
# Il carcinoma gastrico avanzato nel 2015

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# Cosa non sappiamo esattamente…qual è il regime migliore?



## Il miglior regime non è ancora stato individuato…

…ma sappiamo che:

- La doppietta è meglio della monoterapia (RR; PFS ma non OS)
- La tripletta potrebbe essere più attiva, ma occorre prestare attenzione alla tossicità.
- 5FU/capecitabina + cisplatino/oxaliplatino rappresentano regimi comuni.

# Chemioterapia di I linea

- STATO DELL'ARTE
- NOVITA' 2015
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**Trattamento malattia avanzata e recidive**

| Qualità dell'evidenza SIGN | Raccomandazione | Forza della raccomandazione clinica |
|---|---|---|
| A | La chemioterapia eseguita in pazienti asintomatici risulta più efficace in termini di qualità di vita e di sopravvivenza rispetto alla somministrazione della chemioterapia a comparsa dei sintomi (69). | **Positiva forte** |
| A | I regimi di combinazione offrono un significativo miglioramento della sopravvivenza rispetto alla monochemioterapia (69). | **Positiva forte** |
| B | L'impiego di regimi a tre farmaci in pazienti in buone condizioni cliniche generali e senza comorbidità significative risulta più efficace rispetto a regimi a due farmaci (69). | **Positiva debole** |
| A | La somministrazione di fluoropirimidine orali può sostituire il 5FU, in considerazione della sovrapponibile attività e tollerabilità ed al risparmio di accessi venosi centrali necessari per la somministrazione infusionale di 5FU (71,74,75). | **Positiva forte** |
| A | La somministrazione di oxaliplatino può sostituire il cisplatino, in considerazione della sovrapponibile efficacia e della minore tossicità rispetto all'impiego del cisplatino (72,73). | **Positiva forte** |
| A | I pazienti con tumore che presentano iperespressione e amplificazione di HER-2 devono ricevere una combinazione di Fluoropirimidine/cisplatino e trastuzumab (77). | **Positiva forte** |

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# La terapia di I linea…dalle linee guida alla vita reale…

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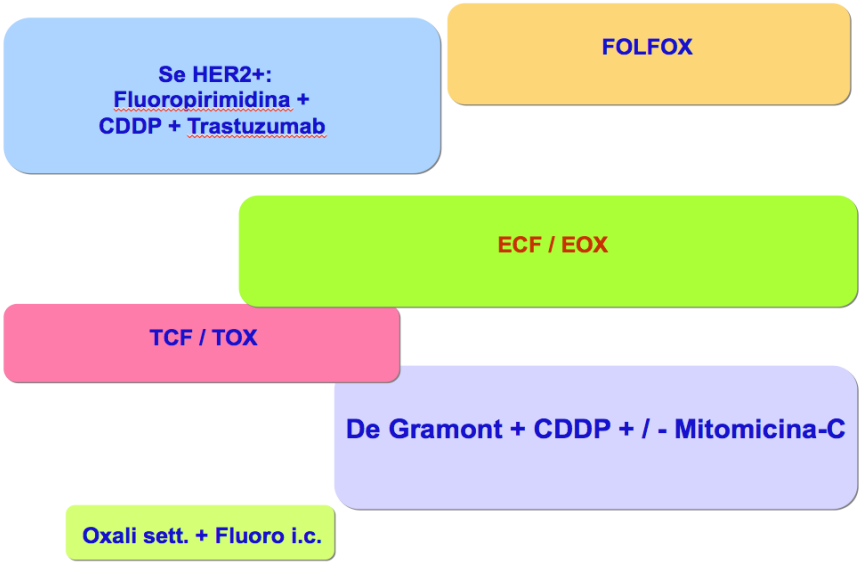
| Qualità dell'evidenza SIGN | Raccomandazione | Forza della raccomandazione clinica |
|---|---|---|
| B | Regimi a base di oxaliplatino e 5-fluororacile possono essere considerati nel paziente anziano (≥65 anni) nell'ambito di una valutazione multidimensionale che definisca i soggetti "fit" e con un attento monitoraggio della tossicità (78,79,85). | **Positiva debole** |
| B | La capecitabina può sostituire il 5-fluorouracile in presenza di care-giver ed in assenza di insufficienza renale (74). | **Positiva debole** |
| D | L'irinotecan può essere un'alternativa all'impiego dell'oxaliplatino (84). | **Positiva debole** |

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# Efficacia della chemioterapia e di trastuzumab (I linea)

