Asian Gynecologic Oncology Group

GYNECOLOGIC CANCER INTERGROUP
An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

Concept/trial design presentation

A Phase 2 Trial of Pembrolizumab Combined with Chemoradiation for Patients with [^{18}F]-FDG PET/CT-defined Poor-prognostic Cervical Cancer

Chun-Chieh Wang, MD and Feng-Yuan Liu, MD/ Prof. Chyong-Huey Lai, MD

Poor survival for advanced cervical cancer (FIGO Annual Report)

FIGO Stage	5-Year Overall Survival
IIB	55.9%
IIIB	23.7%
IVA	16.7%

Quinn MA et al. Int J Gynecol Obstet 2006; 95:S43-S103.

AGOG 09-001 Trial

- CCRT with single-agent cisplatin (arm C) versus cisplatin plus gemcitabine (arm CG)

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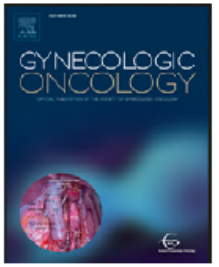

A randomized trial comparing concurrent chemoradiotherapy with single-agent cisplatin versus cisplatin plus gemcitabine in patients with advanced cervical cancer: An Asian Gynecologic Oncology Group study ☆

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AGOG 09-001 Eligibility criteria

- New pathological diagnosis of cervical cancer with squamous cell carcinoma
- FIGO stage III–IVA or any stage with [^{18}F]-FDG PET-defined positive pelvic or para-aortic lymph node
- Between 35 and 70 years old
- ECOG performance status 0 or 1
- Adequate bone marrow, liver and renal function
- Exclusion criteria
  - prior pelvic radiation
  - prior systemic chemotherapy
  - evidence of distant metastasis other than PALN

