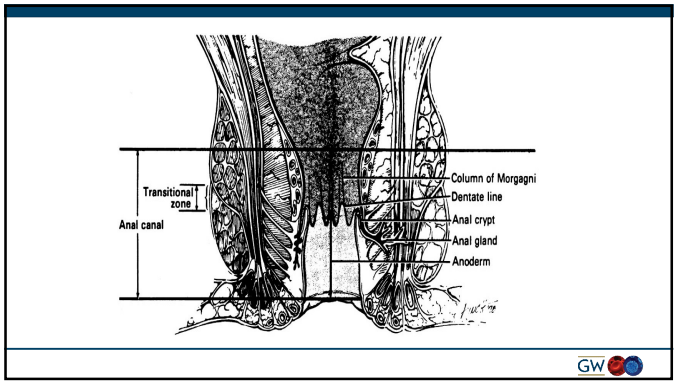
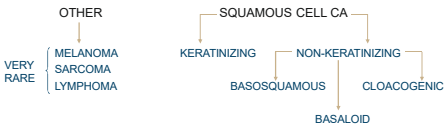


ANAL CANCER EPIDEMIOLOGY

- 9090 new cases (3020 men and 6070 women) of anal cancer involving the anus, anal canal, or anorectum will occur in the United States in 2021, accounting for approximately 2.7% of digestive system cancers
- It has been estimated that 1430 deaths due to anal cancer will occur in the United States in 2021
- the incidence rate of invasive anal carcinoma in the United States increased by approximately 1.9-fold for men and 1.5-fold for women from the period of 1973 through 1979 to 1994 through 2000 and has continued to increase since that time

GW

ANAL CANCER CELL TYPES



AJCC Anatomic Stage

	T	N	M
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T2	N0	M0
Stage IIB	T3	N0	M0
Stage IIIA	T1-2	N1	M0
Stage IIIB	T4	N0	M0
Stage IIIC	T3-4	N1	M0
Stage IV	Tany	Nany	M1

T1=2 cm or less; T2=2-<5 cm; T3=5 cm or greater

Prognosis

- The prognosis of anal carcinoma is related to the size of the primary tumor and the presence of lymph node metastases
- According to the SEER database, ~50% of anal carcinomas were localized at initial diagnosis (Stage I-IIB); these patients had an 80% 5-year survival rate
- Approximately 29% of patients had anal carcinoma that had already spread to regional lymph nodes at diagnosis (Stage III); these patients had a 60% 5-year survival rate
- The 12% of patients presenting with distant metastasis demonstrated a 30.5% 5-year survival rate

ANAL CANCER ETIOLOGY non-HPV ASSOCIATIONS

- Herpes Virus Type 2
- Immunosuppression (Transplant)
- Smoking (RR 9.4)
- HIV alone not associated

ANAL CANCER Anal Ca/AIN are STDs

Population	Multiple partners	Anal receptive intercourse	V.D. in partner
324 patients 554 controls	P < .001	3.4 (O.R.)	2.4 (O.R.)

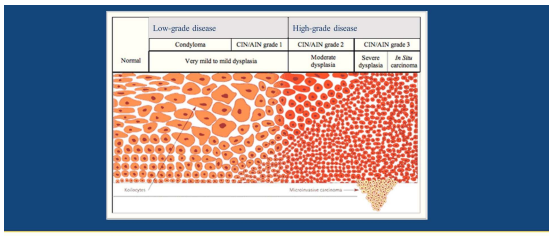
Frisch, et al., *NEJM* 337:1350, 1997

ANAL CANCER STD Anal Ca. or AIN

Population	Tumor (+) HPV-16
324 ♀ 93 ♂	84%

Frisch, et al., *NEJM* 337:1350, 1997

Anal HSIL is a cancer precursor



HSIL = High grade squamous intraepithelial lesion

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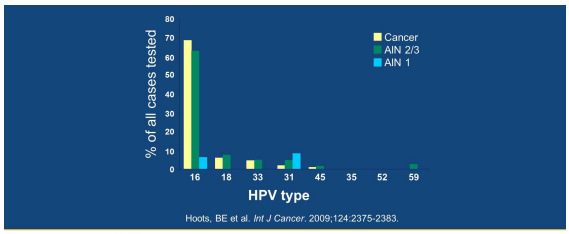
HPV types in anal LSIL, HSIL and cancer



Hoots, BE et al. *Int J Cancer*. 2009;124:2375-2383.