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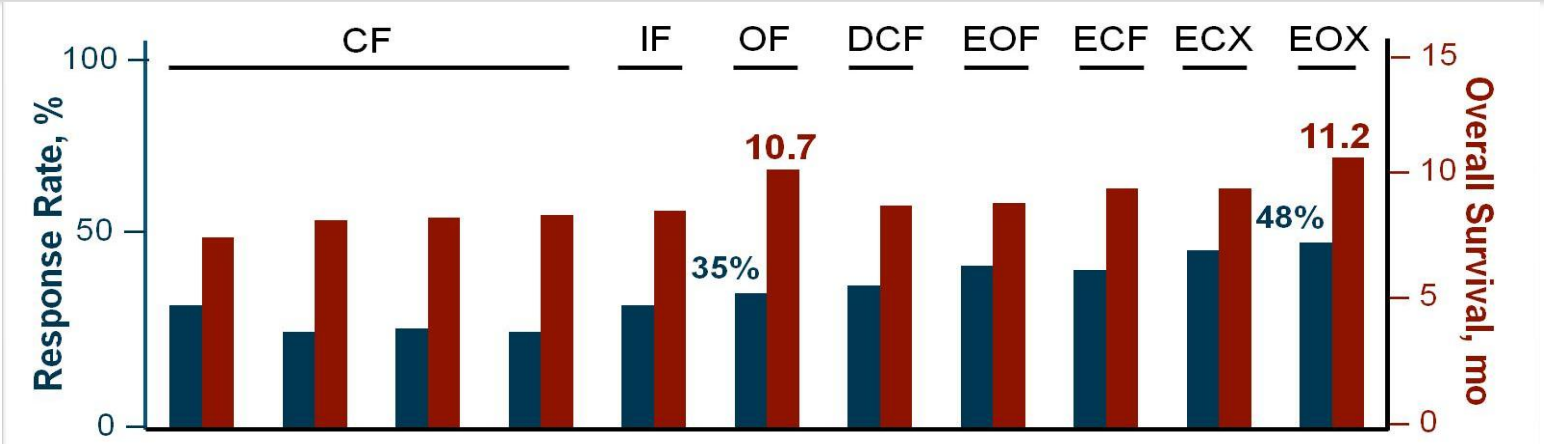
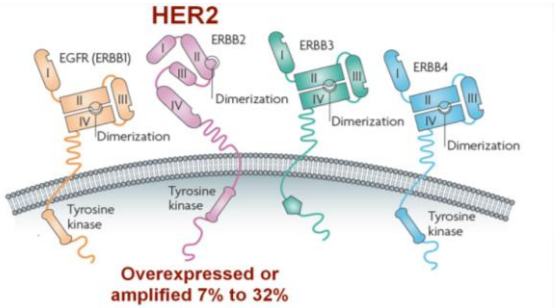
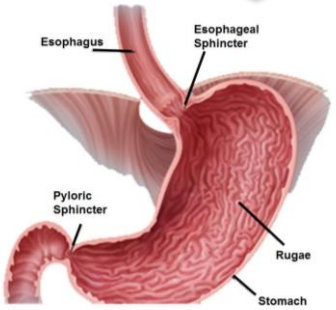
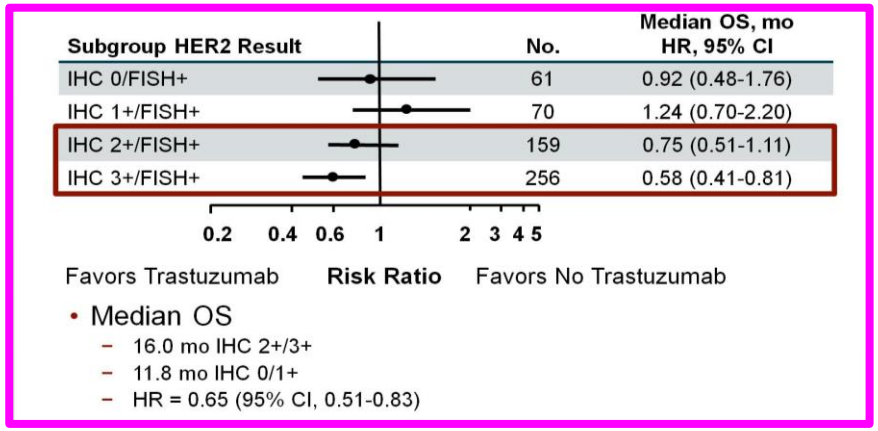



- Esophageal adenocarcinoma
  - **23%**, well-moderate
  - 8%, poor or undifferentiated
- Gastric adenocarcinoma
  - **33%**, intestinal
  - 8%, diffuse/mixed




- Median OS
  - 16.0 mo IHC 2+/3+
  - 11.8 mo IHC 0/1+
  - HR = 0.65 (95% CI, 0.51-0.83)

# Chemioterapia di II linea



## Gli studi clinici hanno mostrato beneficio dei seguenti agenti :

- Docetaxel 75 mg/m2, N=168 pz: COUGAR-02
  - OS 5.2 mesi vs 3.6 mesi (BSC), HR=0.67, p=0.01
- Irinotecan (vs BSC: mOS= 4.0 vs 2.4 mesi)
- Paclitaxel: mOS= 5.03 mesi
- Irinotecan or taxane
  - Chemioterapia di salvataggio (docetaxel o irinotecan vs BSC: mOS= 5.3 vs 3.8 mesi)

**Significativo miglioramento in OS con la chemioterapia**

# Terapia di II linea: polichemioterapia



## Confronto "Head-to-head" per OS:

- Paclitaxel è simile ad irinotecan[a]
- L'aggiunta di cisplatino ad irinotecan: non superiore[b]
- FOLFIRI non superiore ad irinotecan[c]

a. Hironaka S, et al. *J Clin Oncol*. 2013;31:4438-4444.[32]
b. Higuchi K, et al. *Eur J Cancer*. 2014;50:1437-1445.[33]
c. Sym SJ, et al. *Cancer Chemother Pharmacol*. 2013; 71:481-488.[34]

