

Supplementary Online Content

Pietrantonio F, Morano F, Corallo S, et al. Maintenance therapy with panitumumab vs panitumumab plus fluorouracil-leucovorin in patients with *RAS* wild-type metastatic colorectal cancer: a phase 2 randomized clinical trial. *JAMA Oncol*. Published online July 3, 2019. doi: 10.1001/jamaoncol.2019.1467

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Baseline Characteristics

	panitumumab plus 5-FU/LV (n = 117)	panitumumab (n = 112)	*p
Median age (years, IQR)	62.6 (55-71)	62.4 (64-70)	0.638
Gender			0.889
Male	79 (67%)	74 (66%)	
Female	38 (33%)	38 (34%)	
ECOG performance status			1.000
0	84 (72%)	81 (72%)	
1	33 (28%)	31 (28%)	
Prior adjuvant treatment			0.718
Yes	17 (14%)	19 (17%)	
No	100 (86%)	93 (83%)	
Primary tumor resected			0.787
Yes	73 (62%)	72 (64%)	
No	44 (38%)	40 (36%)	
Liver-limited disease			0.891
Yes	42 (36%)	39 (35%)	
No	75 (64%)	73 (65%)	
Synchronous metastases			0.273
Yes	94 (80%)	83 (74%)	
No	23 (20%)	29 (26%)	
Number of metastatic sites			0.596
1	63 (53%)	64 (58%)	
> 1	54 (47%)	48 (42%)	
Primary tumor location			0.730
Right	19 (16%)	21 (20%)	
Left	98 (84%)	91 (80%)	
<i>BRAF</i> status			0.325
Wild-type	114 (97%)	106 (95%)	
Mutated	3 (3%)	6 (5%)	

* p value at Mann-Whitney, or chi-square or Fisher test for categorical variables, respectively.

Data are median with interquartile range (IQR) or number (%).

Abbreviations: ECOG, Eastern Cooperative Oncology Group; 5-FU/LV, 5-fluorouracil/leucovorin.

eTable 2. Efficacy and Activity Measures in Intention-to-Treat Population

	panitumumab plus 5-FU/LV (n = 117)	panitumumab (n = 112)	effect size (95% CI)	p value
Progression-Free Survival			HR 1.51 (1.11-2.07)	0.009
Median, months (95% CI)	12.0 (10.4-14.5)	9.9 (8.4 to 11.0)		
10-month estimate (95% CI)	59.9% (51.5-69.8)	49.0% (40.5-59.4)		
Overall Survival			HR 1.13 (0.71-1.81)	0.820
12-month estimate (95% CI)	85.4% (79.0-92.3)	79.7% (72.4-87.7)		
24-month estimate (95% CI)	60.7% (50.6-72.9)	60.0% (49.5-72.7)		
Overall Response Rate (95% CI)	66.7% (57.4-75.1)	67.0% (57.4-75.6)	OR 1.07 (0.61-1.86)	0.817
Complete Response	6.0%	4.5%		
Partial Response	60.7%	62.5%		
Stable Disease	16.2%	17.0%		
Progressive Disease	6.0%	6.2%		
Not Evaluable	11.1%	9.8%		
Disease Control Rate (95% CI)	82.9% (74.8-82.9)	83.9% (75.8-90.2)	OR 1.06 (0.52-2.15)	0.871
Duration of Response			-	0.156
Median, months (IQR)	10.9 (5.8-21.0)	9.0 (5.9-14.7)		

