DANA-FARBER
CANCER INSTITUTE

식도암과 위암
지금 기본 치료는 무엇인가?

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Dana-Farber Cancer Institute
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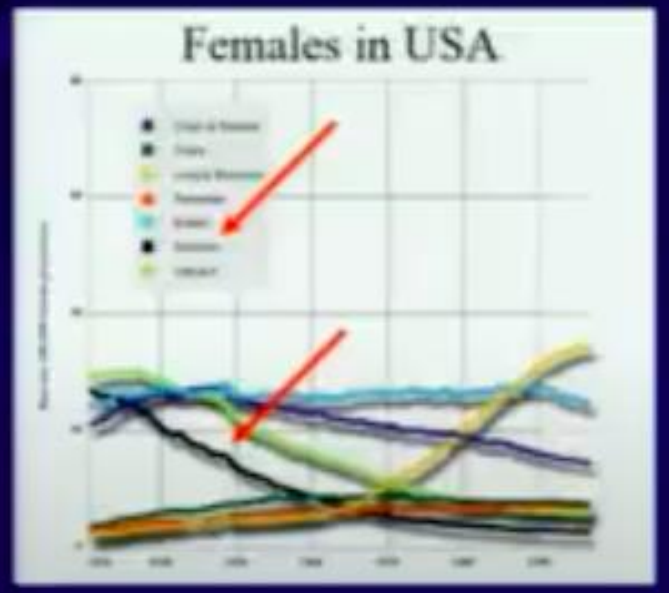
식도암 2019

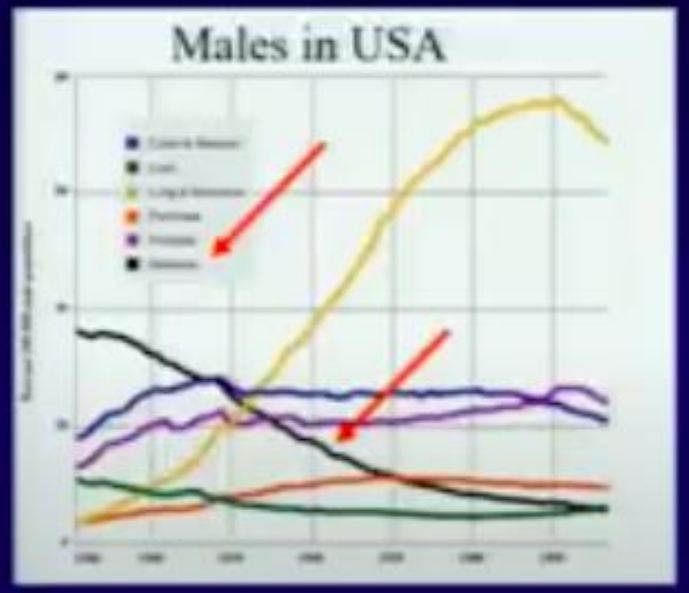
미국

Cancer Site	New Cases:	Men	Women
Esophagus	17,650	13,750	3,900
Stomach	27,510	17,230	10,280

세계적으로

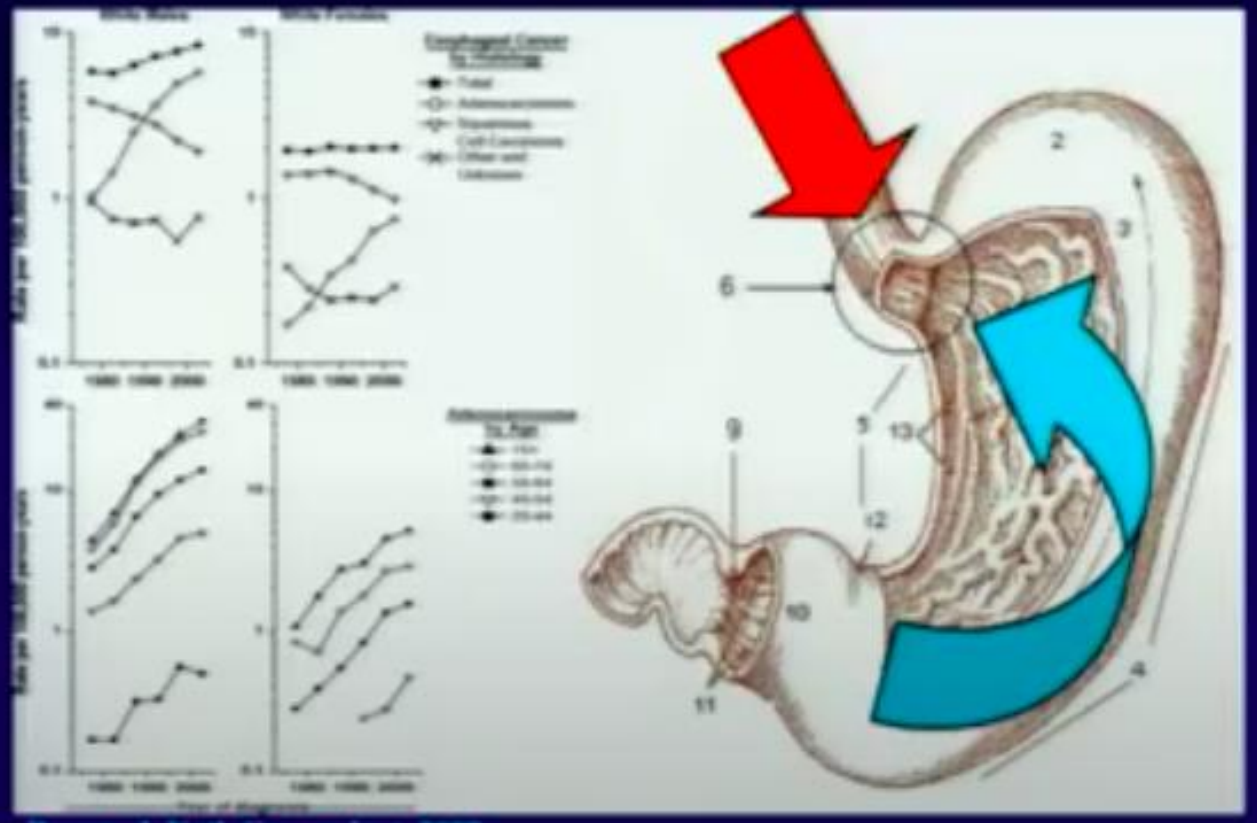
위암의 새 케이스





CA Cancer J Clin '08

식도암의 트렌드



Brown, J. Natl. Cancer Inst. 2008

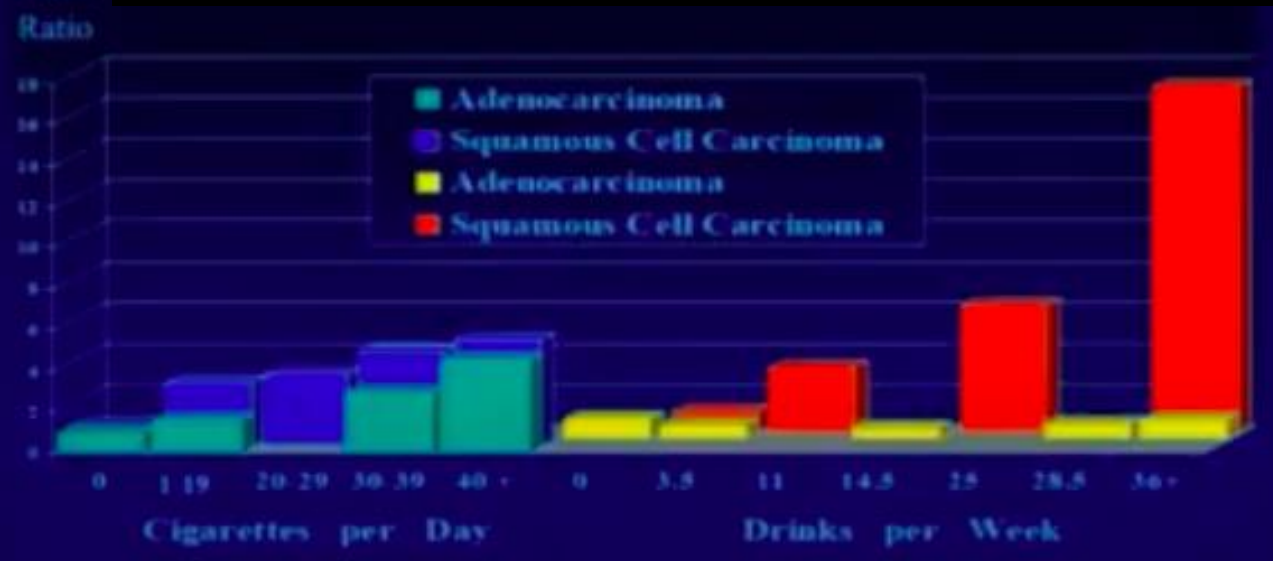
식도암의 위험 요인

Risk Factor	SCC	ADC
Tobacco	+++	++
ETOH	+++	---
Barrett's Esophagus	---	++++
Weekly Reflux Symptoms	---	+++
Obesity	---	++
Poverty	++	---
Achalasia	++++	
Caustic injury to esophagus	++++	---
Tylosis (NEPPK)	++++	---
Plummer-Vinson syndrome	++++	---
History of head & neck cancer	++++	---
H/o breast ca treated with radiotherapy	+++	++
Frequent consumption of hot beverages	+	---
HPV (China, Japan, South Africa)	+/-	---
Beta blocker	---	+/-
Anticholinergics	---	+/-
Aminophylines	---	+/-

++++ > 8-fold risk
+++ 4-8-fold risk
++ 2-4-fold risk
+ < 2-fold risk
+/- Conflicting studies
--- No proven risk