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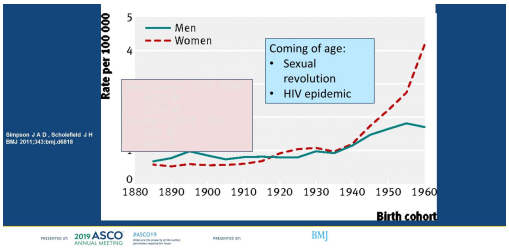
Anal Cancer Rates by Birth Cohort



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High prevalence of anal HPV infection and HSIL in HIV+ men and women

	Anal HPV prevalence	Anal HSIL prevalence	Anal cancer incidence
HIV-infected MSM	96%	43%	131/100,000
HIV-infected MSW	59%	?	46/100,000
HIV-infected women	90%	28%	30/100,000

Chin-Hong et al. *Ann Int Med*. 2008;149:300-6; Silverberg M et al. CID 2012; 54:1026-34
Conley et al. JID 2010; 202:1567-76'Stier EA et al. Presented at International Anal Neoplasia Society (IANS) Scientific Meeting, San Francisco, CA. November 11-13, 2016

The nonavalent HPV vaccine

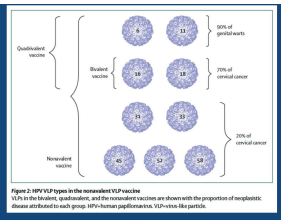
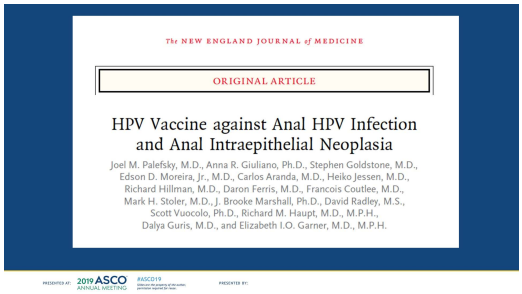
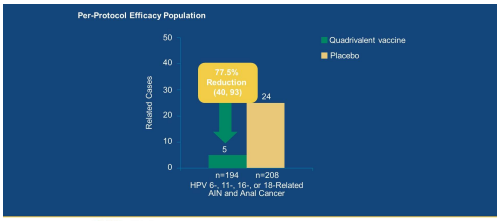


Figure 2: HPV VLP types in the nonavalent VLP vaccine
VLPs in the bivalent, quadrivalent, and the nonavalent vaccines are shown with the proportion of neoplastic disease attributed to each group. HPV=human papillomavirus. VLP=virus-like particle.

Schiller J. Lancet Oncol 2015;16(5):e217-25



Quadrivalent vaccine in males: Efficacy against HPV 6/11/16/18-related AIN and anal cancer in MSM



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Recommendations for HPV vaccine

Recommendations for HPV vaccine

(CDC) Age 9-26

- FDA recently approved vaccination up to age 45 years
- ACIP recommendation pending
- Decision to vaccinate above age 26 is individualized
  - Number of prior sexual partners
  - Likelihood of future sexual exposure
  - Vaccine is safe
  - Vaccine may or may not be costly

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CAIP = Advisory Committee on Immunization Practices

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Who should be screened?