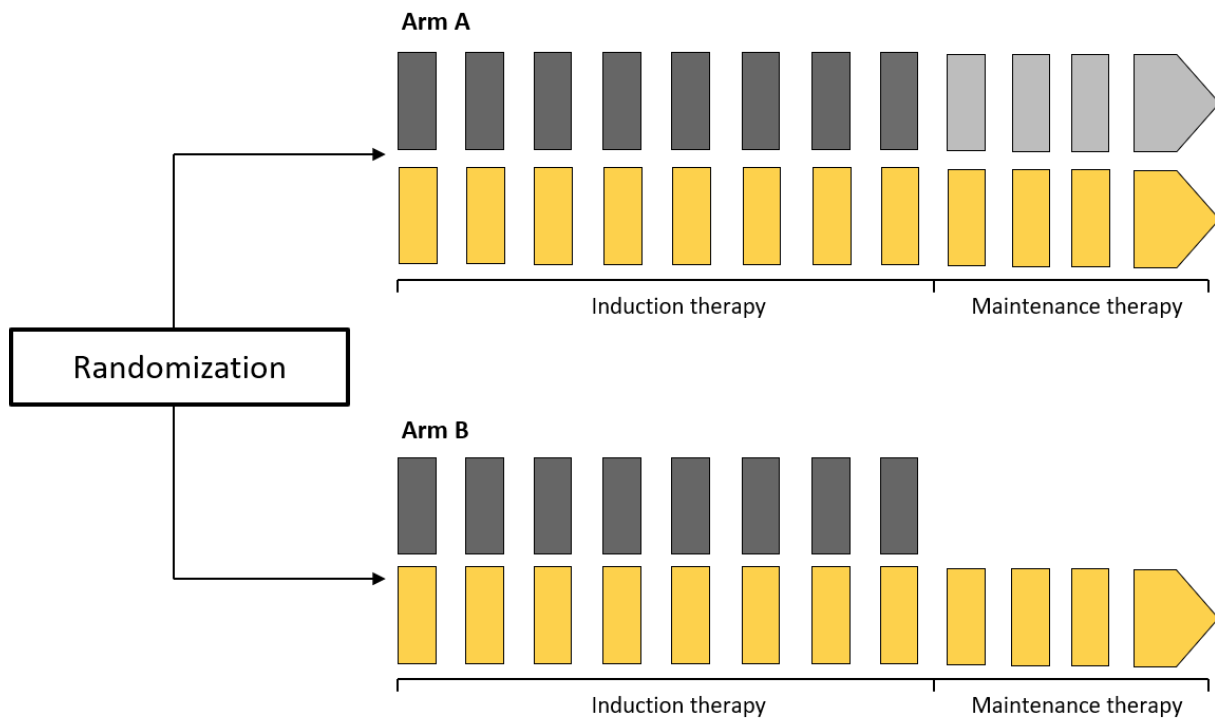
Abbreviations: 5-FU/LV, 5-fluorouracil/leucovorin. CI: confidence interval. HR: hazard ratio estimate (95% CI) of panitumumab vs panitumumab plus 5-FU/LV in the univariable Cox model stratified by prior adjuvant therapy and number of disease sites. OR: pooled response odds ratio (95% CI) of panitumumab vs panitumumab plus 5-FU/LV across the strata determined according to the stratification factors (prior adjuvant therapy and number of disease sites), and corresponding 95% CI.

Table 3. Safety Analysis: Adverse Events During Induction and Maintenance and During Maintenance

