2. SYNOPSIS

Name of Company: Pierre Fabre Médicament	**Individual Study Table**	**(For National Authority Use Only)**
Name of finished product: NAVELBINE ORAL®	**Referring to Module 5 of the Dossier**	
Name of active substance: Vinorelbine tartrate	**Vol.: .....Page: .....**	

Title of study:	A phase II study of Navelbine® oral and Arimidex® as neo-adjuvant treatment in post-menopausal women with locally advanced breast carcinoma (PM0259 CA 217 B0)
Investigators:	Coordinating investigator: Kazimierz Drosik (Poland) Investigators: Servienti Patricio (Argentina), Bianconi Maria Ines (Argentina), Lerzo Guillermo Luis (Argentina), Petruzelka Lubos (Czech Republic), Ferrero Jean-Marc (France), Kaufman Bella (Israel), Moreno Lopez Eva Mariea de Los Angeles (Mexico), Tellez Bernal Eduardo (Mexico), Rolski Januz (Poland), Wojtukiewicz Marek (Poland), Louis Goedhals (South Africa).
Study Centres:	12 Active Centres: 3 in Argentina, 1 in Czech Republic, 1 in France, 1 in Israel, 2 in Mexico, 3 in Poland, 1 in South Africa.
Publication (reference):	M. Riggi et al. *Journal of Clinical Oncology*, 2009: 27, 15S, Abs 600. **Oral vinorelbine (NVBo) and anastrozole (A) as neoadjuvant treatment of locally advanced (LA) breast cancer (BC) in hormone receptor positive (HR+) post-menopausal patients: results of an international phase II trial**
Studied period: (date of first enrolment, date of last completed)[cut-off date])	July 11th, 2005 - November19 th, 2008 [February 3rd, 2009]
Phase of development:	**II**

Objectives:

Primary:	To evaluate, in patients with hormone receptor positive (HR+) locally advanced breast cancer, the overall response rate (ORR) by ultra-sound (US) measurement (primary tumour and lymph nodes) with the following chemo-hormonal oral treatment combination: oral vinorelbine (Navelbine Oral®) and anastrozole (Arimidex®)
Secondary:	–ORR by calliper measurement (primary tumour and lymph nodes), ORR on primary tumour (US, calliper) –Pathological Complete Response (pCR) at time of surgery –Toxicity of the treatment schedule (NCI-CTC criteria) –Pharmacokinetics (PK): to search for a potential PK drug-drug interaction (DDI) when oral vinorelbine (NVBo) and Anastrozole (A) are combined. –The rate of conservative surgical resection and the clinical down staging before surgery
Methodology:	Open-label, multicentre, single-arm, phase II study. •**Assessments:** –US (primary criteria) + calliper at cycles 3 and 6 (adapted RECIST) –Physical examination, serum biochemistry, complete blood cell count /cycle –Post trial follow-up every 3 months for 1 year and then every 6 months –The final assessment performed 30 days after surgery date or the last drug administration •**Surgery:** within 4 weeks after the last D1 NVBo intake (after the 3rd cycle in case of complete tumour response or after the 6th cycle if stable disease or partial response) •**Patients showing disease progression** were removed from the study but were included in the analysis.

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Methodology (continued):

•Pharmacokinetics: evaluated on cycle 1 on a subgroup of patients enrolled.

Blood sampling for the PK of vinorelbine (VRL) and its only active metabolite, 4-O-deacetylvinorelbine (DVRL) was performed after administration of VRL on day 1 and day 8 of cycle 1 (after administration of 60mg/m²) according to a limited sampling schedule.

Plasma sampling for the PK of Anastrozole was performed on day 8 and day 21.

	Sampling time	Sample number	Drugs assayed	
			VRL	anastrozole
Day 1	T0 (pre-dose – before the infusion of VFL	B0	✓	
	T0 + 1 h 30 min	B1	✓	
	T0 + 3 h	B2	✓	
	T0 + 24 h	B3	✓	
Day 8	T0 (pre-dose – before the infusion of VFL)	B4	✓	
	T0 + 1 h 30 min	B5	✓	
	T0 + 3 h	B6	✓	
	T0 + 24 h	B7	✓	✓
Day 21	T0 + 24 h	B8		✓

VRL and DVRL were assayed in whole blood by LC/MS-MS method (LLOQ=0.25 ng/ml). [Van Heugen JC, 2001]

Pharmacokinetic parameters were estimated by a bayesian approach. [L. Nguyen, 2001].

