3-4 AE was neutropenia (37%). About 9% of patients were unable to complete cycles due to disease progression [9].

Neoadjuvant chemotherapy (NA CT), consisting of 4 cycles of two-drug CT, mainly based on cisplatin, has been studied in resectable stage I-III patients and has demonstrated an OS benefit similar to adjuvant schedules of 5% at 5 years. Randomized studies have not demonstrated a categorical benefit of NA CT vs adjuvant CT. This may be explained by the heterogeneity of the population included in the various studies (type of CT schedule, treatment duration and patient selection) [10]. Gilligan et al. evaluated the objective response rate (ORR), defined as the proportion of patients achieving partial or complete response on imaging, and its correlation with OS in 519 patients with NSCLC [11]. The ORR was 49%; however, it did not demonstrate a benefit in OS at 5 years (44% in the NA CT arm and 45% in the surgery alone arm). The benefit of NA CT lies in the fact that it may contribute to reduce the volume of disease, optimizing greater disease control with better adherence to treatment cycles, but without having a correlation with greater OS. The risk of progression during NA CT is up to 36%, so there is a risk of the disease progressing and becoming unresectable and/or metastatic [12]. The benefit in OS of both regimens is insufficient for a disease with such a high incidence and mortality, so new strategies have been sought to increase survival in the early stage.

3. Rationale for ICI in NSCLC

The recognition and destruction of neoplastic cells by the immune system involves the identification of tumor antigens by an antigen-presenting cell, which presents them through its major histocompatibility complex (MHC) to a T-cell receptor (TCR) of a naive T lymphocyte. This is primed and activated as a cytotoxic T lymphocyte, which enters the circulation, recognizes and contacts the tumor cell through its TCR to the tumor MHC and destroys it. However, this process can be inhibited both by the organism physiologically and by the tumor cell through the interaction of immune checkpoint proteins in the priming phase, as occurs between the cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) expressed on the T lymphocyte, which binds to CD80/86, expressed on the antigen-presenting cell. This also occurs in the effector phase, between the programmed death molecule 1 (PD-1) expressed on the surface of the T lymphocyte, and the PD-1 ligands (PD-L1 and PD-L2) expressed on the surface of tumor cells and lymphocytes. Anti-PD-1, anti-PD-L1 and anti-CTLA-4 antibodies are the most widely used inhibitors of immune control in oncology and in the treatment of NSCLC [13-15].

The first phase III clinical trial that showed benefit with ICI in NSCLC was in metastatic stage, where the anti PD-1 nivolumab, used in second-line squamous NSCLC, showed a better OS (HR 0.59) and response rate (20%) compared to docetaxel [16]. In the same year, CheckMate 057 [17] was published, which showed benefit in second-line non-squamous NSCLC. The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved its use in both subtypes. Subsequently, the anti PD-1 pembrolizumab and the anti PD-L1 atezolizumab obtained approval in the same setting [18, 19]. In parallel, multiple trials were initiated in metastatic NSCLC, using immune checkpoint inhibitors (ICI) as first-line treatment, either in monotherapy, associated with chemotherapy (CT), or in combination with other ICIs. The

magnitude of benefit depended mainly on the absence of driver mutations and PD-L1 expression. In the KEYNOTE-189 [20] trial, conducted in non-squamous metastatic NSCLC without EGFR or ALK gene disruption, the combination of pembrolizumab plus platinum-based CT had a median OS of 22 months vs. 10 months with CT plus placebo. Independent of PD-L1 expression, the association with pembrolizumab always had an OS benefit, although the magnitude of the benefit was greater in patients with PD-L1 expressing tumors.

Subsequently, it was studied in the setting of unresectable locally advanced cancer, where patients received a chemo-radiotherapy regimen and then maintenance with the anti-PD-1 drug durvalumab or placebo. The experimental arm had a median OS of 47 months vs. 29 months. A post-hoc analysis showed no OS benefit in patients with PD-L1 suppression <1% [21]. These data demonstrate a benefit of ICI treatment in unresectable and metastatic stage NSCLC, positioning it as the current standard of care based on specific biomarkers.

