Randomized Phase II Study Evaluating The Tolerability Of Adjuvant Docetaxel-based Chemotherapy For Completely Resected Stage IB-II Non-Small Cell Lung Cancer (NSCLC): TOLEDO trial

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Toledo-trial: introduction

- **Antwerps Kanker Register 2000:**
  - 989 new cases of lung cancer in the province of Antwerp.
  - 83% were histologically of NSCLC type.
  - About one quarter (27%) of the NSCLCs were resected.

  →≥ 200 resections for NSCLC / year in the province of Antwerp.
- **Long-term survival for resected NSCLC remains disappointing:**
  - 5-year survival rates range from 73% for pathologic stage IA disease to 39% for pathologic pathologic stage IIB disease.
  - Micrometastatic cancer cells are present in bone marrow of >30% of patients with operable NSCLC.
  - The majority of relapses occur at distant sites.

Toledo-trial: introduction

Survival results of adjuvant chemotherapy from 5 recent randomised placebo-controlled trial

	N	Stage	# cycl	OS 5-yr	HR	p value
ALPI	1209	I-IIIA	3	+ 3%	.96	0.6
BLT	381	I-III	3	+0-1%	1	1
IALT	1867	I-IIIA	3-4	+ 4%	.86	<0.03
JBR.10	482	IB-II	4	+ 15%	.69	0.012
CALGB	344	IB	4	+ 12%*	.62	0.028

Furthermore, systematic reviews and meta-analysis confirm that adjuvant chemotherapy is associated with improved survival compared with surgical intervention alone.

Sedrakyan ea. *J Thorac Cardiovasc Surg* 2004, 128: 414-419.

Toledo-trial: introduction

- **Adjuvant chemotherapy is associated with significant morbidity / toxicity:**
  - IALT: 22.6 % grade 4 toxicity
  - ALPI: 12 % grade 4 toxicity
  - BLT: overall 30% grade 3/4 toxicity (55% of patients receiving NP were reported as having grade 3 or 4 toxicity compared to 27% of the MIC and 17% of the MVP patients)
  - CALGB 9633: 28% grade 4 toxicity
  - NCIC trial: reported only combined grade 3 and 4 (i.e. 73% gr 3-4 neutropenia and 7% febrile neutropenia)

Toledo-trial: introduction

Drug delivery results of adjuvant chemotherapy from 5 recent randomised placebo-controlled trial

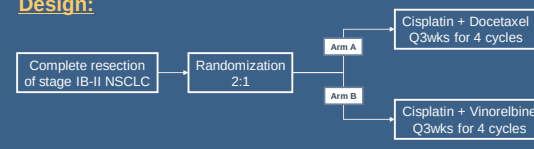
	N	Chemo	Chemo completion	PORT
ALPI	1209	MVdP	69%	43%
IALT	1867	P-Vb, P-Vd, P-Vrb or P-VP16	74%	23%
Big Lung Trial	381	MIP, MVbP P-Vb or P-Vd	64%	-
NCIC JBR.10	482	P-Vrb	65%	-
CALGB 9633	344	Cb-Pacli	85%	-

Toledo-trial: aim and design

Aim:

To evaluate the tolerability of four cycles of adjuvant docetaxel plus cisplatin in patients with completely resected stage IB/II NSCLC.

Design:



Toledo-trial: endpoints

Primary endpoints:

1. Success of delivery treatment
   (To be considered as a "success" a patient should have received at least 3 cycles of chemotherapy, and have a relative dose intensity of 80% or above)
2. Toxicity
   (Occurrence of any grade 4 non-haematological toxicity)

Secondary endpoints:

1. Overall toxicity
2. Progression free survival and overall survival

Toledo-trial: inclusion criteria

1. Completely resected (R0*) pathological stage IB or II NSCLC
2. The first cycle of chemotherapy should be started within 60 days of resection
3. KS 70-100 (see appendix II)
4. Age: 18 – 75 year
5. Weight loss < 10% over previous 6 months
6. Adequate haematological function:
   - ANC > 1,5x 109/L
   - Platelets > 100x 109/L
   - Hgb > 10 g/dl

*R0 resection: a resection is considered a complete resection if microscopic examination shows a radical resection of the primary tumor with tumor-free resction margins and if the highest prelevated mediastinal lymph node is tumor free

Toledo-trial: inclusion criteria

7. Adequate renal and liver function:
   - Creatinine ≤ 1.5 mg/dL, or calculated creatinine clearance ≥ 60 ml/min (see appendix III for calc. creat. clearance)
   - Total bilirubin ≤ ULN
   - Alkaline phosphatase ≤ 5.0x ULN
   - AST/ALT ≤ 2.0x ULN
   - Serum calcium ≤ 1.1x ULN
8. Signed informed consent prior to beginning protocol specific procedures.
9. Women of childbearing potential must be non-pregnant, non-lactating and use adequate contraception during study treatment.