Anastrozole was assayed in plasma by LC/MS-MS method (LLOQ=0.1 ng/ml). [Meyer W]

Number of patients (planned and analysed):

The planned number of evaluable patients was 55 in 12 active investigational centres.

The final analysis was performed on the 60 patients registered in the trial after all patients not prematurely withdrawn completed the final study assessment (30 days after surgery). The cut-off date for the data analysis was February 3rd , 2009 in order patients could have at least one follow-up after main protocol assessments.

POPULATIONS	**N (%)**
Registered in the trial	60 (100)
Eligible	60 (100)
Treated and analysed for safety* (ITT)	59 (98.3)
Evaluable for tumour response (main criteria, US)**	58 (96.7)
Evaluable for tumour response (calliper)**	57 (95.0)

*Intercurrent event between registration and 1st drug administration in 1 pt: discovery of endometrial polyps that compromised treatment initiation[N°520310]; **Assessment missing

- Intent-to-treat (ITT) analysis: pts who received at least one administration of study treatment. They all were analysed for safety. Apart from the absence of any on-study-drug intake, only pts without breast cancer were planned to be excluded from the ITT. This later case was not applicable.
- Evaluable population for response: treated patients being both eligible (no major deviation from inclusion/exclusion criteria) and evaluable as defined as follow:
  - Pts who remain on study until the first evaluation and who are evaluated.
  - Pts who progress before the 1st evaluation will be considered as early progression.
  - Pts who died from malignant disease before the 1st evaluation will be considered as early death.
  - All baseline lesions must have been assessed at least once after the second cycle, with the same method of measurement as baseline.

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Diagnosis and main criteria for inclusion:	Women with: **•Inclusion criteria:** –Locally advanced, measurable BC, tumour size > 3 cm by ultrasound, N0-2, M0. –Previously untreated (chemotherapy, hormonotherapy, radiotherapy or immunotherapy) –Histologically or cytologically proven, ER positive and / or PR positive invasive BC –Defined as post-menopausal : ≥ 60 years ; 45-59 with amenorrhoea ≥ 12 months and an intact uterus **or** amenorrhoea < 12 months with FSH within post-menopausal range **or** bilateral oophorectomy –WHO performance status ≤ 2 –Adequate haematological, hepatic and renal functions –Absence of conditions hampering compliance and written informed consent –Signed written informed consent according to the local Ethics Committee requirements. **•Exclusion criteria:** –Inflammatory BC (T4d) or in ipsilateral, infra/supra clavicular lymph nodes (N3) –Symptoms suggesting brain or other malignancies (except squamous or basal cell carcinoma of the skin or carcinoma In situ of the cervix) –Significant malabsorption syndrome or disease affecting gastro-intestinal tract or inability to swallow tablets –Unwilling to undergo breast surgery at the end of neo-adjuvant treatment –Clinically significant cardiovascular, hepatic, neurological, other systemic,disease, active infections, uncontrolled medical disorder including hypertension, hypercalcemia, diabetes –Participation to another trial within 30 days prior to study screening –Concomitant hormone therapy (except anastrozole) or immunotherapy, prophylactic CSF
Test product, **Dose,** **Mode of administration,** **Batch numbers:**	**Oral Vinorelbine** (Navelbine® Oral) Administered at a dose of 60 mg/m^2 on day 1 and 8 every 3 weeks according to body surface area with no adjustment to "ideal weight" (but not exceeding 120 mg total dose). The dose was subsequently increased to 80 mg/m^2, (not exceeding 160 mg total dose) given day 1 and 8, every 3 weeks for the following cycles in the absence of any grade 3 or 4 haematological toxicity. Then adjustments in the dose of oral vinorelbine (dose decreased or dose delayed) were applied on the basis of haematological/non-haematological toxicity. Oral Vinorelbine batch numbers: - 20 mg form: AQ20114, AQ20116, AQ20118, AQ20122, AQ20139 - 30 mg form: AQ30117, AQ30119, AQ30125, AQ30138, AQ30146
Other product, **Dose,** **Mode of administration,** **Batch numbers:**	**Anastrozole** (Arimidex®): One daily tablet of anastrozole (1 mg/day) was administered orally, from day 1 of the 1st cycle of vinorelbine until the last day of the last neo-adjuvant chemotherapy cycle (i.e. day 21 of the cycle 3 for pts who showed a CR or a PD at 3rd cycle, or at day 21 of the cycle 6 for pts who received 3 more cycles after showing a SD or a PR at 3rd cycle assessment). Anastrozole batch numbers, 1mg: 200014406, 2000855979, 7501H There was no dose adjustment for anastrozole.
Prophylactic treatments and concomitant medication:	- Anti-emetic prophylaxis with an 5-HT$_3$ antagonist was recommended before each oral vinorelbine administration. Adequate oral anti-emetic was to be provided at home. - The prophylactic use of Colony Stimulating Factor (CSF) was not allowed during the study treatment. Granulocytes stimulating growth factors could only be given to patients who experienced febrile neutropenia, grade 4 asymptomatic neutropenia or neutropenic infection according to institutional rules. - Patients requiring radiotherapy during the neo-adjuvant treatment were considered to have had disease progression and should come off study treatment before receiving radiotherapy. - The use of other cytotoxic agents, investigational drugs, breast cancer active or passive immunotherapy or hormonal therapy (except the study drug) was not allowed.