Adverse event	Induction and Maintenance						Maintenance					
	pan plus 5-FU/LV (n = 115)		pan (n = 111)		Overall (n = 226)		pan plus 5-FU/LV (n = 85)		pan (n = 79)		Overall (n = 164)	
	Any Grade n (%)	≥ 3 Grade n (%)	Any Grade n (%)	≥ 3 Grade n (%)	Any Grade n (%)	≥ 3 Grade n (%)	Any Grade n (%)	≥ 3 Grade n (%)	Any Grade n (%)	≥ 3 Grade n (%)	Any Grade n (%)	≥ 3 Grade n (%)
Stomatitis/Oral mucositis	54 (47)	11 (10)	44 (40)	8 (7)	98 (43)	19 (8)	28 (33)	6 (7)	6 (8)	1 (1)	34 (21)	7 (4)
Nausea	36 (31)	3 (3)	41 (37)	2 (2)	77 (34)	5 (2)	8 (9)	0	6 (8)	0	14 (9)	0
Vomiting	23 (20)	2 (2)	17 (15)	1 (1)	40 (18)	3 (1)	5 (6)	1 (1)	0	0	5 (3)	1 (1)
Diarrhea	59 (51)	15 (13)	59 (53)	15 (14)	118 (52)	30 (13)	21 (25)	4 (5)	8 (10)	1 (1)	29 (18)	5 (3)
Hand-foot syndrome	28 (24)	4 (3)	19 (17)	2 (2)	47 (21)	6 (3)	14 (16)	3 (4)	9 (11)	2 (3)	23 (14)	5 (3)
Peripheral Neuropathy	48 (42)	3 (3)	36 (32)	4 (4)	84 (37)	7 (3)	25 (29)	0	12 (15)	1 (1)	37 (23)	1 (1)
Anemia	22 (19)	2 (2)	16 (14)	2 (2)	38 (17)	4 (2)	8 (9)	1 (1)	5 (6)	1 (1)	13 (8)	2 (1)
Thrombocytopenia	28 (24)	2 (2)	22 (20)	4 (4)	50 (22)	6 (3)	7 (8)	0	2 (3)	0	9 (5)	0
Neutropenia	46 (40)	26 (23)	48 (43)	31 (28)	94 (42)	57 (25)	9 (11)	2 (2)	1 (1)	0	10 (6)	2 (1)
Febrile Neutropenia	3 (3)	3 (3)	3 (3)	3 (3)	6 (3)	6 (3)	0	0	0	0	0	0
Fatigue	51 (44)	5 (4)	48 (43)	6 (5)	99 (44)	11 (5)	18 (21)	1 (1)	13 (16)	1 (1)	31 (19)	2 (1)
Infusion Reaction	12 (10)	2 (2)	12 (11)	1 (1)	24 (11)	3 (1)	2 (2)	0	1 (1)	0	3 (2)	0
<i>Pan-related AE</i>	102 (89)	46 (40)	101 (91)	42 (38)	203 (90)	88 (39)	65 (76)	27 (32)	33 (42)	13 (16)	108 (66)	40 (24)
Skin rash	96 (83)	27 (23)	95 (86)	33 (28)	191 (85)	60 (27)	52 (61)	21 (25)	35 (44)	12 (15)	87 (53)	33 (20)
Paronychia	20 (17)	2 (2)	16 (14)	1 (1)	36 (16)	3 (1)	13 (15)	2 (2)	10 (13)	1 (1)	23 (14)	3 (2)
Hypomagnesemia	45 (39)	4 (3)	42 (38)	1 (1)	87 (38)	5 (2)	23 (27)	3 (4)	16 (20)	1 (1)	39 (24)	4 (2)
Conjunctivitis	21 (18)	3 (3)	20 (18)	0	41 (18)	3 (1)	14 (16)	3 (4)	8 (10)	0	22 (13)	3 (2)
<i>AE Non-treatment related of interest</i>	37 (32)	18 (16)	29 (26)	8 (7)	66 (29)	26 (12)	18 (21)	5 (6)	10 (13)	2 (3)	28 (17)	7 (4)
Thromboembolic event	13 (11)	8 (7)	7 (6)	1 (1)	20 (9)	9 (4)	5 (6)	3 (4)	0	0	5 (3)	3 (2)
Gastrointestinal Obstruction	8 (7)	5 (4)	11 (10)	3 (3)	19 (8)	8 (4)	3 (4)	2 (2)	3 (4)	0	6 (4)	2 (1)
Infection	24 (21)	7 (6)	21 (19)	5 (5)	45 (20)	12 (5)	13 (15)	2 (2)	8 (10)	2 (3)	21 (13)	4 (2)

