Pazopanib or placebo in completely resected stage I NSCLC patients: survival results of the phase II trial IFCT-0703

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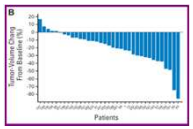
Abstract 7511 - ASCO 2015

ABSTRACT

Background: P is an anti-angiogenic agent approved in metastatic renal cell carcinoma and sarcoma. We have previously reported compliance of adjuvant P (i.e. % of patients (pts) able to receive at least 3 months (m.) of P, whatever the dose) in stage I NSCLC. Compliance has already been reported (WCLC 2013) and has been found adequate at the dose 400 mg/d (69% [95%CI 50-84] (p = 0.027, compared to 38% in P 800 mg/d) vs 93% [95%CI 77-99] in placebo. Here we report survival data. Methods: In this double-blind non-comparative randomized multicenter phase II trial, 143 pts with resected stage I NSCLC (7thTNM edition) were randomized to receive placebo or P 800 mg/d during 6 m. The Fleming's two-stage primary endpoint was compliance. After 64 pts included (interim analysis), IDMC recommended to start with P 400 mg/d because of initial insufficient compliance. A one-step Fleming design was used with the new dose. Here, we present survival data for which the intent to treat analysis was performed in 142 pts (1 consent withdrawal). Results: Between Mar 2009 and Aug 2012, 71 pts were enrolled in each arm. Most pts were male (61%) and smokers (91%), median age was 60. Pathological stage was IA in 103 pts (72%) and 16% were squamous cell carcinomas. No toxic deaths were observed. 2 pts had grade (G) 4 toxicities in P800 (fatigue in P arm, GGT in the placebo arm). Most common G3 toxicities in P800 were diarrhea (9%), hypertension (13%), and increased transaminases (16% vs. 0% in P400); in P400 gastro-intestinal disorders (16%, 6% diarrhea) and hypertension (6%). Median follow-up was 47 m. The number of events for disease free survival (DFS) is 17 in the P arm and 13 in the placebo arm: 3 yrs DFS rates were 77% [95%CI 67%-87%] and 83% [95%CI 74%-92%] respectively (Hazard Ratio (HR) = 1.3 [95%CI 0.6-2.8], p = 0.53). Among the 14 deaths, 9 occurred in the P arm and 5 in the placebo arm. All deaths were secondary to tumor recurrence but 2, related to cardiac events (1 in each arm). 5 yrs overall survival rates were 83% [95%CI 72-94] in the P arm and 94% [95%CI 88-100] in the placebo arm (HR = 1.9 [95%CI 0.6-5.5], p = 0.27, unplanned analysis). Conclusions: Although comparison of survival was unplanned in this phase II, our results do not support a phase III trial. Clinical trial information: NCT00775307

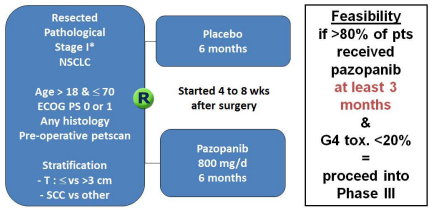
RATIONALE

- There is no standard adjuvant treatment after resection of stage I NSCLC :
  - Adjuvant cisplatin-based chemotherapy is an option if tumor size ≥ 4 cm
  - Adjuvant UFT is only approved in Asia
- Pazopanib is an oral angiogenesis inhibitor targeting VEGFR, PDGFR and c-Kit
- Neoadjuvant pazopanib in 35 stage I-II NSCLC induced a volume reduction in 86% of the cases
- We previously reported the compliance rate (primary endpoint) of the study (Besse, ECCO 2013)



