Supplementary material

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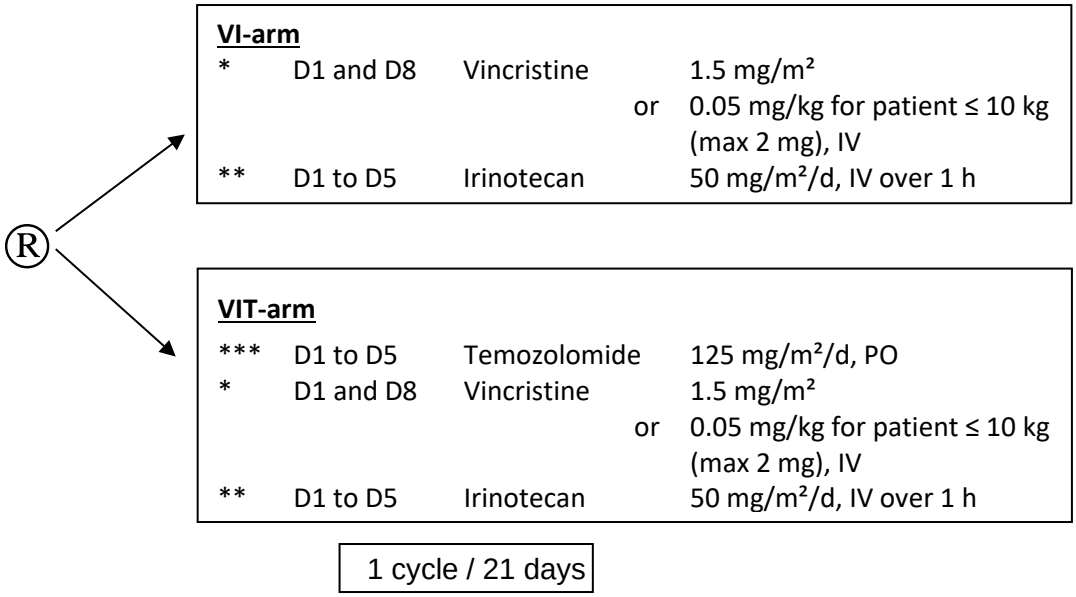
On-line Table S1: List of participating countries, cooperative groups and centers

Country (cooperative group) and participating center	VIT (N=60)		VI (N=60)		Total (N=120)	
France: French Society of Pediatric Oncology (SFCE) & French Sarcoma Group (GSF)	**28**	**47%**	**29**	**48%**	**57**	**48%**
Centre Oscar Lambret, Lille	4		8		12	
Institut Gustave Roussy, Villejuif	5		2		7	
Centre Léon Bérard, Lyon	3		2		5	
Institut Curie, Paris	3		2		5	
Hôpital des enfants, Toulouse	1		4		5	
CHU, Hôpital d'Enfants de la Timone, Marseille	1		2		3	
CHU Hôpital Mère enfants, Nantes	2		1		3	
Hôpital Arnaud de Villeneuve, Montpellier	1		2		3	
CHU - Hôpital Sud, Rennes	2		1		3	
Hôpital des Enfants, Groupe Hospitalier Pellegrin, Bordeaux	1		1		2	
Hôpital Armand Trousseau, Paris	0		2		2	
CHR-U, Tours	2		0		2	
CHU d'Amiens-Picardie, Amiens	1		1		2	
CHRU Hôpital d'Enfants, Vandoeuvre Les Nancy	0		1		1	
Hôpital Jean Bernard, Poitiers	1		0		1	
CHU - Hôpital Nord, St Etienne	1		0		1	
United Kingdom: Children's Cancer and Leukaemia Group (UKCCSG)	**17**	**28%**	**17**	**28%**	**34**	**28%**
Royal Marsden NHS Foundation Trust, London	5		3		8	
Univerity college London hospitals, London	4		2		6	
Royal Manchester Children's Hospital, Manchester	1		4		5	
The Christie NHS Foundation Trust, Manchester	3		1		4	
University Hospitals NHS Trust, Nottingham	0		3		3	
Teaching Hospitals NHS Trust, Leeds	0		2		2	
Alder Hey Children's NHS Foundation, Merseyside	2		0		2	
Royal Hospital for Children, Bristol	1		0		1	
Children's Hospital, Birmingham	1		0		1	
Addenbrooke`s Hospital, Cambridge	0		1		1	
Royal Victoria Infirmary, Newcastle	0		1		1	
Netherlands: Dutch Childhood Oncology Group (DCOG)	**9**	**15%**	**7**	**12%**	**16**	**13%**
Emma Children's Hospital, Amsterdam	4		4		8	
University Medical Center, Gröningen	4		1		5	
Erasmus MC-Sophia Children's Hospital, Rotterdam	1		2		3	
Italy: Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP)	**5**	**8%**	**6**	**10%**	**11**	**9%**
Istituto Nazionale Tumori, Milano	1		2		3	
Ospedale Pediatrico Bambino Gesù IRCCS, Roma	1		2		3	
Istituto G. Gaslini" Children Hospital, Genoa	1		1		2	
Clinica di Oncoematologia Pediatrica, Padova	2		0		2	
Ospedale Infantile Regina Margherita, Torino	0		1		1	
Spain: Sociedad Espanola de Oncologia Pediatrica (SEOP)	**1**	**2%**	**1**	**2%**	**2**	**2%**
Hospital Vall d'Hebron, Barcelona	1		1		2	

On-line Figure S1: Details of treatment schedule



Patients had to have evidence of recovery from all prior cycle toxicity and the ANC must be > 1.0 x 10^9/L and platelets > 100 x 10^9/L before starting a new cycle.

Repeated 3-week cycles until disease progression, unacceptable toxicity or the patient's desire to discontinue therapy

* The dose of vincristine was 1.5 mg/m² or 0.05 mg/kg for patient ≤ 10 kg (max 2 mg), and was administered by direct intravenous infusion on day 1 of each course, before irinotecan. Administration must comply with guidance on administration of vinca alkaloids as per NPSA/2008/RRR004.