4. ICI with Adjuvant Intent

In view of the positive results with ICI in unresectable and metastatic stage NSCLC, its efficacy was studied in early stage in postoperative patients. In the phase III IMpower010 trial [22, 23], 1,005 patients with stage IB-IIIA NSCLC (American Joint Committee on Cancer version 7 [AJCCv7]) resected and treated with adjuvant CT were randomized to receive atezolizumab for 1 year or standard care. The primary outcome was SLE. The use of ICI demonstrated a benefit for group II-IIIA with PD-L1 >1% (HR 0.66 [0.50-0.88; p=0.0039]), thereby gaining FDA approval. However, this benefit was lost in the subgroup with PD-L1 >50%, so the EMA approved its use in PD-L1 > 50%. An update of this trial showed an OS benefit in the II-IIIA subgroup with PD-L1 >50%. Grade 3-4 AEs occurred in 22% in the experimental arm and 18% required continued ICI.

The phase III PEARLS trial [24] had a similar design to IMpower010, although adjuvant CT was optional. A total of 1,955 patients were randomized to pembrolizumab vs placebo. The primary endpoints were SLE in the intention-to-treat (ITT) group and SLE in the PD-L1 subgroup with Tumor Proportion Score (TPS), a PD-L1 expression score, >50%. In the ITT group, the median duration of SLE was 53 months vs. 42 months in the control group (HR 0.76). However, the PD-L1 subgroup >50% did not have a benefit in SLE and when analyzing the subgroups it seems that the benefit in the ITT was dragged down by the PD-L1 1-49% subgroup. This result casts doubt on the predictive value of PD-L1, although it could be explained by heterogeneity in the population studied, who received adjuvant CT and the presence of driver mutations between both arms [25-27]. The ICI arm obtained a benefit in DFS in the ITT population (HR 0.76 [0.63-0.91; p = 0.0014]), and therefore obtained FDA and EMA approval, independent of PD-L1. Table 1 summarizes the characteristics and results of the studies that used ICI with adjuvant intent.

Table 1. Phase III clinical trials using immune checkpoint inhibitors (ICIs) with adjuvant intent in early-stage non-small cell lung cancer (NSCLC)

Essay	IMpower010, Sept. 2021	PEARLS, Sept. 2022
Drug (duration)	Atezolizumab (1 year)	Pembrolizumab (1 year)
Stage	IB-IIIA (AJCCv7) > 4 cm	IB-IIIA (AJCCv7) > 4 cm
Patients	N: 1,005; PD-L1 > 1%: 56%; Cisplatin: 100%.	N: 1,955; PD-L1 > 1%: 61%; Cisplatin: 51%
Treatment	Exp: Atezolizumab for 16 cycles; Ctrl: Pbo	Exp: Pembrolizumab for 18 cycles; Ctrl: Pbo
Primary outcome	DFS	DFS
DFS	PD-L1 > 1%: HR 0.66	ITT: HR 0.76; PD-L1 > 50%: NS
EA	G3-4: 22%; Discontinuation: 8%.	G3-4: 34%; Discontinuation: 19%.
Approval	FDA: II-IIIA PD-L1 TPS > 1% EMA: II-IIIA PD-L1 TPS > 50%	FDA: IB-IIIA independent of PD-L1 EMA: IB-IIIA independent of PD-L1

Note: AJCC: American Joint Commission on Cancer; NSCLC: non-small cell lung cancer; Ctrl: control; Pbo: placebo; EA: adverse events; EMA: European Medicines Agency; Exp: experimental; DFS: disease-free survival; FDA: Food and Drug Administration (EEUU); TPS: Tumor Proportion Score.

5. ICI with Neoadjuvant Intent

ICIs increase immune surveillance, so their activity depends on the exposure of the antigen-presenting cell to tumor antigens. The antigenic load before tumor resection is greater, so we could expect a greater activation of the immune system, with a greater eradication of residual micrometastatic disease. Neoadjuvant (NA) with ICI also allows us to evaluate the efficacy, tolerance and pathological response in that specific patient and tumor.

Murine models have demonstrated the superior efficacy of ICI in AN vs adjuvant. This is due to both the number of T lymphocytes and interferon levels after treatment with anti-PD-1, where there is evidence of an increase in CD8 T lymphocytes directed against the tumor in blood and tissues, capable of producing interferon gamma and tumor necrosis factor [28].

