Article

Intraoperative Adjuvant Hyperthermic Intraperitoneal Chemotherapy in Patients with Locally Advanced Colon Cancer: A Prospective Parallel Phase II Study.

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Abstract.

Background: Prophylactic hyperthermic intraperitoneal chemotherapy (HIPEC) showed promising results in patients with colorectal carcinoma at high risk of recurrence but still without clinically and radiologically evident signs of peritoneal spread. This study aims to analyze the feasibility of this proactive, early phase, multimodality approach.
Methods: A mono-institutional, prospective, parallel, two-stage phase II trial enrolled 49 patients to standard surgery or surgery plus intraoperative HIPEC. Before the procedure and during surgery, patients received intravenous fluorouracil (and leucovorin to potentiate oxaliplatin activity. Data analysis included length of hospital stay, surgery duration, type of surgery and chemotherapy-related complications risk score.
Results: No significant difference was seen in the median time spent in the hospital with a median stay of 7 days in both groups (p=0.5720). The surgical procedure's median duration was longer in the HIPEC group than in the control one. Side-effects and surgical complications did not cross at any time the Pocock-type boundary for side/effect monitoring (p=0.80, N.S.). Conclusions: The present prospective study results demonstrate the feasibility and safety of the colorectal surgery plus HIPEC treatment in patients with colorectal cancer patients at high-risk for peritoneal invasion, although clinically and radiologically undetectable.

Keywords. Colorectal cancer, peritoneal metastasis, HIPEC, surgery, feasibility.

1.   Introduction

Globally, colorectal cancer (CRC) is the third most common cancer in males and the second in females, with 1.8 million new cases and almost 861,000 deaths in 2018 (1). Its incidence and mortality rates vary markedly around the world (1). The usual recurrence sites include anastomotic site, mesentery or nodal basin, retroperitoneum, and peritoneum (2). Peritoneal carcinomatosis (P.C.) may reach up to 25-30% of all recurrences after potentially curative resection (3) and carries a dismal prognosis with a survival of 5 months if untreated and has a range between 5 and 15 months if treated with palliative systemic therapy (4). The peritoneal spread is an event that involves 10-15% of CRC patients at the time of surgery. Occult PC due to the spread of metastatic cells from full-thickness bowel wall invasion or "in transit" from lymphatic vessels during surgical dissection is the main problem. Several features of the primary colorectal tumor represent risk factors in developing PC. These features include mucinous or signet ring cell carcinoma, locally advanced disease (T4 stage), tumor perforation, nodal stage, right-sided tumor location, and non-radical resection (R1 or R2) (5-9). At present, surgery followed by hyperthermic intraperitoneal chemotherapy (HIPEC) represents one of the best therapeutic options for patients with PC. The rationale of this multimodality strategy is to remove all visible peritoneal tumor deposits surgically and to eradicate microscopic residual disease with HIPEC (10). The effectiveness of HIPEC depends on the grade of completeness of cytoreduction and the extension of peritoneal disease spread, which is quantified by the Peritoneal Cancer Index (PCI) scoring system. PCI is a diagnostic and prognostic system that is a sum of scores in thirteen abdominal regions. Each receives a score of 0-3 based on the largest tumor size in each area, with a range from 0 to 39. Higher scores indicate more widespread and larger tumors in the peritoneal cavity. A large study by Klaver et al. showed that patients with low PCI (0-5) might have lower postoperative morbidity and a 5-year survival rate of 70%. In comparison, those of the patients with high PCI (>16) reach only a 10% 5-year survival rate with a higher rate of complications (11). Although this study showed no survival advantage of postoperative HIPEC, prophylactic HIPEC highlighted promising results in patients at high risk of recurrence but still without clinically and radiologically evident signs of peritoneal spread and encouraged the encouraging results as the theoretical benefit of in these patients (12-15).

In this paper, we report the results of a study of the feasibility and safety of colorectal surgery plus simultaneous intraoperative adjuvant hyperthermic intraperitoneal chemotherapy in patients at high risk of recurrence but still without evident signs of peritoneal spread in terms of length of hospital stay, surgical and medical treatment-related toxicity.

