From Cetuxicol to BioRAIDs: Novel strategies for targeted therapies in cervical cancer

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Background: Locally advanced stage cervical cancer (CC) remains a public health issue despite preventive vaccines and screening. EGFR is known to be overexpressed in CC, which suggested that EGFR blockade might be a promising treatment approach. Here we present the final results of the randomized phase II Cetuxicol trial and expand to the ongoing BioRAIDs European study to emphasize potential strategies of targeted therapies in CC.

Cetuxicol: Data from a randomized phase II trial of radio-chemotherapy +/- Cetuximab for advanced cervix carcinoma

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Methodology: **Cetuxicol** enrolled 78 FIGO stage IB2-IIIB CC patients randomized between radio-chemotherapy alone +/- Cetuximab. Mutations were correlated to clinical outcome detected by the Ampliseq cancer panel (Life technology).

Methodology & Patient's Characteristics

Table 1 Characteristics of the population

Patient and tumor characteristics					
Parameter	Arm A		Arm B		p-value
	N = 40	%	N=38	%	
Median age years	49.5 (range, 23-74)		45.5 (range, 25-73)		ns
Performance status					
PS = 0	32		23		ns
PS = 1	5		9		
missing value	2		6		
Smoking habits >10/day	21	52.5	14	36.8	ns
Histological type					
Squamous	33	82.5	33	86.8	ns
Non-squamous	7	17.5	5	13,1	
FIGO Stage					
IB1	0	32.5	1	2.6	ns
IB2	13	10	10	26.3	
IIa	4	45	1	2.6	
IIb	18	5	24	63.1	
IIIa	2	7.5	0	0	
IIIb	3		2	5.2	
Frozen sample					
Yes	10	25	17	45	
no	30	75	21	55	
Median clinical tumor size	44 mm (range, 15-80)		40 mm (range, 20-80)		ns
Median MRI tumor size	53.5 mm (range, 30-90)		47 mm (range, 24-85)		ns
Anemia at diagnosis	13	32.5	9	23.5	ns
Median Renal clearance (ml/mn)	102.7 (range, 71-220)		102.7 (range, 57-174)		ns

Table 2 Treatment

Treatment dose	Arm A		Arm B		
	N=38	%	N=38	%	
Median RT dose (Gy)	45 (range 28.8-50)		45 (range 36-46.6)		ns
Full treatment					
Yes	29	72.5	25	65.8	
	9	22.5	13	34.2	
Median CDDP mg/ per week	38.9 (range 34.5-40.5)		39.8 (range 20.8-62.3)		ns

Table 3 Additional treatment following radio-chemotherapy

Additional treatment following pelvic RTCT					
	Arm A (N=37)		Arm B (N=37)		
	N	%	N	%	
Brachytherapy					
Yes	33	89	34	92	ns
No	4	11	3	8	
Median dose	15 Gy (range 5-60)		15 Gy (range 6-60)		ns
Surgery after RTCT	24	65	26	70	
Hysterectomy	7		6		ns
Radical Hysterectomy	17		20		ns
Lymphadenectomy	14		14		
pN0	12	86	13	93	ns
pN1	2	14	1	8	
Residual T or pN1	9/24	37.5	12/26	46	ns
Complete response	15/24	62.5	14/26	54	

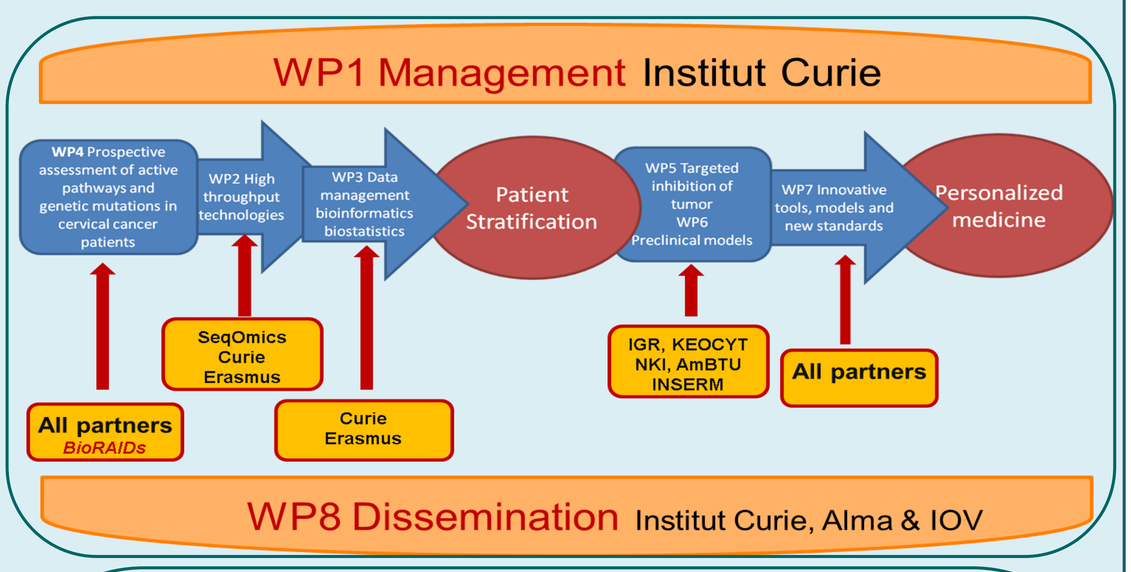
RAIDs: Rational molecular Assessment Innovative Drug selection: 7 EU countries

RAIDs is a multidisciplinary co-operation between academic clinical centers, SMEs and translational research platforms. It combines Next Generation Sequencing (NGS) and Reverse Phase Protein array (RPPA) in a large patient population prior to standard therapy.