The first phase III trial to show a benefit in using ICI NA was CheckMate 816 [29], which randomized 505 patients with stage IB-IIIA NSCLC (AJCC v7) to receive 3 cycles of nivolumab 360 mg plus platinum-based CT vs CT plus placebo every 3 weeks for 3 cycles and then surgery. The primary outcomes were event-free survival (EFSv), defined as the time from randomization to progression, recurrence or death, and complete pathological response (CPR) defined as the absence of viable tumor cells in the primary tumor and in the resected lymph nodes. The median age was 64 years, 63% patients with stage IIIA disease,, 89% with PD-L1 >1%. Median EFS was 31 months in the experimental group vs 20 months in the control group (HR 0.63 [0.45-0.87; p=0.0052]). The PCR was 24% vs 2.2%. Surgery was performed in 83% of the experimental group vs 75% of the control group. Surgery cancellations due to disease progression were 6.7% in the experimental group vs. 9.5% in the control group. All PD-L1 subgroups benefited from ICI NA, with a more evident trend towards higher PD-L1 expression. OS did not reach statistical significance. Table 2 summarizes the characteristics and results of the studies that used ICI with neoadjuvant intent.

Table 2. Phase III trials using immune checkpoint inhibitors (ICI) with neoadjuvant intent in early stage non-small cell lung cancer (NSCLC)

Essay (date of publication)	CheckMate 816 (May 2022)
Drug (duration)	Nivolumab (9 weeks)
Stage	IB-IIIA (AJCCv7) > 4 cm
Patients	N: 505; PD-L1 > 1%: 49%; Cisplatin: 74%
Treatment	Exp: Nivolumab + platinum-based CT for 3 cycles Ctrl: CT + Pbo
Primary outcome	EFSv; CPR
RPC	Exp: 24%; Ctrl: 2.2%
EFSv	EFSv 3a: HR 0.63
Progression during neoadjuvant therapy	Exp: 6.7%; Ctrl: 9.5%

Note: AJCC: American Joint Commission on Cancer; NSCLC: non-small cell lung cancer; Ctrl: control; EA: adverse events; EFSv: event-free survival; EMA: European Medicines Agency; Exp: experimental; FDA: Food and Drug Administration (EEUU); G: grade; HR: hazard ratio; ITT: intent to treat; N: number; NS: Not significant; Pbo: placebo; CPR: complete pathological response; CT: chemotherapy; TPS: Tumor Proportion Score.

6. ICI with Perioperative Intent

In the phase II NADIM II trial [30, 31], 86 patients with resectable stage IIIA-IIIA-IIIB NSCLC (AJCCv8) were randomized to receive NA with carboplatin-based CT plus nivolumab 360 mg or CT plus placebo every 3 weeks for 3 cycles, followed by surgery and adjuvant nivolumab 480 mg every 4 weeks for 6 cycles or placebo. The primary endpoint was complete pathological response. The median age was 65 years. The median tumor size was 5 cm and 72% of the experimental arm were N2 vs. 55% of the control arm. At the last available update (median follow-up of 21.9 months), the complete pathological response was 36.2% in the experimental arm vs. 6.8% in the control arm. Progression-free survival (PFS), defined as the time from randomization to disease progression or death, at 2 years was 63% vs. 52%, a non-significant difference. OS at 2 years was 85.3% vs. 64.8% in the control arm. Grade 3-4 AEs occurred of 22% in the experimental arm vs. 10% in the control arm. 93% of the experimental arm underwent surgery vs. 69% in the control arm. Interestingly, no patients in the experimental arm progressed during NA vs. 13.7% in the control arm and no patients who had complete pathological response progressed or died.

In the phase III KEYNOTE-671 [32, 33] trial, 797 patients with stage IIA-IIIB NSCLC (AJCCv8) were randomized to receive cisplatin-based CT with pembrolizumab 200 mg or CT plus placebo every 3 weeks for 4 cycles, surgery, and adjuvant pembrolizumab or placebo every 3 weeks for 13 cycles. The primary outcomes were EFSv and OS. Median age was 63 years, 70% male, 42% were N2, PD-L1 >1% in 65% of the experimental arm vs 62% in the control arm. About 82% of the experimental arm was underwent surgery vs 79% in the control arm. In the latest available update (mean follow-up 36.6 months), the mean DFS was 47.2 months in the experimental arm and 18.3 months in the control arm (HR 0.59 [0.48-0.72]). There is a statistically significant benefit in OS in favor of the experimental arm (HR 0.72 [0.56-0.93; p=0.00517]), with a 3-year OS of 71.3% in the experimental arm vs. 64% in the control arm. This is the first phase III trial to demonstrate an OS benefit using ICI with perioperative intention. The CPR was 18.1% in the experimental arm vs. 4% in the control arm. AE grade >3 was in 45.2% in the experimental arm (1% deaths) vs 37.8% in the control arm (0.8% deaths). Discontinuation due to toxicity was 20.2% in the experimental arm vs. 9.3% in the control arm. Among those who did not undergo surgery, 3.8% in the experimental arm vs. 6.5% in the control arm were due to disease progression.

