Debbie's Dream Foundation
CURING STOMACH CANCER

제 8차 연례 위암 교육 심포지움

위암: 유전학과 표적치료의 시대

데이비드 일슨 박사

데비의 꿈 재단 의료 자문단

메모리얼 슬론 케터링 암센타 의사

위암.위식도암 미 발병률 2018

- 미국 43,530 새 케이스 (2.7% 미국 캐나다)
- 위암 26,240 (60%)
- 위식도암 17,290 (40%)
- 위암 발병률 줄어듬
- 위식도암 발병률 늘어남
- 생존률 좋아짐
- 1975-77, 1984-86, 1999-2006
  - 위암 : 16% ➔ 18% ➔ 27%
  - 위식도암 : 5% ➔ 10% ➔ 19%

Siegel et al, CA 68: 7-30; 2018

위암 국제적 발병률 : 2012

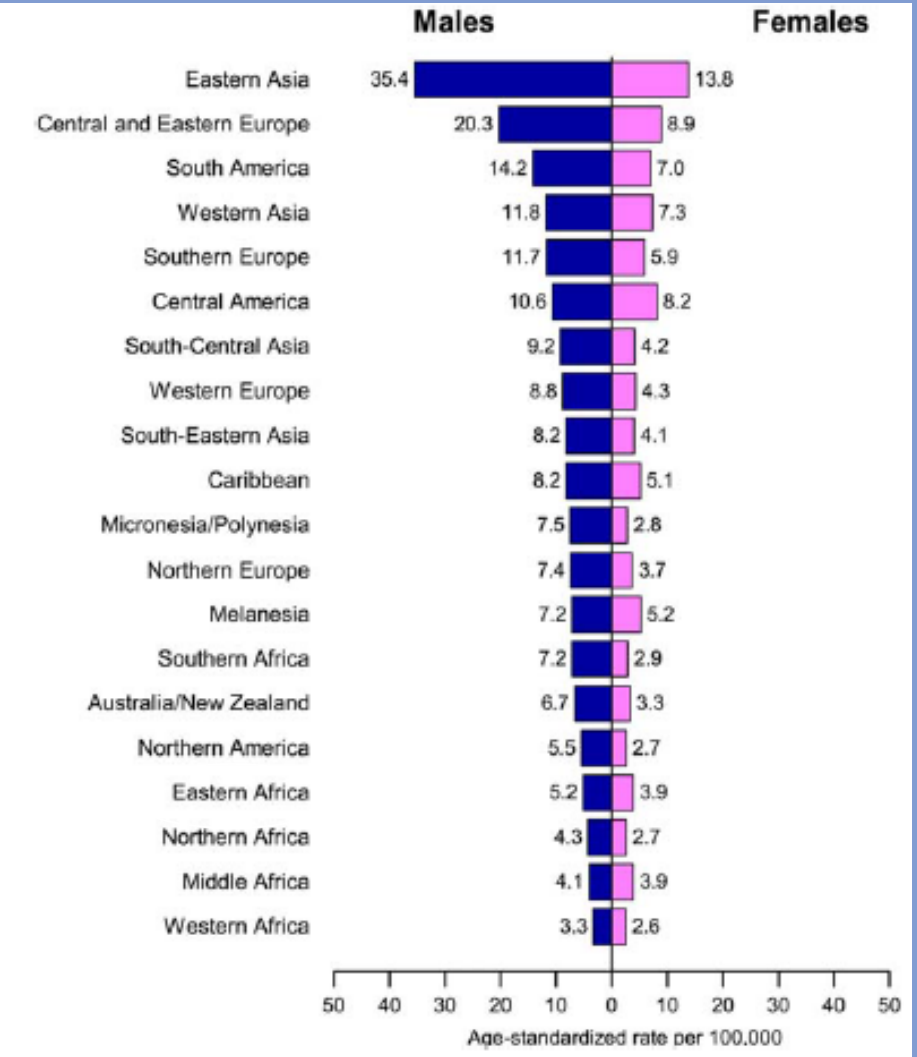


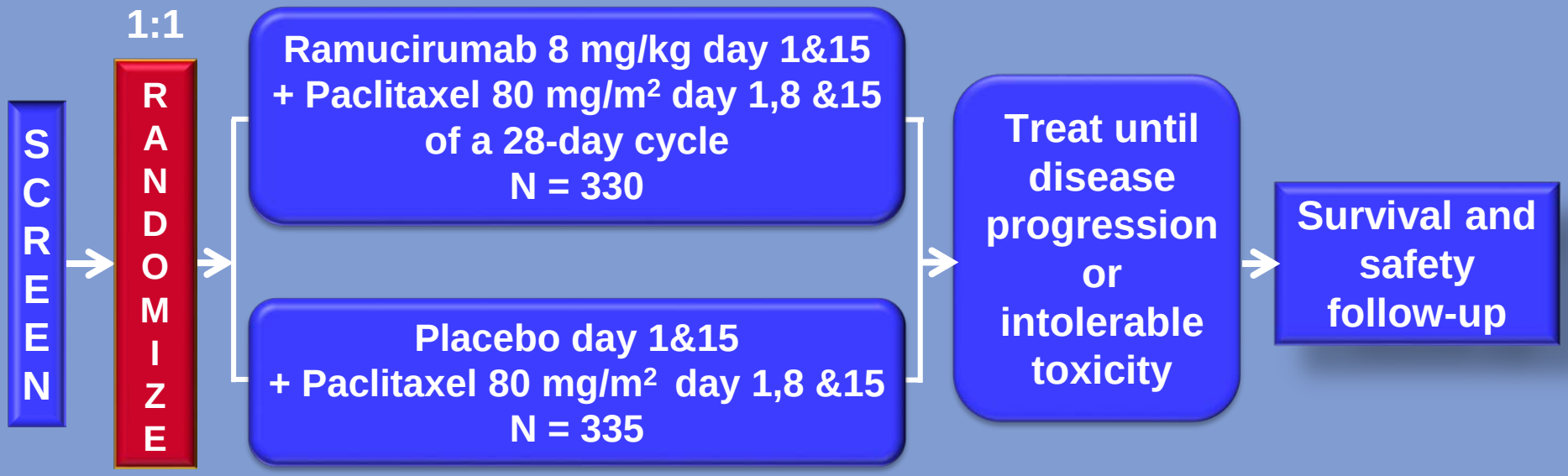
FIGURE 8. Stomach Cancer Incidence Rates by Sex and World Area.