2.   Patients and methods.

2.1 Study design.

This study is a mono-institutional, prospective, parallel, two-stage phase II trial aimed to evaluate the safety and efficacy of adjuvant intraoperative adjuvant hyperthermic intraperitoneal chemotherapy in patients with locally advanced colon cancer who were at high-risk for peritoneal carcinomatosis and underwent cytoreductive surgery. After the approval by the local Ethics Committee of Palermo University (n°10/18 – 14/11/2018), this study was carried out according to the Declaration of Helsinki. All participants included in the study signed a specific, informed consent.

Patients with colon cancer or intraperitoneal rectosigmoid cancer (15 cm from the anal verge) with clinical T3/T4 N0-2 M0 stage or perforated colon cancer were prospectively enrolled between January 2019 and October 2020. Eligibility criteria also included: age between 18 and 75 years; ECOG performance status of 0-2, adequate renal, hepatic and bone marrow function, no major uncontrolled metabolic, cardiovascular or neurologic diseases, histologically proven adenocarcinoma, cancer with mucinous or signet ring cell components, minimal synchronous P.C. - nodules < 1 cm in the omentum and close to the primary tumor - synchronous ovarian metastases. PC and ovarian tumor deposits must have been macroscopically wholly resected at the same time as the primary tumor. Exclusion criteria were a distant metastatic disease, extensive P.C., second malignancies, and-active infection or severe associated medical conditions.

2.2 Clinical outcomes evaluation.

The study endpoints of the first-stage were length of hospital stay, surgical and medical treatment-related toxicity after adjuvant HIPEC.

Safety was reported according to the Dindo et al. classification for surgically related complications and to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 4.0 for chemotherapy-related adverse events (16,17). The surgical complication observation period included 30 days after the surgical procedure. Surgical complications and adverse events occurring within 30 postoperative days or during the same hospital stay were graded from zero to five. Follow-up assessments took place every three months with clinical evaluation, thoracic/abdominal C.T. scan and markers measurements, endoscopic procedures, or as needed accordingly to oncologists' evaluation.

2.3 Treatments.

Potentially eligible patients were identified through an intensive preoperatory workup, including clinical history, colonoscopy, thoracic, abdominal, pelvic C.T. scan, and serum markers (CEA; Ca19.9). Colon resection was done according to the oncological principles of adequate lymphadenectomy; tumor deposits on visceral and parietal surfaces were surgically removed and organ resections as surgically needed. Intraoperative pathologic evaluation assessed tumor depth, and the histologic feature was mandatory to include patients in the study. At the end of the surgery, patients who had signed informed consent and acceptance of receiving intraperitoneal chemotherapy received HIPEC.

HIPEC was delivered with the closed technique with oxaliplatin at the dose of 460 mg/m2 in 2 l/m2 of dextrose solution over 30 minutes at a flow rate of 2 L/min and a temperature of 43°C. Before the HIPEC procedure and during surgery, patients received intravenous fluorouracil of 400 mg/m2 and leucovorin of 20 mg/m2 to potentiate oxaliplatin activity. Systemic adjuvant chemotherapy with FOLFOX or XELOX regimens was also given to patients treated with HIPEC and control ones if indicated according to treatment guidelines.

2.4 Statistics.

The size of this study (two independent samples) was calculated employing a probability of a type-1 error 10% cutoff (alpha 0.1), and a probability of a type-2 error related to the study power (power $1-\beta$) cutoff of 20% cutoff (beta 0.80) (18). The endpoints were binomial, therefore for an anticipated mean of 3.5 ± 1.5 in the control group and an assumed 35% increase in complication rate in the experimental arm with an enrollment ratio of 2:1, a total of 49 evaluable patients had to be enrolled, at least 14 and 38 in the experimental group and the control one respectively.

Continuous monitoring for toxicity using a Pocock-type boundary was employed with an event probability (θ) of 0.2 and the desired probability of early stopping of 0.05 (19). The trial will be stopped if the number of dose-limiting toxicities is equal to or exceeds b_n out of n patients with completed follow-up. This boundary is equivalent to testing the null hypothesis; after each patient, the event rate is equal to 0.1, using a one-sided level 0.026846 test. Sequential boundaries were used to monitor the dose-limiting toxicity rate. The accrual will be halted if excessive numbers of dose-limiting toxicities were seen: if the number of dose-limiting toxicities is equal to or exceeds b_n out of n patients with full follow-up. As shown in Figure n. 1, this is a Pocock-type stopping boundary that yields the probability of crossing the boundary at most [probability of early stopping] when the dose-limiting toxicity rate is equal to the acceptable rate [event probability θ].