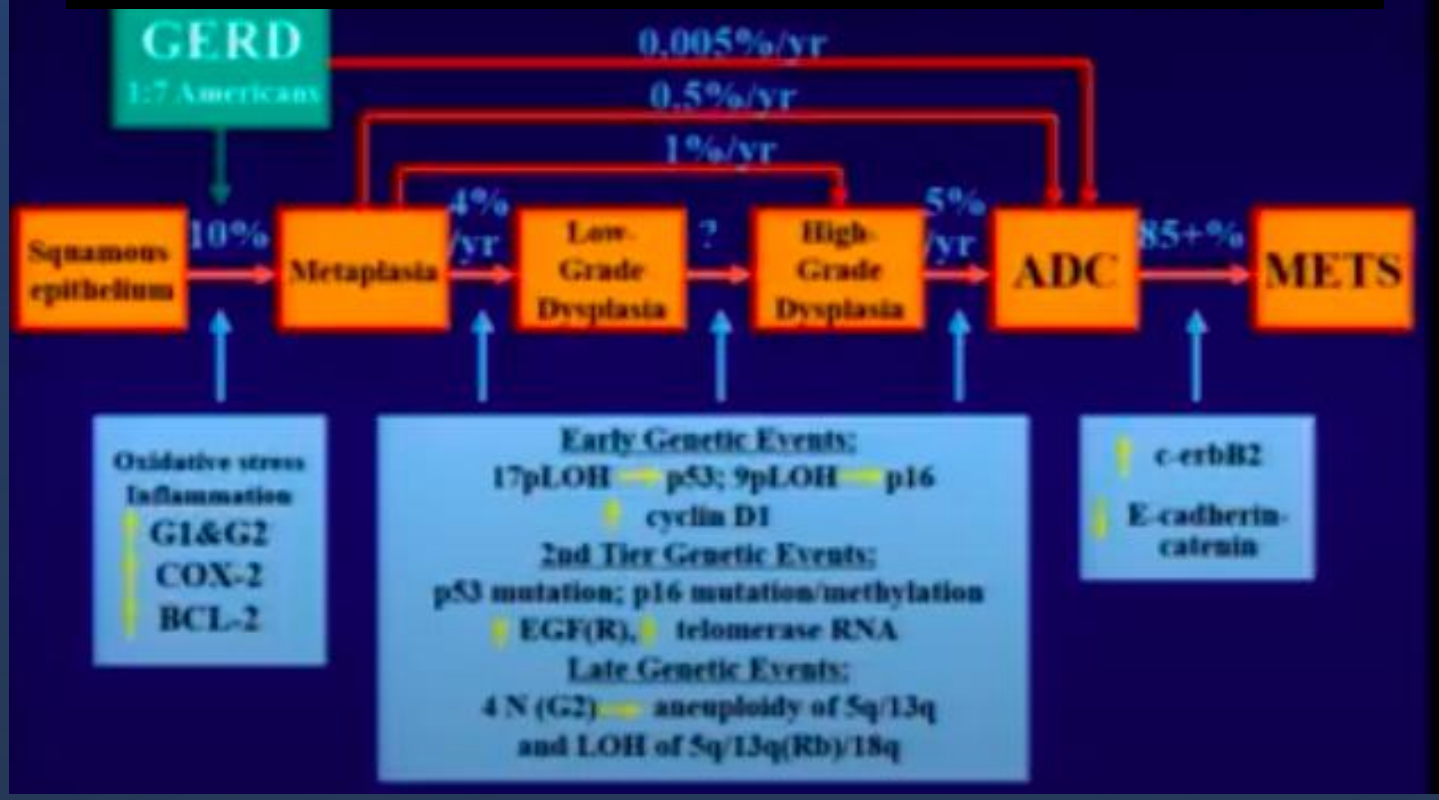
Enzinger & Mayer. N Engl J Med 2003

식도암과 담배/술



Data from Takezaki 2000, Wu 2001 and Brown 2001

바렛의 식도의 네오플라지아 진행



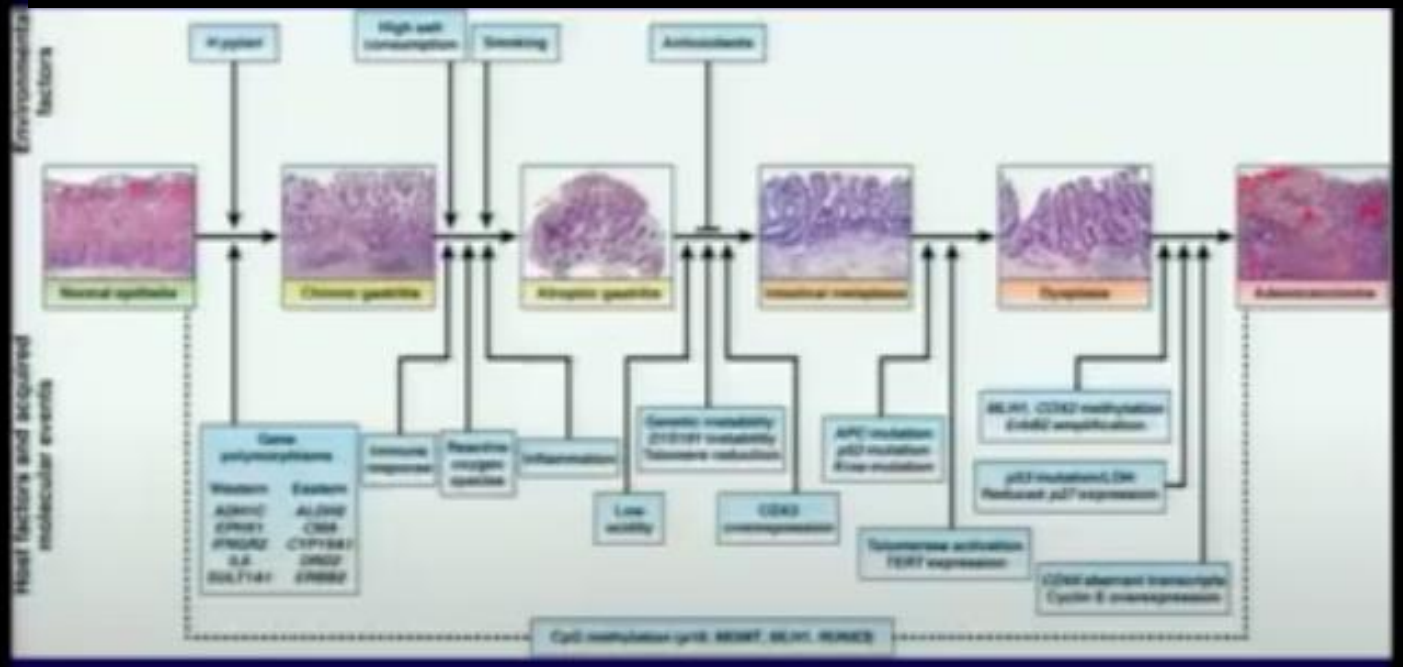
위암의 위험 요인

영양
저지방, 저 단백 섭취
절인 고기나 생선
나트레이트 고 섭취

환경
안 좋은 음식 준비 (훈제)
냉장 잘 안됨
물 부족
담배
낮은 사회적 지위

의료
전 위 수술
위 아트로피나 위염

장 타입의 위암 발달


Environmental factors
Host factors and acquired molecular events
Tan and Yeoh. Gastroenterology 2015;149:1153–1162

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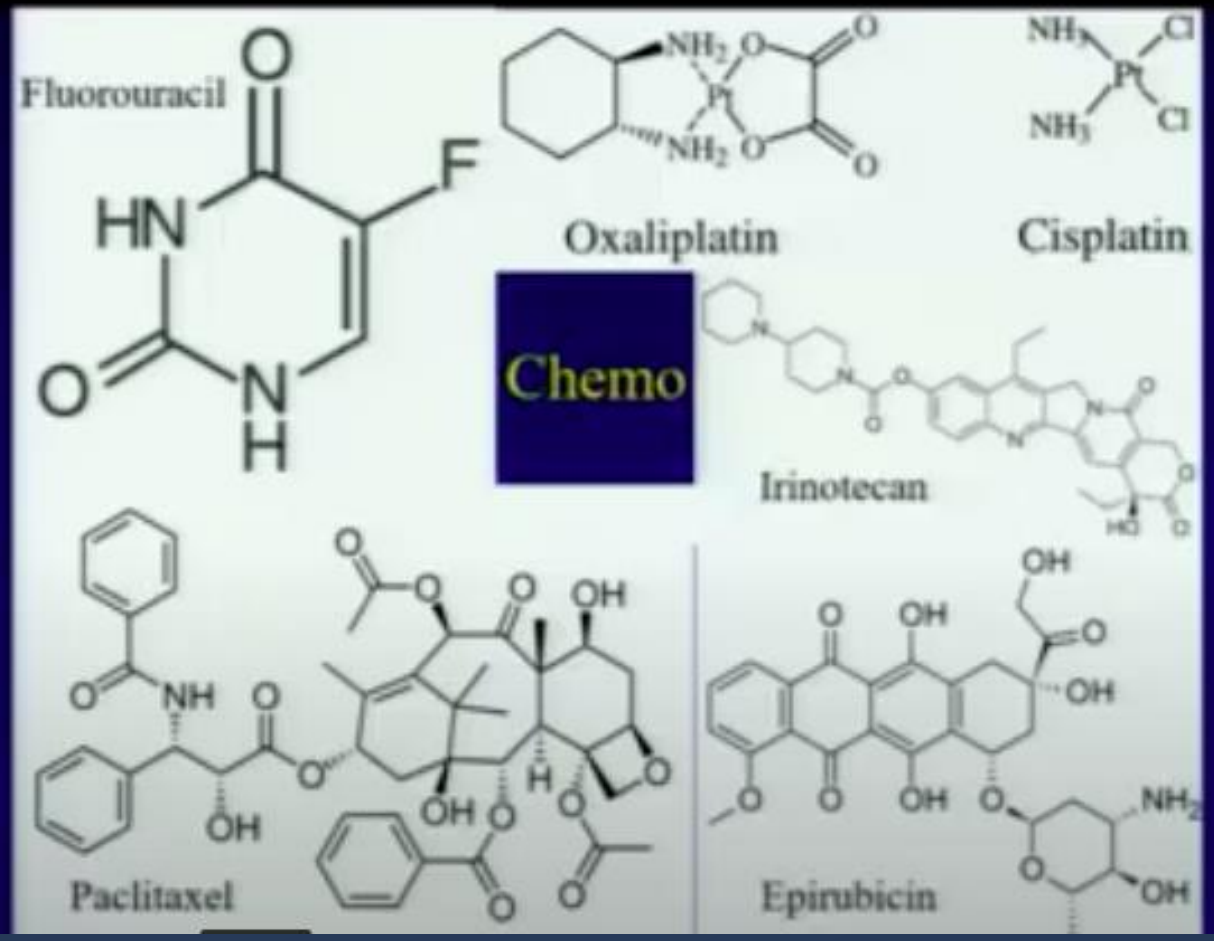
전이성 식도암

식도암 과 위암에 쓸 약?


Fluorouracil
Oxaliplatin
Cisplatin
Chemo
Irinotecan
Paclitaxel
Epirubicin

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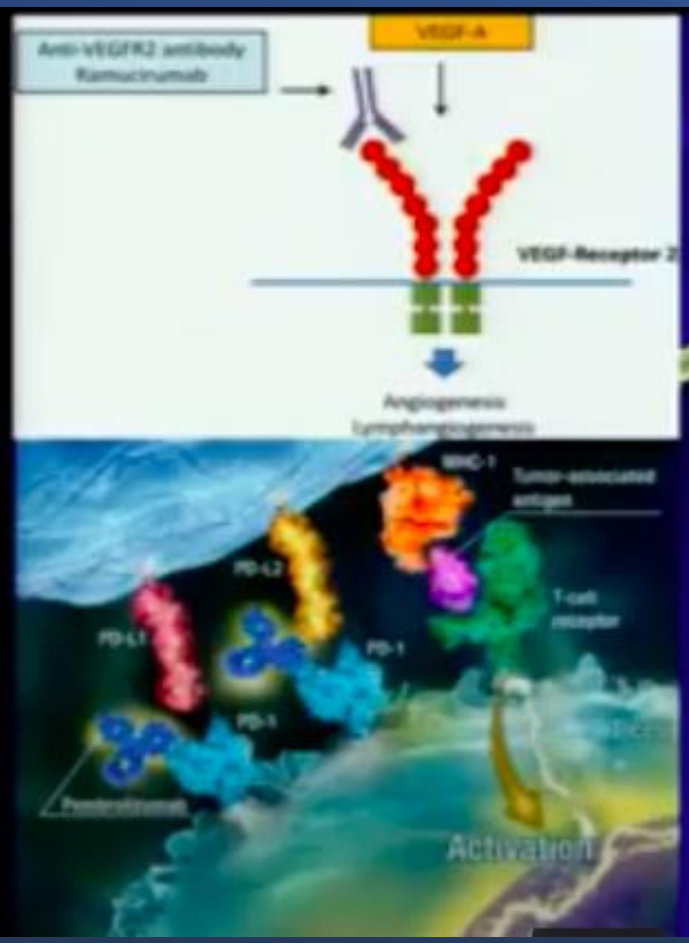
알킬레이팅 약

