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RESEARCH PAPER

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Intercalated chemotherapy and erlotinib for non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) mutations

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ABSTRACT

Among attempts to delay development of resistance to tyrosine kinase inhibitors (TKIs) in patients with advanced non-small cell lung cancer (NSCLC) with activating mutations of epidermal growth factor receptor (EGFR), intercalated therapy has not been properly evaluated. In a phase II trial, 38 patients with EGFR mutated NSCLC in advanced stage were treated with 4 to 6 3-weekly cycles of intercalated schedule with gemcitabine (1250 mg/m2, days 1 and 4), cisplatin (75 mg/m2, day 2) and erlotinib (150 mg, days 5 – 15), followed by continuous erlotinib as maintenance. In addition to standard radiologic evaluation according to RECIST, PET/CT was done prior to treatment and at 6 months, using PERCIST as a method for assessment of response. The primary endpoint was progression-free survival (PFS). In general, tolerance to treatment was good, even among 8 patients with performance status 2–3 and 13 patients with brain metastases; grade 4 toxicity included 2 cases of neutropenia and 4 thrombo-embolic events. Complete response (CR) or partial response (PR) were seen in 15 (39.5%) and 17 (44.7%) cases, respectively. All cases of CR were confirmed also by PET/CT. Median PFS was 23.4 months and median overall survival (OS) was 38.3 months. After a median follow-up of 35 months, 8 patients are still in CR and on maintenance erlotinib. In conclusion, intercalated treatment for treatment-naive patients with EGFR activating mutations leads to excellent response rate and prolonged PFS and survival. Comparison of the intercalated schedule to monotherapy with TKIs in a randomized trial is warranted.

Abbreviations: 18F-FDG, 18-fluorodeoksyglucose; CI, confidence interval; CR, complete response; CT, computer tomography; EGFR, epidermal growth factor receptor; Mcr, metabolic complete remission; mPD, metabolic progressive disease; mPR, metabolic partial response; mSD, metabolic stable disease; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PERCIST, PET response criteria in solid tumors; PET, positron emission tomography; PFS, progression-free survival; PR, partial response; PS, performance status; RECIST, response evaluation criteria for solid tumors; SUV, standard uptake value; TKI, tyrosine kinase inhibitor

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Introduction

Discovery of activating mutations of epidermal growth factor receptor (EGFR) has changed dramatically the treatment of a relatively small subset of patients with non-small cell lung cancer (NSCLC). In these patients, treatment with tyrosine kinase inhibitors (TKIs) such as erlotinib, gefitinib or afatinib offers excellent quality of life with over 70% objective remissions, a figure clearly superior to treatment with chemotherapy. In randomized trials, superiority of TKIs against treatment with cytotoxic drugs has been confirmed.[1,2]

In spite of high proportion of remissions, treatment with TKIs almost invariably leads to resistance. Most of current pre-clinical and clinical research focuses on intercalated application of targeted and cytotoxic drugs, and on new targeted drugs designed to overcome acquired TKI resistance.[3-5]

The concept of intercalated therapy arose after 4 large trials failed to show any benefit of adding TKIs to cytotoxic drugs in a continuous schedule.[6-9] Suspected mutual antagonism between the 2 classes of drugs was confirmed in laboratory experiments: TKIs cause G1 cell cycle arrest, leading to resistance of tumor cells to cycle-specific cytotoxic drugs.[10] An interval of 6 d without TKIs is needed to restore sensitivity of tumor cells to cytotoxic agents.[11] After treatment with cytotoxic drugs, reversed or delayed development of resistance to TKIs were reported.[12,13] With intercalated treatment, patients would therefore benefit from the 2 classes of drugs. In addition, treatment with TKIs would reduce tumor repopulation during gaps between individual applications of cytotoxic drugs.

In our recent Phase II trial, gemcitabine, cisplatin and erlotinib were applied in an intercalated schedule.[14] Here we present mature data on responses, PFS and OS, including analysis for 30 patients who had PET/CT scanning prior to treatment and after 6 months.

Patients and methods

Patients eligible for the trial had histologically confirmed NSCLC with activating mutations of EGFR; were in advanced stage (IIIB or IV) not suitable for treatment with radical radio-

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chemotherapy; did not receive previous chemotherapy or treatment with TKIs; were in fair performance status (PS 0 – 3 according to Eastern Cooperative Oncology Group); fulfilled standard criteria for platin-based chemotherapy; and gave written informed consent.