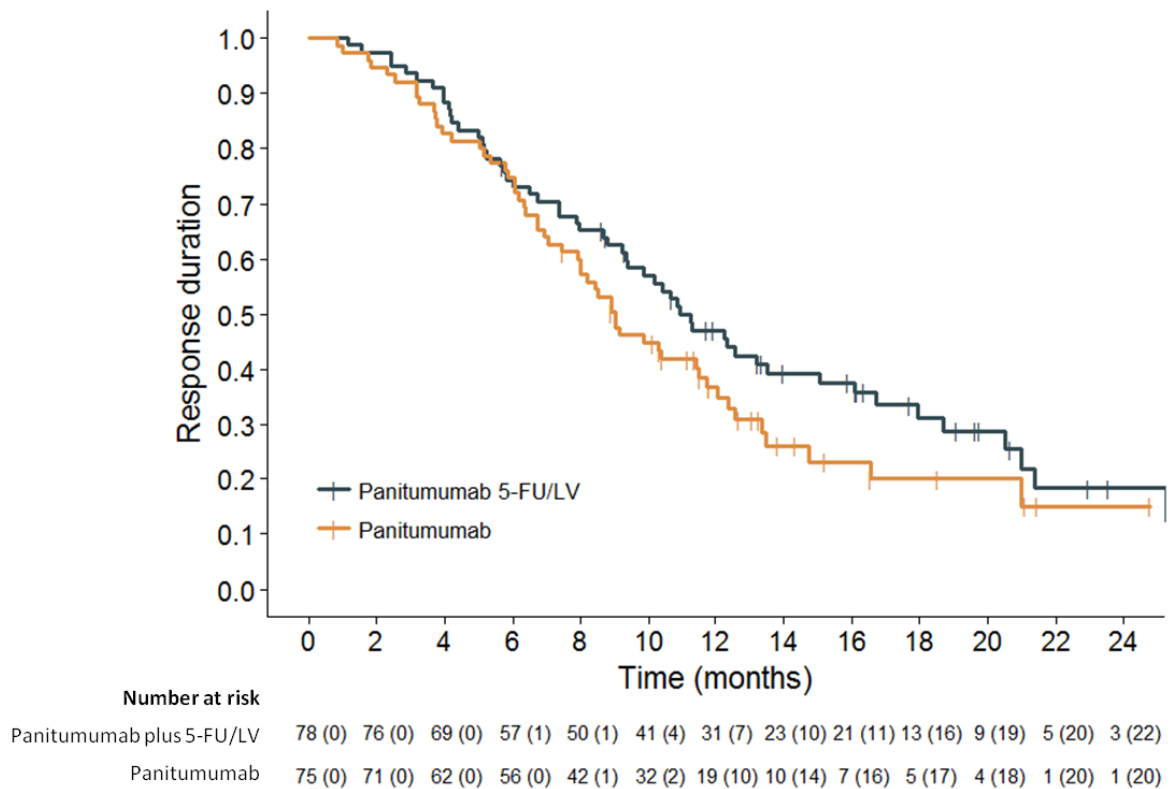
Abbreviations: pan, panitumumab; 5-FU/LV, 5-fluorouracil/leucovorin; AE, adverse event

eFigure 1. Trial Design



This figure depicts the graphic representation of the Valentino trial design, considering both induction and maintenance treatment. Specifically, yellow boxes represent panitumumab cycles, black boxes FOLFOX-4 chemotherapy cycles, and grey boxes 5-FU/LV chemotherapy cycles.

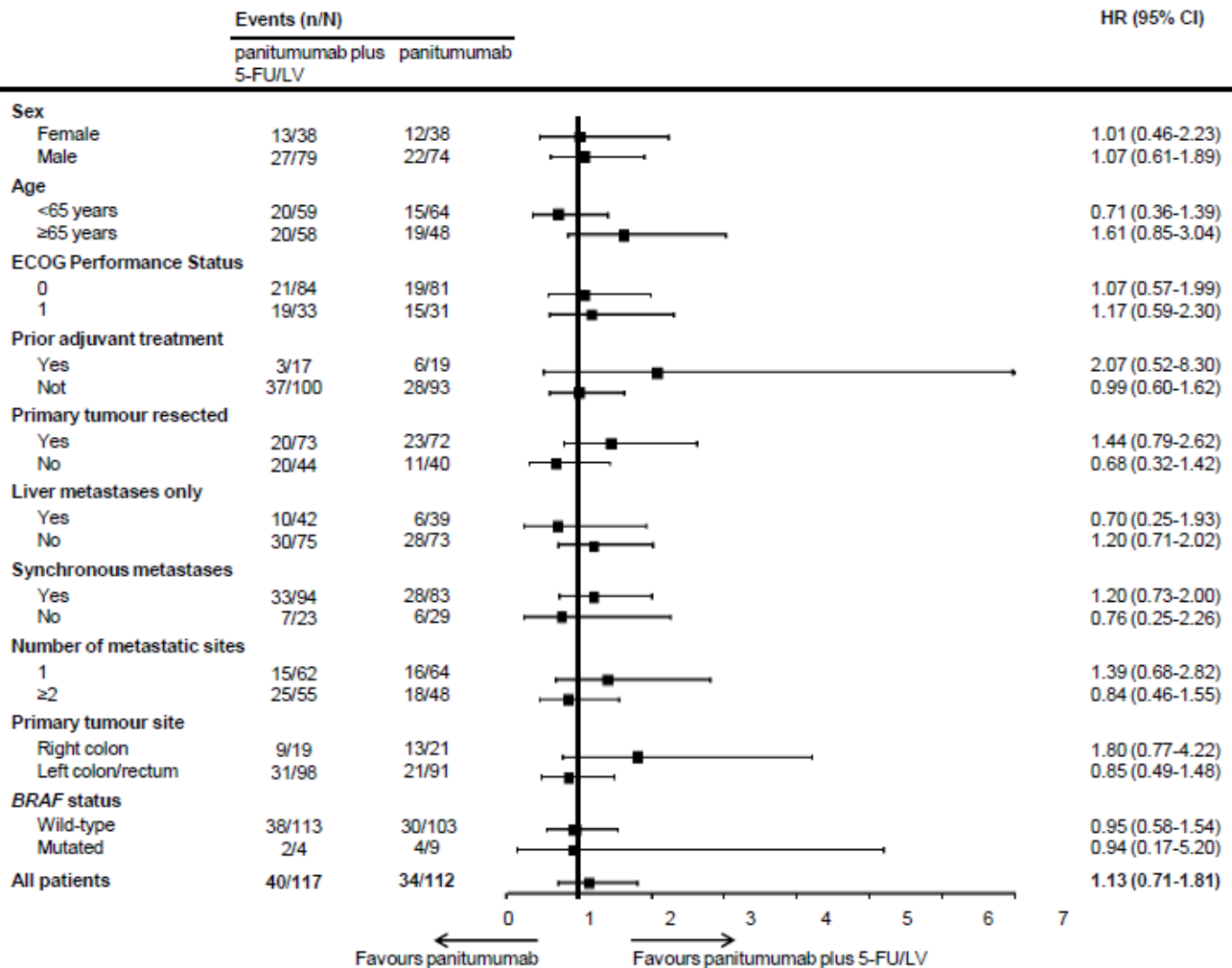
eFigure 2. Duration of Response According to Treatment Arm in the Subgroup of Patients With Objective Tumor Response According to RECIST, Version 1.1