Toledo-trial: exclusion criteria

1. Previous chemo- or radiotherapy for NSCLC
2. Bronchoalveolar cell subtype (ie those cases which show no stromal, pleural, or lymphatic invasion according to the WHO classification of 1999).
3. Second active primary malignancy (except basocellular CA of the skin, adequately treated CA in situ of the cervix, low-grade prostate cancer or other cancer from which the patient has been disease free for at least five years)
4. Serious concomitant medical disease (i.e. active infection, preexisting neuropathy, AMI less than 6 months old), immunosuppression or psychiatric disease that, in the opinion of the investigator, would compromise the safety of the patient or compromise the patient's ability to complete the study.
5. Pregnant or breast-feeding females.
6. Difficulties with adequate follow-up

Toledo-trial: randomization procedure

- Patients will be randomized on a 2:1 basis, with stratification according to clinical stage: IB versus II (using two computer-generated randomization lists). Centralized randomization was used to conceal the allocation sequence to the investigator at time of enrolment.
- The Registration/Randomization center will inform the investigator of the treatment sequence: arm A or arm B. The study treatment had to start within 7 days from randomization and within 60 days of resection.
- The study was not blinded. Commercially available products were used.

Toledo-trial: treatment administration

Arm A:

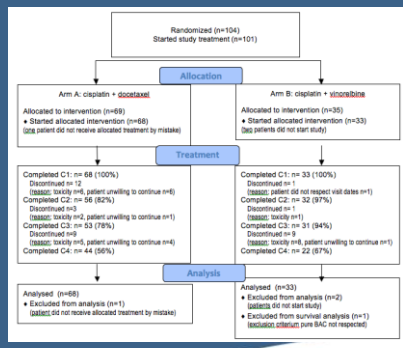
cisplatin 75 mg/m2 on **day 1** and **docetaxel 75 mg/m2** on **day 1** of each cycle

Arm B:

cisplatin 80 mg/m2 on **day 1** and **vinorelbine 25 mg/m2** on **day 1 and 8** of each cycle

- A cycle is defined as an interval of 21 days
- All patients will be treated with 4 cycles of adjuvant chemotherapy, unless there is the occurrence of unacceptable toxicity or early progression.

Patient disposition



Patient demographics

N	all patients 101	Cis-Doc 68	Cis-VRB 33
Age (Y):			
Median	61	61	62
(range)	(37-75)	(37-75)	(43-75)
Gender:			
Male	68	49	19
Female	33	19	14
Performance status:			
KPS 90-100	88	62	26
KPS 70-80	13	6	7
Lung function:			
FEV_1 (L): median	1,88	2,20	1,79
(range)	(1,02-4,60)	(1,02-4,60)	(1,10-2,39)
FEV_1 (%pred): median	66	70	60
(range)	(32-117)	(32-117)	(41-94)
DLCO (%pred): median	56	56	56
(range)	(20-130)	(20-125)	(35-130)
BSA (mg/m^2):			
Median	1,85	1,86	1,85
(range)	(1,41-2,66)	(1,49-2,66)	(1,41-2,29)

Patient demographics

N	all patients 101	Cis-Doc 68	Cis-VRB 33
Interval between surgery and randomization (in days):			
Median	38	36	40
(range)	(14-69)	(14-69)	(25-69)
Type of surgery	n (%)	n (%)	n (%)
pneumonectomy right lung	5 (5)	3 (4)	2 (6)
pneumonectomy left lung	14 (14)	11 (16)	3 (9)
lobectomy RUL	12 (12)	9 (13)	3 (9)
lobectomy RML	2 (2)	2 (3)	-
lobectomy RLL	14 (14)	9 (13)	5 (15)
lobectomy LUL	24 (24)	13 (19)	11 (33)
lobectomy LLL	14 (14)	10 (15)	4 (12)
bilobectomy RUL+RML	5 (5)	3 (4)	2 (6)
bilobectomy RML+RLL	2 (2)	1 (1)	1 (3)
bilobectomy RUL+RLL	1 (1)	1 (1)	-
bilobectomy RUL+RML+RLL	1 (1)	1 (1)	-
limited resection wedge	2 (2)	2 (3)	-
limited resection segmentectomy	1 (1)	-	1 (3)
sleeve lobectomy RUL	2 (2)	2 (3)	-
pneumonectomy left lung+partial thorax wall	1 (1)	-	1 (3)
RUL +part of 2 ribs	1 (1)	1 (1)	-