Treatment consisted of induction and maintenance. Patients started with 4 to 6 3-weekly cycles of intercalated therapy with gemcitabine (1250 mg/m2, i.v. infusion, days 1 and 4), cisplatin (75 mg/m2, i.v. infusion with appropriate hydration and antiemetics, day 2) and erlotinib (150 mg daily p.o., days 5 – 15). After induction phase, treatment continued with uninterrupted erlotinib (150 mg daily p.o.) as maintenance. Effect of treatment was monitored with standard radiological examinations and assessed according to Response Evaluation Criteria for Solid Tumors (RECIST).

PET/CT scanning was recommended as an optional additional instrument for evaluation of treatment. 18F-FDG PET/CT was performed prior to any treatment and at 6 months after entering the trial. At baseline and for control examination, the patient was referred to the same institution – either to Institute of Oncology Ljubljana or to Department of Nuclear Medicine, University Medical Center Ljubljana. European Association of Nuclear Medicine procedure guidelines for tumor PET imaging were used for patient preparation and PET/CT acquisition protocols. Control PET/CT examinations included all initial sites of disease, with measurement of corresponding maximal standardized uptake value (SUVmax). Appearance of any new lesion or increase in SUV of a previously known lesion together with $\geq$ 20% increase in its size was declared as metabolic progression (mPD). For metabolic partial remission (mPR), all previously known lesions should either disappear or show at least 50% reduction in uptake. Patients between progression and partial response were classified as metabolic stable disease (mSD). Finally, normalization of PET/CT and disappearance of all lesions with initially increased SUV were required to declare a metabolic complete remission (mCR).[15]

The primary endpoint of the trial was PFS. Taking 20 months as the expected PFS for the intercalated regimen, 35 patients were needed for a 80% power to confirm, at the one-sided 0.10 significance level, a difference to the reported 12 months as median PFS for monotherapy with TKIs.[16] Progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan-Meier method. Differences between subgroups were compared by the log-rank test.

The trial was approved by the Institutional Review Board Committee (Institute of Oncology Ljubljana) and by the National Committee for Medical Ethics, and was registered with the European Medicines Agency, EudraCT Number 2010-023362-44.

Results

Between September 2005 and October 2013, 38 patients (17 male, 21 female) with EGFR mutant NSCLC with non-squamous histology entered the trial. All patients were Caucasians. With the exception of one patient in Stage IIIB, all other patients had distant metastases, including 12 after whole-brain radiotherapy for multiple brain metastases and one with untreated brain disease. Six patients were in PS 2, and 2 in PS 3. Demographics, sites of metastatic disease and types of EGFR mutations are presented in Table 1.

The actual number of cycles of intercalated therapy was from 1 to 6 (median: 4 cycles).

Grade 4 toxicity was limited to the induction phase of the treatment and was seen in 6 patients: 2 with neutropenia and 4 who developed deep vein thrombosis and/or pulmonary embolisms. Due to toxicity, 10 patients received only 1 – 3 cycles of the intercalated regimen and continued with erlotinib as maintenance. During the maintenance phase of the treatment, the only serious and common side effect was skin toxicity, with grades 2 and 3 in 11 and 13 patients, respectively, leading to a lower dose of erlotinib in 21 patients (Table 2).

The first evaluation for response according to RECIST was performed during the 3rd cycle of intercalated therapy, with confirmation 6 weeks later. Radiologic assessment confirmed complete response (CR) in 15 (39.5%) and partial response (PR) in 17 (44.7%). Four patients had minimal response or stable disease, and one progressed.

Seven patients did not have PET/CT at baseline and an additional patient failed to undergo control PET/CT scanning due to Grade 4 deep venous thrombosis. Thus, data on 30 patients are available for analysis of metabolic response to treatment. According to PERCIST criteria, mCR was confirmed in 17 patients and mPR in 7, with good correlation between radiological response and metabolic response (Table 3).

A total of 149 lesions were examined for maximal SUV prior to treatment and at 6 months. It appears that sensitivity does not depend on the organ of metastasis (Fig. 1). On the basis of PET/CT, 5 patients were classified as mPD. Among these 5 patients, 4 had new lesions but also showed marked reduction of the metabolic activity in most other lesions – evidence on

Table 1. Demographics, prognostic factors, extent of disease and type of EGFR mutations.