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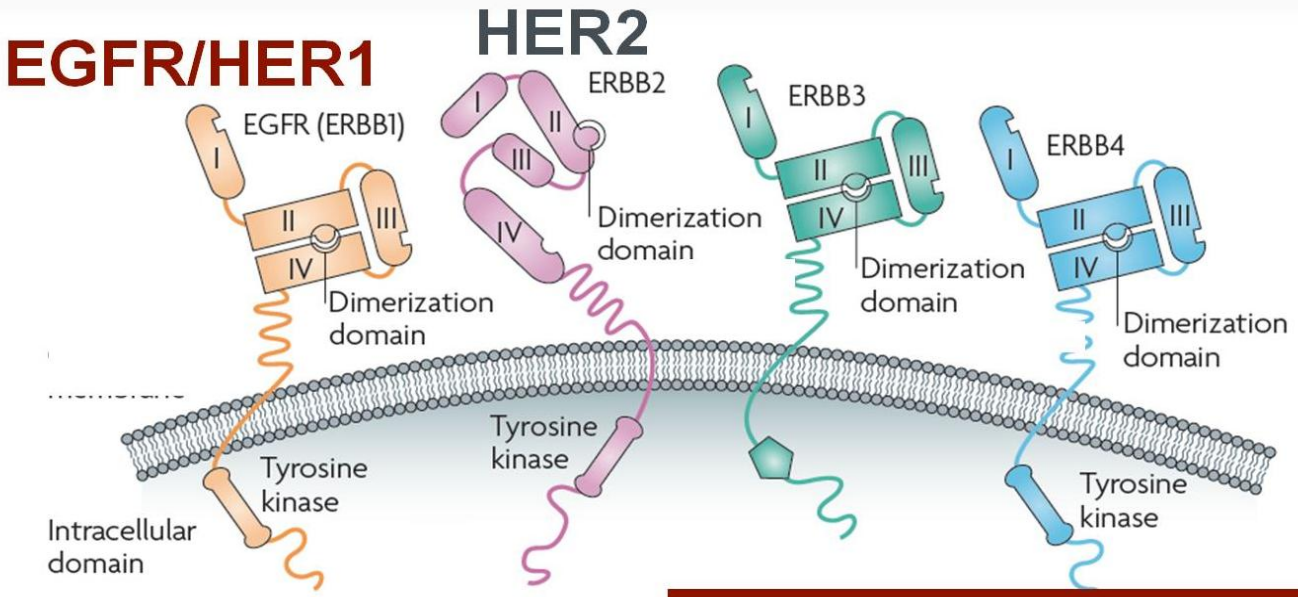
| Qualità dell'evidenza SIGN | Raccomandazione | Forza della raccomandazione clinica |
|---|---|---|
| A | La chemioterapia di seconda linea dovrebbe essere considerata nei pazienti in buone condizioni cliniche generali (PS 0-1) in progressione di malattia dopo un trattamento chemioterapico di prima linea (88-91). | Positiva Forte |
| D* | La scelta del trattamento chemioterapico di seconda linea dipende dal trattamento praticato in prima linea (88-91). | Positiva Debole |

*opinione espressa dal panel.

# HER/ErbB nelle neplasie gastriche






EGFR Overexpressed in 32%-59%
*EGFR* Amplified in 0-50%
*KRAS* mutation in < 5%

- **Phase 3 results**
  - Panitumumab (REAL-3): ***adverse***
  - Cetuximab (EXPAND): ***null***
  - Lapatinib (LOGiC): ***null***
  - Lapatinib (Tytan): ***null***

# Antiangiogenetici nelle neplasie gastriche

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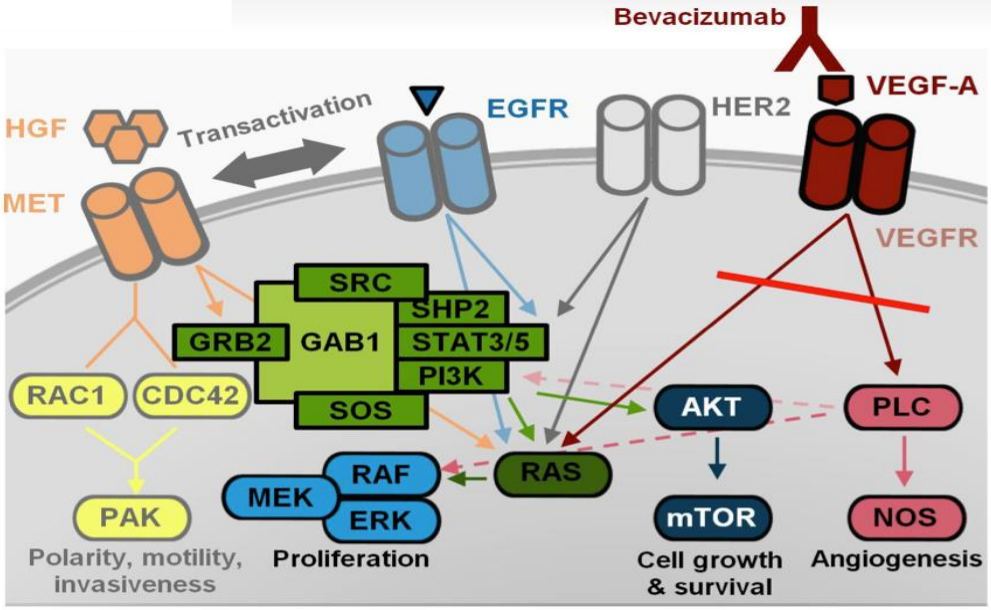
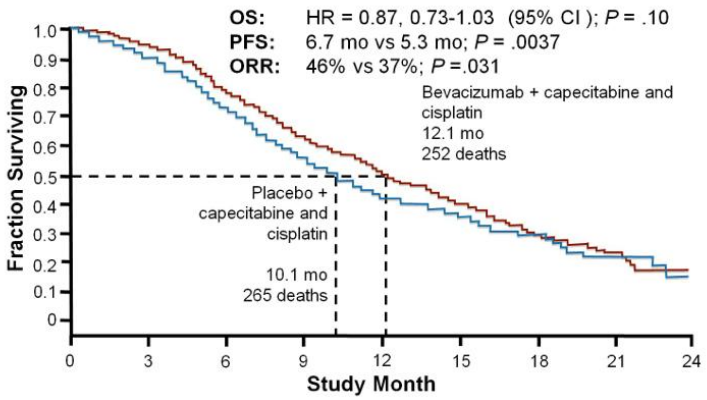