Torre L, Bray F, Siegel R et al. CA Cancer J Clin 65: 87-108; 2015

위식도암 : 전이

- **대장암 화학요법 부작용 적음 : 플폭스, 폴피리, 제록스**
- **세번째 약 더함 :**
  - 에피루비신 (E+CF), 도시텍실 (DCF or FLOT)
  - 10% 반응 증가
  - 1 달 생존률 증가
  - 부작용 증가
  - 에피루비신 는 혜택 없는 듯

VEGFr2: 레인보우 : 2차 라인



- **Important inclusion criteria:**
  - Metastatic or loc. adv. unresectable gastric or GEJ* adenocarcinoma
  - Progression after 1st line platinum/fluoropyrimidine based chemotherapy
- **Stratification factors:**
  - Geographic region,
  - Measurable vs non-measurable disease,
  - Time to progression on 1st line therapy (< 6 mos vs. ≥ 6 mos)

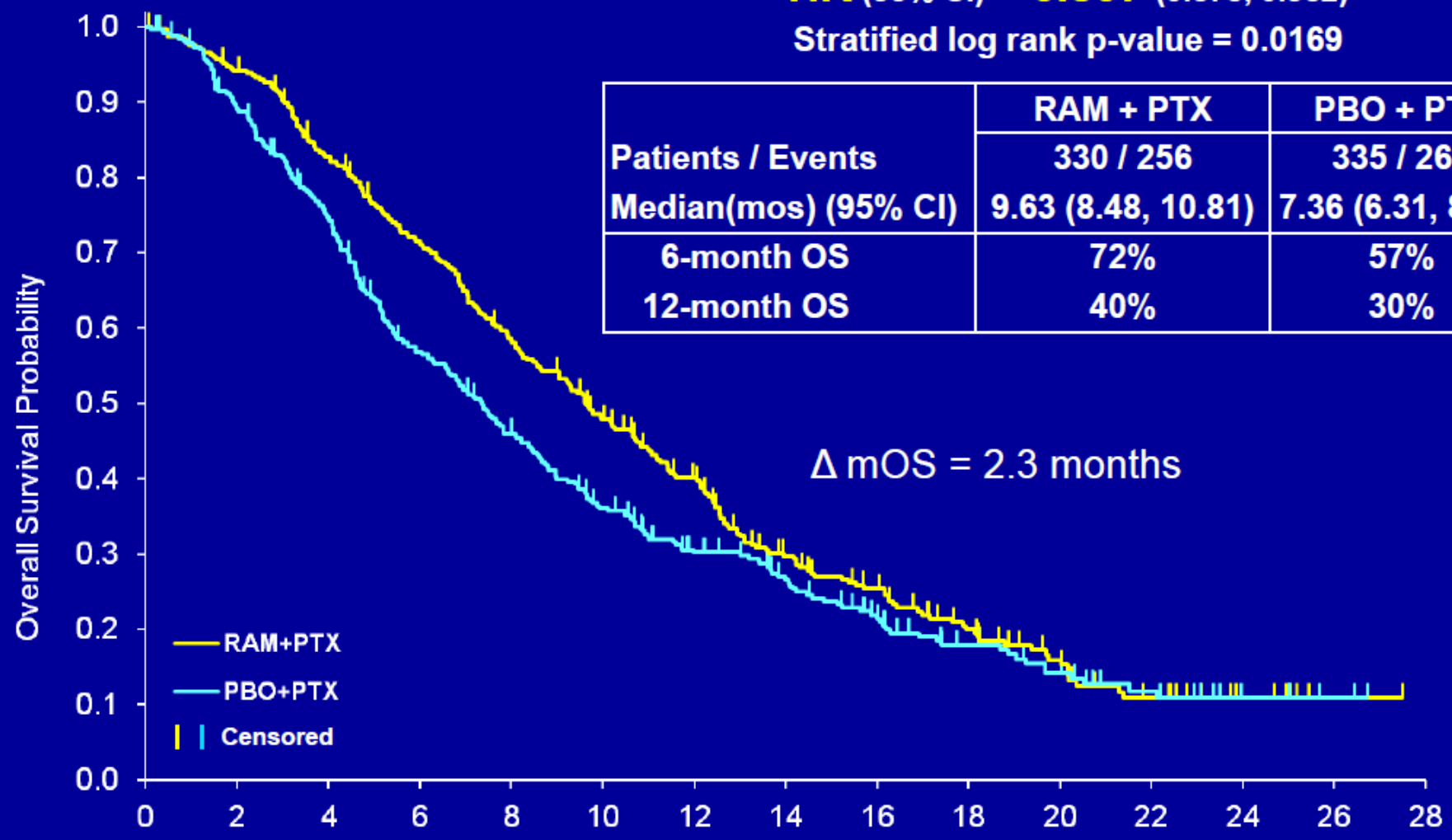
Wilke Lancet Oncol 15: 1224; 2014

레인보우: 생존률

HR (95% CI) = **0.807** (0.678, 0.962)

Stratified log rank p-value = 0.0169

	RAM + PTX	PBO + PTX
Patients / Events	330 / 256	335 / 260
Median(mos) (95% CI)	9.63 (8.48, 10.81)	7.36 (6.31, 8.38)
6-month OS	72%	57%
12-month OS	40%	30%



No. at risk

RAM + PTX	330	308	267	228	185	148	116	78	60	41	24	13	6	1	0
PBO + PTX	335	294	241	180	143	109	81	64	47	30	22	13	5	2	0

표적치료

- 기존 화학치료는 혜택이 제한적
- 반응률 40%, 생존률 1 년 이하
- 표적치료약 : 암의 특정 기작 막음
  - 리셉터 타겟 항원 (트라츄즈맙, 라무기루맙)
  - 타이로신 카이네제 억제제
  - 하위 기작
- 유전자 연구: 새 약 혹은 기존의 약 타겟을 밝힘 to

위암의 유전자 프로파일링? 어떻게 무슨 방법으로?

- 조직학적 염색으로 단백질 발현 : 조직 염색
  - 모든 환자 다 HER2, PDL-1 조직 염색 필요
- 유전자 카피 넘버 결정 위해 FISH
  - 조직학적 염색이 불확실 시 HER2 스크린
- 돌연변이, 증폭은 전체 엑솜 시퀀싱 으로
- 유전자 발현 RNA 정도로
- 유전자 발현 DNA 에레이로

TCGA: 위암

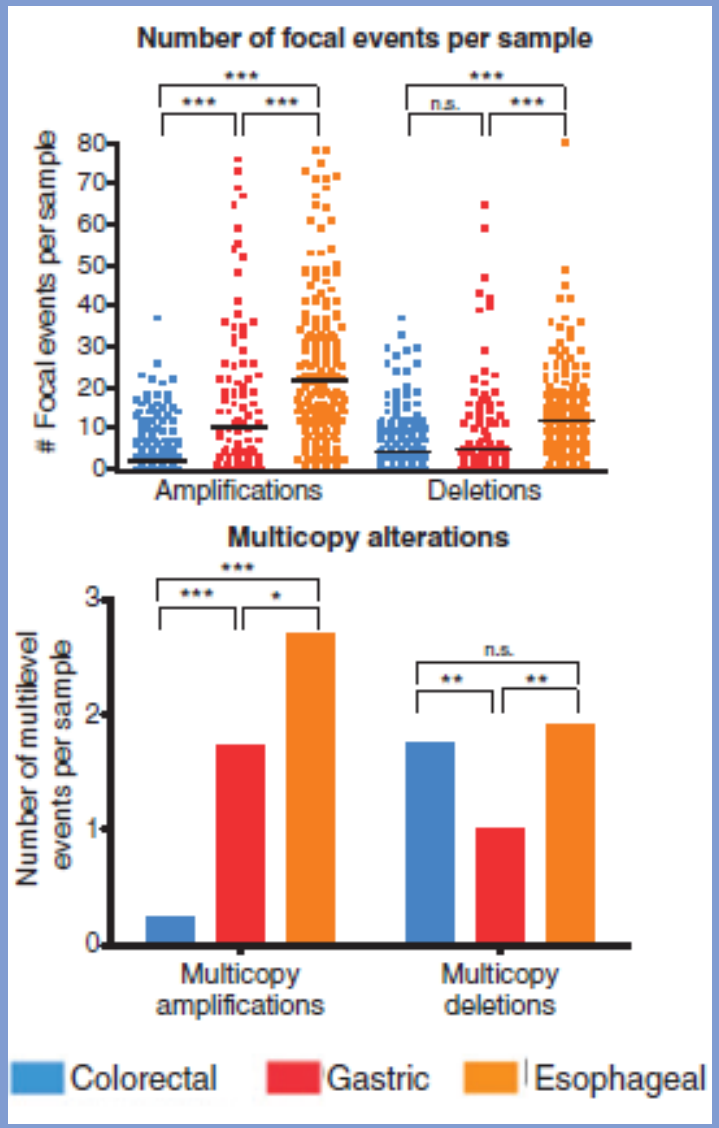
- **295 개의 급속 냉동한 위암 위식도암**
- **6개의 방법으로 연구**
  - **카피 넘버 결정**
  - **전체 엑솜 시퀀싱**
  - DNA 메틀화
  - mRNA, microRNA **시퀀싱**
  - 단백질 어레이