		38 patients
AGE	median	61
	range	37 – 74
GENDER	male	17
	female	21
SMOKING	never smoker	24
	light smoker (< 10 pack years)	5
	smoker	9
PERFORMANCE STATUS	EGOG PS 0	10
	1	20
	2	6
	3	2
STAGE	III B	1
	IV	37
SITE(S) OF METASTATIC DISEASE	bone	24
	distant lung	18
	pleura and pericardium	16
	liver and/or suprarenals	11
	brain (after whole-brain radiotherapy)	13 [a]
	distant lymph nodes and/or soft tissues	10
NUMBER OF METASTATIC SITES	1	10
	2	14
	3 or more	14
TYPE OF EGFR MUTATION	Exon 19 deletion [b]	25
	G719X [b]	4
	L858R	9
	S 768i	1

[a]Includes 1 patient with asymptomatic untreated multiple brain metastases
[b]One patient had deletions and G719X mutation

Table 2. Treatment toxicity.

	Grade	INDUCTION	MAINTENANCE
Anemia	2	11	2
	3	1	0
Neutropenia	2	12	0
	3	4	0
	4	2	0
Thrombocytopenia	2	3	0
	3	2	0
Nephotoxicity	2	1	0
Skin toxicity [a]	2	8	11
	3	3	13
Nausea/vomiting	2	4	0
Asthenia	2	1	2
Thrombo-embolic events	2	1	0
	4	4	0
Diarrhea	2	3	1

[a]Leading to reduced daily dose of erlotinib to 100 mg (12 patients), 75 mg (4 patients) or 50 mg (5 patients)

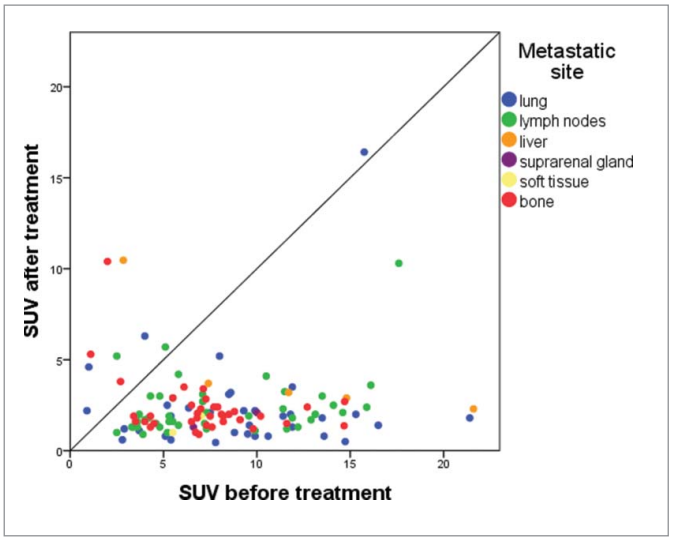

Figure 1. Metabolic response to treatment for individual lesions. For each patient, 2 – 6 lesions are shown. Colors of the dots indicate the metastatic site.

tumor heterogeneiety in sensitivity to anti-cancer treatment (Fig. 2).

Median PFS for all patients was 23.4 months (95% CI 17.6 – 29.2 months) (Fig. 3). For patients in PS 0 or 1, median PFS was 25.0 months (95% CI 19.8 – 30.2), to be compared to 15.3 months (95% CI 2.9 – 27.6) for those in PS 2 or 3 (p = 0.28). Patients with initial SUVmax lower than 12 had longer median PFS, when compared to those with higher initial SUVmax (25.6 months, 95% CI 13.1 – 38.1 vs 17.7 months, 95% CI 6.7 – 28.6; p=0.09). No difference in PFS was seen between patients with exon 19 deletions and those with other mutations (data not shown).

The most frequent sites of progression were bone (10), lung (10), brain (6), liver (3), or distant lymph nodes (3). Two patients with brain metastases and one patient with diffuse progression in the liver did not receive additional systemic treatment. Seventeen patients continued with erlotinib beyond progression. Other choices were gefitinib or afatinib (8 patients) or different combinations of cytotoxic chemotherapy (6 patients); more than one treatment option per patient may apply.