**AVAGAST**




| | Docetaxel 60 mg ± Sunitinib 37.5 mg | |
|---|---|---|
| | N = 107 | |
| Primary PFS (mo) | 3.9 vs 2.6 | NSS |
| Secondary OS (mo) | 8.0 vs 6.6 | NSS |
| ORR improved, % | 41.1 vs 15.3 | *P* = .002 |

Yi JH et al. Br J Cancer 2012

# RAMUCIRUMAB nel 2014



## FDA Approval History for Cyramza

| Date | Article |
|---|---|
| Nov 5, 2014 | APPROVAL FDA Approves Cyramza (ramucirumab) in Combination with Paclitaxel for Advanced Gastric Cancer after Prior Chemotherapy |
| Apr 21, 2014 | APPROVAL FDA Approves Cyramza for Stomach Cancer |

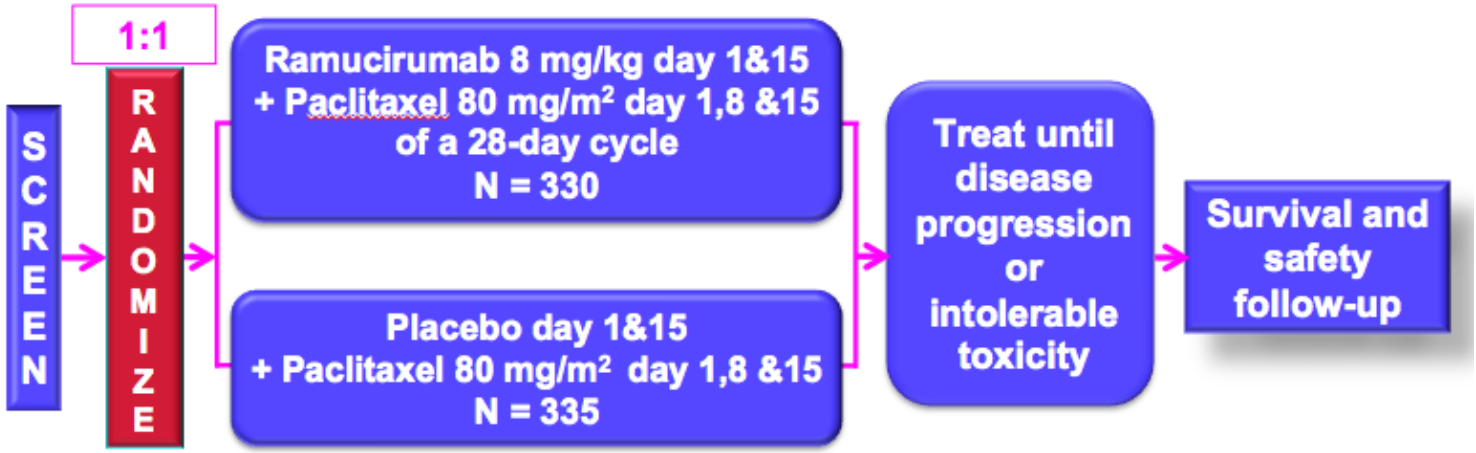
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Committee for Orphan Medicinal Products (COMP) meeting report on the review of applications for orphan designation