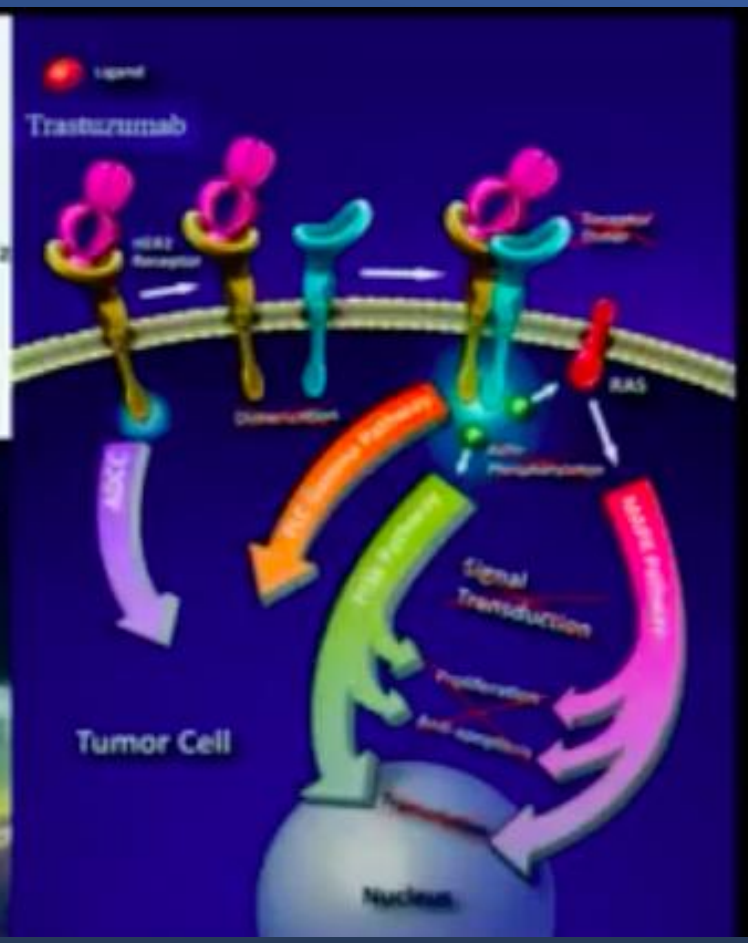
안트라싸이클린

안티메타볼라이트

토포아이소머라아제

마이토틱 억제제


Anti-VEGFR2 antibody
Ramucirumab
VEGF-A
VEGF-Receptor 2
Angiogenesis
MHC-1
Tumor-associated antigen
PD-L2
PD-L1
PD-1
T-cell receptor
Activation


Ligand
Trastuzumab
RAS
ADCC
Signal Transduction
Tumor Cell
Nucleus

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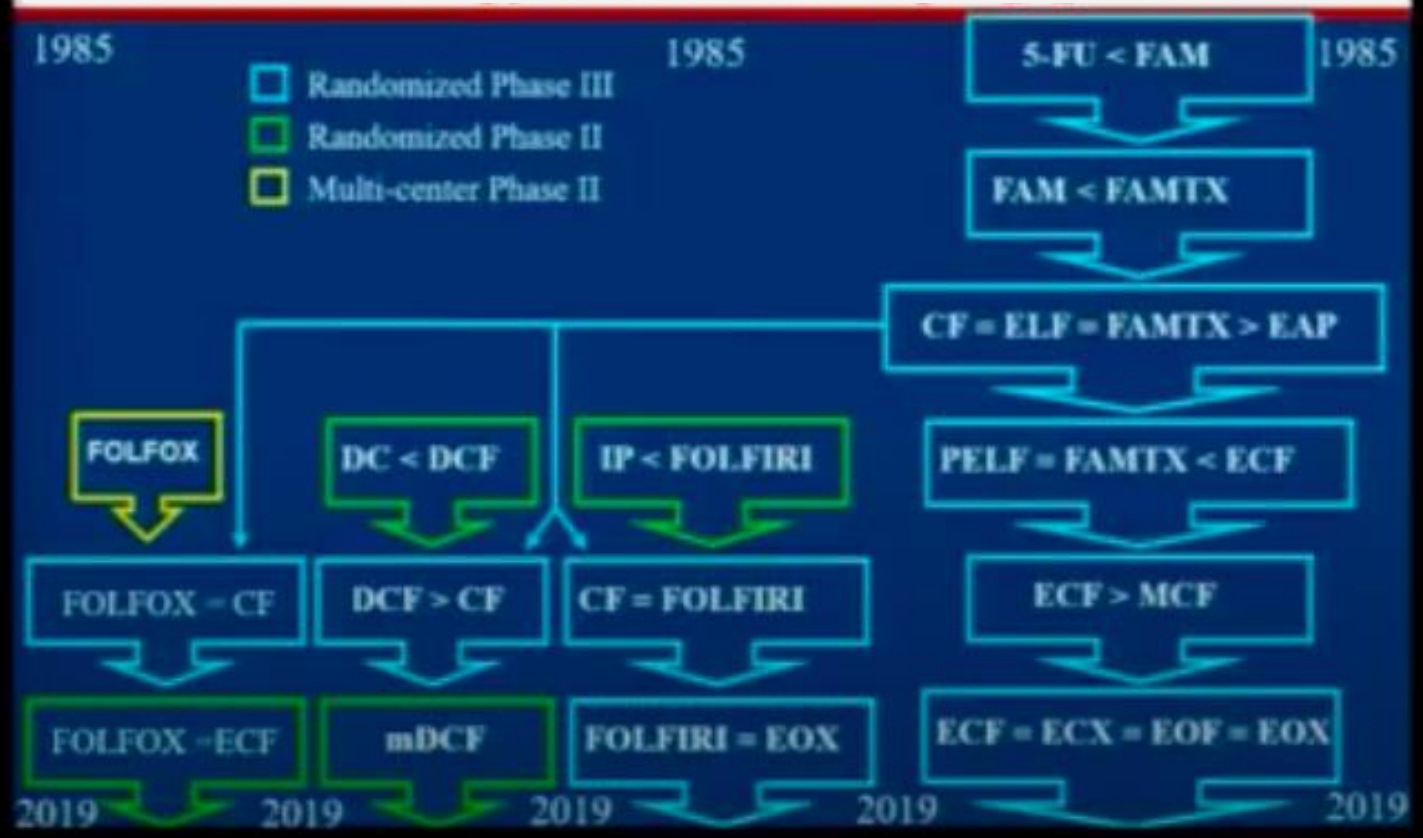
진행성 식도암 요법의 진화



CALGB 80403 / ECOG E1206: Design

Stratification:
ECOG 0-1 vs 2
ADC vs. SCC

ARM A: (ECF + C); 1 cycle = 21 days

Epirubicin 50 mg/m2 IV, day 1
Cisplatin 60mg/m2 IV, day 1
Fluorouracil 200mg/m2/day, days 1-21

ARM B: (IC + C); 1 cycle = 21 days

Cisplatin 30 mg/m2 IV, days 1 and 8
Irinotecan 65 mg/m2 IV, days 1 and 8

ARM C: (FOLFOX + C); 1 cycle = 14 days

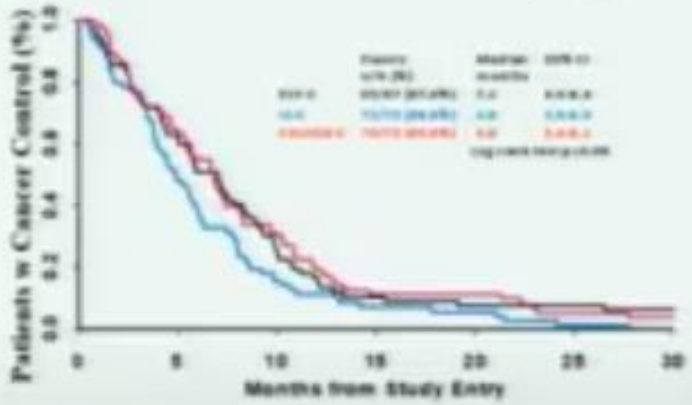
Oxaliplatin 85 mg/m2 IV, day 1
Leucovorin 400 mg/m2, day 1
Fluorouracil 400 mg/m2 IV bolus, day 1
Fluorouracil 2400 mg/m2 IV over 46hrs (days 1-2)

C: Cetuximab 400 → 250mg/m2 IV, weekly added to each arm.

Enzinger. J Clin Oncol 2016

CALGB 80403 / E1206: 암 조절

FOLFOX 는 식도암과 접합암에서 ECF 와 비슷한 암 조절

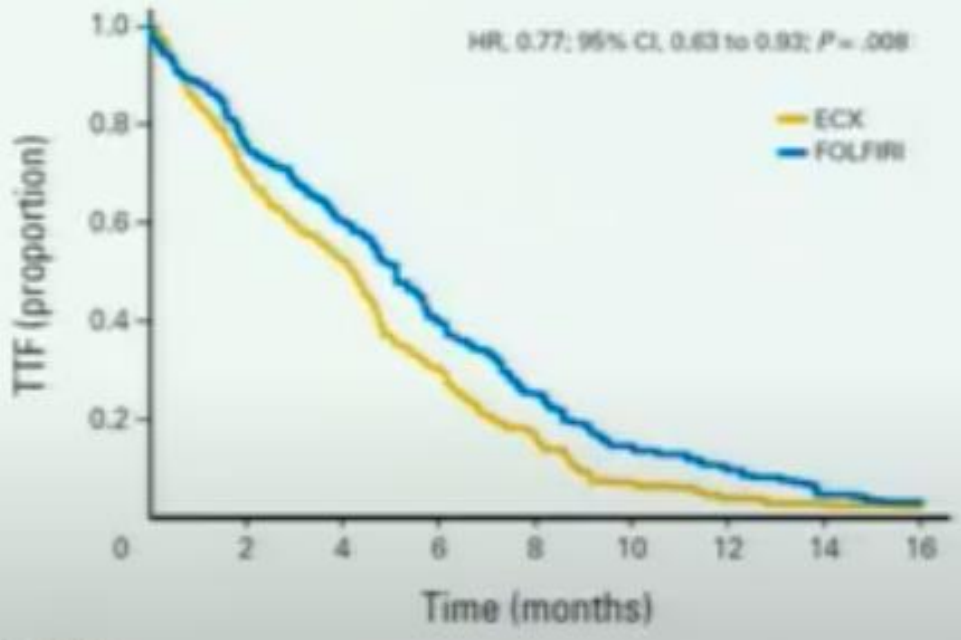


Treatment had to be reduced:
FOLFOX-C (73%) vs IC-C (85%) vs ECF-C (91%) (χ^2, p=0.013).

Discontinued treatment for severe side effects:
FOLFOX-C (11%) vs. ECF-C (19%) vs IC-C (26%) (χ^2, p=0.17).