Nature Genetics 24: 2903; 2014

유전자 증폭은 위식도암에 흔함 : TCGA

296개 위식도암, 190 개 대장암

- 유전자 증폭
- 37%의 위식도암
  - EGFR
  - MET
  - FGFR1-2
  - HER2
  - RAS
  - 표적치료: 타겟으로 리셉터, 타이로신 카이네제

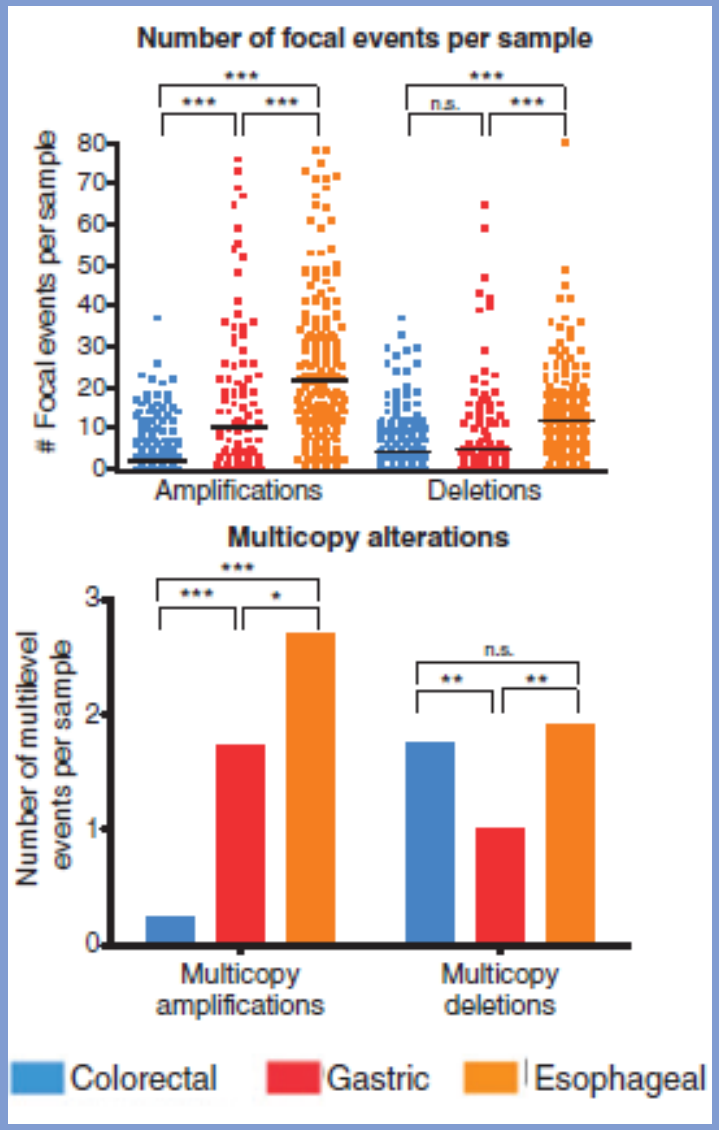


Dulak AM et al Can Res 72: 4383; 2012

유전자 증폭은 식도암에 더욱 흔함

296개 위식도암, 190 개 대장암

- 유전자 증폭
- 37%의 위식도암
  - EGFR: 실패
  - MET: 실패
  - FGFR1-2: 진행
  - HER2: ?
  - RAS
  - 표적치료: 타겟으로 리셉터, 타이로신 카이네제



Dulak AM et al Can Res 72: 4383; 2012

TCGA: 4개의 위암 유전학적 종류

- **유전학적으로 불안정 (50%)**
  - 95% 의 **식도암**
  - p53 **돌연변이,** HER2 **돌연변이**
  - **MSI 높음 (22%)**
- **유전학적으로 안정 (20%)**
  - 디퓨즈 암, CDH-1, RHOA **돌연변이**
- **엡스타인 바 바이러스 (9%)**
  - PD-L1 and 2 **증폭**

Nature Genetics 24: 2903; 2014

왜 유전자 프로파일링을 해야 하는가?

- **MSI 를 알아내기**
  - 유전자 불안정성을 알아내고자

- **타이로신 카이네제 유전자 증폭**
    - HER2
- **엡스타인 바 바이러스 높음**
  - PD-L1 and 2 **증폭** : 면역 치료에 효과 상승

- **연구 임상 시험 전, 스크린**

3상 임상 시험 EGFr: 실패

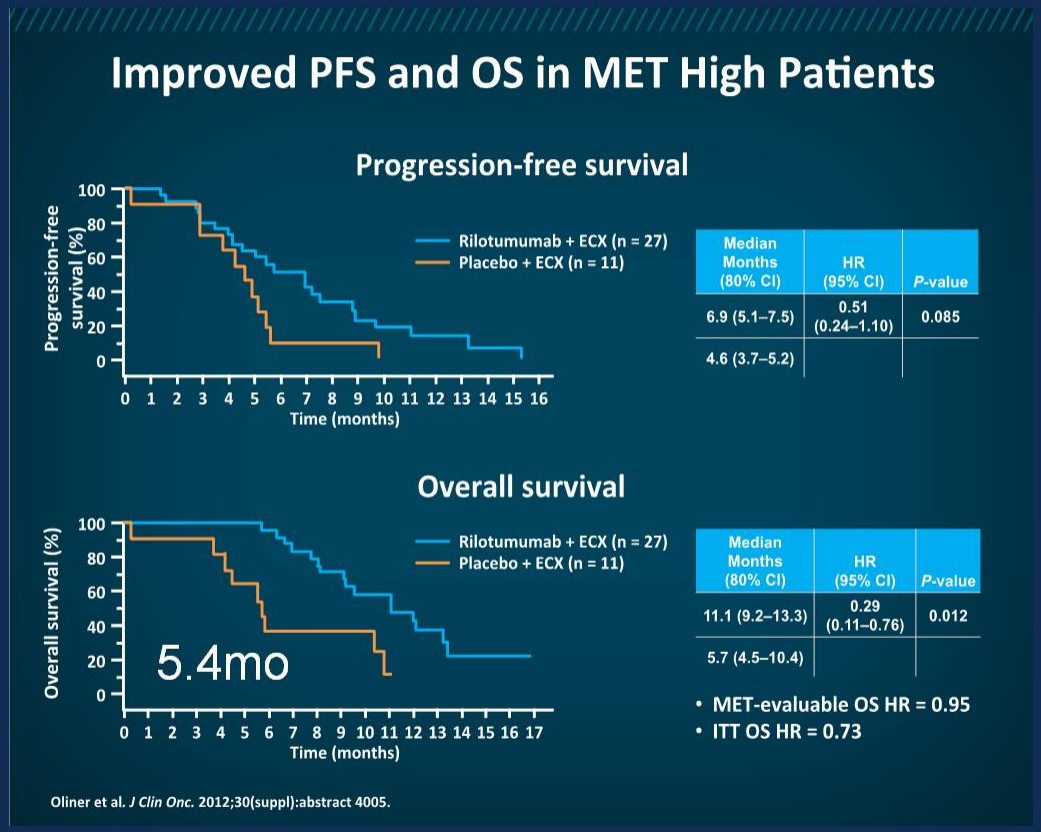
- **REAL 3: ECX + / - Panitumumab (U.K.)**
  - Negative: Panitumumab had inferior outcomes
- **EXPAND: Cape-Cis + / Cetuximab (E.U.)**
  - Negative: Cetuximab trended inferior
- **COG: BSC vs Gefitinib (U.K.): Negative**
- **Irinotecan + / - Nimotuzumab: Negative**