November 2014

# Studio RAINBOW



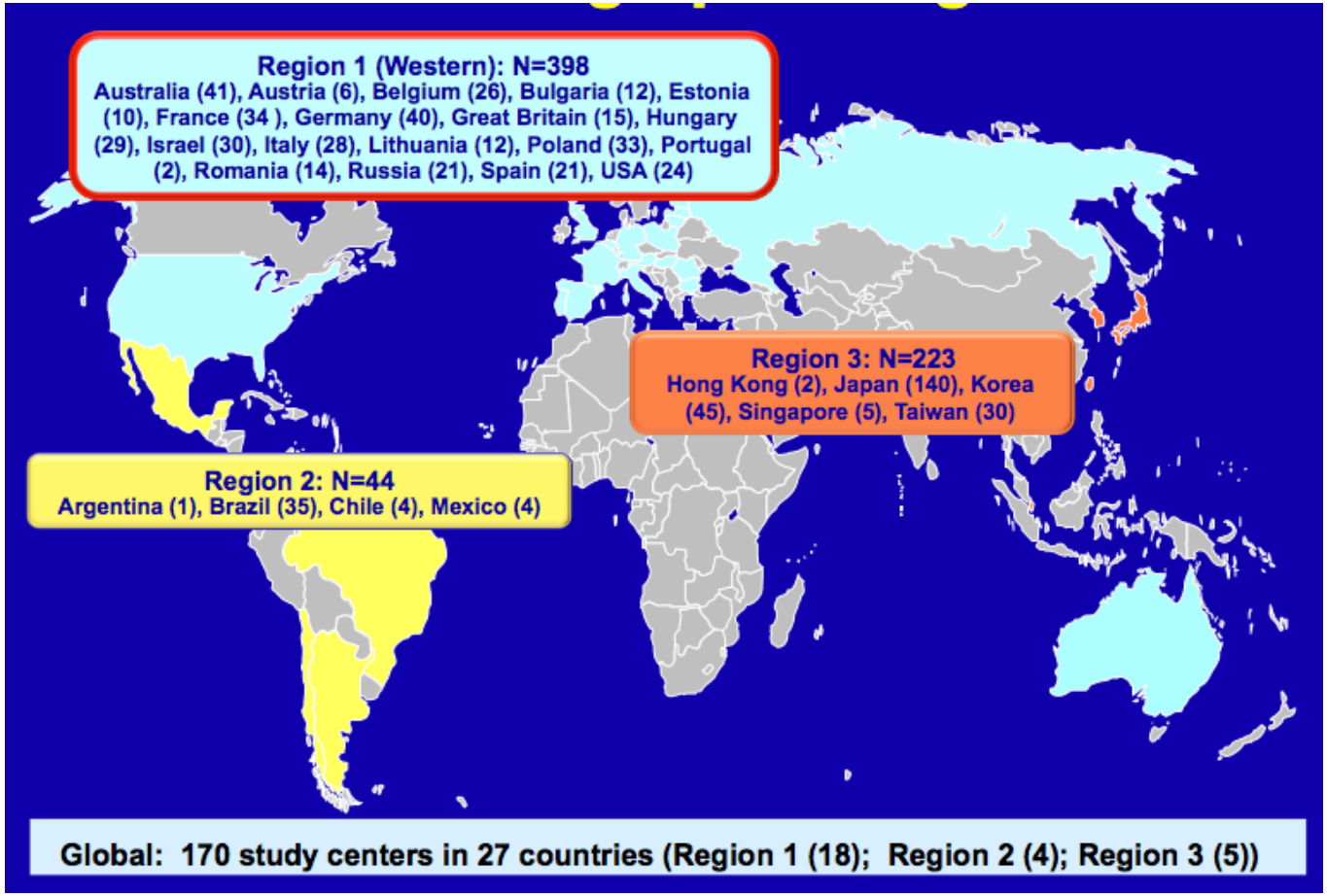



- **Important inclusion criteria:**
  - Metastatic or loc. adv. unresectable gastric or GEJ* adenocarcinoma
  - Progression after 1st line platinum/fluoropyrimidine based chemotherapy
- **Stratification factors:**
  - Geographic region,
  - Measurable vs non-measurable disease,
  - Time to progression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

Wilke H, Lancet Oncology 2014

# Studio RAINBOW: nazioni partecipanti






Berardi R et al, AIOM 2014

# Studio RAINBOW: OS e PFS

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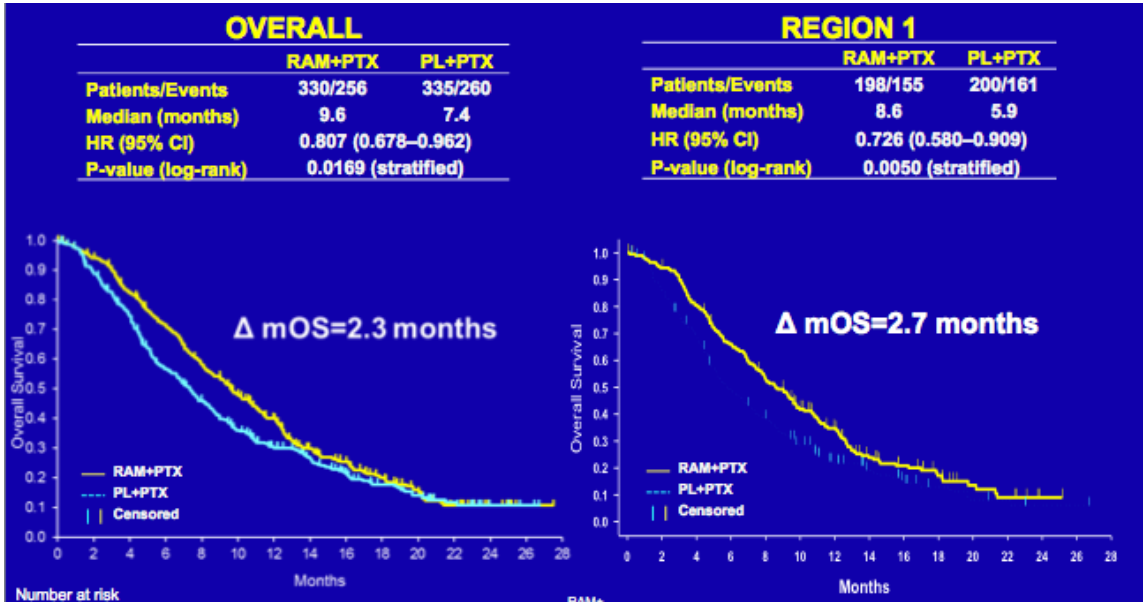