** The dose of irinotecan was 50 mg/m² and was administered by 60 min intravenous infusion one hour following the administration of temozolomide

*** Temozolomide was administered orally, 1 hour before irinotecan and vincristine infusion. The starting dose was 125 mg/m². The dose was escalated to 150 mg/m² at cycle 2 for patients who do not experience ≥ grade 3 toxicity (NCI-CTCAE v4.0). The dose of temozolomide should be rounded off the nearest 5 mg. For patients who had difficulty to swallowing or young children, the daily dose of temozolomide capsules should be placed in 10-30 ml fruit juice or compote and administered after the capsules have been allowed to soften for 15-20 minutes. If the patient vomits within 20 minutes after temozolomide, the dose was re-administered.

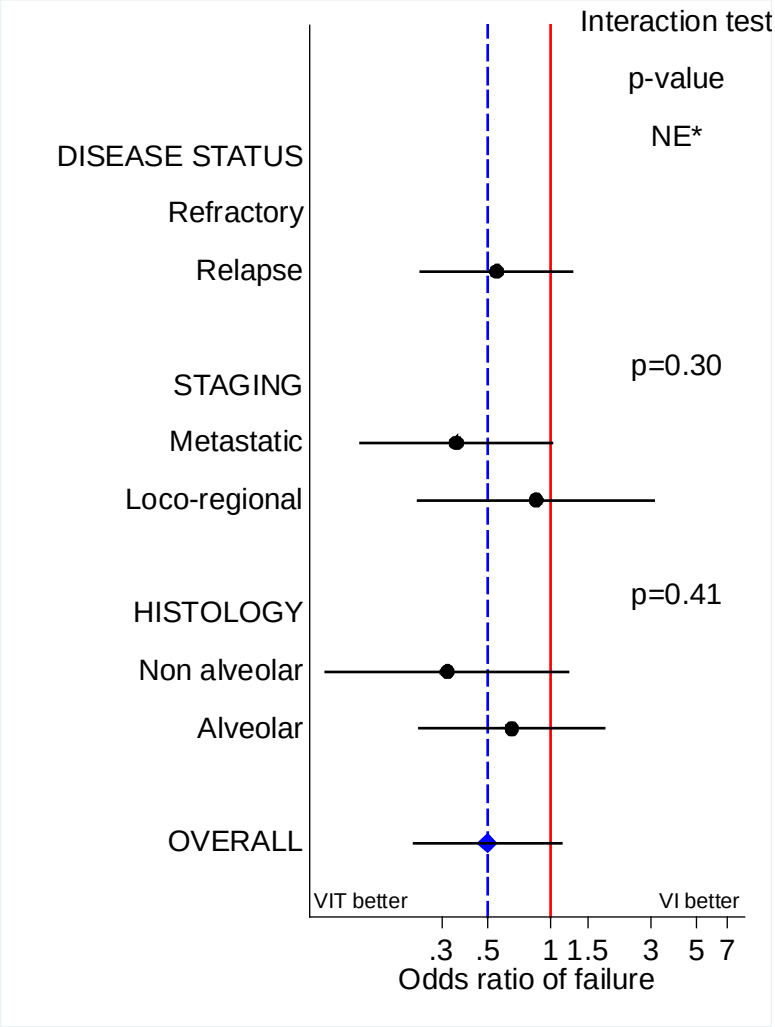
Dose reductions were planned in case of severe toxicities (details in the full protocol).

Systematic treatment with oral cefixime 8 mg/kg once a day (max daily dose 400 mg) was recommended and was started 2 days before chemotherapy until day 7.
If diarrhea occurred, a specific treatment had to be started as soon as possible, based on atropine if occurrence in the first 8 hours (cholinergic symptoms), and based on loperamide if delayed occurrence.

Prophylactic use of granulocyte colony stimulating factor (G-CSF) was not recommended during the trial but G-CSF could be used for patients presenting with severe infection with neutropenia and in subsequent cycles after infectious complications.

Evaluation of heterogeneity of treatment effect across main subgroups

On-line Figure S2: Forest-Plot of Objective Response at 2 cycles (adjusted odd-ratio of failure on the whole population)



Legend

* NE = p-value not estimable because there was no patient with an objective response in the group VI, in the strata of patients with refractory disease.

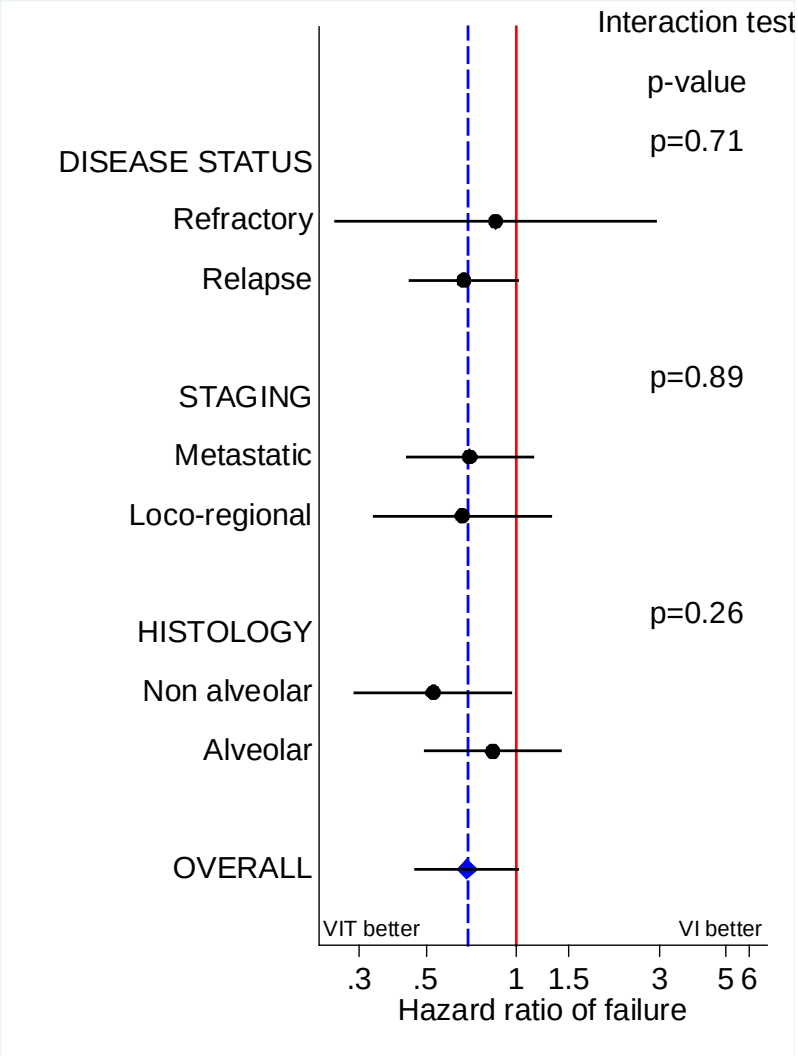
For each variable successively, the model included the treatment effect, the predefined covariates (disease status, staging and histology) and the interaction term between treatment arm and the evaluated variable.