- **이 임상 시험들은 환자들을 바이오 마커로 고르지 않고 실시 - 위암 바이오 마커 아직 발견되지 않음**

Waddell T Lance Oncol 14: 481; 2013 Lordick F et al Lancet 14:490; 2013 Sutton JCO 30: 2012 (suppl 34 abstr 6)

MET 리셉터 억제제 : 리로투무맙, 오나츄즈맙

다른 3상 --- 위암에서 실패



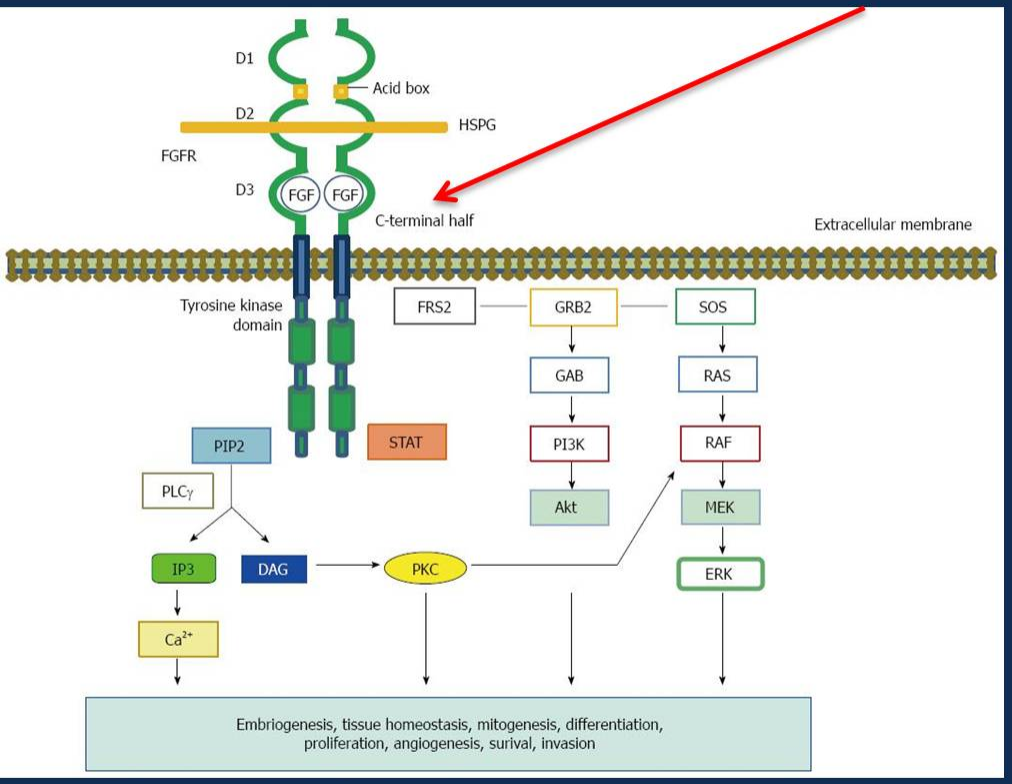
RILOMET-1: OS
Experimental: 9.6mo
Control Arm: 11.5mo
HR 1.37; p = 0.016

MetGastric: OS ITT
Experimental: 11.0mo
Control Arm: 11.3mo

MetGastric: OS MET2+/3+
Experimental: 11.0mo
Control Arm: 9.7mo
HR 0.64; p = 0.062