It includes:

1. a cognitive cohort study (**BioRAIDs**) intended to define patient stratification for targeted therapies
2. targeted clinical trials using an HPV directed vaccine trial or direct viral targeting in association with standard therapy and
3. preclinical studies using cell lines and mouse models to identify new molecules of relevance for CC or CC microenvironment targeting.

Phase I HPV DNA vaccination trial (Principal Investigator G. Kenter, NKI) in VIN patients is ongoing: 5 from 12 patients have been included.



Results

Table 4. Response by treatment arm

Response at 4 months	Arm A N=38	Arm B N=38	
Complete response	16	15	p=0.82
Absence of complete response	22	23	

Figure 1. Response & treatment arm

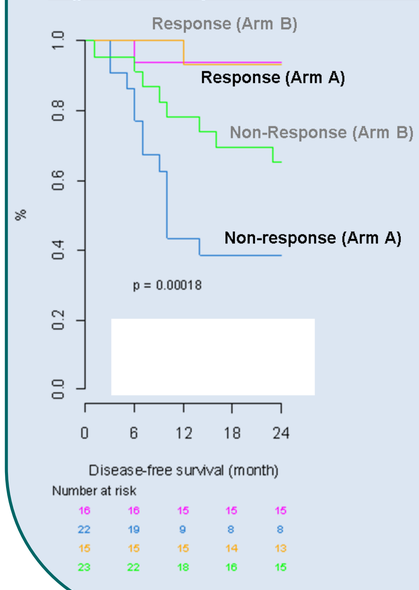


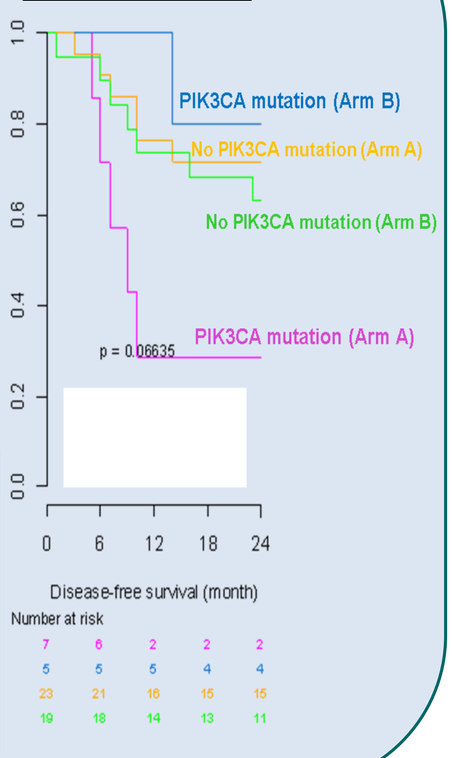
Table 5. Mutational landscape

Mutations	N=54	Arm A	Arm B
PI3KCA	12 (22%)	7	5
BRAF	1 (3%)	1	0
KRAS	5 (10%)	3	2
STK11	1 (3%)	1	0
PI3KCA & KRAS	14 (26%)	8	6

Table 6. Response by mutational status

Mutation	Complete Response	No complete Response	p-value
	(n=31)	(n=45)	
PI3KCA	N(%)	N(%)	0.042
Present	0 (0)	12 (23)	
Absent	14 (27)	26 (50)	
PI3KCA & KRAS			0.021
Present	0 (0)	14 (27)	
Absent	14 (27)	24 (46)	
Any mutation			0.009
Present	0 (0)	16 (31)	
Absent	14 (27)	22 (42)	

Figure 2. DFS by treatment arm & PIK3CA mutation



Methodology: **BioRAIDs** "Biomarker evaluation in advanced stage cervical cancer by an international working group-tumor Stages (1B2 – 4)".

700 Patients - 7 European countries (> 25 centers) will receive primary "standard" treatment. Frozen and fixed biopsies as well as serum/plasma samples are collected before and after treatment in case of residual disease for molecular and proteomics analysis.

Primary Objective :

Assessment of dominant mutations and activation of signaling pathways which may allow to predict treatment response.

Secondary Objectives :

- Evaluation of the PFS at 18 months in correlation with dominant genetic and protein alterations.
- Descriptive analysis of standard treatment modalities which are applied in the participating EU countries.
- Descriptive analysis of adverse events (grade 3 and 4).
- Descriptive analysis of the frequency and geographic distribution of dominant molecular alterations.

Conclusions and perspectives : The study of the mutational profile of CC patients in the Cetuxicol trial suggested that mutations in the PIK3 pathway lead to a resistance to standard therapy and that single EGFR inhibition in the presence of a downstream mutation may aggravate the outcome. These results will be further assessed through a large prospective population in the BioRAIDs protocol which started July 2013 with a plan to enroll 700 patients from 7 European countries.

Specific molecular or protein alterations as well as microenvironment patterns will be assessed. Results should enable the identification of predictive biomarkers in CC and define new strategies for targeted therapies in CC. Immunological data from trials involving vaccine or direct viral targeting will provide information on immune rejection or tolerance of this virally transmitted disease.

The RAIDs consortium seeks to involve other clinical centers in concertation with EORTC. It will liaise with international societies [ESGO (European society for gynaecological oncology), ECCA (European cervical cancer association)] for interactions on patient advocacy groups and with translational groups from within IGCS (International gynaecological cancer society) who may wish to join this initiative for scientific exchanges.

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