Median survival was 38.3 months (95% CI 27.1 – 49.4). Patients with initial PS 0–1 had longer OS, when compared to those with PS 2–3 (38.7 months, 95% CI 29.8 – 47.5 vs 23.9 months, 95% CI 13.4 – 34.4; p = 0.42). Similarly, patients with initial SUVmax lower than 12 had longer survival, when compared to those with higher initial SUVmax (48.1 months, 95% CI 35.9 – 60.3 vs, 29.8 months, 95% CI 20.6 – 38.9; p = 0.10). At the close-out date (February 3, 2016), 13 patients are alive, of whom 8 are still in complete remission and continue with maintenance erlotinib.

Table 3. Response to treatment according to RECIST and metabolic response.

		18F-FDG PET/CT (PERCIST)				
		mCR	mPR	mSD	mPD	Not performed
RADIOLOGY (RECIST)	CR	15				
	PR	2	7		2[a]	6
	SD				3	2
	PD			1		

[a]Partial response according to RECIST during cycle 3 and confirmed in cycle 5; new lesions on PET-CT at 6 months

Discussion

A survey of 17 published trials of intercalated therapy for advanced NSCLC reveals significant differences in inclusion criteria and in treatment schedules.[17-33] Nine trials recruited patients in progression after first-line treatment.[17-25] None of these trials could offer convincing evidence for advantage of intercalated schedule over standard second-line treatment. Of the remaining 8 trials on treatment-naive disease, only 2 reported a meaningful proportion of patients with EGFR mutations. One of these 2 trials (FASTACT 2)[32] used treatment with no gap after erlotinib, a schedule which is not in line with the proposed 6 d for wash-out period before application of cytotoxic drugs. In addition, interpretation of experience of the FASTACT 2 trial is difficult since the intercalated arm was compared to chemotherapy alone, a treatment which is currently not the optimal approach for EGFR mutated NSCLC. Thus, only one trial with 31 EGFR mutant treatment-naive patients remains which is fully in line with the theoretical background for intercalated treatment. This trial indeed reported very high objective response rate (ORR) of 76.9% and a promising curve of PFS, with no figure for median value due to relatively short follow-up.[33]

In a recent phase II randomized trial of concurrent vs. sequential application of pemetrexed, carboplatin and gefitinib for patients with sensitive EGFR mutations, both arms had excellent response rate of over 80%.[34] While this trial did not include an intercalated schedule, its experience confirmed the value of combining TKIs and cytotoxic drugs in the treatment of advanced EGFR mutant lung cancer.

Turning to our trial, small number of patients is obviously its weak point. Since the proportion of patients with EGFR mutant NSCLC among Caucasians is relatively small, we decided to recruit also patients with poor performance status. Also eligible were patients with brain metastases – a frequent occurrence in EGFR mutant disease.[35] In spite of such wide eligibility criteria, our experience with intercalated treatment is very good. Objective response in 84.2%, median PFS 23.4 months and median OS 38.3 months