- All HIV-positive men regardless of sexual orientation
- All HIV-negative MSM
- Women with high-grade cervical or vulvar lesions or cancer
- All HIV+ women
- All men and women with perianal condyloma
- Solid organ transplant recipients
- Over 25 years if immunosuppressed, inc. HIV
- Over 40 years if immunocompetent

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Controversies in Anal Cancer Screening

- General acceptance that anal HSIL precedes anal cancer, but anal HSIL is highly prevalent.
- Most people with anal HSIL will never develop cancer.
- Treatment for anal HSIL is not well studied and are clearly less effective than those for cervical HSIL
  - Recurrent HSIL is the norm; multiple treatments are usually needed to clear HSIL
- Accessing high resolution anoscopy and treatment for anal HSIL is difficult
- Not yet recommended by organizations setting standards for health care maintenance
  - Cost effectiveness is unclear
- No data that treating anal HSIL will reduce the risk of anal cancer

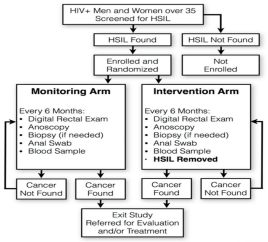
ANCHOR TRIAL

Screen > 17,385

Enroll 5,058

Retain for 5-8 years

Estimated < 50 develop cancer



the ANCHOR study

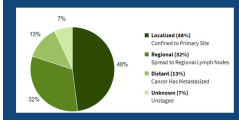
ANAL CANCER CURRENT THERAPIES

Local resection (early lesions with sphincter sparing)
T_1-T_2 N_0

Combined modality therapy
1) 5-FU/Mitomycin-C/XRT
2) Any Rx better than FU-Mito-C?

Salient Facts of Surgically Unresectable Metastatic Anal Cancer

- The majority of patients will present with locally advanced disease and will be treated with concurrent chemoXRT with curative intent.
  - Risk factors for residual or recurrent disease include T>4 cm and N+



- Metastatic disease will develop in < 20% of patients
- **Historically, no** well established chemotherapy regimen for metastatic pts
  - 5-yr OS = 30%

C. Eng: MD Anderson Manual of Clinical Oncology, 2006; Frisch et al: J Natl Cancer Inst 92:1500-10, 2000; Frisch M, et al: J Natl Cancer Inst 91:708-15, 1999; Eng et al: OncoTarget 2014; www.seer.gov Gunderson et al., JCO, 2012.

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ANAL CANCER RESULTS OF ABDOMINAL PERINEAL RESECTION

No. Pts.*	Operative Mortality (%)	5-yr Survival (%)	Local-Regional Failure (%)
460	5.5 (2.5-8)	55 (45-66)	30 (27-35)

* 5 Series

Harter & Ahlgren, GI *Oncology*, 1992

ANAL CANCER
RADIOTHERAPY ALONE AS TREATMENT FOR ANAL CANCER

Series	No. of Pts.	Dose (cGy)	Complications Requiring Surgery (%)	Local Control (%)	5-Yr Survival (%)	Retention of Functional Anus (%)
Inst. Curie	158	6500-7500	8	67	59	73
Inst. Gustave Roussy	64	6000-6500	14	91 ($T_{1,2}$) 76 (T_1)	46	74
Princess Margaret	51	4500-6000	12	57	59	76
Centre Léon Bérard	222	3000-4200 (Ext) 1500-2000 (Implt) 4500-6200	3	79	65	--

ANAL CANCER
5-FU + MITO-C + XRT

5-FU:	1000 mg/m^2 x 4 days CI
MMC:	10-15 mg/m^2 day 1 i.v.
XRT:	3000-4000 R

- 11 pts all bx-proved NED (median f/u 1 yr)
- 1 pt dead p.e. NED at autopsy

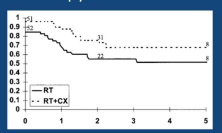
Flam, et al., ASCO 1:97, 1982

ANAL CANCER
5-FU + MITO-C + XRT

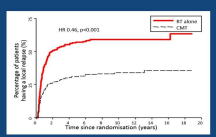
Institution	Regimen	No. Pts	CR (%)
Wayne State	5-FU + Mitomycin-C + 30 GY XRT (Simul)	122	113/122 (93%)
Memorial	5-FU + Mitomycin-C + 30 G **(Sequential)**	37	19/37 **(52%)**
Princess Margaret	5-FU + Mitomycin-C + 50 GY vs. **60 GY only**	30 25	27/30 (93%) **15/25 (60%)**

Squamous Cell Carcinoma of the Anus

- Chemoradiation more effective in achieving local control than radiotherapy alone.