FGF 리셉터 타겟

FPA 144



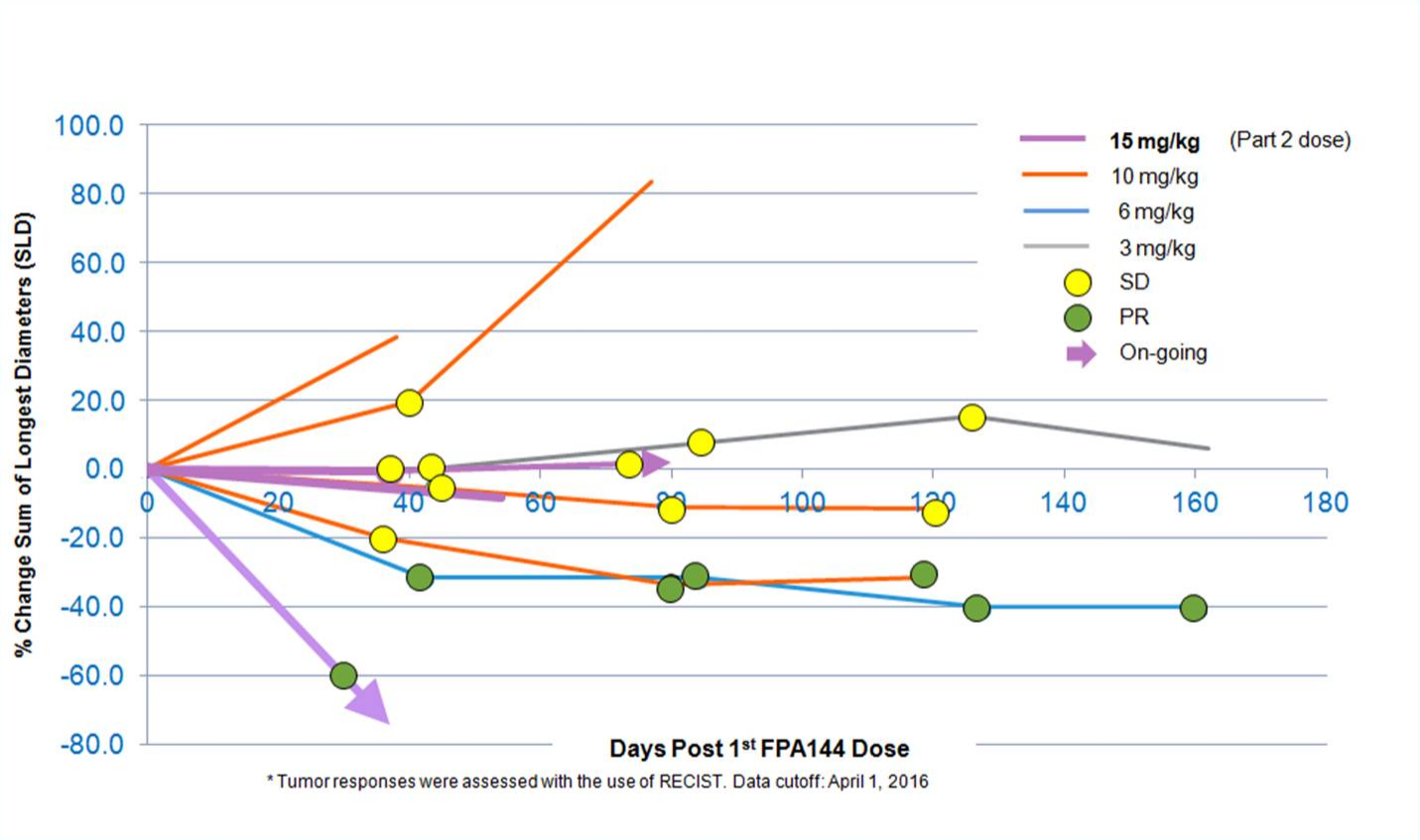
항체

FGF 리셉터에 붙음

NK 세포 끌어와서 ADCC 활성

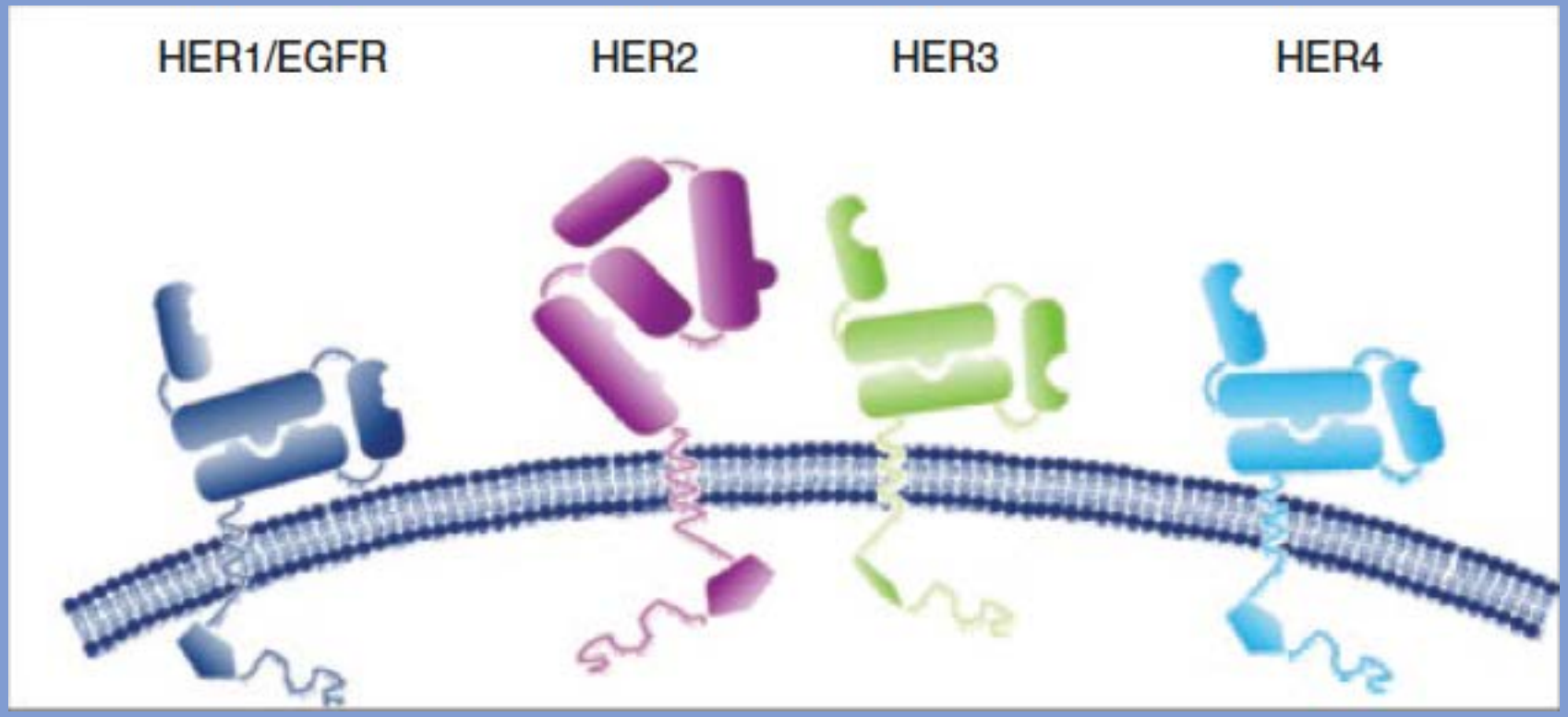
2-9% 위암만이 **FGF 리셉터가 증폭**

1상: FPA144에 반응도



HER2 타겟

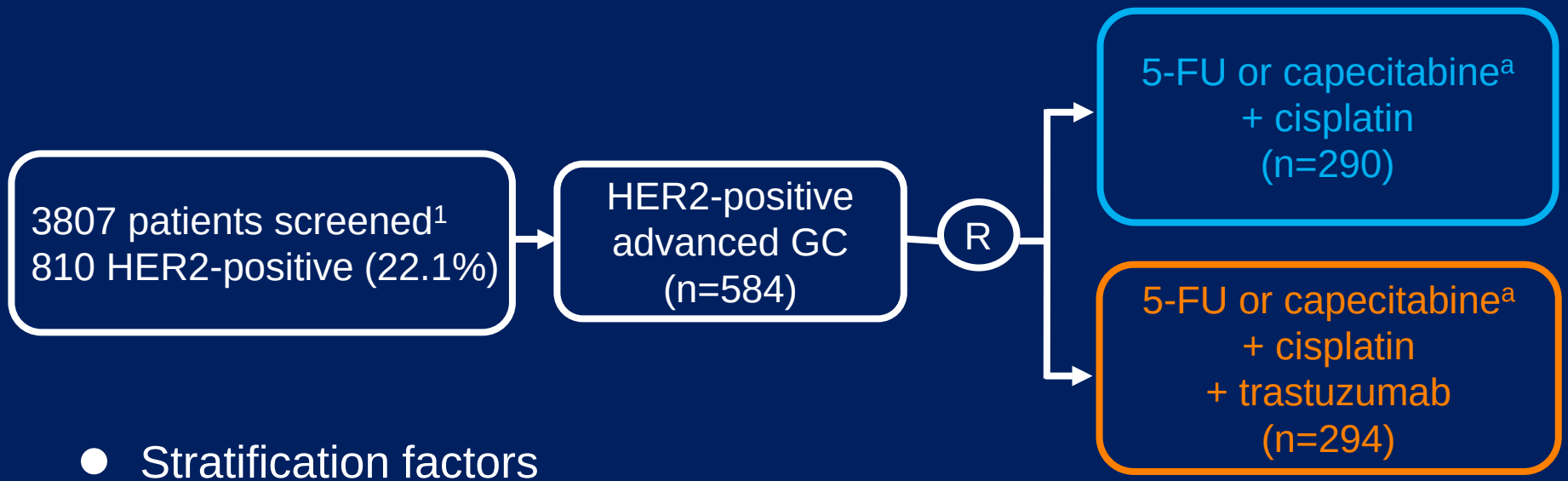
HER 리셉터 구조



Fine et al, 2009; Rowinsky, 2003; Yarden et al, 2001.