This figure illustrates the curve of duration of response to treatment in the subgroup of patients that achieved an objective tumor response according to RECIST vers 1.1. criteria. In green are reported data of patients in Arm A (panitumumab plus 5-FU/LV) and in yellow data of Arm B (panitumumab).

Abbreviations: 5-FU/LV= 5-fluorouracil plus leucovorin.

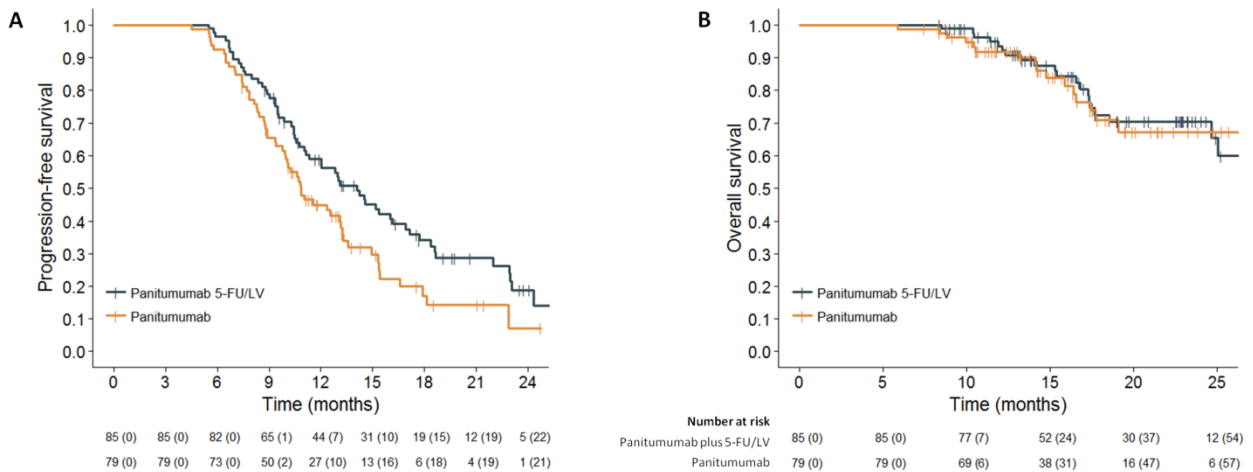
eFigure 3. Forest Plots of Overall Survival by Patient Subgroups Within the Intention-to-Treat Population



This figure depicts the Forest plots of overall survival in the intention-to-treat population, considering several patients subgroups.

Abbreviations: HR=Hazard ratio. ECOG: Eastern Cooperative Oncology Group. 5-FU/LV: 5-Fluorouracil and Leucovorin.

eFigure 4. Kaplan-Meier Curves for Progression Free-Survival and Overall Survival According to Treatment Arm in the Per Protocol Population



This figure illustrates the progression-free survival in part A and overall survival in part B curves in the per-protocol population at the date of first data cut-off (July 30, 2018), in green are reported data of patients in Arm A (panitumumab plus 5-FU/LV) and in yellow data of Arm B (panitumumab).