EORTC 22861 Bartelink H et al J Clin Oncol 1997



ACT I Trial UKCCR Lancet 1996

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Squamous Cell Carcinoma of the Anus

- Chemoradiation more effective in achieving local control than radiotherapy alone.
- Addition of MMC to 5FU CRT essential component
- No benefit from addition of induction chemotherapy (5FU/cisplatin prior to CRT
- No benefit from consolidation chemotherapy after CRT
- No benefit for 5FU/cisplatin vs 5FU/MMC

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No benefits and excessive toxicity from cetuximab

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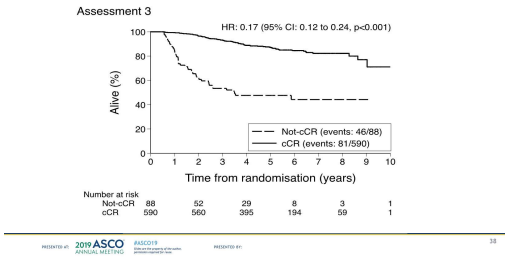
Outcomes if in CCR at 26 weeks (ACT II)



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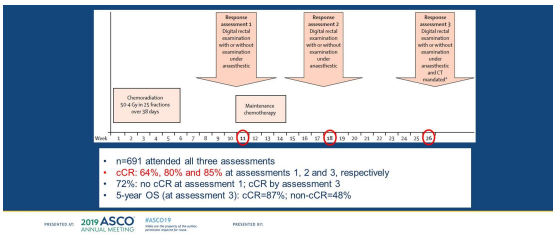
Best time to assess complete clinical response (cCR) after CRT: ACT II data



- n=691 attended all three assessments
- cCR: 64%, 80% and 85% at assessments 1, 2 and 3, respectively
- 72%: no cCR at assessment 1; cCR by assessment 3
- 5-year OS (at assessment 3): cCR=87%; non-cCR=48%

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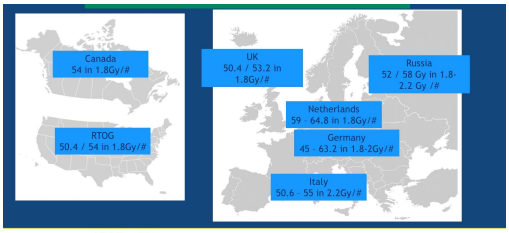
To biopsy or not?

- Needle biopsy may have false negative
- Biopsy before 26 weeks may be too soon: false positive
- Excisional biopsy may increase risk of sphincter incompetence

Radiotherapy Doses to Primary Tumour



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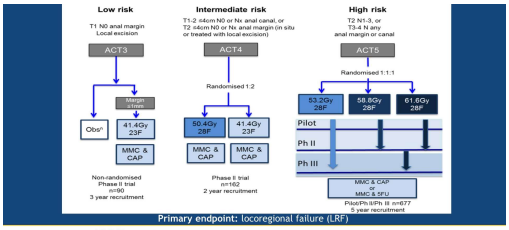
Risk-adapted RT: the PLATO trial



PLATO is a UK integrated protocol, comprising 3 separate trials (ACT3, ACT4 and ACT5) which aims to optimise radiotherapy dose (in combination with chemotherapy) for low-, intermediate- and high-risk anal cancer.