Enzinger. J Clin Oncol 2016

3상: 식도암과 접합암에서 FOLFIRI 대 ECX



No. at risk									
ECX	209	145	108	61	33	14	8	5	4
FOLFIRI	207	157	123	81	50	28	19	9	6

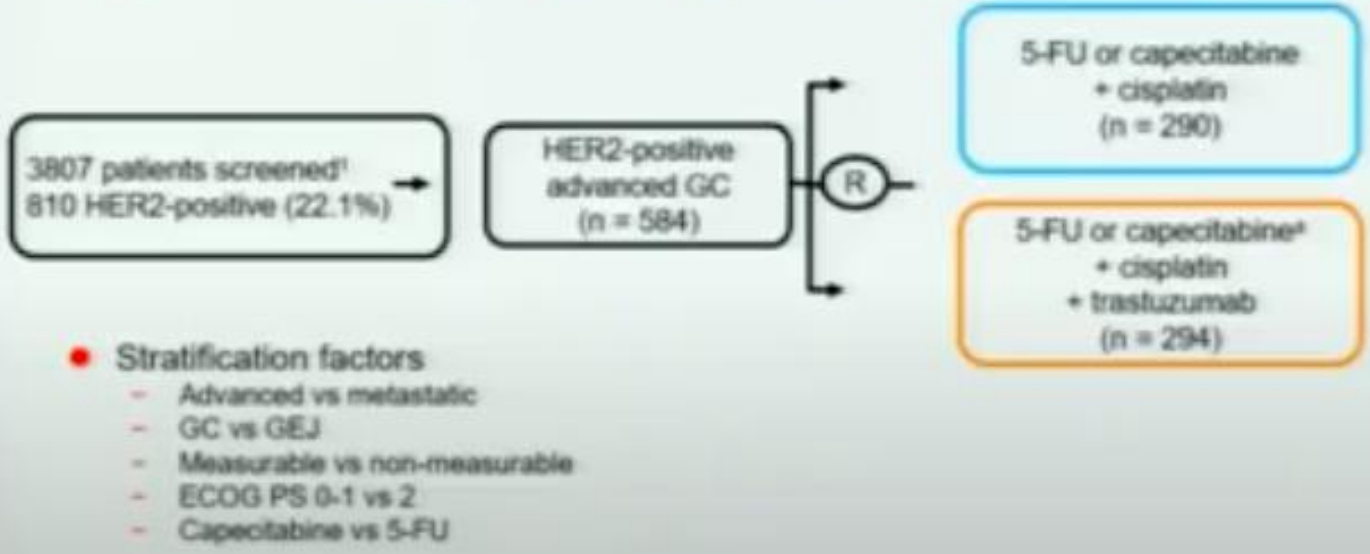
Time to Treatment Failure

*Irinotecan
Fluorouracil
Leucovorin

Guimbaud. J Clin Oncol 2014

토가 시험

3상 무작위, 오픈 라벨, 국제적, 다센터 시험

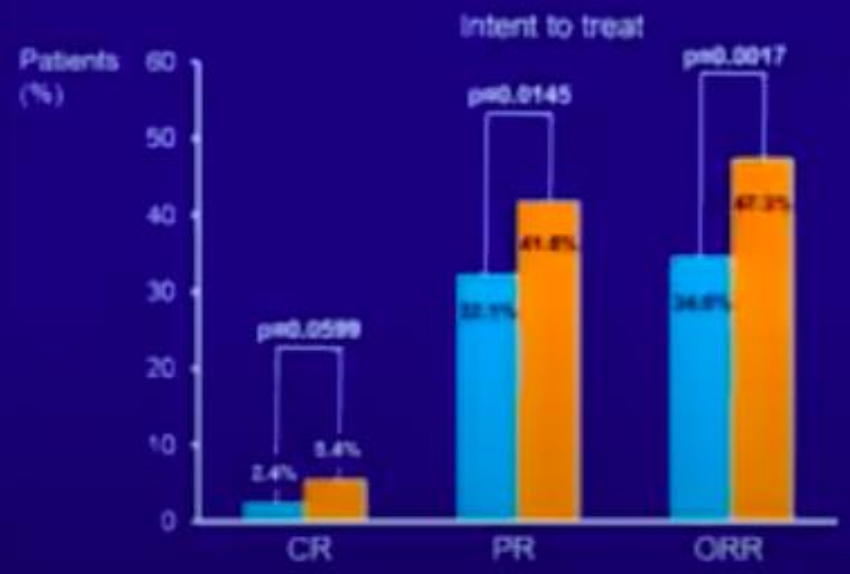


- Stratification factors
  - Advanced vs metastatic
  - GC vs GEJ
  - Measurable vs non-measurable
  - ECOG PS 0-1 vs 2
  - Capecitabine vs 5-FU

*Chosen at investigator's discretion
GEJ, gastroesophagealjunction

Bang, Y-J et al. Lancet 2010; 376:687

토가 시험: 반응율 과 생존율

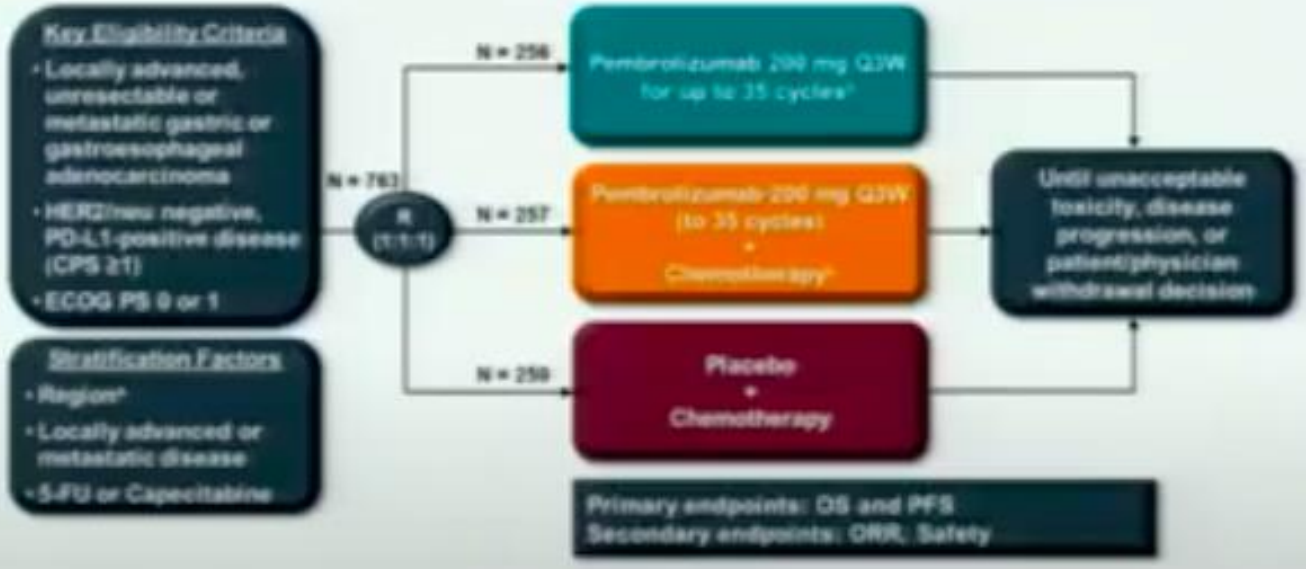


5.2 month improvement in survival for patients with HER2 3+ or 2+/FISH+ tumors

ORR= CR + PR
CR, complete response; PR, partial response

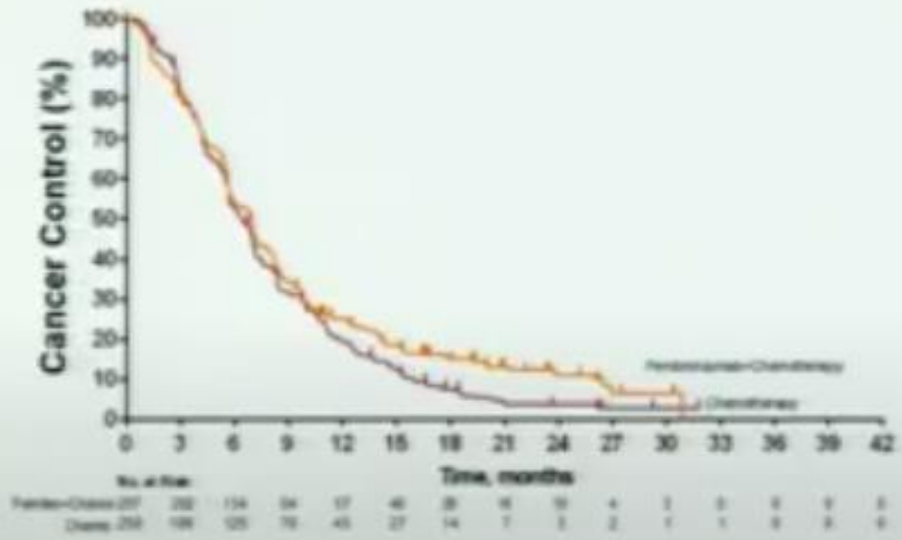
Van Cutsem. ASCO 2009

키노트 -062 시험 디자인



Presented By Josep Tabernero at 2019 ASCO Annual Meeting

키노트 -062 암 조절 – 화학 +/- 면역 요법



Presented By Joseph Tabernero at 2019 ASCO Annual Meeting

코가 -02: 재발된 식도암에서 도세텍실 대 BSC 무작위 시험

168 patients :

RANDOMIZE

- Docetaxel 75 mg/m² q 3 weeks
- Best supportive care

Primary Endpoint:
Overall Survival

Ford et al. Lancet Oncol. 2014 Jan;15(1):78-86.

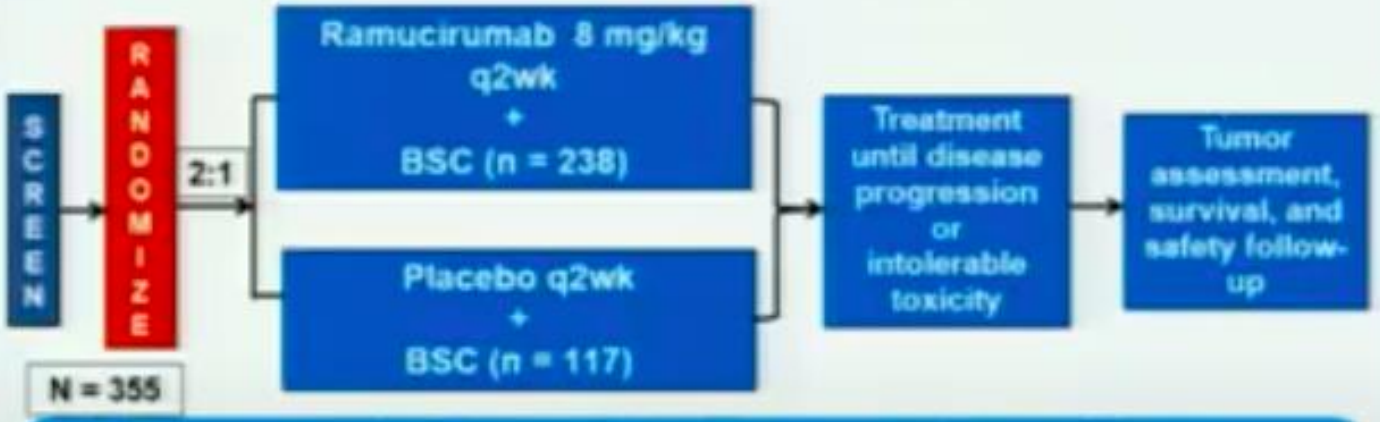
코가 -02: 2차 라인 도세텍실 대 BSC

도세텍실:
7% 환자에서 주 반응
46% 환자에서 안정된 병
29% 환자에서 6개월에 병 조절

도세텍실 대 BSC:
70% 환자에서 6개월에 병 조절
45% 환자에서 전체 생존율 향상

Ford et al. Lancet Oncol. 2014 Jan;15(1):78-86.