ToGA 임상 시험

3기, 무작위, 오픈 레이블, 국제적, 여러 센터

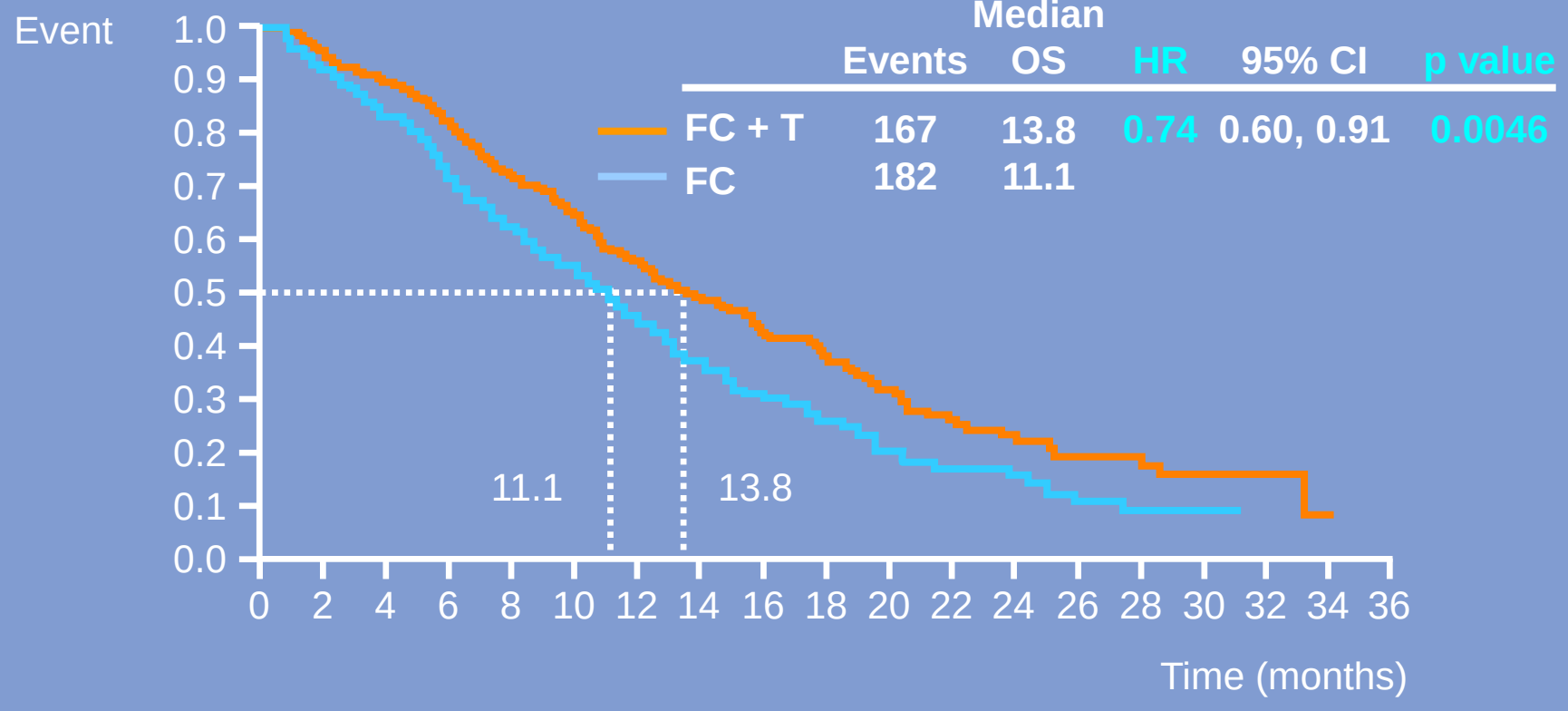


- Stratification factors
  - advanced vs metastatic
  - GC vs GEJ
  - measurable vs non-measurable
  - ECOG PS 0-1 vs 2
  - capecitabine vs 5-FU

Bang et al Lancet 376: 687-697; 2010

[a]Chosen at investigator's discretion
GEJ, gastroesophageal junction

1차 결과 : 생존률



	Events	Median OS	HR	95% CI	p value
FC + T	167	13.8	0.74	0.60, 0.91	0.0046
FC	182	11.1			

No. at risk																		
FC + T	294	277	246	209	173	147	113	90	71	56	43	30	21	13	12	6	4	1	0
FC	290	266	223	185	143	117	90	64	47	32	24	16	14	7	6	5	0	0	0

T, trastuzumab

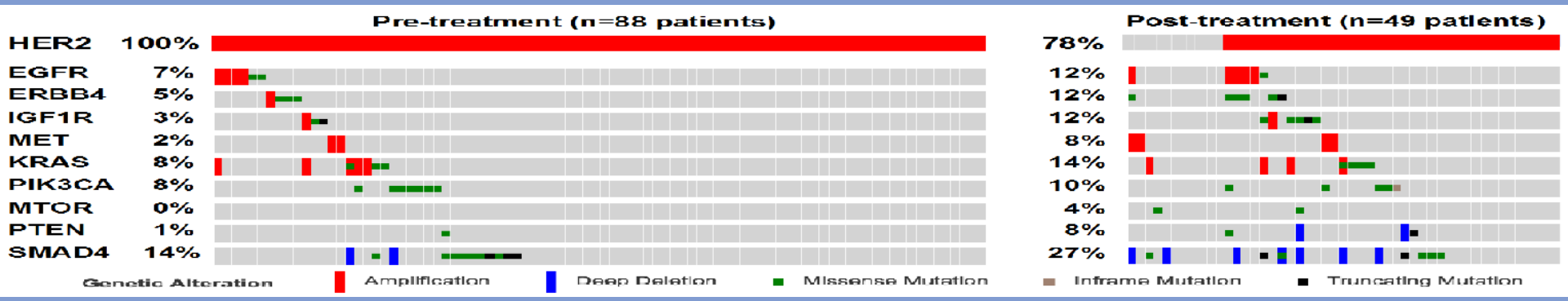
HER2 타겟 약 : 위식도암 은 유방암이 아님

- **트라츄츠맙 은 1차 라인 약 –약간의 효과**
- TOGA: Cape-Cis + **트라츄츠맙 효과**
- **1차 라인: 라무기루맙 (LOGIC), 퍼튜츄맙 (JACOB) 생존률 향상 실패**
- **1차 라인: 트라츄츠맙, 엠탄신 (TDM-1) 은 팍리탁실보다 낫지는 않음**
- **HER2 저항성**

Bang Lancet 376: 1302; 2010, Hecht JCO 34: 443; 2016, Tabernero Ann Oncol 28: 2017, Thuss-Patience Lancet Oncol 18: 640; 2017