For each modality, the figure represents the adjusted odds-ratio of treatment failure (VIT versus VI) and its 95% confidence interval.

The p-value corresponds to the p-value of the interaction test in the multivariable model.

All details are available in Supplementary Table S1, on the whole study population, as well as considering patients enrolled at relapse only.

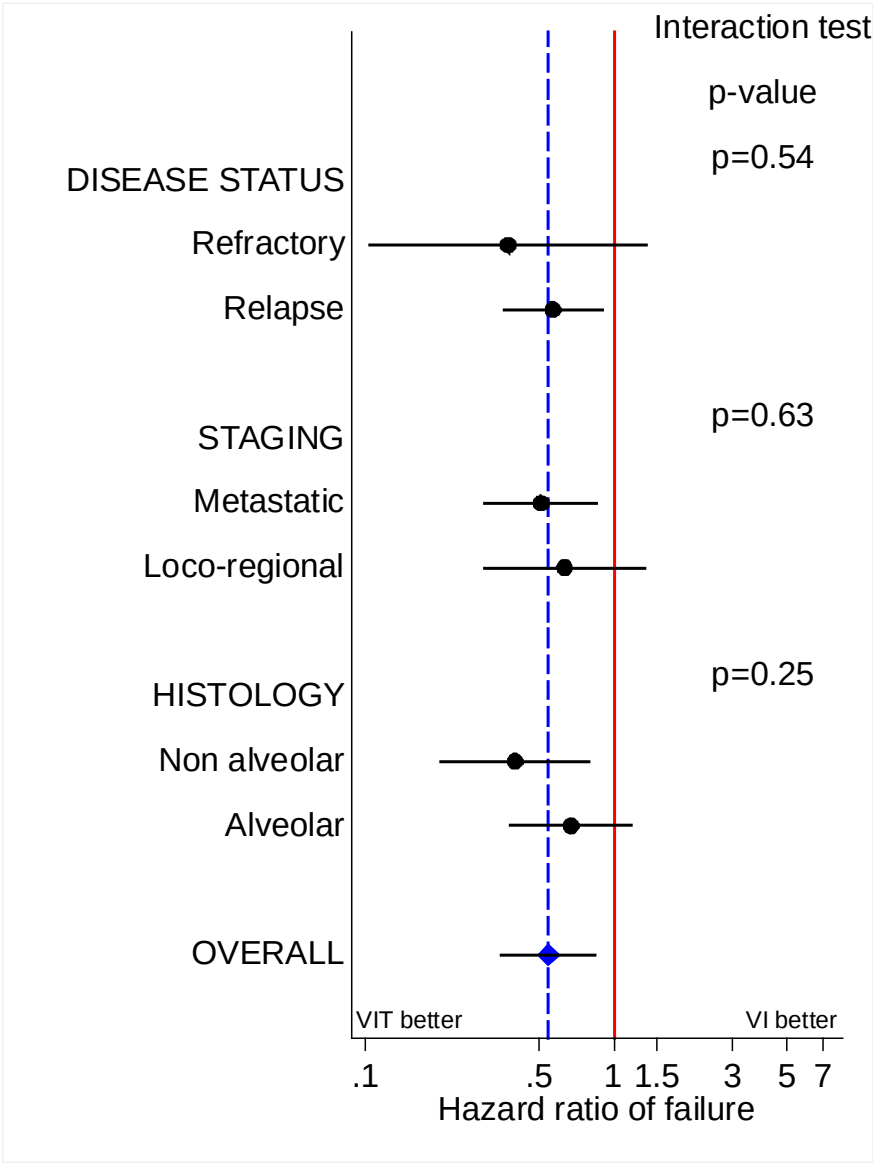
On-line Figure S3: Forest-Plot of Progression-Free Survival (adjusted HR of PFS on the whole population)



Legend

For each variable successively, the model included the treatment effect, the predefined covariates (disease status, staging and histology) and the interaction term between treatment arm and the evaluated variable.
For each modality, the figure represents the adjusted hazard ratio of progression or relapse (VIT versus VI) and its 95% confidence interval.
The p-value corresponds to the p-value of the interaction test in the multivariable model.
All details are available in Supplementary Table S1, on the whole study population, as well as considering patients enrolled at relapse only.

On-line Figure S4: Forest-Plot of Overall Survival (adjusted HR of OS on the whole population)



Legend

For each variable successively, the model included the treatment effect, the predefined covariates (disease status, staging and histology) and the interaction term between treatment arm and the evaluated variable.
For each modality, the figure represents the adjusted hazard ratio of death (VIT versus VI) and its 95% confidence interval.
The p-value corresponds to the p-value of the interaction test in the multivariable model.
All details are available in Supplementary Table S1, on the whole study population, as well as considering patients enrolled at relapse only.