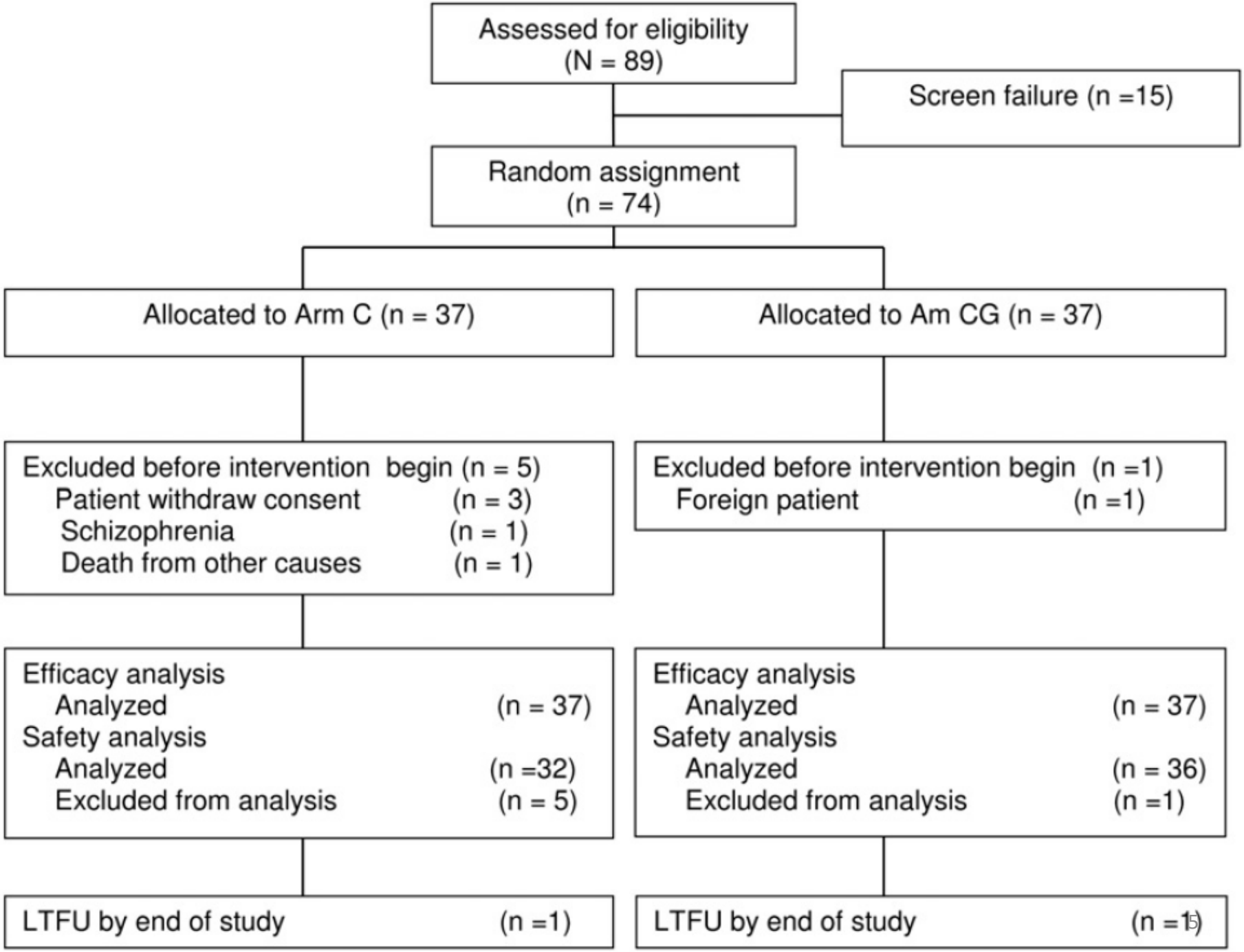

Assessed for eligibility
(N = 89)
Screen failure (n =15)
Random assignment
(n = 74)
Allocated to Arm C (n = 37)
Allocated to Am CG (n = 37)
Excluded before intervention begin (n = 5)
Patient withdraw consent (n = 3)
Schizophrenia (n = 1)
Death from other causes (n = 1)
Excluded before intervention begin (n =1)
Foreign patient (n =1)
Efficacy analysis
Analyzed (n = 37)
Safety analysis
Analyzed (n =32)
Excluded from analysis (n = 5)
Efficacy analysis
Analyzed (n = 37)
Safety analysis
Analyzed (n = 36)
Excluded from analysis (n =1)
LTFU by end of study (n =1)
LTFU by end of study (n =1)

Table 1
Patient demographics and clinical characteristics.