리가드 연구 디자인

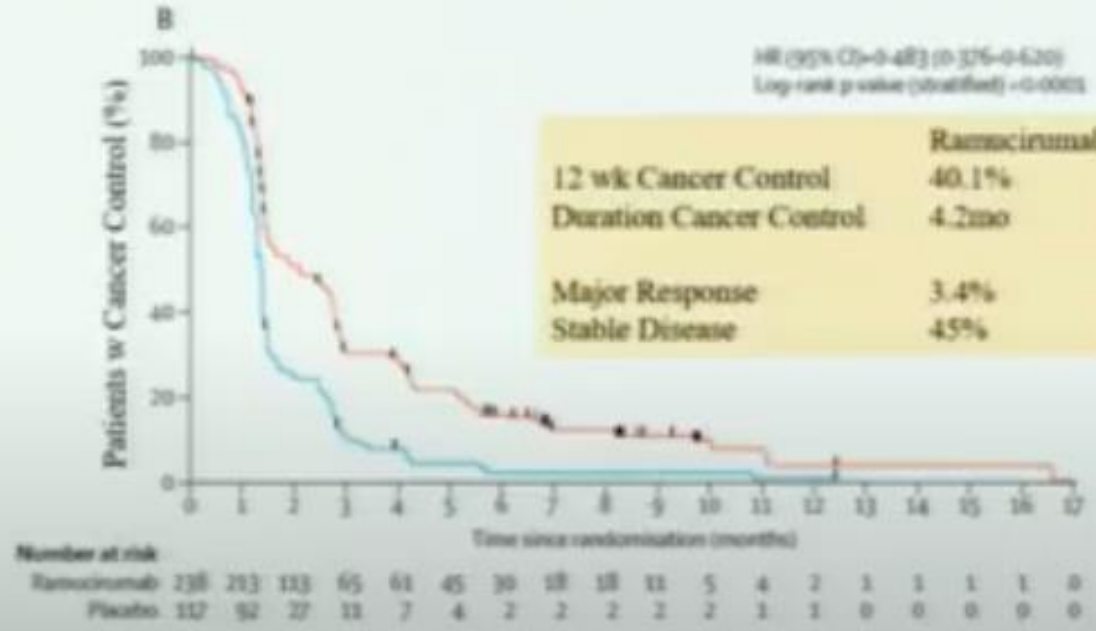


- Multicenter, randomized, double-blind, placebo-controlled, phase 3 trial
- Gastric or GEJ adenocarcinoma
- Stratification factors: region, weight loss (≥10% vs. <10% over 3 months), location of primary tumor (gastric vs. GEJ)
- Global: 6 continents, 30 countries, 120 study centers

Abbreviations: BSC=best supportive care; GEJ= gastroesophageal junction

Fuchs et al. Lancet. 2014 Jan 4;383(9911):31-9.

리가드: 병 조절 과 반응율



	Ramucirumab	Placebo
12 wk Cancer Control	40.1%	15.8%
Duration Cancer Control	4.2mo	2.9mo
Major Response	3.4%	2.6%
Stable Disease	45%	21%

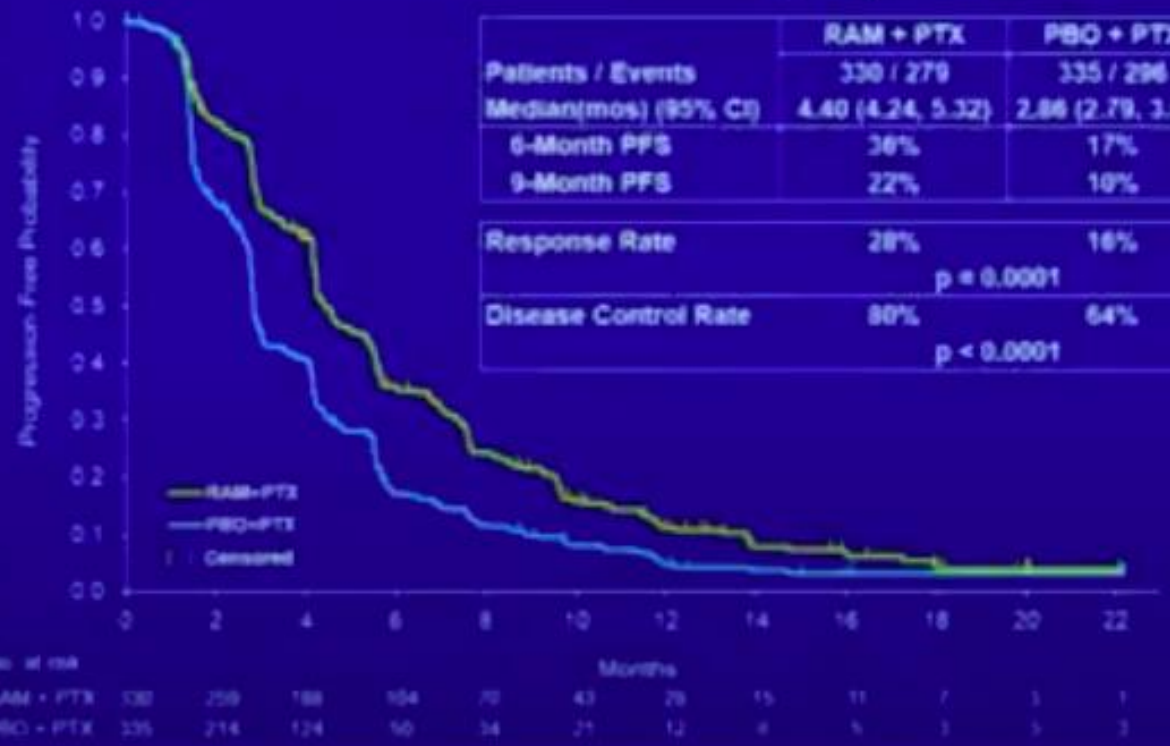
Fuchs et al. Lancet. 2014 Jan 4;383(9911):31-9.

레인보우: 병 조절 과 반응율

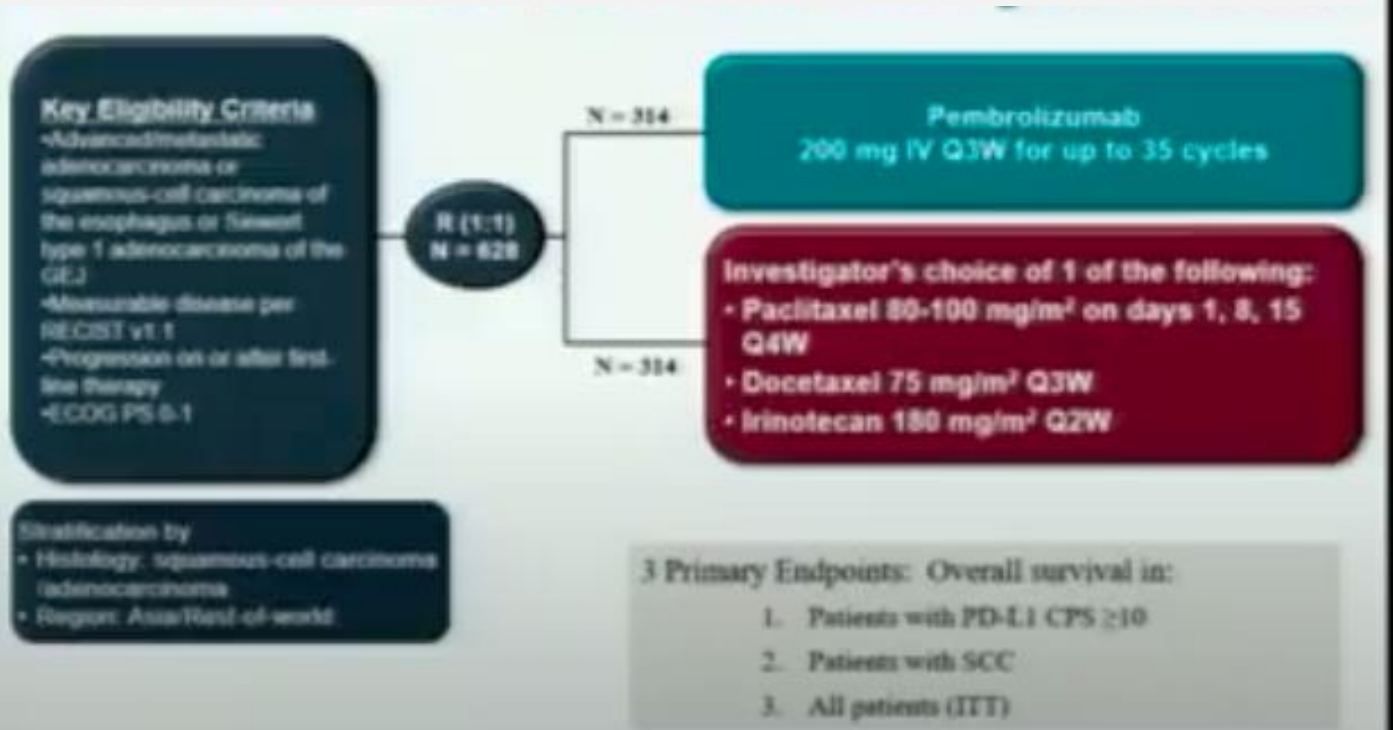
HR (95% CI) = 0.635 (0.536, 0.752)

Stratified log rank p-value < 0.0001

	RAM + PTX	PBO + PTX
Patients / Events	330 / 279	335 / 296
Median(mos) (95% CI)	4.40 (4.24, 5.32)	2.86 (2.79, 3.02)
6-Month PFS	36%	17%
9-Month PFS	22%	10%
Response Rate	28%	16%
	p = 0.0001	
Disease Control Rate	80%	64%
	p < 0.0001	



3상 키노트 - 181 연구


Key Eligibility Criteria
•Advanced/metastatic adenocarcinoma or squamous-cell carcinoma of the esophagus or Siewert type 1 adenocarcinoma of the GEJ
•Measurable disease per RECIST v1.1
•Progression on or after first-line therapy
•ECOG PS 0-1
R (1:1)
N = 628
N = 314
Pembrolizumab
200 mg IV Q3W for up to 35 cycles
N = 314
Investigator's choice of 1 of the following:
• Paclitaxel 80-100 mg/m² on days 1, 8, 15 Q4W
• Docetaxel 75 mg/m² Q3W
• Irinotecan 180 mg/m² Q2W
Stratification by
• Histology: squamous-cell carcinoma/adenocarcinoma
• Region: Asia/Rest-of-world
3 Primary Endpoints: Overall survival in:
1. Patients with PD-L1 CPS ≥10
2. Patients with SCC
3. All patients (ITT)