HER2 저항성 : 획득성

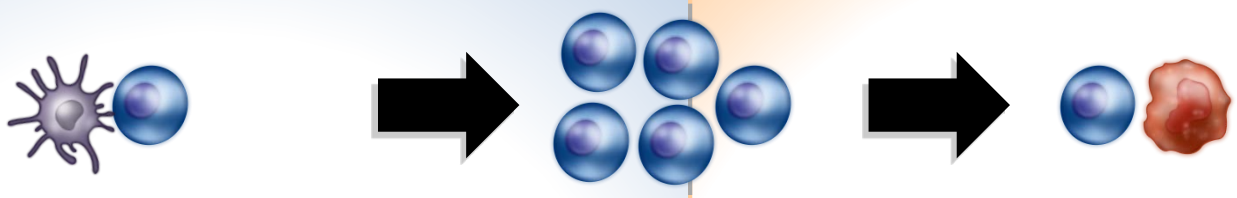
- **MSK: NGS IMPACT**
- **88 HER2+ patients: 57% Eso/GEJ and 43% gastric**
  - 49 pts post Trastuzumab
- **At progression**
  - 12/49 (24%) lost HER-2 expression (FISH and IHC)
  - Increase amplification/mutation in EGFR, ERBB4, IGF1R, MET
  - Increase amplification or mutation of SMAD4, KRAS, PIK3CA, PTEN, MTOR



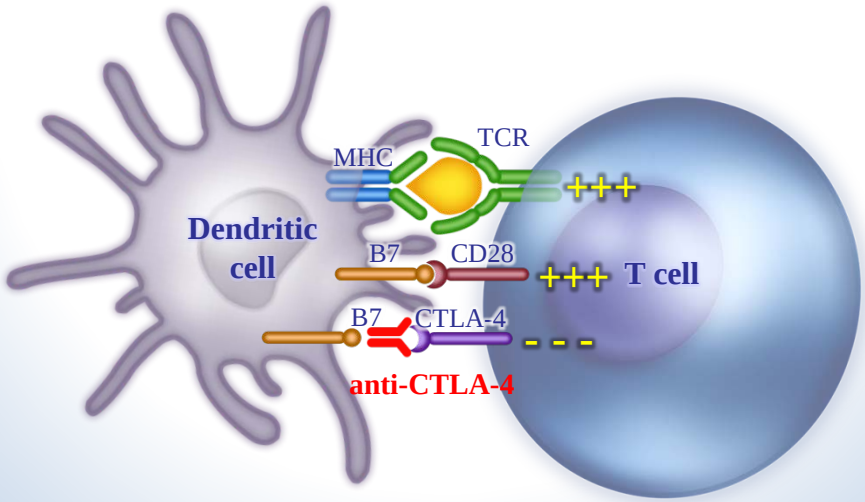
Janjigian JCO 34, 2016, abstract 11608

CTLA-4과 PD-1 억제

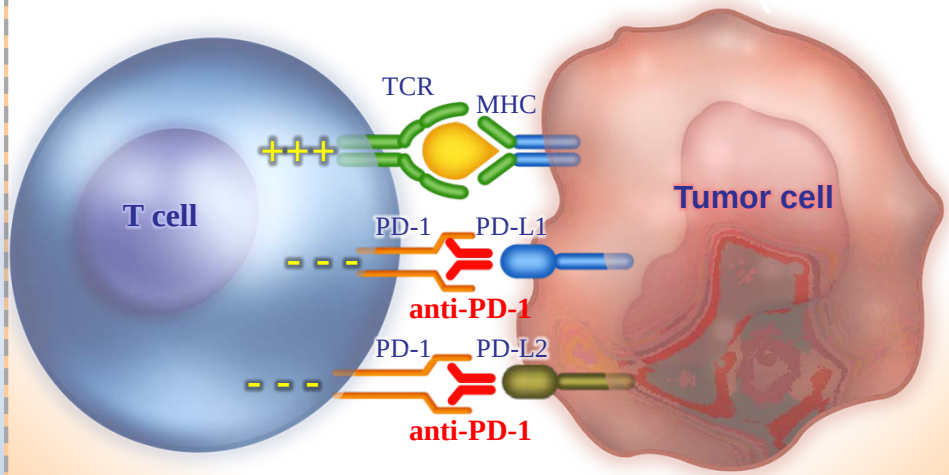
Tumor Microenvironment



Activation
(cytokines, lysis, proliferation,
migration to tumor)



CTLA-4 Blockade (ipilimumab)



PD-1 Blockade (nivolumab)

주요 면역치료 시험

- **키노트 059**
  - 재발 위암의 펌브로리츄맙 코호트 증폭
- **어트렉션 02 연구**
  - 재발 위암
  - 니보루맙 대 보조 케어 비교

관련 논문

KEYNOTE-059 Cohort 1: Efficacy and Safety of Pembrolizumab Monotherapy in Patients With Previously Treated Advanced Gastric Cancer

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반응률

Response in All Patients

Response[a]	N = 259	
	%	95% CI
ORR (CR + PR)	11.6	8.0-16.1
CR	2.3	0.9-5.0
PR	9.3	6.0-13.5
SD	16.2	11.9-21.3
PD	56.0	49.7-62.1
DCR[b]	27.0	21.7-32.9

- Median (range) follow-up: 5.8 months (0.5-21.6)

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[a]Only confirmed responses were included
[b]CR + PR + SD≥2 months
Data cutoff: January 16, 2017

PD-L1 발현과 반응률

Response by PD-L1 Expression

Response[a]	PD-L1 Positive (n = 148)		PD-L1 Negative (n = 109)	
	%	95% CI	%	95% CI
ORR	15.5	10.1-22.4	6.4	2.6-12.8
CR	2.0	0.4-5.8	2.8	0.6-7.8
PR	13.5	8.5-20.1	3.7	1.0-9.1
DCR[b]	33.1	25.6-41.3	19.3	12.3-27.9

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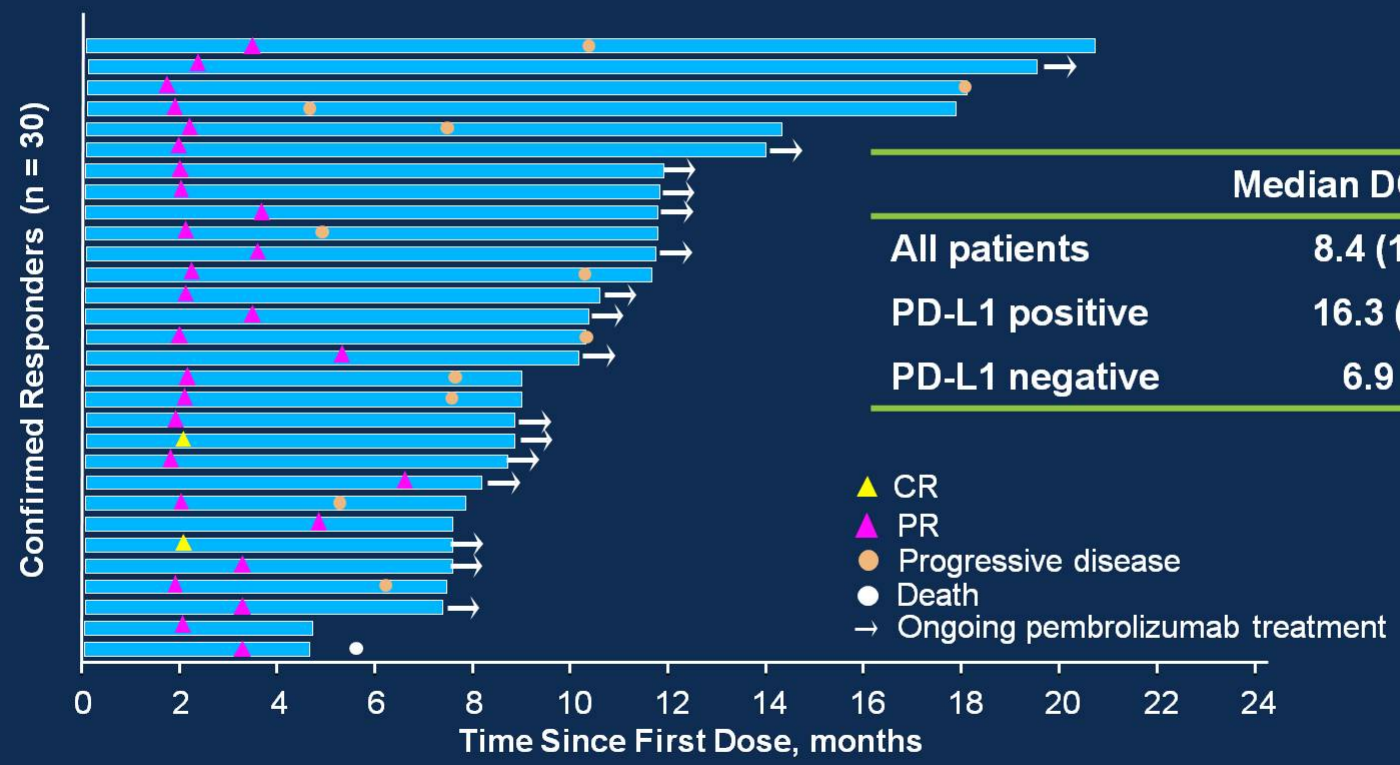
[a]Only confirmed responses were included
[b]CR + PR + SD≥2 months
Data cutoff: January 16, 2017