Patient demographics

N	all patients 101	Cis-Doc 68	Cis-VRB 33
Histological tumor type	n (%)	n (%)	n (%)
adenocarcinoma	53 (52)	36 (53)	17 (52)
squamous cell	33 (33)	25 (37)	8 (24)
large cell	9 (9)	6 (9)	3 (9)
adenocarcinoma + squamous	1 (1)	1 (1)	-
adenocarcinoma + BAC	2 (2)	-	2 (6)
adenocarcinoma + large cell	1 (1)	-	1 (3)
muco-epidermoid	1 (1)	-	1 (3)
BAC	1 (1)	-	1 (3)
Histology differentiation			
well differentiated	12 (12)	8 (12)	4 (12)
moderately differentiated	49 (49)	34 (50)	15 (45)
poorly differentiated	32 (32)	23 (34)	9 (27)
unknown	8 (8)	3 (4)	5 (15)
Pathological TNM*			
T1N1M0	10 (10)	7 (10)	3 (9)
T2N0M0	56 (55)	37 (54)	19 (58)
T2N1M0	29 (29)	18 (26)	11 (33)
T3N0M0	6 (6)	6 (9)	-
Cancer stage*			
IB	56 (55)	37 (54)	19 (58)
IIA	12 (12)	8 (12)	4 (12)
IIB	33 (33)	23 (34)	10 (30)

* according to 6th TNM classification

Succes of treatment delivery
(≥3 cycles with RDI ≥80%)

Succes of delivery treatment	Cis-Doc n = 68		Cis-VRB n = 33
Succes cisplatinum: n (%)	52 (76)	Succes cisplatinum: n (%)	26 (79)
Succes docetaxel: n (%)	52 (76)	Succes vinorelbine: n (%)	25 (76)
Succes Cis-Doc: n (%)	52 (76)	Succes Cis-VRB: n (%)	23 (70)

Reason for dose modification or delay

	Cis-Doc					Cis-VRB				
	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Total	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Total
Adverse event drug related:										
-hematological toxicity	-	4	3	-	7	-	11	8	14	33
-non-hematological toxicity	1	5	4	8	18	-	2	4	3	9
Adverse event not drug related	-	-	1	1	2	-	-	-	1	1
Patient unwilling/unable to continue	-	6	1	4	11	-	-	-	1	1
Organizational reason or other	-	2	4	3	9	2	3	1	-	6
Total	1	17	13	16	47	2	16	13	19	50

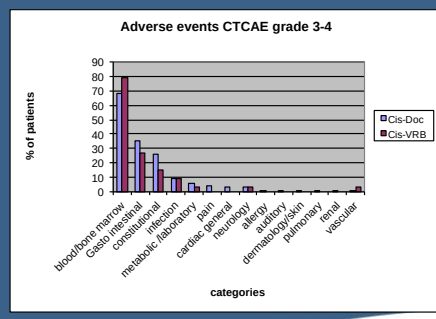
Reason for withdrawal from chemotherapy

	Cis-Doc					Cis-VRB			
	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Total	Cycle 2	Cycle 3	Cycle 4	Total
Adverse event drug related:									
-hematological toxicity	-	2	1	-	3	-	-	4	4
-non-hematological toxicity	1	3	1	5	10	-	1	3	4
-hematologic+non-hematologic	-	-	-	-	-	-	-	1	1
Patient unwilling/unable to continue	-	6	1	4	11	-	-	1	1
Investigator decision because patient did not respect visit dates	-	-	-	-	-	1	-	-	1
Total	1	11	3	9	24	1	1	9	11

Grade 3-4 adverse events

CTCAE categories	Cis-Doc Grade 3 n	Grade 4 n	Grade 3-4 n	%	Cis-VRB Grade 3 n	Grade 4 n	Grade 3-4 n	%
Blood/bone marrow	17	29	46	(68)	10	16	26	(79)
Gastro intestinal	24		24	(35)	9		9	(27)
Constitutional	18		18	(26)	5		5	(15)
Infection	6		6	(9)	3		3	(9)
Metabolic /laboratory	4		4	(6)	1		1	(3)
Pain	3		3	(4)	-		-	
Cardiac general	2		2	(3)	-		-	
Neurology	1	1	2	(3)	1		1	(3)
Allergy	1		1	(1)	-		-	
Auditory	1		1	(1)	-		-	
Dermatology/skin	1		1	(1)	-		-	
Pulmonary	1		1	(1)	-		-	
Renal	1		1	(1)	-		-	
Vascular	1		1	(1)	1		1	(3)
Hematological			46	(68)			26	(79)
Non hematological			36	(53)			14	(42)
Hematological + non hematological events			57	(84)			28	(85)