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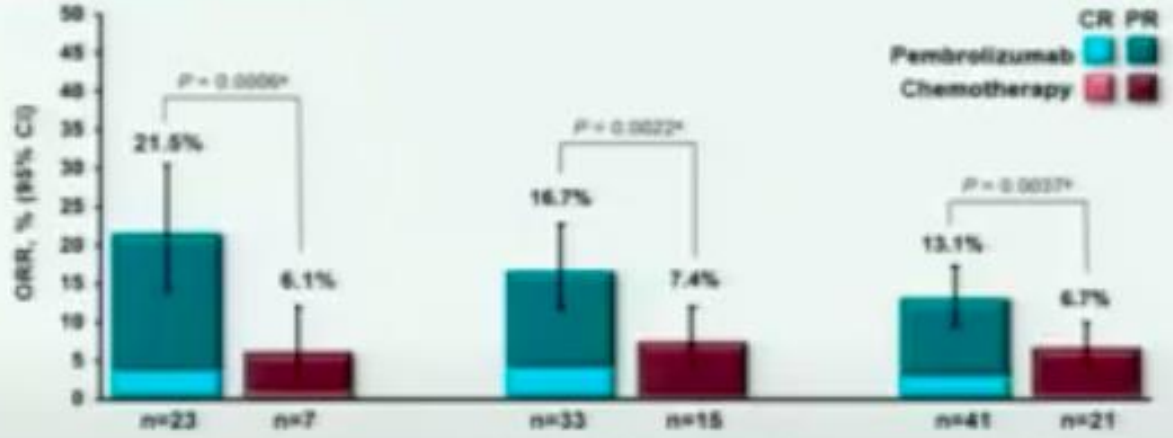
병 조절 과 기간

(RECIST v1.1, BICR)



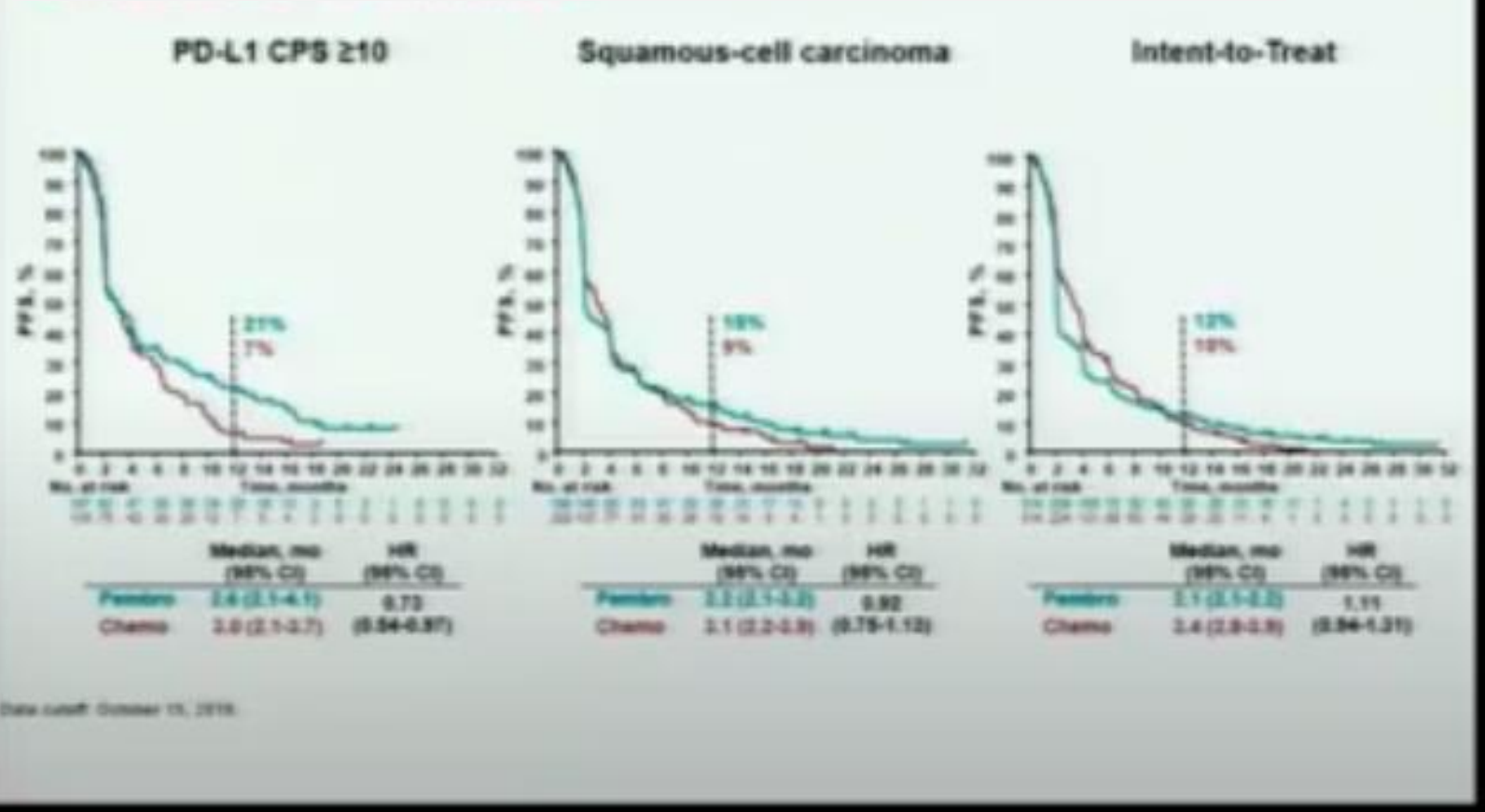
Duration	Median, mo (range)	≥ 6 mo, %
Pembro	9.3 (2.1+ to 22.6+)	77
Chemo	7.7 (4.2 to 16.8+)	57

Duration	Median, mo (range)	≥ 6 mo, %
Pembro	8.8 (2.1+ to 26.8+)	68
Chemo	10.7 (2.1+ to 16.8+)	79

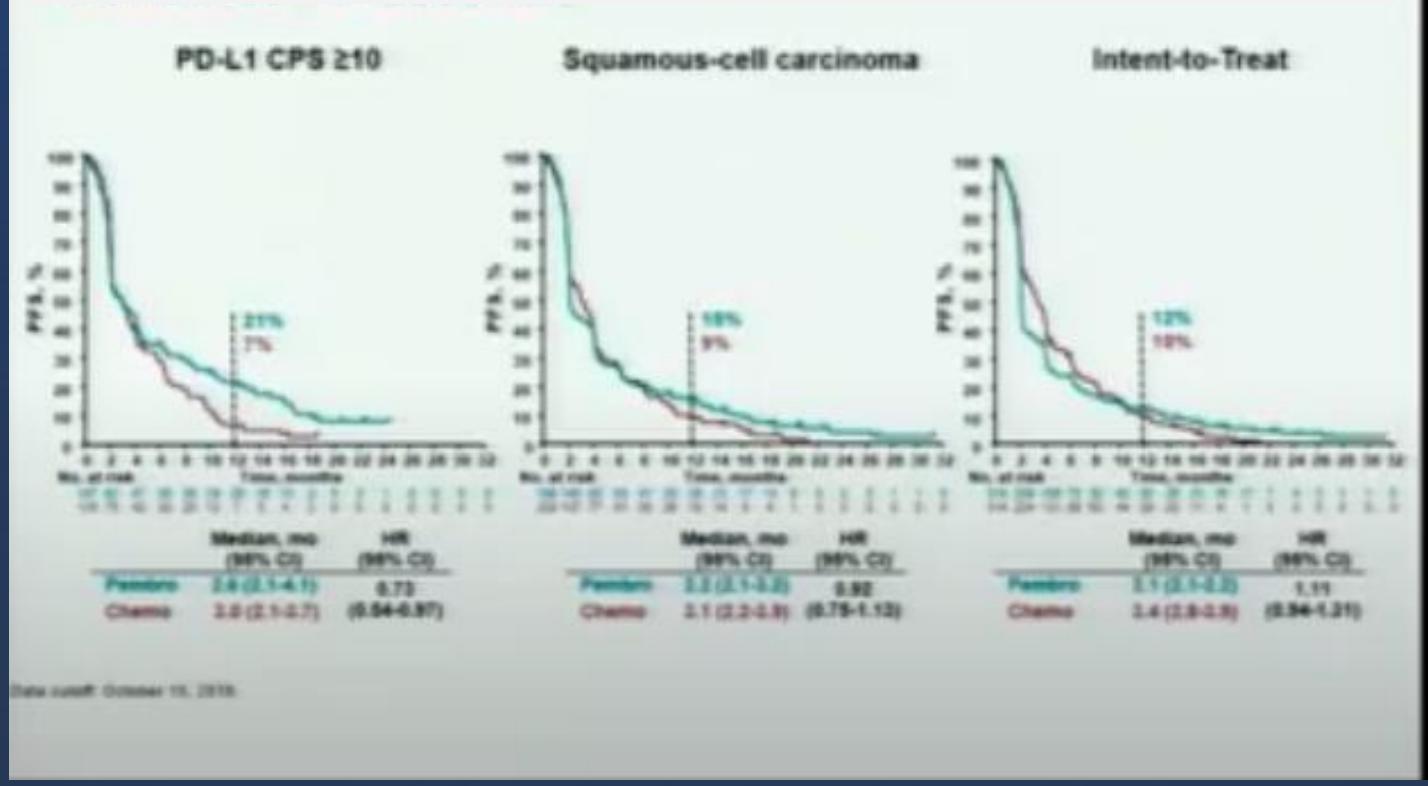
Duration	Median, mo (range)	≥ 6 mo, %
Pembro	8.8 (2.1+ to 26.8+)	72
Chemo	10.7 (1.8+ to 16.8+)	62

*Binomial, one-sided.
Data cutoff: October 15, 2016.

암 조절


PD-L1 CPS ≥10
Squamous-cell carcinoma
Intent-to-Treat
PFS, %
21%
7%
10%
9%
12%
10%
Median, mo (95% CI)
HR (95% CI)
Pembro
Chemo
0.73
(0.54-0.97)
0.92
(0.75-1.12)
1.11
(0.94-1.31)

암 조절


PD-L1 CPS ≥10
Squamous-cell carcinoma
Intent-to-Treat
PFS, %
Time, months
No. at risk
21%
7%
18%
9%
12%
10%
Median, mo (95% CI)
HR (95% CI)
Pembro
Chemo
0.73
(0.54-0.97)
0.92
(0.75-1.13)
1.11
(0.94-1.31)

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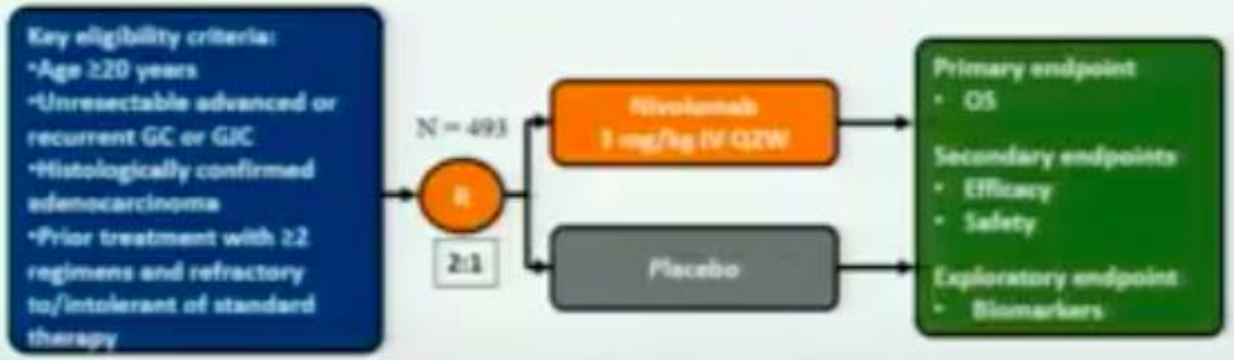
오노-4538-12 : 재발된 식도암에서 3상 니보루맙 대 위약