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Duration of treatment:	Patients had to receive 3 or 6 cycles of treatment (3 weeks = 1 cycle). Patients with objective complete response (mammary ultrasound and calliper) at the 3rd cycle assessment had to undergo surgery 4 weeks later (between day 22 and 35 after the day 1 of cycle 3). Patients with partial response or stable disease at cycle 3 continued treatment for 3 more cycles, having surgery performed 4 weeks after the last day 1 NVBo intake of the final cycle. Patients showing progression were removed from the trial.
Reference therapy, Dose, Mode of administration, Batch number:	Not applicable.
Criteria for evaluation:	Primary endpoint: • Overall response rate (ORR) by ultra-sound measurement (primary tumour and nodes) Secondary objectives: • ORR by calliper measurement (primary tumour and lymph nodes) • ORR on primary tumor by both ultra-sound and calliper measurement • Pathological Complete Response (pCR) at time of surgery • Toxicity of the treatment schedule (NCI-CTC criteria) • Pharmacokinetics (PK): to search for a potential PK drug-drug interaction (DDI) when oral vinorelbine (NVBo) and Anastrozole (A) are combined. Mutual interaction was explored. Anastrozole interaction on NVBo: Apparent VRL clearance (Cltot/F) was compared graphically between days (D1 vs D8) and with reference phase I and II monotherapy; DVRL concentrations were compared graphically with reference phase II monotherapy data. NVBo interaction on Anastrozole was assessed by comparing trough concentrations of Anastrozole between D8 (with vinorelbine) and D 21(alone). • Rate of conservative surgical resection • Clinical down staging before surgery
Statistical methods:	Sample size: The one-sample multiple testing procedure for phase II clinical trials described by Fleming was used. A sample size of 55 evaluable pts was needed. Assuming that 60 % was the minimum desirable response rate for an active agent therapy in this population, $\alpha \leq 0.05$, $\beta \leq 0.10$, the first test was performed after 25 evaluable pts: if >15 and < 22 responses were observed, 30 additional pts were supposed to be recruited. The second test was planned on 55 evaluable pts: if ≥ 40 responses were observed further investigation was warranted. Analyses: The statistical analysis was performed by the Institut de Recherche Pierre Fabre, using the SAS® system software version 8.2 (or later if available) for Windows. Pharmacokinetics analysis: The potential effect of Anastrozole on PK of Navelbine oral was studied by comparing NVBo PK first between day 1 and day 8 and then with reference phase I and II monotherapy. Apparent vinorelbine clearance (Cltot/F) was compared graphically and using a Wilcoxon test. The reference population was made of Cltot/F values from patients who received NVBo as a single agent (n=121). [PM0259 IN M108] [PM0259 IN M156] [PM0259 IN M161] [9 PM0259 96 CA 201] [9 PM0259 97 CA CA 205] [9 PM0259 CA 206] DVRL concentrations were compared graphically with reference phase II monotherapy data (n=78).[9 PM0259 96 CA 201] [9 PM0259 97 CA CA 205] [9 PM0259 CA 206]. NVBo potential interaction on Anastrozole PK was evaluated by comparing steady state trough concentrations between D8 (with VRL) and D21 (alone) using a t-test. In addition, concentrations were compared to those of the literature. [ATAC trialists' group, 2001].