On-line Table S2: Summary of the treatment effect heterogeneity across main subgroups for objective response at 2 cycles, PFS and OS

	Objective response at 2 cycles								Progression Free Survival (PFS)						Overall Survival (OS)					
	Nb response / Nb pts				Adjusted treatment effect			Inter° test	Nb events / Nb pts		Adjusted treatment effect			Inter° test	Nb events / Nb pts		Adjusted treatment effect			Inter° test
	VIT		VI		OR	95% CI		P	VIT	VI	HR	95% CI		P	VIT	VI	HR	95% CI		P
Whole population (N=120)																				
Disease status								-						0.71						0.54
Refractory	2/8	25%	0/4	0%	-	-	-		8/8	4/5	0.85	0.25	2.91		7/8	4/5	0.37	0.10	1.35	
Relapse	22/47	47%	18/54	33%	0.55	0.24	1.26		44/52	49/55	0.67	0.44	1.01		36/52	44/55	0.57	0.36	0.90	
Disease staging								0.30						0.89						0.63
Metastatic (or combined)	17/37	46%	8/33	24%	0.35	0.12	1.01		37/41	31/33	0.70	0.43	1.13		31/41	29/33	0.51	0.30	0.85	
Loco-regional only	7/18	39%	10/25	40%	0.85	0.23	3.12		15/19	22/27	0.66	0.34	1.30		12/19	19/27	0.63	0.30	1.34	
Histology								0.41						0.26						0.25
Non alveolar	9/25	36%	5/25	20%	0.32	0.08	1.22		23/26	24/26	0.53	0.29	0.96		19/26	21/26	0.40	0.20	0.79	
Alveolar	15/30	50%	13/33	39%	0.65	0.23	1.80		29/34	29/34	0.83	0.49	1.40		24/34	27/34	0.67	0.38	1.18	
Overall	24/55	44%	18/58	31%	0.50	0.22	1.12		52/60	53/60	0.68	0.46	1.01		43/60	48/60	0.55	0.35	0.84	
Relapsed patients (N=107)																				
Disease staging								0.64						0.92						0.61
Metastatic	15/33	45%	8/30	27%	0.45	0.15	1.32		33/37	28/30	0.69	0.41	1.15		27/37	26/30	0.53	0.31	0.91	
Loco-regional	7/14	50%	10/24	42%	0.68	0.17	2.66		11/15	21/25	0.66	0.32	1.37		9/15	18/25	0.68	0.30	1.51	
Histology								0.56						0.23						0.35
Non alveolar	7/18	39%	5/24	21%	0.38	0.09	1.52		16/19	23/24	0.50	0.26	0.96		13/19	20/24	0.44	0.21	0.90	
Alveolar	15/29	52%	13/30	43%	0.63	0.22	1.81		28/33	26/31	0.84	0.49	1.43		23/33	24/31	0.68	0.38	1.21	
Overall	22/47	47%	18/54	33%	0.53	0.23	1.22		44/52	49/55	0.68	0.45	1.03		36/52	44/55	0.57	0.36	0.90	

For each variable successively, the model on the whole population included the treatment effect, the predefined covariates (disease status, staging and histology) and the interaction term between treatment arm and the evaluated variable; the model on patients at relapse included the treatment effect, the predefined covariates (staging and histology) and the interaction term between treatment arm and the variable.
For each modality, the table displays the number of responses and the adjusted odd ratio of failure (VIT versus VI) for the objective response at 2 cycles, or the adjusted hazard ratio for OS and PFS, and their corresponding 95% confidence intervals.
The p-value corresponds to the p-value of the interaction test in the multivariable model.

Details of the safety analysis

On-line Table S3: Distribution of the maximum grade of adverse events over the whole treatment duration, by treatment group and by type of adverse event (classified by preferred term and pooled by system organ class)

	Arm VIT (N=58)									Arm VI (N=54)								
Maximum grade per type of adverse events	**G 0**	**G 1**	**G 2**	**G 3**	**G 4**	**G≥1**		**G≥3**		**G 0**	**G 1**	**G 2**	**G 3**	**G 4**	**G≥1**		**G≥3**	
Biological	46	6	0	6	0	12	21%	6	10%	46	3	1	4	0	8	15%	4	7%
Hypercalcaemia	57	1	0	0	0	1	2%	0	0%	54	0	0	0	0	0	0%	0	0%
Hyperglycaemia	56	2	0	0	0	2	3%	0	0%	54	0	0	0	0	0	0%	0	0%
Hyperkalaemia	57	1	0	0	0	1	2%	0	0%	53	0	0	1	0	1	2%	1	2%
Hypermagnesaemia	58	0	0	0	0	0	0%	0	0%	53	1	0	0	0	1	2%	0	0%
Hypoalbuminemia	57	0	0	1	0	1	2%	1	2%	50	2	1	1	0	4	7%	1	2%
Hypocalcaemia	56	2	0	0	0	2	3%	0	0%	52	2	0	0	0	2	4%	0	0%
Hypokalaemia	53	1	0	4	0	5	9%	4	7%	51	2	0	1	0	3	6%	1	2%
Hypomagnesaemia	58	0	0	0	0	0	0%	0	0%	53	1	0	0	0	1	2%	0	0%
Hyponatraemia	53	4	0	1	0	5	9%	1	2%	53	0	0	1	0	1	2%	1	2%
Hypophosphataemia	55	3	0	0	0	3	5%	0	0%	52	0	0	2	0	2	4%	2	4%
Cardiac disorders	**55**	**2**	**1**	**0**	**0**	**3**	**5%**	**0**	**0%**	**50**	**3**	**1**	**0**	**0**	**4**	**7%**	**0**	**0%**
Bradycardia	57	1	0	0	0	1	2%	0	0%	53	0	1	0	0	1	2%	0	0%
Palpitations	58	0	0	0	0	0	0%	0	0%	53	1	0	0	0	1	2%	0	0%
Tachycardia	55	2	1	0	0	3	5%	0	0%	52	2	0	0	0	2	4%	0	0%
Ear and labyrinth disorders	**57**	**0**	**1**	**0**	**0**	**1**	**2%**	**0**	**0%**	**54**	**0**	**0**	**0**	**0**	**0**	**0%**	**0**	**0%**
Deafness unilateral	57	0	1	0	0	1	2%	0	0%	54	0	0	0	0	0	0%	0	0%
Eye disorders	**55**	**3**	**0**	**0**	**0**	**3**	**5%**	**0**	**0%**	**50**	**3**	**1**	**0**	**0**	**4**	**7%**	**0**	**0%**
Diplopia	58	0	0	0	0	0	0%	0	0%	53	0	1	0	0	1	2%	0	0%
Dry eye	57	1	0	0	0	1	2%	0	0%	54	0	0	0	0	0	0%	0	0%
Eye disorder	58	0	0	0	0	0	0%	0	0%	53	1	0	0	0	1	2%	0	0%
Eyelid oedema	58	0	0	0	0	0	0%	0	0%	53	1	0	0	0	1	2%	0	0%