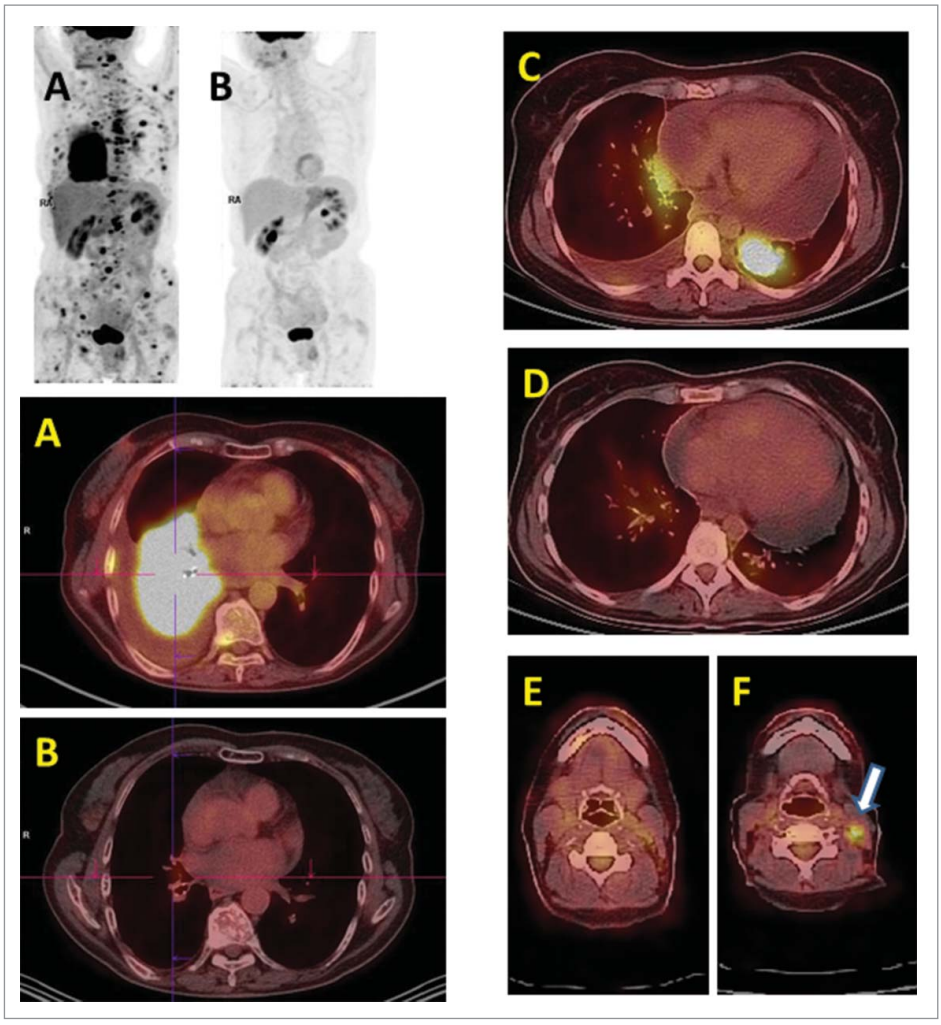

Figure 2. (A, B) Complete response to treatment in a woman aged 72, with initial PS 2; EGFR deletions. PET/CT scan with representative sections before treatment (A) and after treatment (B). C, D, E, F: Mixed response to treatment in a woman aged 41, EGFR deletions. At 6 months, comparison of PET/CT scans before treatment (C) and after treatment (D) reveals complete metabolic response on the site of the primary tumor. However, a new lesion (F) is visible in a previously uninvolved site on the neck (E). In accordance with the rules for assessment of metabolic response to treatment, this was classified as progression.

are figures which have not been reported in any other trial of advanced NSCLC, at least not in Caucasian patients. CR was confirmed in 39.5% of patients – a striking difference to virtually all reports on monotherapy with TKIs where the proportion of patients with CR remains below 5%.[16,36] Two explanations are offered for high efficacy of intercalated therapy. This schedule combines 3 drugs with proven activity, a different mechanism of action, and a different toxicity profile and applies the principle of pharmaco-dynamic separation to avoid their mutual antagonism. In addition, erlotinib fills the gaps between individual applications of cytotoxic drugs and prevents tumor repopulation, a decisive factor for failure of standard chemotherapy schedules for solid tumors.[37] Significantly inferior results of other trials support the opinion that intercalated treatment should be reserved for patients who are sensitive to both classes of drugs: it is unlikely that the intercalated schedule would be effective for EGFR wild-type disease, or for patients who developed resistance to either treatment alone. In our opinion, only treatment-naive EGFR-mutant patients are candidates for this treatment.

While some patients in PS 2 or 3 had durable responses, their survival was inferior when compared to those in PS 0 or 1. The benefit of adding cytotoxic drugs to TKIs for this subset of patients is questionnable. Until more experience is available, future trials on intercalated treatment should limit inclusion to patients in PS 0 and 1.

The cytotoxic part of our regimen was designed at the time when gemcitabin in combination with platin was widely accepted as the first-line treatment for advanced NSCLC. An obvious option for future trials is pemetrexed with platin, currently the preferred doublet for adenocarcinoma.

Another promising approach toward more effective treatment for patients with advanced EGFR mutant tumors is combination of erlotinib with bevacuzimab. In a randomized trial, addition of bevacuzimab to erlotinib significantly improved the results.[38] The possibility of a triple combination – intercalated regimen of cytotoxic and targeted drugs with additional bevacuzimab – remains a challenge for future research.

This report illustrates the role of PET/CT in 4 important aspects: meaningful interpretation of small clinical trials; assessment of response for lesions not evaluable by classical radiology such as bone metastases or pleural invasion; prognostic information; and rational approach to heterogeneiety of cancer.