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Summary - Conclusions:

Patients disposition

Patients and tumour characteristics

Sixty patients from 12 centres were enrolled from July 2005 to June 2008.

Out of these, 59 received at least one dose of treatment and 58 could be evaluable for the main end point (US response rate).

Pharmacokinetics analysis was performed in 9 patients.

Protocol deviations:

No major deviation was considered at study entry.

Four patients were considered to present major protocol violation during the course of study: all were withdrawn from the study for reasons not planned by the protocol [N°270104, 760304, 760305, 760312] (see premature withdrawals section for details).

2 patients presented some minor protocol deviations at study entry:

- 1 case of primary breast tumour < 30mm (28mm) [N°760101]
- 1 case of serum Creatinine ≥ 130 µmol/L (153µmol/L) [N°050301]

Some investigations at baseline were performed > 21 days before 1st drug administration in 5 patients (minor violation): [N°050303, 520301, 760309, 760311, 760312].

During the course of the study, minor protocol violations were recorded in 5 patients:

- One case of NVBo underdosing during first cycle by calculation mistake [N°760102]
- One NVBo administration cancelled in absence of toxicity in 3 patients [N°050301, 050303, 760305]
- Dose of NVBo not reduced despite of haematotoxicity in 1 patient[N°380203]

Premature study withdrawals:

- One pt never received the study treatment because an intercurrent event between registration and 1st treatment administration: discovery of endometrial polyps that compromised treatment initiation [N°520310]
- One pt withdrew her consent [N°520201].
- One pt was withdrawn because of a major protocol deviation (treatment administration delayed over 2 weeks because of concurrent additional investigations) [N°760312].
- Three (5%) pts stopped the treatment upon their physicians decision:
  - 1 pt~~s~~ with complete response on mammography only[N°270104]
  - 1 pt with a decision of treatment modification on stable disease[760304]
  - 1pt in which the decision was taken because of a discrepancy between primary tumour and overall tumour response [760305]
- Seven pts (11.7%) discontinued the treatment because of an adverse event:
  - Six due to non serious adverse events (SAE): only Grade 1-2 toxicities except 2 grade 3 events in one patient (myalgia and increased hepatic enzymes) and another pt with grade 4 musculoskeletal pain) [N°050301, 520105, 600101, 760306, 760310, 760311].
  - One patient due to a SAE: she died because of a cerebral haemorrhage that was not considered related to progression neither toxicity. [N°520308]
- Withdrawal due to progressive disease was observed in 6 pts [270106, 520102, 520205, 760102, 760104, 760105].

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Summary – Conclusions (continued):

Patients and tumour characteristics (continued)	**Patients characteristics**	**N (%)**
	Number of treated patients	**59**
	Median Age, years[Range]	64.9 [51.7-87.3]
	Median BSA, m^2[Range]	1.7 [1.2-2.1]
	HER 2 testing	55 (100.0)
	IHC 3+	9 (16)
	IHC 2+	13(24)
	IHC 0-1+	33 (59)
	ER+ status	59 (100)
	PR + status	44 (75)
	Primary Tumor Diameter(PTD), by ultrasound, cm	
	Mean[SD]	4 (1.2)
	Median[Range]	3.7 [2.8-9.0]
	>5 cm	7 (12)
	>3 cm to ≤ 5 cm	41(70)
	= 3cm	10 (17)
	< 3 cm	1(2)
	Primary Tumor Diameter(PTD), by calliper, cm	
	Mean[SD]	6.3 (2.3)
	Median[Range]	6 [3-15]
	Nodal invasion, %	
	N0, N1, N2	40.7 / 40.7 / 18.6
	Target lesions size at baseline, by ultrasound, cm	
	Mean[SD]	4.8 (2.1)
	Median[Range]	4.1 [2.8-14.5]
Treatment administrations:	**Number of patients with drug exposure**	**59**
	Total number of cycles	304
	Median (Range) / pt	6 [2-6]
	Mean (SD) / pt	5.2 (1.3)
	Treatment duration (weeks) / pt	
	Median (Range)	17.9 [6.0-22.9]
	Mean (SD)	15.9 (4.3)
	Oral vinorelbine relative dose intensity / pt	
	Median (Range)	98% [69-109]
	Mean (SD)	94% (11)
	Cumulative dose of anastrozole (mg) / pt	
	Median (Range)	126.0 [29-165]
	Mean (SD)	112.7 (31.5)
	• Median relative dose intensity for NVBo was 98%. In 57/59 patients the dose was escalated to 80 mg/m2 at cycle 2. • Fifty eight pts (98%) received at least 3 cycles of NVBo and 40 (68%) received 6 cycles. • Over 304 cycles, only 2 (0.7%) were delayed for more than 2 weeks and only 25 (8.2%) were delayed for more than 7 days but less than 2 weeks, mainly due to haematological adverse event, elevated hepatic enzymes in 2 pts, personal convenience in 2 pts, and various non drug-related events in 5 other pts.	