In the phase III AEGEAN trial [34], 802 patients with stage IIA-IIIB NSCLC (AJCCv8), without EGFR or ALK mutation, were randomized to receive NA with platinum-based CT plus durvalumab 1,500 mg or CT plus placebo every 3 weeks for 4 cycles, surgery and adjuvant durvalumab every 4 weeks for 12 cycles or placebo. The primary outcomes were event-free survival and complete pathological response. Median age was 65 years, 71% male, 49% with N2, 66% with PD-L1 >1%. Seventy-three percent received carboplatin and 27% received cisplatin. EFSv was statistically superior in the experimental arm (HR of 0.68 [0.53-0.88, p=0.004]). The 2-year EFSv was 62% in the experimental arm vs 53% in the control. When stratified by PD-L1 expression, durvalumab use showed a trend toward benefit, independent of whether or not PD-L1 was expressed. CPR was also higher in the experimental arm, 17.2% vs 4.3% in the control arm. In each arm, approximately 80% of patients underwent surgery. Patients who did not undergo or did not complete surgery due to disease progression were 8.8% in the experimental arm vs. 10.5% in the control arm. The frequency of grade 3-4 AEs was similar in each arm (approximately 42%) and AEs leading to discontinuation of durvalumab were 12% vs 6% with placebo.

In the phase III CheckMate 77T [35] and Neotorch [36] trials, the efficacy of nivolumab and toripalimab (anti-PD-1) perioperative intent-to-treat schemes was evaluated, respectively. In CheckMate 77T, 461 patients with stage IIA-IIIB NSCLC (AJCC v8) were randomized to NA with CT plus nivolumab for 4 cycles or CT plus placebo, followed by surgery and adjuvant nivolumab for 1 year vs placebo. The primary outcome was event-free survival, which was positive (HR 0.58 [0.42-0.81; p=0.00025]). The complete pathological response was 25.3% in the experimental arm vs 4.7% in the control

arm. 78% of the experimental arm was a surgery vs 77% in the control arm. Grade 3-4 AEs were 32% in the experimental arm vs 25% in the control arm. In the Neotorch trial, 404 patients with resectable stage II-III NSCLC (AJCCv8) were randomized to NA with CT plus toripalimab for 3 cycles or CT plus placebo, then surgery and adjuvant toripalimab for 13 cycles vs placebo. The primary outcomes were event-free survival and major pathologic response (MPR). Event-free survival and major pathologic response were higher in the experimental arm, EFSv with a HR 0.40 [0.27-0.56] and MPR of 48% in the experimental arm vs. 8% in the control, and MPR was higher in the experimental arm with 24.8% vs. 1%. Grade >3 AEs occurred in 63% in the experimental branch vs 54% in the control branch, with a discontinuation of 9.4% in the experimental branch vs 7.4% in the control branch. Table 3 summarizes the characteristics and results of the studies that used ICI with perioperative intent.

Table 3. Trials using immune checkpoint inhibitors (ICI) with perioperative intent in early stage non-small cell lung cancer (NSCLC)