Maximum grade per type of adverse events	Arm VIT (N=58)									Arm VI (N=54)								
	G 0	G 1	G 2	G 3	G 4	G≥1		G≥3		G 0	G 1	G 2	G 3	G 4	G≥1		G≥3	
Papilloedema	58	0	0	0	0	0	0%	0	0%	53	1	0	0	0	1	2%	0	0%
Photophobia	57	1	0	0	0	1	2%	0	0%	54	0	0	0	0	0	0%	0	0%
Visual impairment	57	1	0	0	0	1	2%	0	0%	53	1	0	0	0	1	2%	0	0%
Gastrointestinal disorders	**4**	**6**	**22**	**25**	**1**	**54**	**93%**	**26**	**45%**	**3**	**12**	**22**	**16**	**1**	**51**	**94%**	**17**	**31%**
Abdominal distension	57	0	1	0	0	1	2%	0	0%	53	0	1	0	0	1	2%	0	0%
Abdominal pain	29	9	17	3	0	29	50%	3	5%	33	10	10	1	0	21	39%	1	2%
Anal haemorrhage	58	0	0	0	0	0	0%	0	0%	53	1	0	0	0	1	2%	0	0%
Anal incontinence	58	0	0	0	0	0	0%	0	0%	53	0	1	0	0	1	2%	0	0%
Anorectal disorder	55	3	0	0	0	3	5%	0	0%	53	1	0	0	0	1	2%	0	0%
Ascites	58	0	0	0	0	0	0%	0	0%	53	0	0	1	0	1	2%	1	2%
Colitis	58	0	0	0	0	0	0%	0	0%	53	0	0	1	0	1	2%	1	2%
Constipation	36	14	6	2	0	22	38%	2	3%	44	5	4	1	0	10	19%	1	2%
Diarrhoea	10	13	21	13	1	48	83%	14	24%	11	20	14	9	0	43	80%	9	17%
Dyspepsia	57	0	1	0	0	1	2%	0	0%	54	0	0	0	0	0	0%	0	0%
Gastro-esophageal reflux disease	58	0	0	0	0	0	0%	0	0%	53	1	0	0	0	1	2%	0	0%
Intussusception	57	0	0	1	0	1	2%	1	2%	54	0	0	0	0	0	0%	0	0%
Large intestine perforation	58	0	0	0	0	0	0%	0	0%	53	0	0	0	1	1	2%	1	2%
Nausea	24	14	16	4	0	34	59%	4	7%	30	10	12	2	0	24	44%	2	4%
Oesophagitis	57	1	0	0	0	1	2%	0	0%	53	0	1	0	0	1	2%	0	0%
Pancreatitis	58	0	0	0	0	0	0%	0	0%	52	0	0	2	0	2	4%	2	4%
Salivary hypersecretion	58	0	0	0	0	0	0%	0	0%	53	0	1	0	0	1	2%	0	0%
Small intestinal obstruction	57	0	0	1	0	1	2%	1	2%	54	0	0	0	0	0	0%	0	0%
Stomatitis	48	5	3	2	0	10	17%	2	3%	51	3	0	0	0	3	6%	0	0%

Maximum grade per type of adverse events	Arm VIT (N=58)									Arm VI (N=54)								
	G 0	G 1	G 2	G 3	G 4	G≥1		G≥3		G 0	G 1	G 2	G 3	G 4	G≥1		G≥3	
Vomiting	12	12	20	14	0	46	79%	14	24 %	19	17	9	9	0	35	65%	9	17 %
General disorders and administration site conditions	**19**	**11**	**18**	**8**	**1**	**39**	**67%**	**10**	**17 %**	**19**	**16**	**13**	**6**	**0**	**35**	**65%**	**6**	**11 %**
Anorexia	42	5	5	5	1	16	28%	6	10 %	46	6	1	1	0	8	15%	1	2%
Asthenia	29	12	13	4	0	29	50%	4	7%	37	7	10	0	0	17	31%	0	0%
Face oedema	57	0	1	0	0	1	2%	0	0%	54	0	0	0	0	0	0%	0	0%
General physical health deterioration	57	0	0	0	0	1	2%	1	2%	52	0	0	2	0	2	4%	2	4%
Hyperthermia	51	5	2	0	0	7	12%	0	0%	47	2	4	1	0	7	13%	1	2%
Malaise	57	1	0	0	0	1	2%	0	0%	53	1	0	0	0	1	2%	0	0%
Oedema peripheral	57	1	0	0	0	1	2%	0	0%	52	0	2	0	0	2	4%	0	0%
Pain, other	50	6	1	1	0	8	14%	1	2%	45	4	2	3	0	9	17%	3	6%
Weight decreased	47	2	8	1	0	11	19%	1	2%	46	6	1	1	0	8	15%	1	2%
Haematological	**0**	**3**	**8**	**23**	**24**	**58**	**100 %**	**47**	**81 %**	**0**	**8**	**13**	**18**	**15**	**54**	**100 %**	**33**	**61 %**
Anaemia	0	17	25	15	1	58	100 %	16	28 %	0	23	20	11	0	54	100 %	11	20 %
Leukopenia	38	1	8	9	2	20	34%	11	19 %	41	1	4	4	4	13	24%	8	15 %
Lymphocytosis	57	0	1	0	0	1	2%	0	0%	54	0	0	0	0	0	0%	0	0%
Lymphopenia	45	1	2	6	4	13	22%	10	17 %	44	0	3	5	2	10	19%	7	13 %
Neutropenia	0	8	4	25	21	58	100 %	46	79 %	0	10	16	14	14	54	100 %	28	52 %
Thrombocytopenia	51	0	6	0	1	7	12%	1	2%	47	2	1	2	2	7	13%	4	7%