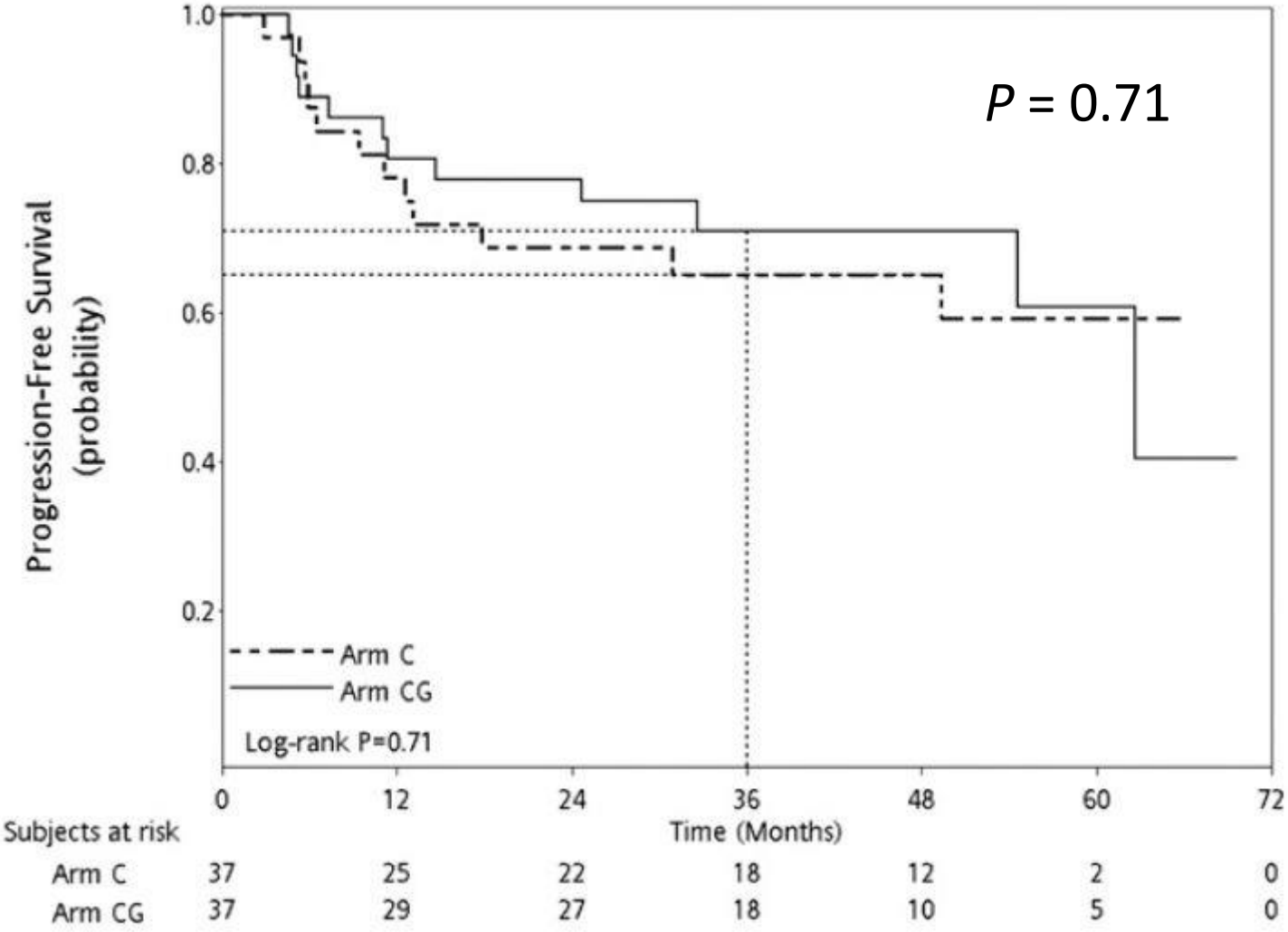
Characteristic	All patients		Arm C[a]		Arm CG[b]		p-Value
	N = 74	%	N = 37	%	N = 37	%	
Age (years)							0.366
Median	55.0		56		53		
Range	38–69		39–69		38–69		
ECOG performance status							0.790
0	55	74.3	28	75.7	27	73.0	
1	19	25.7	9	24.3	10	27.0	
Hemoglobin level							0.401
≧10	51	75.0	24	70.6	27	79.4	
<10	17	25.0	10	29.4	7	20.6	
Differentiation							0.698
Moderate	27	44.3	14	46.7	13	41.9	
Poor	33	54.1	15	50.0	18	58.1	
Unknown	1	1.6	1	3.3	0	0.0	
FIGO stage							0.669
IB	7	9.6	5	13.5	2	5.6	
IIA	2	2.7	1	2.7	1	2.8	
IIB	31	42.5	17	45.9	14	38.9	
IIIB	31	42.5	13	35.1	18	50.0	
IVA	2	2.7	1	2.7	1	2.8	
Pelvic node							
Yes	59	79.7	28	75.7	31	83.8	0.386
No	15	20.3	9	24.3	6	16.2	
Paraaortic node							
Yes	16	21.6	9	24.3	7	18.9	0.572
No	58	78.4	28	75.7	30	81.1	
Largest diameter							0.440
Mean	5.61		5.44		5.78		
Range	1.1–10.6		1.1–10.6		3.3–10		

[a] Arm C: radiotherapy with cisplatin.
[b] Arm CG: radiotherapy with cisplatin and gemcitabine.