치료와 반응률 지속도

Treatment Exposure[a] and Duration of Response



	Median DOR (95% CI), mos
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 postbaseline assessment (n = 30). Bar length indicates time to last imaging assessment.
[b]No progressive disease at last disease assessment. Data cutoff: January 16, 2017.

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MSI 와 반응률

Response by MSI Status (n = 174)

4.0% of patients were MSI-High

Response[a]	MSI-High (n = 7)		Non–MSI-High (n = 167)	
	%	95% CI	%	95% CI
ORR	57.1	18.4-90.1	9.0	5.1-14.4
CR	14.3	0.4-57.9	2.4	0.7-6.0
PR	42.9	9.9-81.6	6.6	3.3-11.5
DCR[b]	71.4	29.0-96.3	22.2	16.1-29.2

[a]Only confirmed responses were included
[b]CR + PR + SD≥2 months
Data cutoff: January 16, 2017

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ONO-4538 / BMS- 936558 임상 시험

Study Design and Endpoints

Key eligibility criteria:
- Age ≥ 20 years
- Unresectable advanced or recurrent gastric or gastroesophageal junction cancer
- Histologically confirmed adenocarcinoma
- Prior treatment with ≥ 2 regimens and refractory to/intolerant of standard therapy
- ECOG PS of 0 or 1

→ **R 2:1**

→ **Nivolumab 3 mg/kg IV Q2W**

Stratification based on:
- Country (Japan vs Korea vs Taiwan)
- ECOG PS (0 vs 1)
- Number of organs with metastases (< 2 vs ≥ 2)

→ **Placebo**

Primary endpoint:
- OS

Secondary endpoints:
- Efficacy (PFS, BOR, ORR, TTR, DOR, DCR)
- Safety

Exploratory endpoint:
- Biomarkers

- 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

BOR, best overall response; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IV; intravenous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q2W, every 2 weeks; R, randomization; RECIST, Response Evaluation Criteria In Solid Tumors; TTR, time to tumor response.

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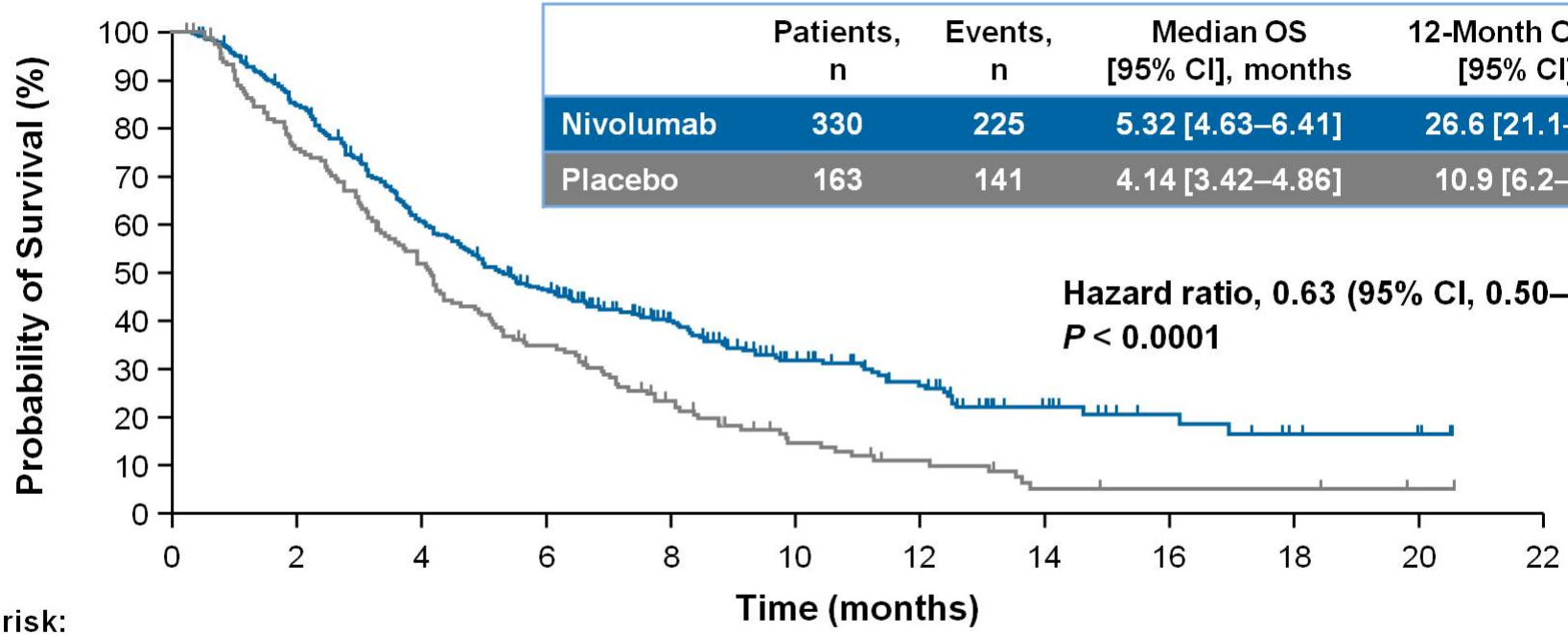
생존률

Overall Survival

	Patients, n	Events, n	Median OS [95% CI], months	12-Month OS Rate [95% CI], %
Nivolumab	330	225	5.32 [4.63–6.41]	26.6 [21.1–32.4]
Placebo	163	141	4.14 [3.42–4.86]	10.9 [6.2–17.0]



At risk:												
Nivolumab	330	275	193	142	95	57	39	19	10	5	3	0
Placebo	163	121	82	53	32	16	10	4	3	3	1	0

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유전학: 핵심 메세지

- 화학 치료는 약간의 잇점
- 폴폭스, 폴피리 기본
- 모든 환자 조직: HER2, PDL-1 염색
- 유전자 테스트
  - HER2 (트라츄츠맙)
  - MSI, (퍼튜츄맙)
  - 약의 타겟을 보기 위해

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