Essay (date of publication)	Drug (duration)	Stage	Patients	Treatment (neoadjuvant phase)	Treatment (adjuvant phase)	Primary outcome	RPC	EFSv	Progression during neoadjuvant therapy
Neotorch (Abstract April 2023)	Toripalimab (1 year)	II-III (AJCCv8)	N: 404 PD-L1 > 1%: ND Cisplatin: ND	Exp: Platinum-based CT + Toripalimab for 3 cycles Ctrl: CT based on platinum + Pbo	Exp: Toripalimab for 13 cycles Ctrl: Pbo	EFSv MPR	Exp: 24.8% Ctrl: 1%.	HR 0.4	ND
KEYNOTE 671 (August 2023)	Pembrolizumab (1 year)	IIA-IIIB (AJCCv8)	N: 797 PD-L1 > 1%: 65.2%. Cisplatin: 100%	Exp: Platinum-based CT + Pembrolizumab for 4 cycles Ctrl: CT + Pbo	Exp: Pembrolizumab for 13 cycles Ctrl: Pbo	EFSv	Exp: 18.1% Ctrl: 4%	HR 0.59	Exp: 3.8% Ctrl: 6.5%
NADIM II (August 2023)	Nivolumab (1 year)	IIIA-IIIB (AJCCv8)	N: 86 PD-L1 > 1%: 52.3%. Carboplatin: 100%	Exp: carboplatin-based CT + Nivolumab for 3 cycles Ctrl: CT + Pbo for 3 cycles	Exp: Nivolumab for 6 cycles Ctrl: Pbo	CPR	Exp 36.2% Ctrl: 6.8%	PFS 2a: NS	Exp: 0% Ctrl: 13.7%
CheckMate 77T (Abstract October 2023)	Nivolumab (1 year)	IIA-IIIB (AJCCv8)	N: 461 PD-L1 > 1%: 52.3%. Cisplatin: ND	Exp: Platinum-based CT + Nivolumab Ctrl: CT + Pbo	Exp: Nivolumab for 12 cycles Ctrl: Pbo	EFSv	Exp: 25.3% Ctrl: 4.7%	HR 0.58	ND
AEGEAN (November 2023)	Durvalumab (1 year)	IIA-IIIB (AJCCv8)	N: 802 PD-L1 > 1%: 66.7 Carboplatin: 73.5%.	Exp: Platinum-based CT + Durvalumab for 4 cycles Ctrl: CT + Pbo	Exp: Durvalumab for 12 cycles Ctrl: Pbo	EFSv CPR	Exp: 17.2% Ctrl: 4.3%.	HR 0.68	Exp: 8.8%. Ctrl: 10.5%.

Note: AJCC: American Joint Commission on Cancer; NSCLC: non-small cell lung cancer; Ctrl: control; EA: adverse events; EFSv: event-free survival; EMA: European Medicines Agency; Exp: experimental; FDA: Food and Drug Administration (EEUU); G: grade; HR: hazard ratio; ITT: intent to treat; N: number; NS: Not significant; Pbo: placebo; CPR: complete pathological response; MPR: major pathologic response; CT: chemotherapy; TPS: Tumor Proportion Score.

7. Discussion

Recent trials have demonstrated a benefit of ICI in early stage of patients diagnosed with lung cancer. However, several questions arise in order to optimize the selection of biomarkers, schedule and duration of treatment.

The time it takes for a trial to demonstrate a benefit in OS tends to be longer in trials with curative intent than in palliative intent. In the trials of ICI with perioperative intent presented, only KEYNOTE 671 has demonstrated a benefit in OS. Most trials have demonstrated benefits in EFSv and DFS, which, while they may reflect a reduction in the likelihood of disease progression, recurrence or death, have not been shown to be surrogates of OS in patients with early-stage NSCLC treated with ICI. Nevertheless, the benefits in these links raise the hypothesis that they will correlate in the future with a benefit in OS and will therefore be the new standard of care.

Another question is which scheme to choose: neoadjuvant, adjuvant or perioperative ICI? Since there are no prospective trials comparing these strategies, each case should be discussed in a multidisciplinary committee, where patient willingness, systemic toxicity and economic impact are considered. While strategies with demonstrated benefit in OS should be favored, i.e., adjuvant atezolizumab in stage II-IIIAIA (AJCCv7) PD-L1 >50%, pembrolizumab with perioperative intent in stage IIA-IIIB (AJCCv8) and NA and adjuvant CT, the other strategies presented in this review should be taken into consideration due to their clinical and pathologic benefits.

Regarding the duration of treatment, it is not clear who benefits from one year of adjuvant treatment and, considering the good prognosis of patients who present post-NA CRP, the possibility of de-escalating and suspending adjuvant ICI to reduce toxicity and costs could be considered. However, it is necessary to analyze biomarkers and perform prospective studies to validate the de-escalation of treatment in this group of patients.

In advanced stages, there is evidence of resistance to ICIs in tumors with driver mutations. For this reason, most trials excluded those with a mutation in the EGFR gene or rearrangement of the ALK gene and, therefore, the importance of molecular study is established as a necessity in early stage NSCLC prior to the initiation of treatment. Retrospective analyses of advanced stage NSCLC suggest that some mutations in genes such as TP53 would confer greater sensitivity to ICI, while mutations in the KEAP1 and STK11 genes would confer resistance, so it is necessary to evaluate the role of these biomarkers at an early stage [37, 38].

ICIs have optimized the management of both advanced and localized NSCLC. With the new therapeutic strategies mentioned in this review, treatment strategies should be individualized to optimize OS results and safety profile, with discussion in multidisciplinary committees being of vital importance. New questions regarding biomarkers of resistance and optimization of treatment duration should be answered in prospective trials and/or meta-analyses.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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