3-year PFS of stage IIIB 69.6%

Arm C: 3-year PFS 65.1%

Arm CG: 3-year PFS 71.0%



Eur J Nucl Med Mol Imaging (2016) 43:1812–1823
DOI 10.1007/s00259-016-3384-7

ORIGINAL ARTICLE

Utility of ^{18}F-FDG PET/CT in patients with advanced squamous cell carcinoma of the uterine cervix receiving concurrent chemoradiotherapy: a parallel study of a prospective randomized trial

Feng-Yuan Liu[1,2] · Chyong-Huey Lai[2,3] · Lan-Yan Yang[4,5] · Chun-Chieh Wang[2,6] · Gigin Lin[2,7] · Chee-Jen Chang[5,8] · Wei-Yang Chang[4] · Shu-Hua Huang[9] · Yu-Erh Huang[10] · Nan-Jing Peng[11] · Ji-Hong Hong[2,6] · Angel Chao[2,3] · Hung-Hsueh Chou[2,3] · Yu-Chen Chang[1,2,12] · Tzu-Chen Yen[1,2]

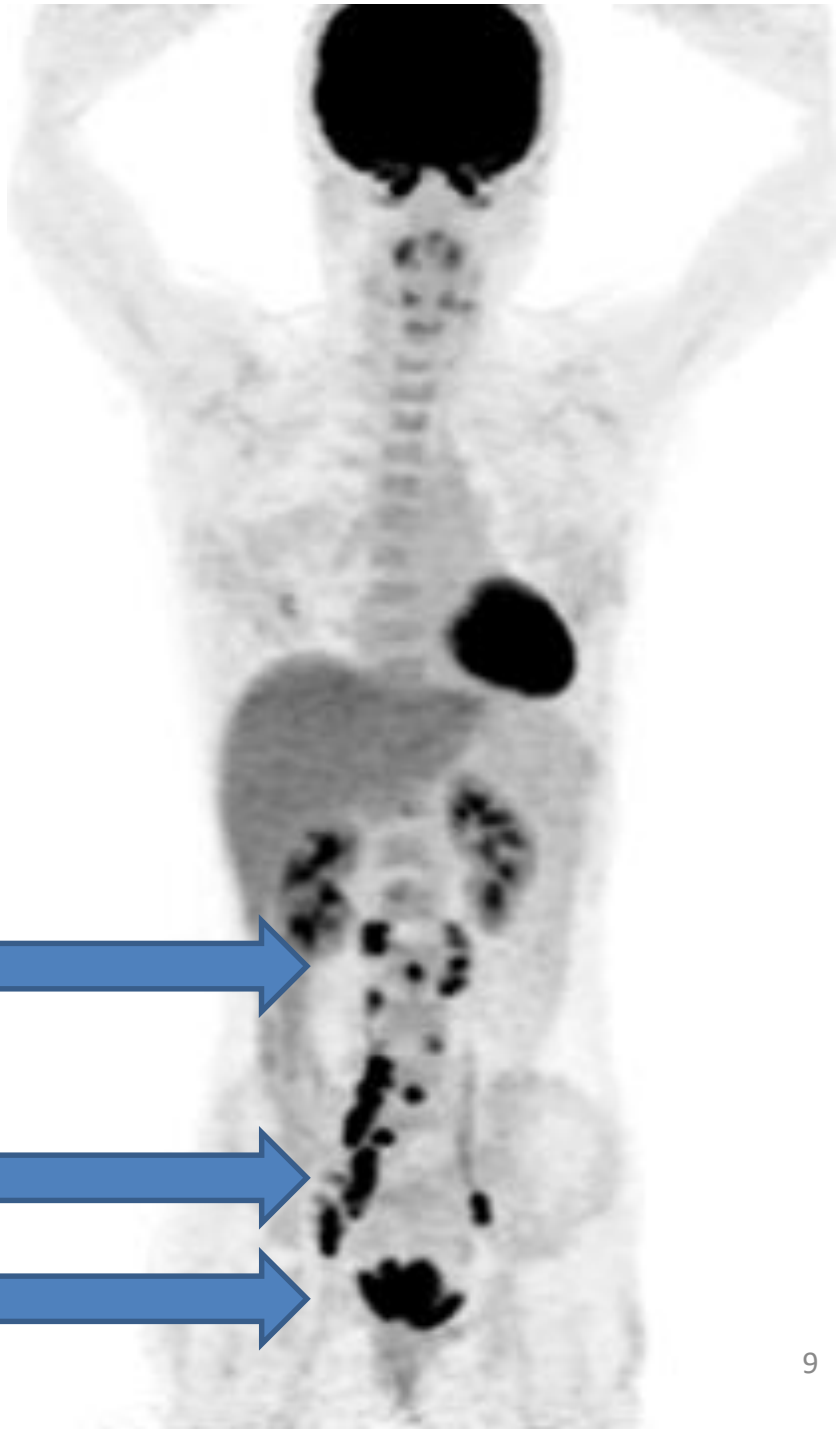
European Journal of Nuclear Medicine and Molecular Imaging (2018) 45:727–734
https://doi.org/10.1007/s00259-017-3884-0