Number of patients	n	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Boundary	b_n	-	-	3	4	4	4	5	5	5	6	6	6	7	7

Figure n. 1. Pocock-type boundary for side/effect monitoring.The trial will be stopped if the number of severe complications and toxicity is equal or exceed b_n out of n patients with complete follow-up.

A descriptive analysis of all included patients was performed. Patient characteristics, tumor characteristics, and operative findings by lymphadenectomy or other surgical maneuvers were compared using Wilcoxon's test for quantitative variables and chi-square or Fisher's exact tests for qualitative variables. The time-dependent comparison was constructed using the Kaplan–Meier method with the log-rank test and the Gehan-Breslow-Wilcoxon test to detect differences between groups.

3. Results.

3.1 Patient population.

Overall, 49 patients were enrolled in the study. Table 1 reports the main clinical, demographic, and clinical characteristics of enrolled patients. Eighteen patients were candidate to receive post-surgery HIPEC, and 31 patients had surgery only. Fifteen out of the eighteen patients who were candidates for HIPEC were evaluable (83%). Table 1 reports no statistically significant differences between the two groups of patients in terms of gender, median age, the primary tumor site, percentage of patients treated with neoadjuvant chemotherapy or radiotherapy. Nearly one-third of patients had the primary tumor in the ascending colon/hepatic flexure, while the remaining had to descending colon/splenic flexure or sigmoid colon. Three patients had neoadjuvant chemotherapy and only one pre-operative radiotherapy. Video-laparoscopic surgery was done in 33% and 39% of HIPEC and control groups, respectively. In some patients it was necessary to combine the resection of other organs with the standard colectomy. Peritoneal washing was cytologically negative in all cases.

Table 1. Patients' demographic and clinical characteristics

		HIPEC	CONTROLS	
N. of patients		18 (100%)	31 (100%)	
N. evaluable patients		15 (83%)	31 (100%)	
Age (years)	Median (range)	58 (46-76)	60 (44-78)	
Gender	Male	5 (36%)	17 (55%)	p=0.275787
	Female	9 (64%)	14 (45%)	
Site of primary	ascending colon*	6 (33%)	8 (26%)	p=NS
	transverse colon	0	1 (03%)	
	descending colon**	3 (17%)	10 (32%)	
	sigmoid/rectal colon	9 (50%)	12 (39%)	
CEA at basal > 4		2 (11%)		
Neoadjuvant CT	Yes	1 (6%)	1 (3%)	
	FOLFOX	1	0	
	XELOX	1	0	
	Capecitabine	0	1	
	None	13	30	
Neoadjuvant R.T.		0	1	
Surgery	Open	12 (67%)	19 (61%)	p=0.059126 NS
	VLS	6 (33%)	12 (39%)	
	hemicolectomy	10	17	p=NS
	rectal anterior resection	8	14	
	Ileostomy	6	5	
Other organs resected	Pancreas	1	0	
	gall bladder	1	0	
	uterus/ovary	3	3	
	urinary bladder	2	2	
	Peritoneum	1	3	
	Prostate	1	0	
Peritoneal washing	Negative	14	31	

	Positive	0	0	
Histology	Adenocarcinoma	18 (100%)	31 (100%)	
Post-surgical stage	pT3, N0, M0	5	2	
	pT3, N1a, M0	1	6	
	pT3, N1b, M0	1	11	
	pT3, N2a, M0	2	3	
	pT3, N2b, M0	2	3	
	pT3, N1c, M0	0	1	
	pT3, N2b, M0	0	1	
	pT3, N0,M1 (per)	1	0	
	pT4, N0, M0	0	1	
	pT4a, N1b, M0	0	2	
	pT4b, N0, M0	1	0	
	pT4b, N1a, M0	0	1	
	pT4, N2a, M0	1	0	
	pT4b, N1b, M0	1	1	
	pT4, N2b, M0	1	0	
*Including hepatic flexure; ** Including splenic flexure				