Maximum grade per type of adverse events	Arm VIT (N=58)									Arm VI (N=54)								
	G 0	G 1	G 2	G 3	G 4	G≥1		G≥3		G 0	G 1	G 2	G 3	G 4	G≥1		G≥3	
Hepatobiliary disorders	**44**	**5**	**2**	**7**	**0**	**14**	**24%**	**7**	**12%**	**43**	**6**	**4**	**1**	**0**	**11**	**20%**	**1**	**2%**
Blood alkaline phosphatase increased	56	2	0	0	0	2	3%	0	0%	51	1	2	0	0	3	6%	0	0%
Cholestasis	57	0	0	1	0	1	2%	1	2%	54	0	0	0	0	0	0%	0	0%
Gamma-glutamyltransferase increased	56	1	0	1	0	2	3%	1	2%	51	0	3	0	0	3	6%	0	0%
Hepatic failure	57	0	1	0	0	1	2%	0	0%	54	0	0	0	0	0	0%	0	0%
Liver disorder	58	0	0	0	0	0	0%	0	0%	53	0	0	1	0	1	2%	1	2%
Transaminases increased	45	4	2	7	0	13	22%	7	12%	45	8	0	1	0	9	17%	1	2%
Immune system disorders	**55**	**1**	**2**	**0**	**0**	**3**	**5%**	**0**	**0%**	**54**	**0**	**0**	**0**	**0**	**0**	**0%**	**0**	**0%**
Cholinergic syndrome	57	0	1	0	0	1	2%	0	0%	54	0	0	0	0	0	0%	0	0%
Dermatitis allergic	57	0	1	0	0	1	2%	0	0%	54	0	0	0	0	0	0%	0	0%
Hypersensitivity	57	0	1	0	0	1	2%	0	0%	54	0	0	0	0	0	0%	0	0%
Seasonal allergy	57	1	0	0	0	1	2%	0	0%	54	0	0	0	0	0	0%	0	0%
Infections and infestations	**30**	**7**	**5**	**14**	**2**	**28**	**48%**	**16**	**28%**	**35**	**0**	**6**	**12**	**1**	**19**	**35%**	**13**	**24%**
Bacterial infection, nos	57	0	0	1	0	1	2%	1	2%	54	0	0	0	0	0	0%	0	0%
Cholecystitis infective	58	0	0	0	0	0	0%	0	0%	53	0	0	1	0	1	2%	1	2%
Clostridium difficile colitis	56	0	0	2	0	2	3%	2	3%	54	0	0	0	0	0	0%	0	0%
Conjunctivitis	54	1	3	0	0	4	7%	0	0%	53	1	0	0	0	1	2%	0	0%
Device related infection	57	0	0	1	0	1	2%	1	2%	53	0	0	0	1	1	2%	1	2%
Ear infection	57	0	1	0	0	1	2%	0	0%	52	1	1	0	0	2	4%	0	0%
Febrile neutropenia	46	0	0	12	0	12	21%	12	21%	45	0	0	9	0	9	17%	9	17%
Fungic infection	57	0	0	0	1	1	2%	1	2%	53	0	1	0	0	1	2%	0	0%
Gastroenteritis	58	0	0	0	0	0	0%	0	0%	52	0	2	0	0	2	4%	0	0%
Infection, nos	54	0	3	1	0	4	7%	1	2%	54	0	0	0	0	0	0%	0	0%
Influenza like illness	57	1	0	0	0	1	2%	0	0%	53	0	1	0	0	1	2%	0	0%
Lower respiratory tract infection	56	0	2	0	0	2	3%	0	0%	53	0	0	1	0	1	2%	1	2%