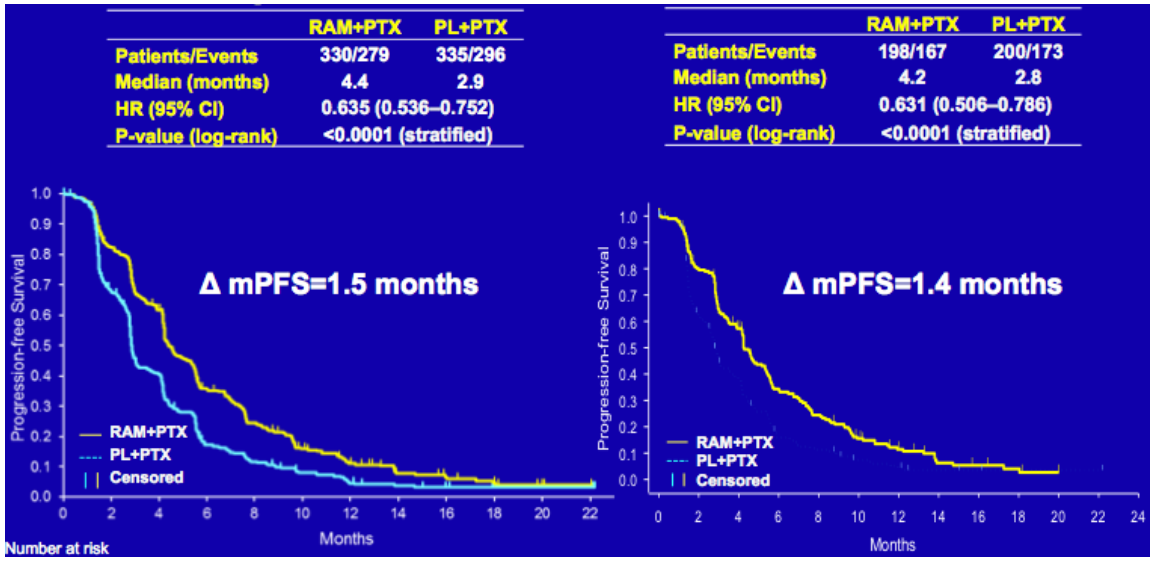

# RAINBOW: OS and PFS by age

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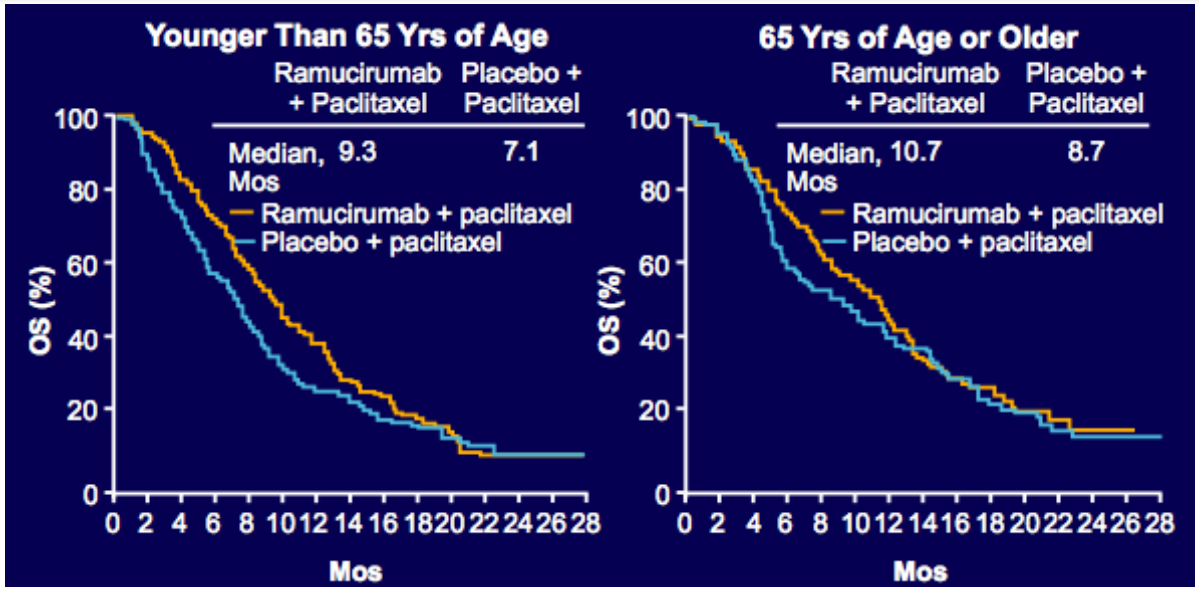