3.2 Outcomes.

Table 2 shows results in terms of duration of surgical procedure subtracting time dedicated to hyperthermic intraperitoneal chemotherapy procedure, length of hospitalization, surgical complications, side-effects related to chemotherapy, and impact of HIPEC on post-surgical chemotherapy. No significant difference was seen in median time spent in the hospital (Figure 2) with a median stay of 7 days in both groups (Gehan-Breslow-Wilcoxon test p=0.5720, N.S.; Mantel-Haenszel HR 0,0922, 9%% CI 0.4282-2.299). As shown in Figure n. 3, the surgical procedure's median duration was longer in the HIPEC group than in the control one (median 192 versus 138 minutes). This difference was statistically significant if the log-rank test applied (p=0.0037), but not if the Gehan-Breslow-Wilcoxon test used (p=0,0810). The rate of surgical complications as well side-effects potentially related to chemotherapy were equally distributed in both groups. Side-effects and surgical complications did not cross at any time the Pocock-type boundary for side/effect monitoring (p=0.80, N.S.). Moreover, HIPEC did not affect subsequent adjuvant chemotherapy's safety being toxicity the same in both groups of patients.

Table 2. Results

		HIPEC	**CONTROLS**	
Duration of surgery (minutes)	median (range)	192 (71-276)	148 (77-221)	p=0.0037
Post-procedure side-effects°	Nausea/vomiting	1	2	p=NS
	None	14	29	
Hospital stay (days)	median (range)	7 (6-21)	7 (5-15)	p=NS
Complications after discharge		1 §	1 ^	
Adjuvant chemotherapy		11(73%)	25(81%)	p=NS
	FOLFOX	2	4	
	XELOX	7	18	
	CAPECITABINE	2	3	
	none	4 (27%)	6 (19%)	
Percent of planned cycles		90%)	87 (%)	p=NS
Side-effects (≥ grade 3)	Mucositis	2 (18%)	4 (16%)	p=NS
	Diarrhea	2 (18%)	3 (12%)	
	Neutropenia	2 (18%)	6 (24%)	
	Febrile neutropenia	0	0	
	Platelets	0	1	
Delays in chemotherapy	yes	4 (27%)	7 (28%)	p=NS

	no			
Adjuvant R.T.		1	1	

° chemotherapy-related; § splenic artery bleeding; ^ dehiscence of the anastomosis
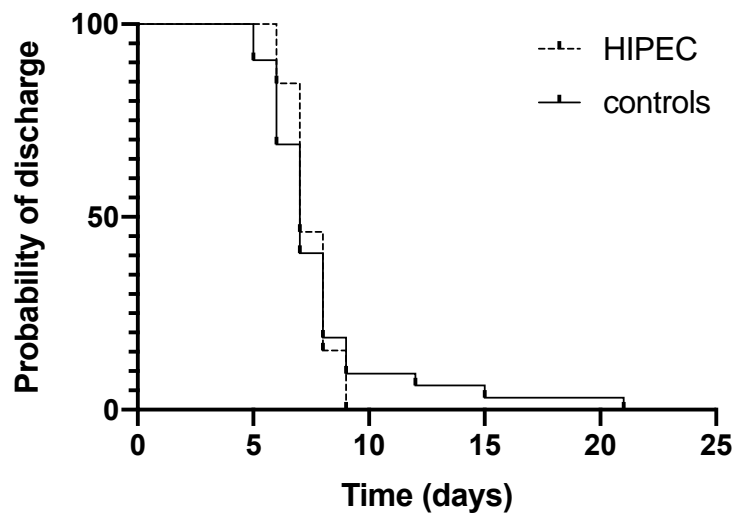
Lenght of hospital stay

Figure 2.

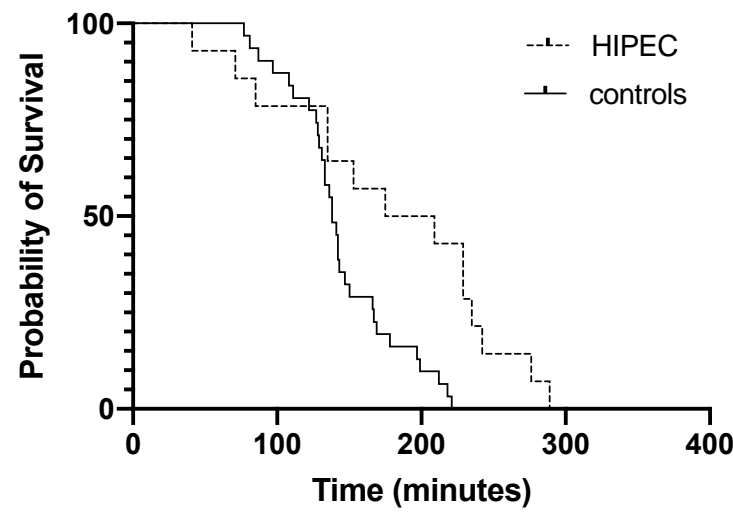## Duration of surgical procedure

Figure 3. Length of surgical procedure was calculated subtracting time lost to set up and to perform HIPEC.