Study Design and Endpoints

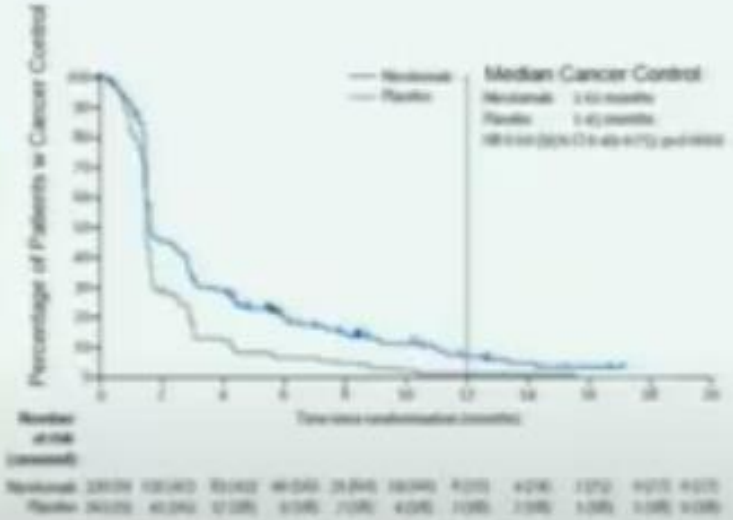


- Stratification based on:
  - Country (Japan vs Korea vs Taiwan)
  - ECOG PS (0 vs 1)
  - Number of organs with metastases (<2 vs ≥2)
- Patients were permitted to continue treatment beyond initial RECIST v1.1-defined disease progression as assessed by the investigator if receiving clinical benefit and tolerating study drug.

Kang YK et al. Lancet 2017 Dec 2;390(10111):2461-2471

오노-4538-12 : 반응 과 조절

	Nivolumab (n=268)
Objective response(%)	30 (33.2%; 27.7-43.4)
Time to confirmed response (range), months	1.61 (1.4-3.0)
Duration of confirmed response (95% CI), months	9.53 (5.14-9.82)



Cancer Control	Nivolumab (n=268)	Placebo (n=131)
6 months	20.2% (15.7-25.1)	6.8% (3.3-11.8)

Kang YK et al. Lancet 2017 Dec 2;390(10111):2461-2471

키노트 -059 : 진행성 위암 혹은 위접합암에서 2상 펨브로리추맙

Primary end point: ORR per RECIST v1.1 by central review

Fuchs CS et al. JAMA Oncol 2018;4(5):e180013

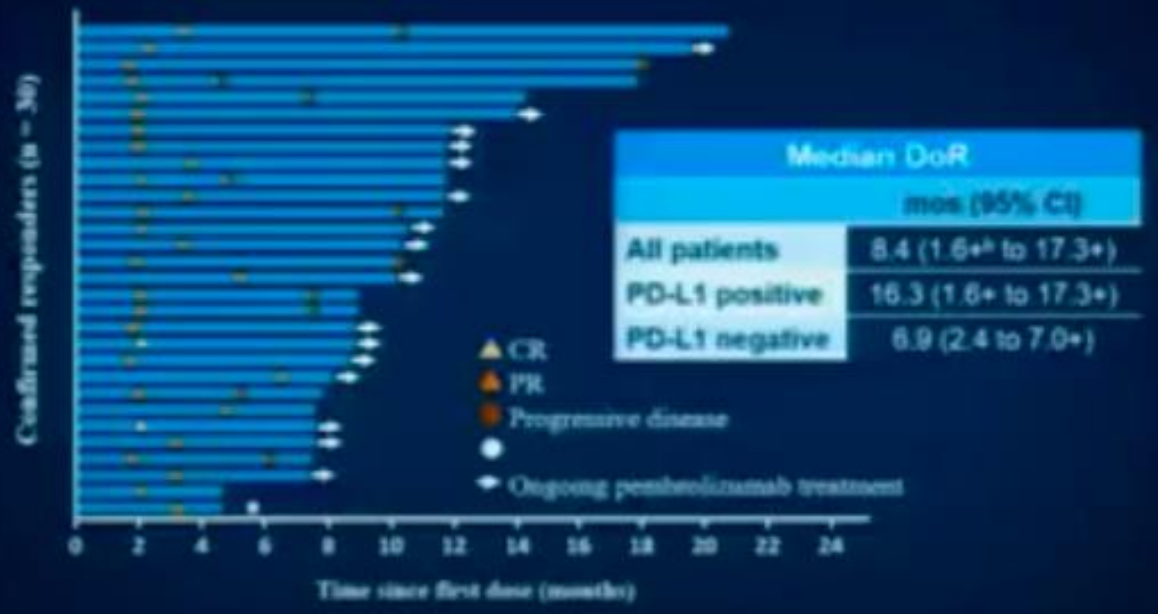
코호트 1 : PD-L1 와 MSI 발현에 따른 반응

Response*	PD-L1 Positive (n = 148)		PD-L1 Negative (n = 109)	
	%	95% CI	%	95% CI
Major	15.5	10.1–22.4	6.4	2.6–12.8
Complete	2.0	0.4–5.8	2.8	0.6–7.8
Partial	13.5	8.5–20.1	3.7	1.0–9.1
Dz Control	33.1	25.6–41.3	19.3	12.3–27.9

Response*	MSI-High (n = 7)		Not MSI-High (n = 167)	
	%	95% CI	%	95% CI
Major	57.1	18.4–90.1	9.0	5.1–14.4
Complete	14.3	0.4–57.9	2.4	0.7–6.0
Partial	42.9	9.9–81.6	6.6	3.3–11.5
Dz Control	71.4	29.0–96.3	22.2	16.1–29.2

Fuchs CS et al. JAMA Oncol 2018;4(5):e180013

코호트 1 : 치료 노출과 반응 기간



Median DoR	
	mos (95% CI)
All patients	8.4 (1.6+[b] to 17.3+)
PD-L1 positive	16.3 (1.6+ to 17.3+)
PD-L1 negative	6.9 (2.4 to 7.0+)

[a]Patients with measurable disease per RECIST v1.1 by central review at baseline who had ≥1 post-baseline assessment were included (n = 30). Bar length indicates time to last imaging assessment. [b]No progressive disease at last disease assessment.
Data cutoff on January 16, 2017.

Fuchs CS et al. JAMA Oncol 2018;4(5):e180013

2상: 키노트 - 180

Participants:

121 patients with advanced, metastatic esophageal cancer, 2 or more prior chemotherapy regimens

Intervention:

Pembrolizumab 200 mg intravenously every 3 weeks

More than 50% shrinkage of tumor burden (Major Response):

10% of all patients, lasting for 2 - 15+ months

14% of patients with squamous cell carcinoma

5% of patients with adenocarcinoma

14% of patients with PD-L1-positive tumors

6% of patients with PD-L1-negative tumors

Safety:

Overall, 12% of patients had severe side effects. Only 4% of patients discontinued due to severe side effects.

There was one pembrolizumab-related death from pneumonitis.

테그스:

Patients with mGC
(including GEJ cancer)
- ≥2 prior regimens:
  - Fluoropyrimidine
  - Platinum
  - Taxane and/or irinotecan
  - HER2 inhibitor, *if available*, for HER2+ disease
  - Refractory to/intolerant of last prior therapy
- ECOG PS of 0 or 1
- Age ≥18 y (≥20 y in Japan)

Target sample size: 500

→ R 2:1

FTD/TPI (TAS-102) + BSC (n=337)
35 mg/m² BID orally on days 1–5 and 8–12 of each 28-day cycle

Placebo + BSC (n=170)
BID orally on days 1–5 and 8–12 of each 28-day cycle

End points
- Primary:
  - OS
- Key secondary:
  - PFS, safety
- Other secondary:
  - ORR
  - DCR
  - QOL
  - Time to ECOG PS ≥2

- Treatment until progression, intolerable toxicity, or patient withdrawal
- Multicenter, randomized, double-blind, placebo-controlled, phase III study
  - Stratification: ECOG PS (0 vs 1), region (Japan vs ROW), prior ramucirumab (yes vs no)
  - Sites: 18 countries, 110 sites; enrollment: February 2016 – January 2018
  - Data cutoff date: March 31, 2018
  - Target 384 events allowed detection of HR for death of 0.70 with 90% power at 1-sided type 1 error of 0.025

BID, twice daily; BSC, best supportive care; ECOG PS, Eastern Cooperative Oncology Group performance status; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; ORR, overall response rate; PFS, progression-free survival; QOL, quality of life; R2:1, ratio of randomization; NCT02314481

Tabernero et al. ESMO GI 2018

40

이 결과들로부터의 결론

전이성 식도암:

모든 환자들은 처음부터 MMR, HER2, CPS 체크

일차 라인: FOLFOX 이 지금 기본 치료. FOLFIRI 이 대체 가능. 에피루비신은 독성이 있고 별 혜택을 못 줌. 트라추추맙이 HER2/neu 3+ 나 2+/FISH+ 에 더해져야 함. MSI-H 나 CPS가 10 이상인 환자는 펨브로리추맙을 고려.