Maximum grade per type of adverse events	Arm VIT (N=58)									Arm VI (N=54)								
	G 0	G 1	G 2	G 3	G 4	G≥1		G≥3		G 0	G 1	G 2	G 3	G 4	G≥1		G≥3	
Paronychia	57	0	1	0	0	1	2%	0	0%	54	0	0	0	0	0	0%	0	0%
Pneumonia	58	0	0	0	0	0	0%	0	0%	53	0	1	0	0	1	2%	0	0%
Sepsis	55	0	2	0	1	3	5%	1	2%	54	0	0	0	0	0	0%	0	0%
Upper respiratory tract infection	52	4	2	0	0	6	10%	0	0%	49	3	2	0	0	5	9%	0	0%
Urinary tract infection	55	1	1	1	0	3	5%	1	2%	51	0	3	0	0	3	6%	0	0%
Viral infection	55	1	2	0	0	3	5%	0	0%	51	0	1	2	0	3	6%	2	4%
Wound infection	57	0	0	1	0	1	2%	1	2%	54	0	0	0	0	0	0%	0	0%
Injury, poisoning and procedural complications	**52**	**3**	**3**	**0**	**0**	**6**	**10%**	**0**	**0%**	**54**	**0**	**0**	**0**	**0**	**0**	**0%**	**0**	**0%**
Infusion related reaction	56	1	1	0	0	2	3%	0	0%	54	0	0	0	0	0	0%	0	0%
Injury	54	2	2	0	0	4	7%	0	0%	54	0	0	0	0	0	0%	0	0%
Metabolism and nutrition disorders	**55**	**0**	**0**	**3**	**0**	**3**	**5%**	**3**	**5%**	**51**	**0**	**1**	**2**	**0**	**3**	**6%**	**2**	**4%**
Dehydration	55	0	0	3	0	3	5%	3	5%	52	0	0	2	0	2	4%	2	4%
Malnutrition	58	0	0	0	0	0	0%	0	0%	53	0	1	0	0	1	2%	0	0%
Musculoskeletal and connective tissue disorders	**40**	**6**	**11**	**1**	**0**	**18**	**31%**	**1**	**2%**	**38**	**9**	**5**	**2**	**0**	**16**	**30%**	**2**	**4%**
Muscle fatigue	57	1	0	0	0	1	2%	0	0%	54	0	0	0	0	0	0%	0	0%
Muscle haemorrhage	58	0	0	0	0	0	0%	0	0%	53	1	0	0	0	1	2%	0	0%
Muscle spasms	56	1	1	0	0	2	3%	0	0%	53	0	1	0	0	1	2%	0	0%
Muscle spasticity	58	0	0	0	0	0	0%	0	0%	53	0	1	0	0	1	2%	0	0%
Muscle twitching	58	0	0	0	0	0	0%	0	0%	53	1	0	0	0	1	2%	0	0%
Musculoskeletal pain	43	4	10	1	0	15	26%	1	2%	42	6	4	2	0	12	22%	2	4%
Trismus	58	0	0	0	0	0	0%	0	0%	53	1	0	0	0	1	2%	0	0%
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**56**	**2**	**0**	**0**	**0**	**2**	**3%**	**0**	**0%**	**49**	**1**	**2**	**2**	**0**	**5**	**9%**	**2**	**4%**
Tumour pain	56	2	0	0	0	2	3%	0	0%	49	1	2	2	0	5	9%	2	4%

Maximum grade per type of adverse events	Arm VIT (N=58)									Arm VI (N=54)								
	G 0	G 1	G 2	G 3	G 4	G≥1		G≥3		G 0	G 1	G 2	G 3	G 4	G≥1		G≥3	
Nervous system disorders	**30**	**12**	**6**	**7**	**2**	**28**	**48%**	**10**	**17%**	**32**	**9**	**10**	**2**	**0**	**22**	**41%**	**3**	**6%**
Ageusia	58	0	0	0	0	0	0%	0	0%	53	1	0	0	0	1	2%	0	0%
Aphasia	58	0	0	0	0	0	0%	0	0%	53	0	1	0	0	1	2%	0	0%
Cranial nerve disorder	57	1	0	0	0	1	2%	0	0%	52	2	0	0	0	2	4%	0	0%
Depressed level of consciousness	56	2	0	0	0	2	3%	0	0%	52	0	1	0	0	2	4%	1	2%
Dizziness	55	3	0	0	0	3	5%	0	0%	53	1	0	0	0	1	2%	0	0%
Dysgeusia	56	1	1	0	0	2	3%	0	0%	54	0	0	0	0	0	0%	0	0%
Headache	48	3	5	2	0	10	17%	2	3%	46	3	4	1	0	8	15%	1	2%
Hemiplegia	57	0	0	0	1	1	2%	1	2%	54	0	0	0	0	0	0%	0	0%
Hydrocephalus	57	0	0	0	0	1	2%	1	2%	54	0	0	0	0	0	0%	0	0%
Hypoaesthesia	57	0	1	0	0	1	2%	0	0%	52	1	1	0	0	2	4%	0	0%
Memory impairment	58	0	0	0	0	0	0%	0	0%	53	1	0	0	0	1	2%	0	0%
Monoplegia	58	0	0	0	0	0	0%	0	0%	53	0	1	0	0	1	2%	0	0%
Myoclonic	58	0	0	0	0	0	0%	0	0%	53	0	1	0	0	1	2%	0	0%
Neuralgia	57	1	0	0	0	1	2%	0	0%	52	1	1	0	0	2	4%	0	0%
Neurotoxicity, nos	58	0	0	0	0	0	0%	0	0%	53	1	0	0	0	1	2%	0	0%
Peripheral neuropathy	41	10	3	4	0	17	29%	4	7%	46	6	2	0	0	8	15%	0	0%
Psychomotor hyperactivity	58	0	0	0	0	0	0%	0	0%	53	0	1	0	0	1	2%	0	0%
Seizure	57	0	0	0	1	1	2%	1	2%	52	0	1	1	0	2	4%	1	2%
Syncope	56	0	0	2	0	2	3%	2	3%	54	0	0	0	0	0	0%	0	0%
Tremor	58	0	0	0	0	0	0%	0	0%	53	1	0	0	0	1	2%	0	0%
Psychiatric disorders	**53**	**2**	**2**	**1**	**0**	**5**	**9%**	**1**	**2%**	**48**	**1**	**2**	**3**	**0**	**6**	**11%**	**3**	**6%**
Affect lability	58	0	0	0	0	0	0%	0	0%	53	0	1	0	0	1	2%	0	0%
Agitation	57	0	1	0	0	1	2%	0	0%	53	0	0	1	0	1	2%	1	2%
Anxiety	54	2	1	1	0	4	7%	1	2%	52	0	1	1	0	2	4%	1	2%
Delirium	58	0	0	0	0	0	0%	0	0%	53	1	0	0	0	1	2%	0	0%
Depression	58	0	0	0	0	0	0%	0	0%	53	0	0	1	0	1	2%	1	2%