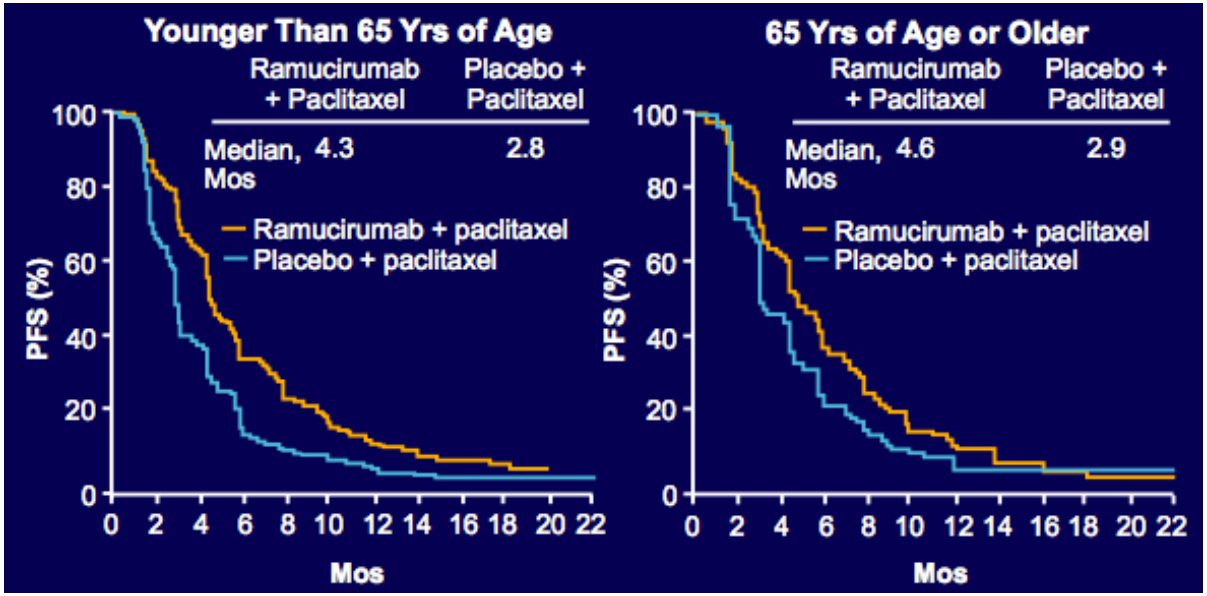


Muro K, et al. ASCO GI 2015

# RAMUCIRUMAB nel paziente anziano

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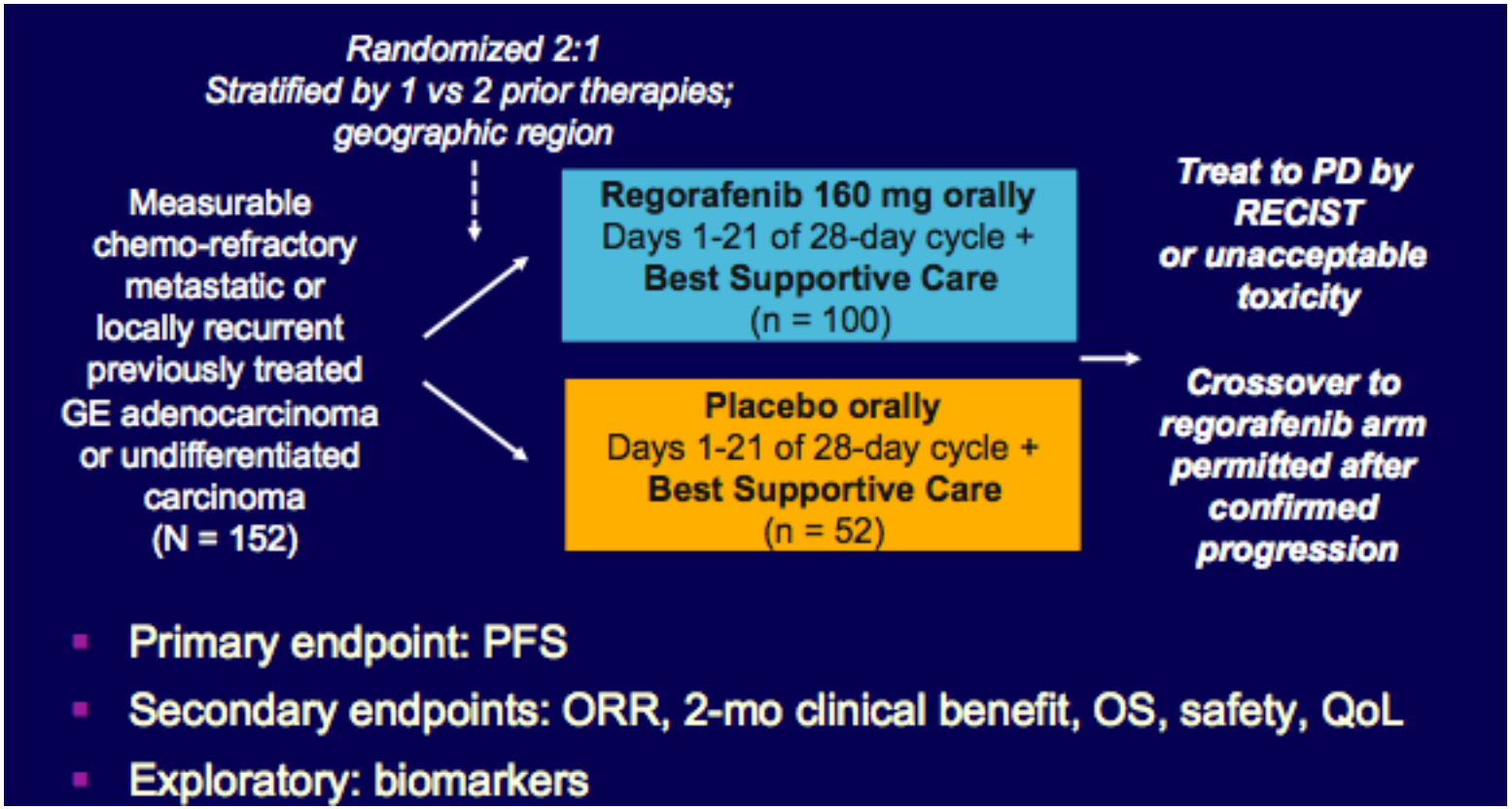
**E nel paziente anziano?**