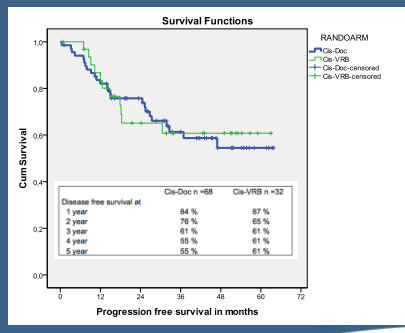
Grade 3-4 adverse events



Site of disease recurrence

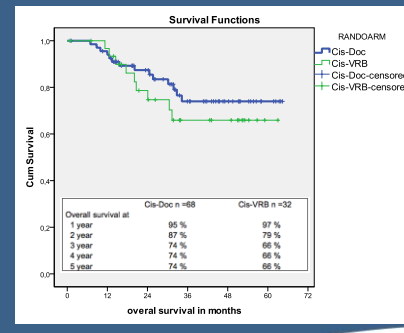
	Cis-Doc n =68	Cis-VRB n =32
Type of recurrence	n (%)	n (%)
Local (ipsilateral lung and/or hilum)	3 (4,4)	1 (3,1)
Regional mediastinum	1 (1,5)	1 (3,1)
Local + regional mediastinum	1 (1,5)	
Local + metastasis	2 (2,9)	2 (6,3)
Regional mediastinum + metastasis	1 (1,5)	1 (3,1)
Regional supraclavicular	1 (1,5)	1 (3,1)
Second primary tumor in contralateral lung	3 (4,4)	
Metastasis	11 (16,2)	4 (12,5)
Died from lung cancer		1 (3,1)
Died non lung cancer related	2 (2,9)	
Total number of recurrence	25 (36,8)	11 (34,4)

TOLEDO: disease-free survival ~ arm



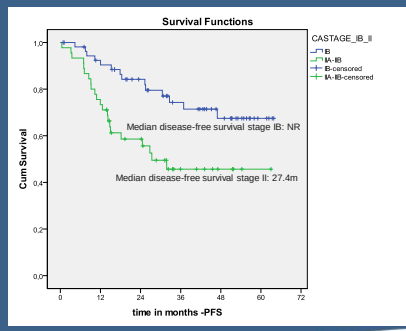
Median follow-up 63 months

TOLEDO: overall survival ~ arm



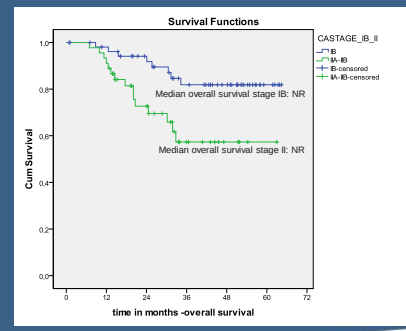
Median follow-up 63 months

TOLEDO: disease-free survival ~ stage



Median follow-up 63 months

TOLEDO: overall survival ~ stage



Median follow-up 63 months

TOLEDO trial: conclusions

- Adjuvant treatment with 3 week schedule Pt-TXT is :
  - feasible, tolerable
  - 1st endpoints reached: 76% delivery success
- 3 W schedule Adjuvant treatment PT- NVB shows
  - A better tolerability than a historical 4 w schedule
  - A 70% delivery success
- Data robust enough to propose a Random PhIII study based on DFS and Survival

Investigational sites: 15 in Belgium - 3 in Holland

Site	Principal investigator	N° patients
Centre Hospitalier Universitaire de Liège, B	Dr L Bosquée	13
Amphia ziekenhuis Breda, NI	Dr J Aerts	12
ORBIS medisch centrum Geleen, NI	Dr F Peters	10
Universitair Ziekenhuis Antwerpen, B	Prof Dr P Germonpré	8
AZ Nikolaas, St Niklaas, B	Dr K Deschepper	8
ZNA Middelheim Antwerpen, B	Dr D Galdermans	7
AZ Turnhout, B	Dr P Driesen	7
AZ St Maarten Duffel Mechelen, B	Dr M Lambrechts	6
GZA St Vincentius, Antwerpen, B	Dr I Stappaerts	5
AZ Monica, Antwerpen Deurne, B	Dr T Huybrechs	5
Stedelijk ziekenhuis Aalst, B	Dr L Van Moorter	5
C.H.R de la Citadelle Liège, B	Dr F Bustin	4
GZA St Augustinus, Wilrijk, B	Dr D Verresen	3
AZ St Jozef Bomem Willebroek, B	Dr AM Morel	2
AZ St Elisabeth, Herentals, B	Dr Y Menten	2
Ommelander ziekenhuisgroep Delfzijl Winschoten, NI	Dr R Pieterman	2
ZNA Jan Palfijn, Merksem, B	Dr C Van Schaardenburg	1
AZ OLV Aalst Asse, B	Dr P Vercauter	1