4. Discussion.

Metastatic diffusion into the peritoneal surface carries out a very unfavorable prognosis and a dismal quality of life in many patients with recurrent/metastatic CRC (20). The recent interest in adjuvant HIPEC for CRC at high risk of peritoneal diffusion is a revival of a treatment strategy originating from the 1980s (21). Despite the logical scientific background of adjuvant HIPEC, currently available shreds of evidence are somewhat conflicting. In practice, several factors influence the optimization of this multimodality approach, such as patient characteristics, drug pharmacodynamics, and methodological issues, explaining the outcome differences in published trials (21). Clinical data suggest that one-fifth of patients with locally advanced (T4 stage) or perforated colon cancer are at high risk of developing peritoneal metastases and suitable for surgery

plus HIPEC with a reasonable chance of improving their outcome (22,23). In cases with detectable PC, the surgical procedure involving peritonectomy and visceral resections must be accurate and result in a complete cytoreduction (21). The majority of studies employed a combination of leucovorin-potentiated fluoropyrimidine and oxaliplatin. This choice relies on well-documented drug synergism, the pharmacokinetic analysis of intraperitoneally delivered oxaliplatin, and the well-documented activity of such regimen (FOLFOX) in the treatment of CRC patients in adjuvant and metastatic settings (24-26).

Researchers at the National Cancer Centre in Singapore have recently published an updated review of the state of the art of surgical management and HIPEC for locally advanced CRC (27). The multicenter COLOPEC study was carried out in nine hospitals in the Netherlands and the primary endpoint was peritoneal metastasis free-survival at 18 months, according to an intention-to-treat (11). This study followed a pilot study, which reported a clear advantage for adjuvant delayed laparoscopic HIPEC after a median follow-up of 4.5 years in patients with a high risk of peritoneal spread (28). In the COLOPEC trial, 204 patients with clinical or pathological T4, N0–2, M0 stage or perforated CRC were randomized before surgery in a 1:1 fashion to receive adjuvant systemic chemotherapy alone or HIPEC within 5-8 weeks after primary resection followed by standard adjuvant systemic chemotherapy (11). Patients were stratified for perforation, stage of the disease, age (<65 years or ≥65 years), and surgical approach (open or laparoscopic). Adjuvant HIPEC consisted of systemic leucovorin potentiated fluorouracil followed by intraperitoneal hyperthermic delivery of oxaliplatin by either a laparoscopic or open procedure to allow exploration of the abdominal cavity for peritoneal staging and adhesiolysis when necessary. This technical approach was based on the assumption that second-look surgery, first described more than five decades ago, remains the only method to ascertain the presence of minimal progression at the peritoneal surface (28). This study showed no statistically significant difference being peritoneal metastasis-free survival at 18-months, 80.9% for the HIPEC group versus 76.2% for the control group, respectively. This study's main criticism is the high proportion (91%) of patients who received delayed adjuvant HIPEC 5 to 8 weeks after primary tumor resection when adhesions and tumor cell entrapment may have limited the drug distribution and effectiveness of HIPEC. Also, 9% of the 100 patients in the HIPEC group had peritoneal invasion before delivering HIPEC.

Another recently published prospective open-label, phase III trial (PROPHYLOCHIP-PRODIGE), carried out in France, failed to improve disease-free survival compared to standard surveillance (29). This trial enrolled 150 patients affected by CRC who underwent resection of the primary tumor and synchronous peritoneal or ovarian metastases and treated with adjuvant systemic chemotherapy. Patients were randomized to no further therapy or second-look surgery at the end of chemotherapy, plus, if no recurrence, oxaliplatin- or mitomycin-based HIPEC. The study did not reach the primary endpoint being 3-year disease-free survival 53% (95% CI 41-64) in the surveillance group versus 44% (33-56) in the second-look surgery group (hazard ratio 0·97, 95% CI 0·61-1·56). These results disfavored the use of second-look surgery plus HIPEC in this clinical setting.