Besse, J Clin Oncol 2009,
Altorki, J Clin Oncol 2010

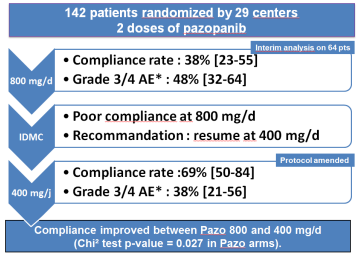
STUDY DESIGN



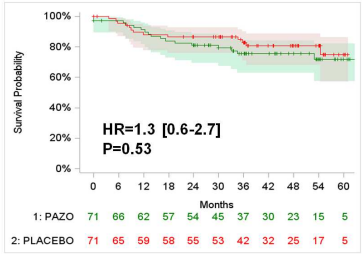
T= tumor size, SCC = squamous cell carcinoma, G4 = grade 4

*WHO 2011 classification

RECRUITMENT & DESIGN



DISEASE-FREE SURVIVAL

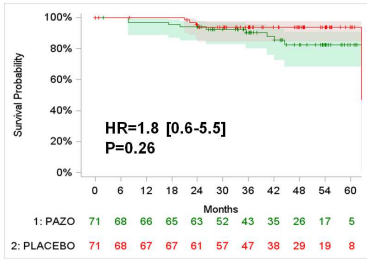


3 year DFS
Placebo 83% [74-92]
Pazo 76% [65-86]

Median follow-up = 3.9 years

30 events

OVERALL SURVIVAL



5 year OS
Placebo 94% [88-100]
Pazo 83% [72-93]

14 deaths

ENDPOINTS

Primary: Proportion of patients that receive pazopanib, or placebo, for at least 12 weeks within 24 weeks of randomization

Secondary :
- Overall survival
- Tolerance/compliance
- Long-term toxicity profiles/safety
- Recurrence site
- Detailed observance
- QoL (EORTC-QLQ-C30 with LC-13)

Exploratory:
identification of intra-tumoural biomarkers

PATIENT CHARACTERISTICS

		Pazopanib n=71		Placebo n=71	
		N	%	N	%
Gender	Female	30	42	26	37
Median age, yrs		57		61	
ECOG PS	0	47	66	58	82
	1	24	34	13	18
Origin	Caucasian	69	97	69	97
	Other	2	3	2	3
Smoker	Never	6	8	6	8
	Current/Former	65	92	64*	92
Stage	I-A	54	76	59	83
	I-B	16**	24	12	17
Pathology	SCC	12	17	11	15
	Adenocarcinoma	51	72	56	79
	Other	8	11	4	6

* Missing data ** one pt pT1pN0M1

AE of special interest, any grade

	Pazo 800 mg/d				Pazo 400 mg/d			
	Pazopanib n=39		Placebo N=41		Pazopanib N=32		Placebo N=30	
	n	%	n	%	n	%	n	%
Any event	39	100	39*	95	32	100	30	100
Anorexia	16	41	5	12	8	25	2	7
Nausea	18	46	5	12	14	44	3	10
Diarrhea	24	62	11	27	21	66	8	27
Hypertension	21	54	11	27	16	50	2	7
Fatigue	23	59	19	46	26	81	15	50
ALAT	17	44	12	29	17	44	4	13
Proteinuria	19	49	16	39	10	31	3	10

*2 patients without any AE did not take any treatment

STATISTICAL ANALYSIS

A two-step Phase II Fleming's design was used to monitor compliance in the pazopanib group.
With probability of compliance: P0 = 60%; Pa = 80%; power = 90%; α (one-sided) = 5%. First evaluation after 32 evaluable patients and, if necessary,
24 additional patients, up to 56 evaluable patients.
After 32 pts (interim analysis, cohort 1), IDMC recommended to start with pazopanib 400 mg/d because of initial insufficient compliance.
Study recruitment not hold → 7 additional patients at 800 mg/d in pazopanib group (cohort 2).
Cohort 1 and 2 reported together.
One-step Fleming design used with the new dose and 31 patients were further included in pazopanib arm (cohort 3).