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Summary – Conclusions (continued):

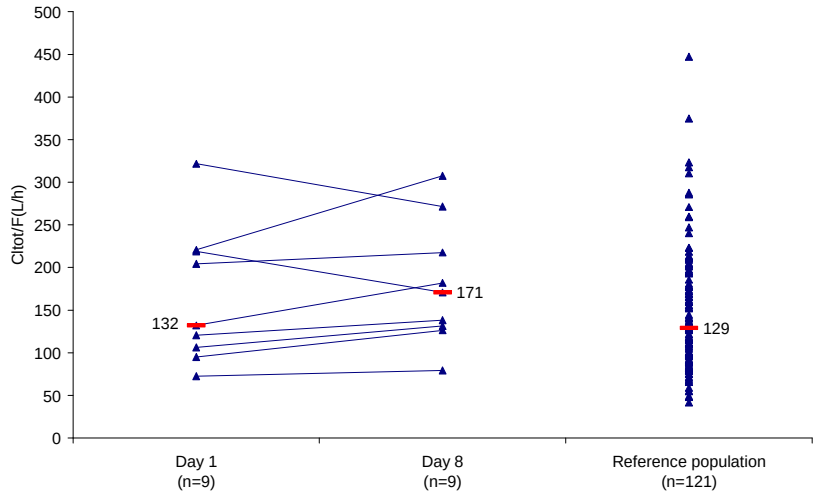
Pharmacokinetics results

Vinorelbine (VRL)

Cltot/F on Day 1 (1st coadministration with Anastrozole) was similar to those obtained on Day 8 (anastrozole steady-state) (p=0.16).

Since no difference was observed pooled data were compared to reference values. Cltot/F values were comparable to the reference values (p=0.80).

Comparison of VRL Cltot/F between days and reference data



DVRL

Concentrations were in the range of concentrations usually observed during phase II monotherapy studies.

Anastrozole: C_{trough} on D 8 (with VRL) were similar to those observed on D21(A. alone). Results are summarized in the following table :

	D8 (n=9)	D21 (n=9)	p value
C_{trough} (ng/ml)	31.6 ± 12.6	30.7 ± 12.7	0.92 (NS)

Concentrations observed were also comparable to those of the literature. (**ATAC Trialists' Group**, British Journal of Cancer (2001) **85**(3), 317–324)

Efficacy results

Primary efficacy results

Primary efficacy results

ITT population (Investigator's assessment): ORR = 59% [95% CI 46-72%]

Evaluable population (Investigator's assessment): ORR = 60% [95% CI 46-72%]

Response rate (%)	US N (%)		Calliper N (%)
	All targets	Primary Tumour	All targets
Nb of analysed patients	59	59	59
Complete response (CR)	3 (5.1)	3 (5.1)	5 (8.5)
Partial response (PR)	32 (54.2)	33 (55.9)	36 (61.0)
Stable Disease (SD)	18 (30.5)	17 (28.8)	11(18.6)
Progressive disease (PD)	5 (8.5)	5 (8.5)	5 (8.5)
Non evaluable (NE)	1 (1.7)	1 (1.7)	2 (3.4)
Objective response (CR+ PR)	35 (59.3)	36 (61.0)	41 (69.5)
[95% CI]	[45.8-71.9]	[47.4-73.5]	[56.1-80.8]

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Summary – Conclusions (continued):

Efficacy results

Secondary efficacy endpoints

Secondary efficacy endpoints:

- **pCR (pT0-pN0; TA-NA Sataloff Classification) : 3.8%**
- **Clinical down staging : nodal invasion regressed by 43% among the 35 pts ≥ N0**

Clinical Node Status	Baseline	End
0	24 (41%)	35 (59%)
1	24 (41%)	15 (25%)
2	11 (19%)	8 (14%)
Unknown	-	1 (2%)