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Survivorship- late toxicity

- Grade 3 and above (classified as severe) up to 33.3%.
- The most commonly reported late toxicities were faecal incontinence (up to 44%), diarrhea (up to 26.7%), and ulceration (up to 22.6%)
- Intensity-modulated radiation therapy appears to reduce late toxicity.

Pan YB, Maeda Y, Wilson A, Glynne-Jones R, Vaizey CJ. **Late gastrointestinal toxicity after radiotherapy for anal cancer: a systematic literature review.** Acta Oncol. 2018 Nov;57(11):1427-1437

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Nivolumab After Combined Modality Therapy in Patients With High Risk Stage II-IIIB Anal Cancer NCT03233711

ECOG-ACRIN Cancer Research Group

- Nivolumab IV over 30 minutes on day 1. Treatment repeats every 14 days for up to 12 courses in the absence of disease progression or unacceptable toxicity.
- Primary endpoint 5 years DFS
- Started April 2018 - Estimated enrolment -200 by
- 2020

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Prior Published Regimens for Metastatic Anal SCCA

Author	N	Agents	ORR	Med PFS (months)	Med OS (months)
Wilking 1985	15	Vincristine, bleomycin & High-dose methotrexate	3/12 (25%)	2M	NR
Ajani 1989	3	5-FU/CDDP	NA	17M (2 of 3)	NA
Faivre 1999	18	5-FU/CDDP	60% (CR=10%)	4M	NA
Hainsworth 2001	60 (4 with anal cancer)	TPF (max = 4 cycles)	65% (CR = 25%)	26M	NR
Jhawer 2006	20	Mitomycin C, adriamycin, cisplatin, bleomycin-CCNU	12/20 (60%)	8M	15
Alcindor 2008	5	Taxol (1st and 2nd line)	80%	Range: 3-8M	Range: 4-20M
Abbas 2011	7	Taxol (2nd line)	57%	Range: 2-8M	Range: 5-14M
Kim 2013	8	DCF	CR: 50% (3/4 resected)	19-86M	1 yr: 62.53M%
Eng, 2014	77	Carbo/Taxol and 5-FU/CDDP	33% - 57%	7M (6M vs. 16M)	22M (17M vs. 83M)
Kim, 2018	69	Docetaxel, cisplatin, and 5-FU (DCF)	89%	11M	NR

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International Rare Cancer Initiative (IRCI)/ECOG EA#2133 InterAACT: 1st line Met SCCA of the Anal Canal

NCT02560298

- **Arm A**: Cisplatin 75 mg/m2 day 1 + 5FU 1000mg/m2 infusion/24 hours/4 days q28 days
- **Arm B**: Carboplatin (AUC = 5) + Taxol (weekly) q 21 days

R

- Treatment for 6M and cont at the discretion of the investigator
- Substratification: **HIV+/HIV-**, HPV status, and prior XRT
- CT scans: q3M
- N=90

Study PI's – S Rao, US PI: C Eng

Objective: Feasibility and to identify best chemotherapy backbone to build for biologic development
1) Primary endpoint: RR
2) Secondary endpoints: PFS, OS, correlatives, and QOL, etc.

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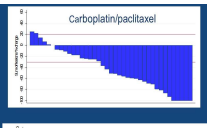
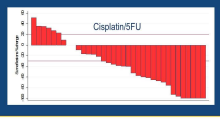
InterAACT/EA#2133 Primary Endpoint

Response (RECIST)	Carboplatin-Paclitaxel N=39		Cisplatin-5FU N=35	
	N	(%) CI	N	(%)
CR	5	12.8	5	14.3
PR	18	46.2	15	42.9
SD	10	25.6	7	20.0
PD	6	15.4	8	22.9
CR/PR	23	59 95% CI: [42.1-74.4]	20	57 95% CI: [39.4-73.7]