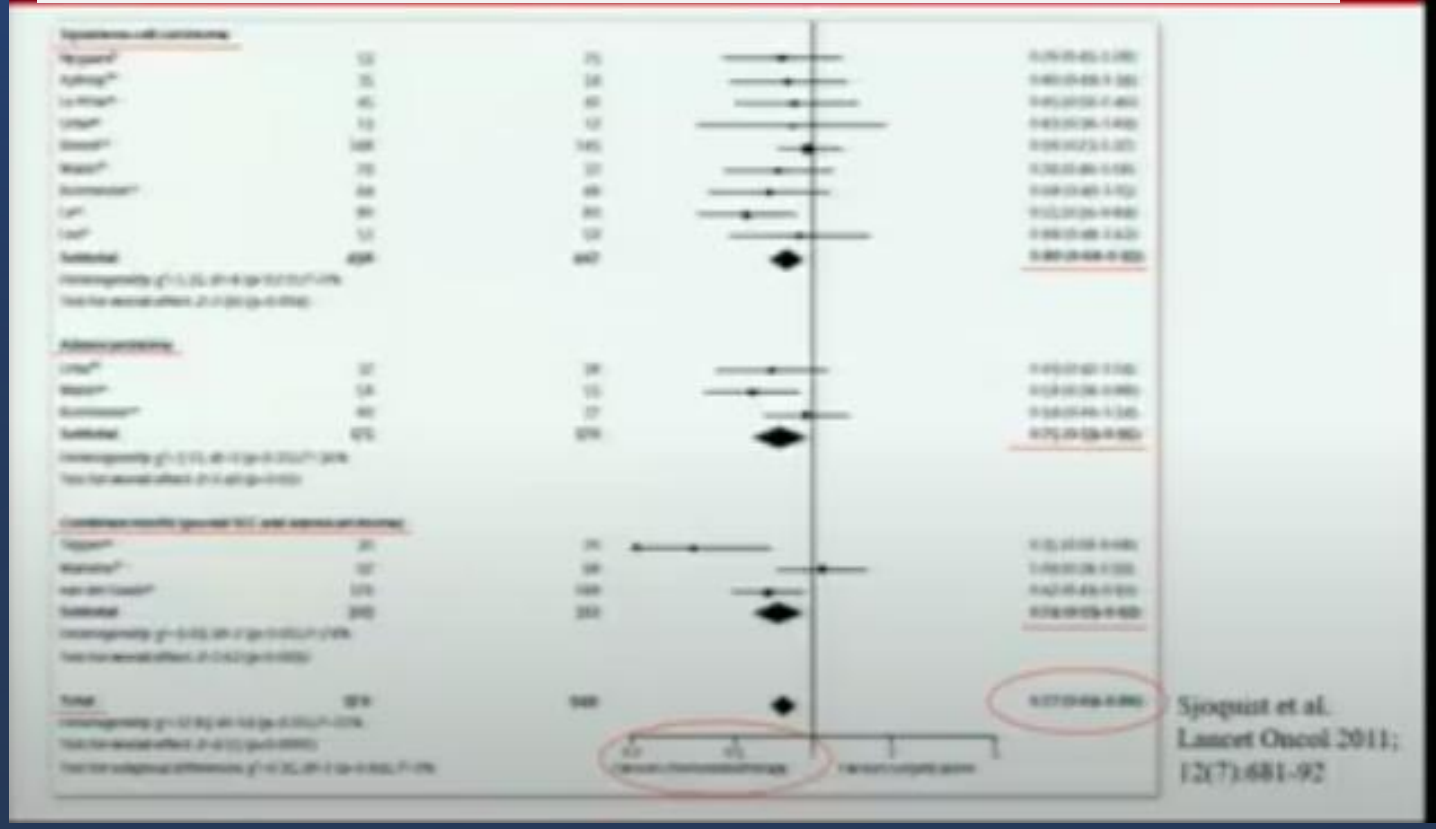
일차 라인: 펙시탁실 과 아무시루맙 이 대부분의 아데노카시노마 환자에 가장 좋은 선택임. 스퀘머스 셀 카시노마 와 CPS가 10 이상인 환자는 펨브로리추맙을 고려.

삼차 라인: 체크포인트 억제제는 모든 양성 환자에게 주어야 한다. 아니면, 아데노카시노마는 FTD/TPI 을 받아야 한다. 스퀘머스 셀 카시노마는 텍산을 받아야 한다.

지역에 있는 식도암

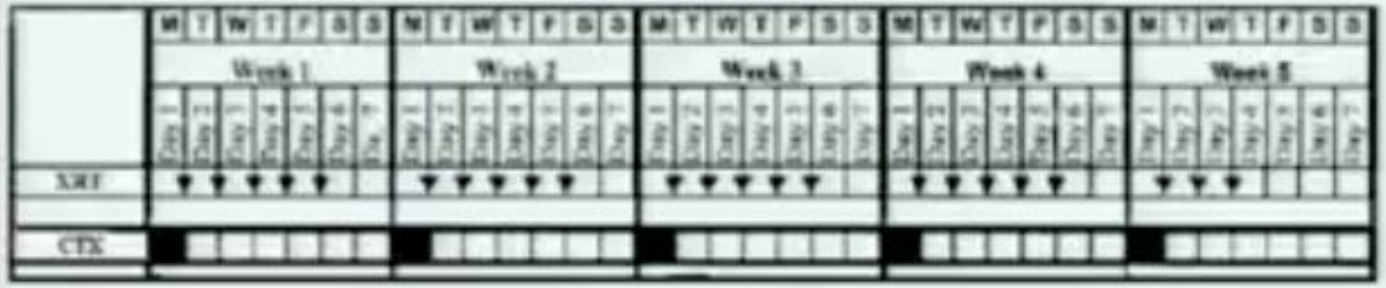
니오 어드저번트
화학 방사선 요법이
수술의 결과를
개선할까?

니오 어드저번트 화학 방사선 요법과 수술 만의 모든 이유의 사망율 예측값



Sjoquist et al.
Lancet Oncol 2011;
12(7):681-92

크로스 연구



- Chemoradiotherapy regimen:
  - Paclitaxel 50mg/m^2 + Carboplatin AUC=2 on days 1, 8, 15, 22 and 29
  - Concurrent radiotherapy of 41.4 Gy in 23 fractions of 1.8 Gy
- Surgery within 6 weeks after completion of chemoradiotherapy (THE/TTE)

Van Hagen et al. N Engl J Med 2012;366:2074-84.

크로스 연구: 전체 생존율

No residual cancer after Chemo+RT: 29%.

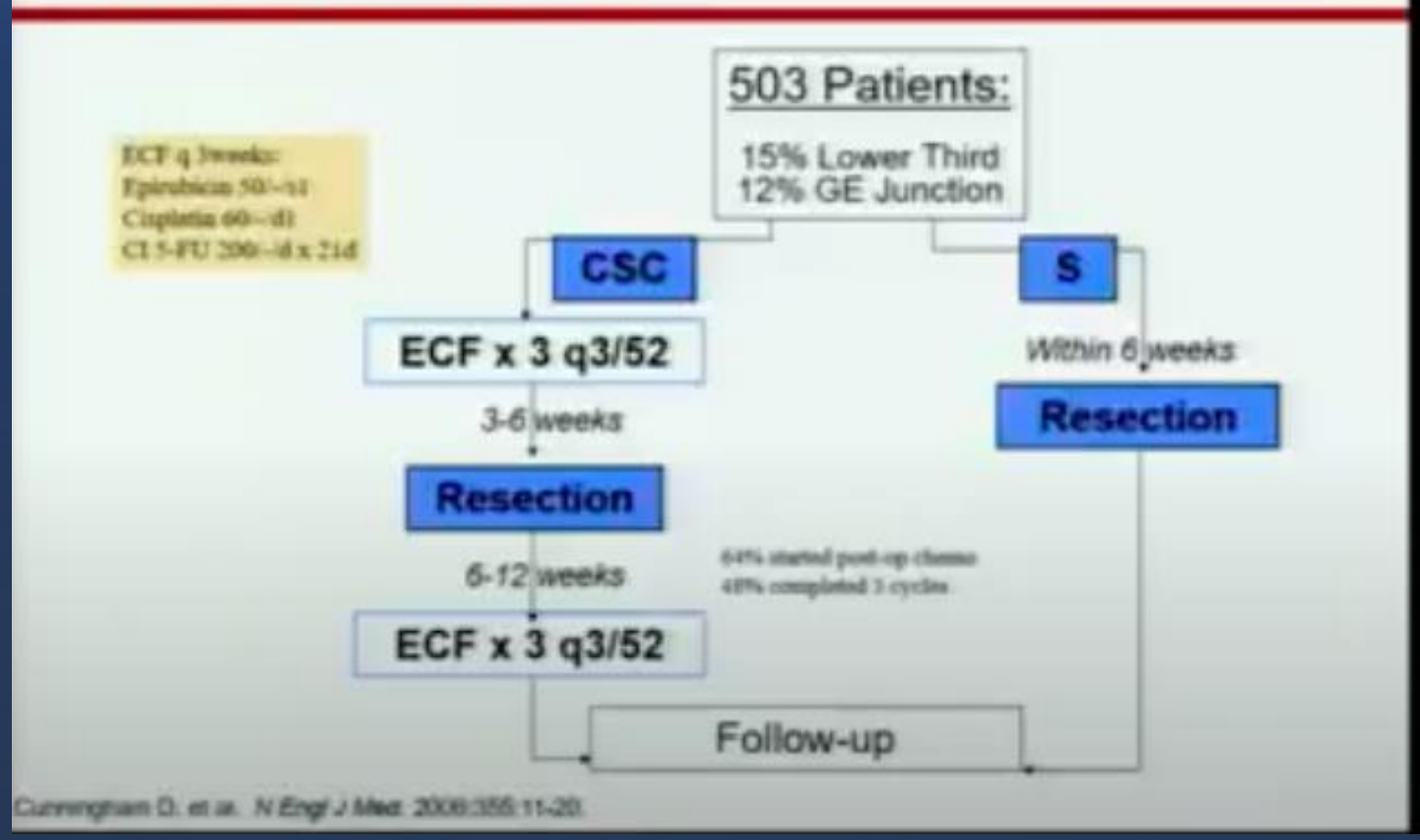
Median Survival was doubled with Chemo+ RT over surgery alone.

Median Survival was nearly quadrupled for patients with squamous cell carcinoma.

Median Survival was improved by 66% in adenocarcinoma patients.

Van Hagen et al. N Engl J Med 2012;366:2074-84.
Shapiro et al. Lancet Oncol 2015; 16: 1090-98

매직 연구:


503 Patients:
15% Lower Third
12% GE Junction
CSC
S
ECF x 3 q3/52
3-6 weeks
Resection
6-12 weeks
ECF x 3 q3/52
Within 6 weeks
Resection
Follow-up
Cunningham D. et al. N Engl J Med. 2006;355:11-20.

Dream
Foundation
Curing Stomach
Dana-Farber

매직 연구: 생존율

2년 생존율: 수술만 했을 때와 수술 전 후 화학요법 하면 23% 향상

5년 생존율: 수술만 했을 때와 수술 전 후 화학요법 하면 57% 향상

중간 생존율: 수술만 했을 때와 비교해서 매직에서는 9개월 향상

Cunningham D, et al.
N Engl J Med 2006;355:11-20

FLOT4 연구 디자인

Randomized, multicenter, investigator-initiated, phase II/III study

- Gastric cancer or adenocarcinoma of the gastro-esophageal junction type I-III
- Medically and technically operable
- cT2-4/cN-any/cM0 or cT-any/cN+/cM0

STRATIFICATION

R

n=716

FLOT x4 - RESECTION - FLOT x4

FLOT: docetaxel 50mg/m2, d1; 5-FU 2600 mg/m², d1, leucovorin 200 mg/m², d1; cisplatin 85 mg/m², d1, every two weeks

ECF/ECX x3 - RESECTION - ECF/ECX x3

ECF/ECX: Epirubicin 50 mg/m2, d1; cisplatin 60 mg/m², d1; 5-FU 200 mg/m² (or capecitabine 1250 mg/m² p.o. divided into two doses d1-d21), every three weeks

Stratification: ECOG (0 or 1 vs. 2), location of primary (GEJ type I vs. type II/III vs. stomach), age (< 60 vs. 60-69 vs. ≥70 years) and nodal status (cN+ vs. cN-)

Presented by: Sarah-Eddin Al-Batran

ASCO ANNUAL MEETING '17 #ASCO17

FLOT4 연구 : 생존율

2년 생존율: 수술 전 후 메직에 비해 수술 전 후 FLOT 하면 15% 향상

5년 생존율: 수술 전 후 메직에 비해 수술 전 후 FLOT 하면 25% 향상

중간 생존율: 수술 전 후 메직에 비해 수술 전 후 FLOT 하면 15달 향상

Cunningham D, et al.
N Engl J Med 2006;355:11-20.

결론

지역 위암:

수술 후 5-FU 기반으로 한 화학 방사선 요법은 림프 노드 양성이거나 근육 침투한 경우의 기준 케어 방법임.

수술 전 후 FLOT 하면 메직에 비해 향상되고 퍼퍼먼스 상태좋은 환자에게 고려되어야.

감사합니다