- **Surgery**

Feasibility of surgery, n=59	Baseline	End	Surgery Performed	
Not currently operable	11 (19%)	3 (5%)	No**	5 (8%)
Mastectomy required	41 (69%)	44 (75%)	Mastectomy	42 (71%)
Breast conservative surgery	7 (12%)	10 (17%)	Breast conservative surgery	10 (17%)
Not applicable*	-	2 (3%)	Not applicable*	2 (3%)

*Not applicable: 1 cerebral haemorrhage, 1 change of chemotherapy on physician decision (tumour assessment quoted as SD after 3 courses)

**2 concurrent events : 1 lost to follow-up and 1 AE (increase of hepatic enzymes)

The median follow-up (from registration, 59 pts) was 18.9 months; 57 pts had at least a 3 month follow-up after study end (up to 35 months). All were alive at last contact. In 4 pts a relapse or progression was reported at 10.6, 13.5, 15.8 and 16.0 months.

Safety results

Haematological G3/4 toxicity:

Grade (G) 3-4 toxicities, observed in only 6 pts (10.2%), were leucopenia, neutropenia without any febrile neutropenia; neither G3/4 anemia , nor thrombopenia.

Related G3/4 haematological toxicities, N(%) n = 59	G3	G4	G3-4
Anemia	-	-	-
Leucopenia	1 (1.7%)	-	1 (1.7%)
Neutropenia	4 (6.9%)	2 (3.4%)	6(10.2%)
Thrombocytopenia	-	-	-
Febrile Neutropenia			-

Biochemical G3/4 toxicity: 1 pt showed an asymptomatic increase(G3) in hepatic enzymes (ALAT/ASAT) from baseline (ALAT G0 /ASAT G1)

Clinical G3/5 toxicity:

- **Only 6 pts experienced related adverse events grade 3/4** (1 pt had 3 different)

Clinical Toxicities N(%) G3/G4	Grade	RELATED ADVERSE EVENT PER PATIENT	RELATED ADVERSE EVENT PER CYCLE
Total Number		59 (100%)	304 (100%)
nausea	G 3	3 (5.1%)	3 (1.0%)
	G 4	-	-
Vomiting	G 3	1 (1.7%)	2 (0.7%)
	G 4	-	
Diarrhoea	G 3	3 (5.1%)	6 (2.0%)
	G 4	-	-
Musculoskeletal pain	G 3	-	-
	G 4	1 (1.7%)	1 (0.3%)

- **5 additional pts had G3-5 non-related toxicities, including 2 pts with SAE:**

- Non-related G3-4 AE: Sinus tachycardia G3, hypertension G3, myalgia G3
- Non-related SAE: 1 pt experienced anaphylactic shock due to the administration of blue colorant leading to G4 hypotension (imaging purposes; recovered) [N°760302] and 1 pt with a known underlying hypertension died from a cerebrovascular haemorrhage [N°520308]. (Assessed by Sponsor as dubiously related and hypertension as possibly related to study drugs).

Serious adverse events (SAE): No related SAE was reported but 2 non-related SAE occurred in 2 pts (see above).

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Summary – Conclusions (continued):

Conclusion

Two recent randomized studies with anastrozole, as single agent or with an unspecified cytotoxic, produced an objective response rate (RR) of 24 and 39.5% by ultra-sound (US) [baseline primary tumor diameters (PTD) of 2.6 cm (median) and 3.6 cm (mean), respectively] in LA BC.

This phase II, open-label, multicentre study was designed to determine the efficacy and safety of the combination of oral vinorelbine (Navelbine Oral®) 60-80 mg/m² every 3 weeks and anastrozole (Arimidex®) 1 mg daily per os in post-menopausal patients with locally advanced, hormone receptor positive breast cancer.

Navelbine Oral® plus Anastrozole led to an increased response rate as compared with previous experiences with Anastrozole alone or not (IMPACT, PROACT trials) in a high risk population with a larger primary tumour diameter (median of 3.7 cm, mean of 4 cm by US) and mainly with nodal invasion: 59%.

From the PK analysis, no mutual drug-drug interaction was suggested in this study.

The operability rate was improved from baseline in this population with unfavourable characteristics and breast conservative surgery slightly increased.

This combination treatment was well tolerated and pts could benefit from an oral therapy allowing preservation of daily living activities.

Date of report: 12th October 2011