ORIGINAL ARTICLE

Comparison of positron emission tomography/computed tomography and magnetic resonance imaging for posttherapy evaluation in patients with advanced cervical cancer receiving definitive concurrent chemoradiotherapy

Tzu-Pei Su[1] · Gigin Lin[2,3] · Yu-Ting Huang[2,4] · Feng-Yuan Liu[2,5] · Chun-Chieh Wang[2,6] · Angel Chao[2,7] · Hung-Hsueh Chou[2,7] · Tzu-Chen Yen[2,5,7] · Chyong-Huey Lai[2,7]

Pre-treatment [^{18}F]-FDG PET/CT



- Para-aortic LNs
- Regional LNs
- Primary Tumor

Pre-treatment PET/CT-defined Prognostic Factors

Parameter	Value	N	3-year PFS	*P*
PALN	Negative	42	83.3%	< .001
	Positive	13	23.1%	
Pre-treatment MTV (mL)	< 90	38	81.6%	.003
	≥ 90	17	39.7%	
Pre-treatment SUVnode	< 6.7 or negative	36	83.2%	.002
	≥ 6.7	19	42.1%	
Low-risk group	None of above	26	96.0%	< .001
High-risk group	Any of above	29	44.3%	

Important trials for locally advanced CC

- ANZGOG-0902_GOG-0724_RTOG-1174-**OUTBACK** (NCT01414608) **phase III adjuvant combination chemotherapy**

Inclusion criteria: stage IB1 & positive nodes, IB2, II, IIIB or IVA cervical cancer suitable for primary treatment with chemo-radiation with curative intent

- ADXS11-001 in Subjects With High Risk Locally Advanced Cervical Cancer **(AIM2CERV)** (NCT02853604) **phase III adjuvant ADXS11-001 after CCRT (maintenance)**
- **Inclusion criteria:** Stage IB2, IIA2, IIB with biopsy proven pelvic node(s); or more positive nodes by MRI/CT ≥1.5 cm, shortest dimension; or more positive pelvic nodes by PET with SUV ≥2.5 or stage III/IVA (estimated **4-y PFS 50%**)

Trials using pembrolizumab for CC-1

- NCT02635360 Dr. **Linda R Duska, University of Virginia**, collaborated with MSD (Pembrolizumab and CCRT, **concurrent or maintenance**, phase II randomize n=88) **locally advanced cervical cancer for primary CCRT**

✓ Arm A: After chemoradiation is complete, subjects will receive the study drug, pembrolizumab

✓ Arm B: pembrolizumab concurrently with CCRT

✓ Drug: Pembrolizumab 200 mg of study drug is given through intravenous (IV) administration once every 21 days for 3 months.

➢ Primary Outcome Measures : **Change in immunologic markers** following combination of study drug with chemoradiation; incidence of **DLT**

Trials using pembrolizumab for CC-3

- NCT03444376 **Genexine, Inc.** collaborated with MSD (GX-188E Vaccination and Pembrolizumab, phase Ib/II, n =46) advanced, inoperable or metastatic cervical cancer who is positive for HPV-16 or HPV-18 AND failed (or not eligible to) standard-of-care chemotherapy and/or radiation.