Abbreviations: Progression-free survival (A) and overall survival (B) at the date of first data cut-off (July 30, 2018). 5-FU/LV= 5-fluorouracil plus leucovorin. HR=hazard ratio. 95% CI=95% confidence interval.

eMethods. Details on Dose Reductions During Study Treatment and Study Centers

A delay in treatment administration for drug-related AEs was necessary in 82 (71%) of the 115 patients treated in Arm A and 74 (67%) of the 111 patients in Arm B. Regarding the maintenance phase, the treatment was delayed for AEs in 36 (42%) of 85 patients in Arm A and 15 (19%) of 79 patients in Arm B. A dose reduction was needed for 79 (69%) patients in Arm A and 71 (64%) patients in Arm B. The drug-related toxicity was manageable in both treatment arms (table 3). Dose reductions at first and second level, as per protocol, were performed in 100 (44%) and 16 (7%) of 226 patients for 5FU, 88 (39%) and 7 (3%) for oxaliplatin and 66 (29%) and 22 (10%) for panitumumab. Considering the two treatment arms, oxaliplatin was reduced at the first and second dose level in 40% and 4% in panitumumab plus 5-FU/LV group and in 38% and 2% in single-agent panitumumab group, respectively, while panitumumab was reduced at the first and second dose level in 30% and 16% in panitumumab plus 5-FU/LV group and in 28% and 4% in single-agent panitumumab group, respectively. In the maintenance phase only, 28 (33%) of 85 patients in the panitumumab plus 5-FU/LV group and 8 (10%) of 79 in the single-agent panitumumab group, respectively, received a dose reduction for drug-related toxicity. Specifically, 5-FU bolus was reduced at the first and second dose level in 9% and 6% of patients, respectively, whereas reductions of 5-FU continuous infusion at the first and second dose level were performed in 12% and 5% of patients, respectively. Panitumumab was reduced at the first and second dose level in 14% and 16% of patients in the panitumumab plus 5-FU/LV arm, and in 9% and 1% of patients in the single-agent panitumumab arm, respectively.

LIST OF ALL PARTICIPATING CENTERS

0001	Fondazione IRCCS Istituto Nazionale dei Tumori (Milano)
0002	Ospedale Fatebenefratelli (Milano)
0003	Ospedale Policlinico San Martino (Genova)
0004	Istituto Oncologico Veneto (Padova)
0005	Azienda Ospedaliero-Universitaria San Luigi Gonzaga (Orbassano)
0006	Azienda Ospedaliera di Valtellina e Valchiavenna (Sondrio)
0007	Humanitas Cancer Center (Rozzano)
0008	Azienda Ospedaliero-Universitaria Pisana (Pisa)
0009	Istituto Europeo di Oncologia (Milano)
0010	Azienda Socio-Sanitaria Territoriale Bergamo Ovest (Treviglio)
0011	Azienda Socio-Sanitaria Territoriale Ospedale di Cremona (Cremona)
0012	Fondazione Poliambulanza (Brescia)
0013	Azienda Ospedaliera Città della Salute e della Scienza 1 (Torino)
0015	Ospedali Galliera (Genova)
0016	Azienda Ospedaliera Città della Salute e della Scienza 2 (Torino)
0017	Ospedale San Gerardo (Monza)
0018	Azienda Socio-Sanitaria Territoriale Lariana (Como)
0019	Azienda Socio-Sanitaria Territoriale Sette Laghi (Varese)
0020	Niguarda Cancer Center (Milano)
0021	Azienda Socio-Sanitaria Territoriale di Vimercate
0022	Ospedale Santissima Annunziata (Chieti)
0023	Ospedale Floraspe Renzetti (Lanciano)
0024	Policlinico Umberto (Roma)
0025	Azienda Ospedaliero-Universitaria Papardo (Messina)
0026	Azienda Ospedaliero-Universitaria Careggi (Firenze)
0027	Ospedale Di Summa Perrino (Brindisi)
0028	Istituto di Ricerca sul Cancro (Candiolo, To)
0029	Policlinico Tor Vergata (Roma)
0030	Nuovo Ospedale di Prato