Rao et al, ESMO 2018





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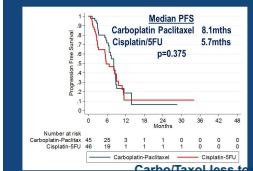
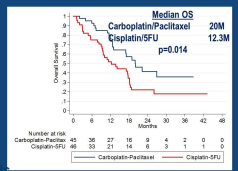
InterAACT/EA#2133: Secondary Endpoints of PFS and OS

Median follow-up of 25.3 M





CarboTaxol less toxic

Rao et al, ESMO 2018

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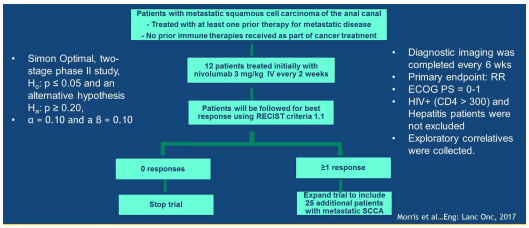
NCI9673 (Part A): Multi-Institutional Phase II ETCTN Study of Nivolumab in Previously Treated Metastatic SCCA



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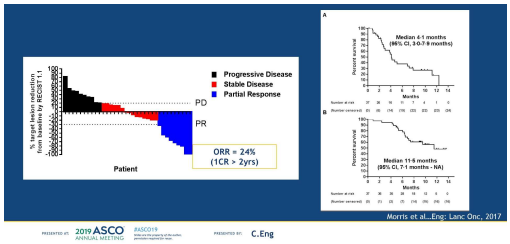
NCI9673 (Part A): Secondary Endpoints- PFS and OS



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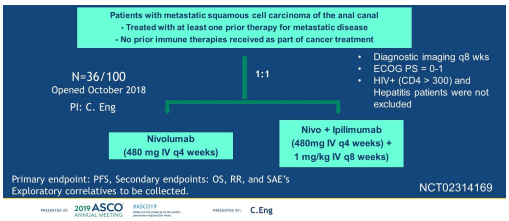
NCI9673 (Part B): Randomized Phase II ETCTN Study of Nivolumab +/- Ipilimumab in Metastatic SCCA
of the Anal Canal



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Expected closure 2/2022; 137 pts

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Pembrolizumab for Advanced Anal Squamous Cell Carcinoma: Results From the Phase 2 KEYNOTE-158 Study

Aurelien Marabelle,[1] Philippe Cassier,[2] Marwan Fakih,[3] Tormod Guren,[4] Antoine Italiano,[5] Steven Kao,[6] Dorte Nielsen,[7] Paolo Ascierto,[8] Giovanni Mendonca Bariani,[9] Armando Santoro,[10] Jamil Asselah,[11] Anthony El-Khoueiry,[12] Kristen Spencer,[13] Shunji Takahashi,[14] Arkendu Chatterjee,[15] Fan Jin,[15] Kevin Norwood,[15] Jean-Pierre Delord[16]

[1]Gustave Roussy, INSERM U1015, Villejuif, France; [2]Centre Léon Bérard, Lyon, France; [3]City of Hope National Medical Center, Duarte, CA, USA; [4]Oslo University Hospital, Oslo, Norway; [5]Institut Bergonie _ Bordeaux, France; [6]Chris O'Brien Lifehouse, Camperdown, NSW, Australia; [7]Herlev Hospital, University of Copenhagen, Copenhagen, Denmark ; [8]Istituto Nazionale Tumori IRCCS Fondazione Pascale, Naples, Italy; [9]Instituto do Câncer do Estado de São Paulo, Universidade de São Paulo, São Paulo, Brazil ; [10]Humanitas Clinical and Research Hospital, IRCCS, Humanitas University, Milan, Italy; [11]McGill University, Montreal, QC, Canada; [12]University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA, USA; [13]Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA; [14]Cancer Institute Hospital of the Japanese Foundation for Cancer Research, Tokyo, Japan; [15]Merck & Co., Inc., Kenilworth, NJ, USA; [16]Institut Claudius Regaud IUCT-Oncopole, Toulouse, France