✓ GX-188E: 1st day of week 1,2,4,7,13,19, 46/ 2mg

✓ pembrolizumab:Day 1 q3 weeks/ 200mg

➢ Primary Outcome Measures : **DLT**; **ORR**

- NCT03367871 **Dr. Brian Slomovitz, University of Miami** (Pembrolizumab, paclitaxel, cisplatin, phase II, n=39) recurrent, persistent or metastatic (primary stage IVB)

➢ Primary Outcome Measures : **DLT**; **ORR**

Trials using pembrolizumab for CC-2

- NCT03144466 (PAPAYA trial) **Royal Marsden NHS Foundation Trust** collaborated with MSD and National Institute for Health Research,UK, phase I, dose escalation, n=26) **cervical cancer stage IB-IVA for primary CCRT (excluding PALN mets)**
- NCT03454451 **Corvus Pharmaceuticals, Inc.** (CPI-006 alone and in combination with CPI-444 and with pembrolizumab for patients with advanced cancers, phase I, n=378)

Other trials using immune check-point inhibitors-1

- Nivolumab plus cisplatin CCRT **(NiCOL): Institut Curie** collaborated with BMS (NCT03298893) **phase I/II** n =21

✓ Nivolumab + radiochemotherapy 5 weeks of radiochemotherapy + nivolumab followed by 5 months of nivolumab alone

✓ Drug: Nivolumab Injection with 2 possible doses : flat dose 240 mg q2 weeks or 1mg/kg q2 weeks

Drug: Cisplatin 40 mg/m2, once a week during RT

✓ Primary Outcome Measures : **rate of occurrence of DLT**

Other trials using immune check-point inhibitors-2

- Atezolizumab plus bevacizumab: National Cancer Institute (NCI), Recurrent, persistent, metastatic CC, phase II, n = 21, (NCT02921269)

✓ primary outcome: antitumor activity

- **Ipilimumab after CCRT**: NCI, CC with **PALN mets** for curative CCRT, CCRT with cisplatin weekly x4, within 2 weeks, patients receive ipilimumab IV over 90 minutes once every 3 weeks x4, phase I dose escalation, n= 34 (NCT01711515)

✓ primary outcome: MTD, DLT

Will Novel Therapy including Pembrolizumab Improve the Outcome and Survival ?

Phase 2 Trial Proposal

- Based on AGOG09-001, only **44.3%** of PET/CT-defined advanced cervical SCC (not including ScLN mets) can be free of persistent or recurrent disease at 3-y .
- The survival of cervical cancer patients with persistent or recurrent disease after primary treatment remains dismal.
- We thus propose a phase II trial of primary CCRT plus pembrolizumab and post-CCRT immunochemotherapy to improve 3-y PFS for such high-risk patients.

Eligibility criteria

- New pathological diagnosis of cervical cancer with SCC
- [^{18}F]-FDG PET/CT-defined high-risk factors (any one)
  - Positive PALN
  - Pre-treatment MTV ≥ 90 mL
  - Pre-treatment SUVnode ≥ 6.7
- Between 35 and 70 years old
- ECOG performance status 0 or 1
- Adequate bone marrow, liver and renal function
- Exclusion criteria
  - prior pelvic radiation
  - prior systemic chemotherapy
  - evidence of distant metastasis other than PALN

Study design

- Multicenter, single-arm, open-label, phase II study
- Primary end point: Progression-free survival
- Secondary end points:

1. Tolerability
2. Overall survival
3. Quality of life

Exploratory: Biomarkers related to outcomes

Estimated patient number

- Test for one exponential mean
- For alpha = 0.05 and power = 0.80

Ref Haz Rate (h1)	HR	Trt. Haz Rate (h2)	Ref mean survival (1/h1)	Trt. Mean survival (1/h2)	single-arm N
65.70%	0.5	32.85%	1.522	3.044	45
	0.55	36.14%		2.767	58
	0.6	39.42%		2.537	77
	0.65	42.71%		2.342	104
	0.7	45.99%		2.174	148

Trial Treatment-1

- Pembrolizumab 200 mg IV 3-weekly and combination chemotherapy with cisplatin 40mg/m^2 with topotecan (0.7 mg/m^2 D1-D3) or paclitaxel (135 mg/m^2), chemotherapy regimen can be determined at the physician's discretion according to local health insurance coverage.
- Target volume RT (conformal or IMRT with or without brachytherapy) concurrently with chemotherapy

Trial Treatment-2

- If treatment delay > 1 week for G3/4 toxicity, chemotherapy will be given with single agent cisplatin alone with pembrolizumab continued.
- Post-CCRT combination chemotherapy with pembrolizumab will continued for 4 courses.