TREATMENT WITHDRAWAL

	Pazo 800 mg/d		Pazo 400 mg/d	
	N=80	100%	N=62	100%
According to protocol	45	56%	45	73%
Disease recurrence	2	3%	0	0%
Study drug toxicity	17	21%	7	11%
Patient's decision	8	10%	5	8%
Investigator's decision	5	6%	1	2%
Intercurrent disease	0	0%	4	6%
Other	3	4%	0	0%

AE of special interest, Grade 3/4

	Pazo 800 mg/d				Pazo 400 mg/d			
	Pazopanib n=39		Placebo N=41		Pazopanib N=32		Placebo N=30	
	n	%	n	%	n	%	n	%
Any event	19$	49	7$	17	12*	38	8*	27
Anorexia	1	3	0	0	2	6	0	0
Nausea	1	3	0	0	0	0	1	3
Diarrhea	3	8	0	0	2	6	1	3
Hypertension	4	10	0	0	2	6	0	0
Fatigue	1	3	0	0	1	3	0	0
ALAT	5	13	0	0	0	0	0	0
Proteinuria	0	0	0	0	1	3	1	3

$ 1 AE G4, GGT, in placebo arm
1 AE G4, fatigue, in pazopanib arm

* No grade 4

CONCLUSIONS

IFCT 0703 is the first feasibility study of adjuvant VEGFR TKI

Compliance rate with pazopanib 800 mg/d was 38% [23-55] vs. 69% [50-84] with pazopanib 400 mg/d

Pazopanib 400 mg/d cohort was feasible and had acceptable toxicity.

The phase III component was cancelled because pazopanib 800 mg/d was not feasible

The number of events are very low, but it is unlikely that adjuvant pazopanib improves OS and DFS in resected stage I NSCLC patient

The role of antiangiogenic agents has not been established, so far, in the adjuvant setting

Poster online
www.ifct.fr

Acknowledgments

All other IFCT-0703 investigators: Dr Lionel MOREAU (Colmar - CH), Pr Denis MORO-SIBILOT (Grenoble - CHU), Dr Olivier MOLINIER (Le Mans - CHG), Pr Pierre-Jean SOUQUET (Lyon - Sud), Dr Henri BERARD (Toulon - Sainte Anne HIA), Dr Jean-Pierre GURY (Vesoul - CH), Dr Stéphane JACQUOT (Montpellier - Clinique), Dr Lidia PETIT (Reims - CHU), Dr Hervé LENA (Rennes - CHU), Dr Frédéric GOUTORBE (Béziers CH), Dr François GUICHARD (Bordeaux - Polyclinique), Dr Gaelle JEANNIN (Clermont-Ferrand - CHU), Dr Jérôme DAUBA (Mont De Marsan - CH), Pr Jean-Louis PUJOL (Montpellier - CHU), Pr Marie WISLEZ (Paris - Tenon), Pr Elisabeth QUOIX (Strasbourg - Nouvel Hôpital Civil), Pr Yves MARTINET (Vandoeuvre-lès-Nancy - CHU), Dr Fabien VAYLET (Clamart - Percy/Armées), Pr Arnaud SCHERPEREEL (Lille - Hôpital Calmette), Dr Dominique HERMAN (Nevers - CH), Dr Adrien DIXMIER (Orléans - CHR), Dr Aldo RENAULT (Pau - CHG), Dr Philippe ROMAND (Thonon-les-Bains - CH), Dr Patrick CHATELLAIN (Annemasse - CH), Pr Jean-François MORERE (Bobigny - Avicenne), Dr Sylvie LABRUNE (Boulogne - Ambroise Paré), Dr Laure GAUTIER-FELIZOT (Dax - CH), Dr Jean Bernard AULIAC (Mantes La Jolie - CH), Dr Denis BRAUN (Metz - Clinique Claude Bernard), Dr Hamid BELHADJ (Moulins - CH), Dr Patrice RAY (Nîmes - CHU), Pr Christos CHOUAID (Paris - Saint-Antoine), Dr Damien POUESSEL (Paris - Saint-Louis), Dr Jean DOMAS (Perpignan - Clinique)

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Version 20/05/2015