Presented By Aurelien Marabelle at 2020 Gastrointestinal Cancer Symposium

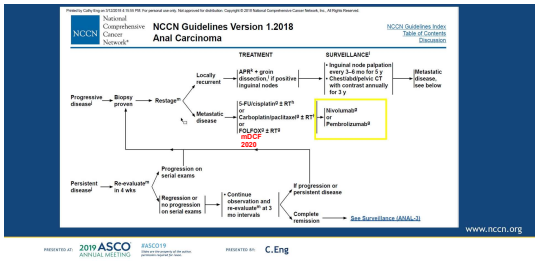
Antitumor Activity (RECIST v1.1, Central Review)

	All Patients N = 112	PD-L1 Positive N = 75	PD-L1 Negative N = 30
ORR, % (95% CI)	10.7 (5.7–18.0)	14.7 (7.6–24.7)	3.3 (0.1–17.2)
Best overall response			
CR	6 (5.4)	6 (8.0)	0
PR	6 (5.4)	5 (6.7)	1 (3.3)
SD	17 (15.2)	11 (14.7)	4 (13.3)
PD	74 (66.1)	48 (64.0)	21 (70.0)
Nonevaluable[a]	1 (0.9)	0	1 (3.3)
No assessment[b]	8 (7.1)	5 (6.7)	3 (10.0)

Data are presented as n (%), unless otherwise noted.
[a]Patients for whom not all target lesions were captured on ≥1 postbaseline imaging assessment.
[b]Patients for whom no postbaseline tumor assessment was performed.
Data cutoff date: June 27, 2019 .

Presented By Aurelien Marabelle at 2020 Gastrointestinal Cancer Symposium

Change in 2018 NCCN v 2.2021 Guidelines



PRESENTED AT: 2019 ASCO ANNUAL MEETING #ASCO19

PRESENTED BY: C.Eng

Presented By Cathy Eng at 2019 ASCO Annual Meeting

Phase 1 study of pembrolizumab in people with HIV and cancer

2019 American Society of Clinical Oncology Annual Meeting
June 2, 2019
Chicago, IL

Thomas S Uldrick MD, MS
Deputy Head, Global Oncology
PI, Cancer Immunotherapy Trials Network-12
Associate Member, Vaccine and Infectious Disease Division
Associate Member, Clinical Research Division
Fred Hutchinson Cancer Research Center

cancer immunotherapy trials network

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Conclusions:

- Pembrolizumab has acceptable safety in cancer patients with HIV on ART and >100 CD4 cells/μL
- Clinical benefit noted in lung cancer, lymphoma, and KS
- Activity noted in liver cancer
- ***Anti-PD-1 therapy is appropriate for FDA-approved indications and cancer clinical trials in this population***
- Prospective evaluation of pembrolizumab as first systemic therapy in Kaposi sarcoma on-going
- Pembrolizumab may be associated with polyclonal KSHV-associated B-cell lymphoproliferation
- Patients with KSHV-associated Castleman disease should not be treated with pembrolizumab

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Conclusions:

- Single agent immune checkpoint inhibition is able to provide durable and prolonged responses with excellent tolerability for previously treated patients.
  - *Change 2018 NCCN Treatment Guidelines
  - Disadvantage: Off-protocol use
- InterAACT/EA2133 indicates carbo/weekly paclitaxel improves RR and OS
  - *Change in 2019 NCCN Treatment Guidelines
- NCI9673 (Part B): Randomized phase II ETCTN study of nivolumab +/- ipilumumab is open for enrollment.
  - Additional correlatives will be collected from all ETCTN sites.
- Pending data:
  - Atezo/Bev
  - MEDI0457/Durvalumab
  - mDCF +/- Atezo
  - Avelumab +/- Cetux
  - EA#2176 for tx naïve patients.
- ****Encourage patients to enroll on clinical trials**

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