Overall, the results of these two-phase III trials challenged the effectiveness of HIPEC protocol with oxaliplatin and raised the question of whether delayed and limited exposure to chemotherapy may negatively affect its antitumor effect. Timing of adjuvant HIPEC is another point of debate since it should be ideally delivered during primary surgical resection to avoid tumor cell entrapment and delayed microscopic disease management. Statistical sample underpowering could be another explanation for the failure to reach study endpoints.

Although surgery plus HIPEC yielded unsatisfactory results in patients with a high PCI score, it showed promising results in patients at high risk of recurrence but still without clinically evident peritoneal spread. Generally, CRC patients with a low PCI score show better survival rates and lower postoperative morbidity after treatment with surgery and HIPEC (20). Therefore, the recognition and management of peritoneal invasion as early as possible may play a pivotal role in maximizing therapeutic results and, ultimately, patients' survival and quality of life (11). Unluckily early detection of peritoneal invasion is a significant challenge due to the lack of signs and symptoms and the relatively low accuracy of imaging techniques. C.T. scan may detect only less than 30% of peritoneal deposits with a size <5 mm (21,22).

In this paper, we report the feasibility and safety of colorectal surgery plus HIPEC in terms of length of hospital stay, surgical, and medical treatment-related toxicity in a mono-institutional series of CRC patients high risk of recurrence but still without evident signs of peritoneal spread who underwent radical surgery. In

our hands, colorectal surgery plus HIPEC was feasible without an increase in surgically- or chemotherapy-related complications. The median length of hospital stay was not statistically different in patients who received HIPEC and those who did not.

Time spent on the surgical procedure was slightly longer in the HIPEC group than in control one. This difference reached statistical significance. Even though other authors reported a 14% rate of postoperative complications after adjuvant HIPEC (11), in our experience, both surgical complications and chemotherapy-related toxicity were low. None of the 14 patients showed peritoneal recurrence or distant metastases after a median follow-up of 12 months. Although the patients' sample size is too small to draw conclusions survival outcomes, these results are, however, in line with the encouraging results of other studies investigating the role of adjuvant HIPEC in high-risk CRC patients. These data support the need for a proper patient selection based on clinical criteria if surgeons plan to deliver HIPEC simultaneously with primary resection. These criteria include data from pre-operative imaging, histological biopsies, and intra-operative findings. However, in our experience, it was difficult to select patients based on clinical staging adequately. A well-defined cT4 stage based on imaging or intraoperative findings frequently turns out to have a pathological T3 stage. Therefore, this proactive management of patients with stage T4 as the only risk factor could represent an overtreatment recently suggested (30). Three trials, the Italian PROMENADE, The Chinese APEC, and the Spanish HIPECT4, are currently investigating the early use of adjuvant HIPEC for locally advanced CRC (31-33). These studies are currently recruiting patients, with the latter using mitomycin-C, and hopefully shed more light on this matter.

5. Conclusions.

Colorectal surgery plus HIPEC treatment is safe and feasible in colorectal cancer patients at high-risk for peritoneal invasion, although clinically and radiologically undetectable. Our data concerning the impact of such a procedure on survival parameters are not available due to follow-up shortness. However, further studies are needed to better identify early peritoneal invasion and optimize the role of colorectal surgery plus HIPEC in patients at risk of peritoneal cancer spread.

Author Contributions
Conceptualization, Ina Macaione, Pietro Mezzatesta and Vittorio Gebbia; Data curation, Ina Macaione, Lucio Mandalà and Vittorio Gebbia; Formal analysis, Dario Piazza; Investigation, Ina Macaione, Lucio Mandalà, Antonella Campisi, Elena Roz, Sebastiano Mercadante and Pietro Mezzatesta; Methodology, Dario Piazza and Vittorio Gebbia; Writing – original draft, Vittorio Gebbia; Writing – review & editing, Ina Macaione, Lucio Mandalà and Vittorio Gebbia.

Conflicts of Interest: V.G. received honoraria from Lilly, Roche, Janssen, GSK, and Pfizer for consultations and lectures unrelated to this project. D.P. has received honoraria from Astra Zeneca for consultations unrelated to this project.

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