Maximum grade per type of adverse events	Arm VIT (N=58)									Arm VI (N=54)								
	G 0	G 1	G 2	G 3	G 4	G≥1		G≥3		G 0	G 1	G 2	G 3	G 4	G≥1		G≥3	
Insomnia	56	2	0	0	0	2	3%	0	0%	53	1	0	0	0	1	2%	0	0%
Sleep terror	58	0	0	0	0	0	0%	0	0%	53	1	0	0	0	1	2%	0	0%
Renal and urinary disorders	**55**	**2**	**1**	**0**	**0**	**3**	**5%**	**0**	**0%**	**48**	**5**	**1**	**0**	**0**	**6**	**11%**	**0**	**0%**
Blood creatinine increased	57	1	0	0	0	1	2%	0	0%	49	5	0	0	0	5	9%	0	0%
Blood urea increased	57	1	0	0	0	1	2%	0	0%	54	0	0	0	0	0	0%	0	0%
Micturition urgency	58	0	0	0	0	0	0%	0	0%	53	0	1	0	0	1	2%	0	0%
Urinary retention	56	1	1	0	0	2	3%	0	0%	54	0	0	0	0	0	0%	0	0%
Respiratory, thoracic and mediastinal disorders	**48**	**7**	**2**	**1**	**0**	**10**	**17%**	**1**	**2%**	**47**	**6**	**1**	**0**	**0**	**7**	**13%**	**0**	**0%**
Cough	52	4	2	0	0	6	10%	0	0%	48	5	1	0	0	6	11%	0	0%
Dyspnoea	56	1	0	1	0	2	3%	1	2%	51	3	0	0	0	3	6%	0	0%
Nasal discomfort	57	1	0	0	0	1	2%	0	0%	54	0	0	0	0	0	0%	0	0%
Throat irritation	57	1	0	0	0	1	2%	0	0%	54	0	0	0	0	0	0%	0	0%
Skin and subcutaneous tissue disorders	**37**	**7**	**11**	**3**	**0**	**21**	**36%**	**3**	**5%**	**37**	**9**	**7**	**1**	**0**	**17**	**31%**	**1**	**2%**
Alopecia	45	3	9	1	0	13	22%	1	2%	44	3	6	1	0	10	19%	1	2%
Decubitus ulcer	57	0	1	0	0	1	2%	0	0%	54	0	0	0	0	0	0%	0	0%
Dry skin	56	1	1	0	0	2	3%	0	0%	53	1	0	0	0	1	2%	0	0%
Eczema	58	0	0	0	0	0	0%	0	0%	53	0	1	0	0	1	2%	0	0%
Pruritus	55	2	1	0	0	3	5%	0	0%	53	1	0	0	0	1	2%	0	0%
Radiodermatitis	56	0	1	1	0	2	3%	1	2%	54	0	0	0	0	0	0%	0	0%
Rash	51	3	3	1	0	7	12%	1	2%	48	4	2	0	0	6	11%	0	0%
Skin exfoliation	57	1	0	0	0	1	2%	0	0%	54	0	0	0	0	0	0%	0	0%
Skin lesion, nos	57	1	0	0	0	1	2%	0	0%	53	1	0	0	0	1	2%	0	0%
Vascular disorders	**49**	**5**	**4**	**0**	**0**	**9**	**16%**	**0**	**0%**	**49**	**4**	**1**	**0**	**0**	**5**	**9%**	**0**	**0%**
Embolism	57	0	1	0	0	1	2%	0	0%	54	0	0	0	0	0	0%	0	0%

Maximum grade per type of adverse events	Arm VIT (N=58)									Arm VI (N=54)								
	G 0	G 1	G 2	G 3	G 4	G≥1		G≥3		G 0	G 1	G 2	G 3	G 4	G≥1		G≥3	
Epistaxis	55	2	1	0	0	3	5%	0	0%	53	1	0	0	0	1	2%	0	0%
Haematoma	58	0	0	0	0	0	0%	0	0%	53	1	0	0	0	1	2%	0	0%
Hot flush	57	1	0	0	0	1	2%	0	0%	54	0	0	0	0	0	0%	0	0%
Hypertension	56	0	2	0	0	2	3%	0	0%	52	1	1	0	0	2	4%	0	0%
Hypotension	57	1	0	0	0	1	2%	0	0%	53	1	0	0	0	1	2%	0	0%
Meno/metrorrhagia	57	1	0	0	0	1	2%	0	0%	53	1	0	0	0	1	2%	0	0%
Purpura	58	0	0	0	0	0	0%	0	0%	53	1	0	0	0	1	2%	0	0%

More than 450 distinct types of clinical, laboratory or ECG events were noted using literal description, but the MedDRA coding dictionary, reduced that number to 235 preferred terms, in 22 system organ classes (SOC). We followed recommendation from the CONSORT Statement to analyze the adverse events (Better Reporting of Harms in Randomized Trials: An Extension of the CONSORT Statement, Ioannidis et al., Annals of Internal Medicine, 2004). In particular, since some adverse events were similar, i.e. fatigue and asthenia, or white blood cell count decreased and leukopenia, they were regrouped. In a clinical perspective, we have also grouped some preferred terms in higher level terms such as AST increased, ALT increased or transaminase increased, reported as transaminase increased, or dysaesthesia, neuropathy peripheral, paraesthesia, peripheral motor neuropathy, peripheral sensory neuropathy reported as peripheral neuropathy. This resulted in 149 terms listed in the table hereinabove, classified in 20 different SOC. For clinical purpose, we also modified some SOC, in particular for terms included in the SOC “Investigations” such as Blood creatinine increased and Blood urea increased reclassified in the SOC “Renal and urinary disorders”, Blood alkaline phosphatase increased, Gamma-glutamyltransferase increased and Transaminases increased reclassified in the SOC “Hepatobiliary disorders”

On-line Figure S5: safety analysis for AE coded as related to study treatment