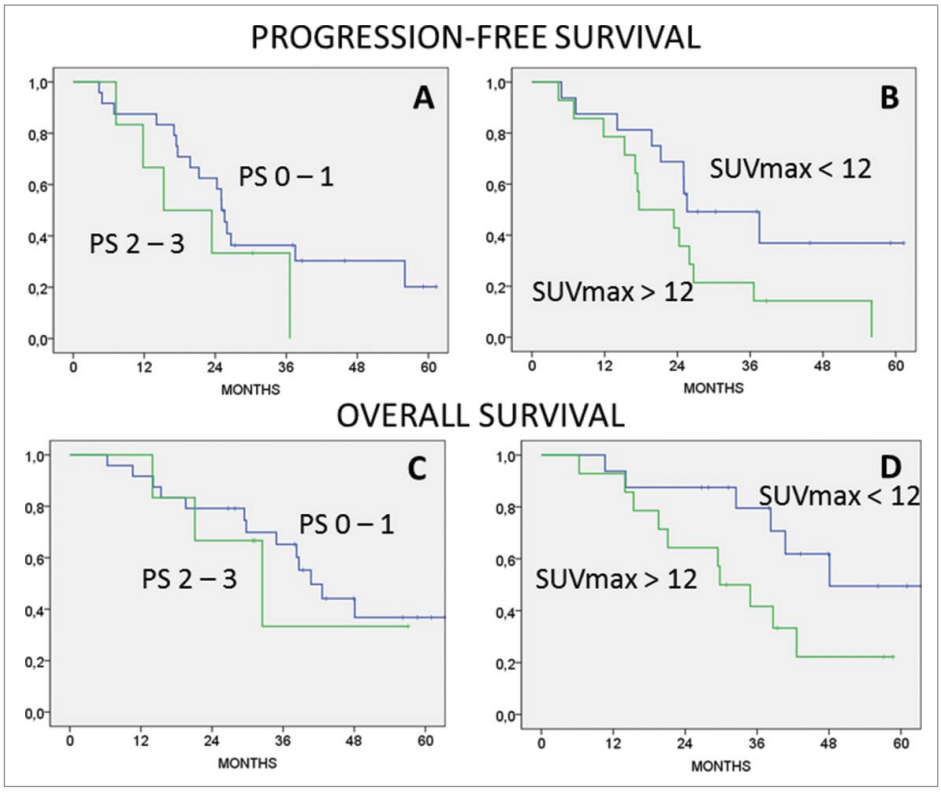

Figure 3. (A) Progression-free survival for patients with initial performance status 0 – 1 and 2 – 3. (B) Progression-free survival for patients with initial SUVmax below or under 12. (C) Overall survival for patients with initial performance status 0 – 1 and 2 – 3. (D) Overall survival for patients with initial SUVmax below or under 12.

Evaluation with PET/CT is of special importance for trials with a limited number of patients, a situation which is likely to become a reality for many diagnostic sub-categories treated with targeted drugs. Small clinical trials demand precise tools for assessment of efficacy of treatment. In comparison to classical radiology and RECIST, PET/CT scanning gives numerical result with little observer's bias and offers better distinction between categories of stable disease, partial remission and complete response.[39,40] In our trial, 15/30 (50%) patients had complete response both according to RECIST and to PET/CT. Without confirmation of metabolic CR, doubt regarding the validity of this report might remain, the more so since a substantial proportion of our patients had bone or pleural metastases – sites which are not evaluable with classical radiology.

Regarding prognostic information, patients with baseline SUV over 12 had shorter survival, when compared to those with lower initial activity. This is in line with previous reports on correlation among poorly differentiated histological pattern, high initial SUV and shorter survival.[41]

Our trial offers a new insight into heterogeneiety of lung cancer. In 4 of the 5 patients with mPD, PET/CT revealed some lesions in progression, concurrently with markedly diminished metabolic activity in other lesions. This observation points to heterogeneiety of the tumor and supports the concept of treatment beyond progression.[42]

In conclusion, intercalated treatment with gemcitabine, cisplatin and erlotinib offers excellent response rate and prolonged survival for treatment-naive patients with advanced EGFR mutant NSCLC. Responses were confirmed by PET/CT scanning. A randomized trial with comparison against monotherapy with TKIs as the standard treatment is warranted.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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Author's Contribution

Conception, design, conduct and analysis: M Zwitter, M Rajer, K Stanic, M Vrankar, I Kern, V Kovac; Statistical evaluation: M Zwitter, M Rajer, K Stanic; PET/CT evaluation and analysis: A Doma, A Cuderman, M Grmek; Manuscript writing: all authors; Final approval of manuscript: all authors

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