- Combination ramucirumab and paclitaxel conferred similar improvements in OS, PFS, and ORR in both age groups compared with placebo and paclitaxel
- Drug exposure for ramucirumab + paclitaxel and paclitaxel + placebo similar for both age groups
- More pts discontinued or modified treatment in the ramucirumab arm

# INTEGRATE: Study Design






Pavlakis et al. ASCO 2015

# INTEGRATE: outcomes

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| Response | Regorafenib (n = 97) | Placebo (n = 50) | |
|---|---|---|---|
| Median PFS, mos | 2.6 | 0.9 | HR 0.40 (95% CI: 0.28-0.59; *P* < .0001) |
| Median OS, mos | 5.8 | 4.5 | HR 0.74 (95% CI: 0.51-1.08; *P* = .11) |
| 2-mo clinical benefit, % | 45 | 18 | |
| CR/PR/SD, % | 0/3/40 | 0/2/14 | |

- 58% pts in placebo arm crossed over to receive regorafenib

- Regorafenib significantly extended PFS compared with placebo in broad pt population
  - Efficacy variable but present in all regions and subgroups
- Nonsignificant OS improvement with regorafenib
- Low number of objective responses but more stable disease with regorafenib compared with placebo
- Regorafenib generally well tolerated with expected safety profile
- Authors suggest phase III trial warranted

# Sviluppo di S1 nei Paesi Occidentali



- Marketed in Japan since 1999
  - Accepted standard of care as first-line treatment of gastric cancer

| | |
|---|---|
| 1996 | |
| 1997 | Jun: Phase I monotherapy (EU) |
| 1998 | Nov: Phase I monotherapy (USA) |
| 1999 | Mar: Phase II gastric and CRC monotherapy (EU + USA) |
| 2003 | Feb: Phase I – First patient enrolled (Teysuno® + cisplatin in AGS) |
| 2005 | May: First patient in FLAGS |
| 2007 | Mar: 1053 patients accrued in FLAGS |
| 2009 | Jan: FLAGS completed |
| 2011 | Mar: EMEA marketing approval granted for Teysuno® + cisplatin in AGS |

**Teysuno® in combination with cisplatin was approved in Europe for the treatment of patients with advanced gastric cancer (AGS) in March 2011**


Ajani JA, *et al. J Clin Oncol* 2006;24:663–7; Ajani JA, *et al. J Clin Oncol* 2010;28:1547–53; Cohen SJ, *et al. Clin Cancer Res* 2002;8:2116–22; Teysuno®. Summary of Product Characteristics. Nordic Group BV

# Studio FLAGS: disegno



**Stratification factors:**
- Type of disease (locally advanced; 1 metastatic site; ≥2 metastatic sites)
- Prior adjuvant therapy (y/n)
- Measurable vs non-measurable disease
- Center

RANDOMIZE

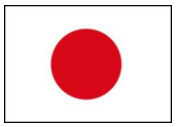
**CS Arm**
- S-1 25 mg/m² PO BID fasting, Days 1-21, recovery on days 22-28, repeated every 4 wks
- Cisplatin 75 mg/m² IV infusion 1-3 hrs, Day 1 (after S-1 administration), repeated every 4 wks for max 6 cycles

**CF Arm**
- 5-FU 1000 mg/m²/24 hrs CI over 120 hrs, Days 1-5, repeated every 4 wks
- Cisplatin 100 mg/m² IV infusion 1-3 hrs, Day 1 (before 5-FU infusion), repeated every 4 wks for max 6 cycles

**Primary Endpoint:**
- Overall Survival (OS)

**Secondary Endpoints:**

| | CS N = 521 | CF N = 508 |
|---|---|---|
| Age (yrs), median (min, max) | 59 (18, 83) | 60 (20, 85) |
| ≥65, n (%) | 160 (31) | 164 (32) |
| Males, n (%) | 382 (73) | 347 (68) |
| Race, n (%) | | |
| White | 447 (86) | 438 (86) |
| Black | 5 (1) | 7 (1) |
| Asian | 4 (1) | 4 (1) |
| Other | 65 (12) | 59 (12) |
| BSA, median (min, max) | 1.8 (1.2, 2.5) | 1.8 (1.2, 2.4) |
| ECOG 0 / 1, n (%) | 226 (43) / 295 (57) | 200 (39) / 308 (61) |
| Weight loss <5% / ≥5%, n (%) | 288 (55) / 233 (45) | 282 (56) / 226 (44) |
| Region, n (%) | | |
| E. Europe | 245 (47) | 209 (41) |
| W. Europe | 96 (18) | 103 (20) |
| Latin America | 114 (22) | 127 (25) |
| N. America | 44 (8) | 47 (9) |
| Other | 22 (4) | 22 (4) |



| Regimen | Asian patients | Western patients |
|---|---|---|
| Teysuno® (+ cisplatin) | 35 mg/m² bid d 1–21 q5w[1] | 25 mg/m² bid d 1–21 q4w[2] |
| Teysuno® monotherapy | 40 mg/m² bid d 1–28 q6w[1] | 30 mg/m² bid d 1–14 q3w[3] |

Ajani JA, JCO 2010

# Studio FLAGS: sopravvivenza globale

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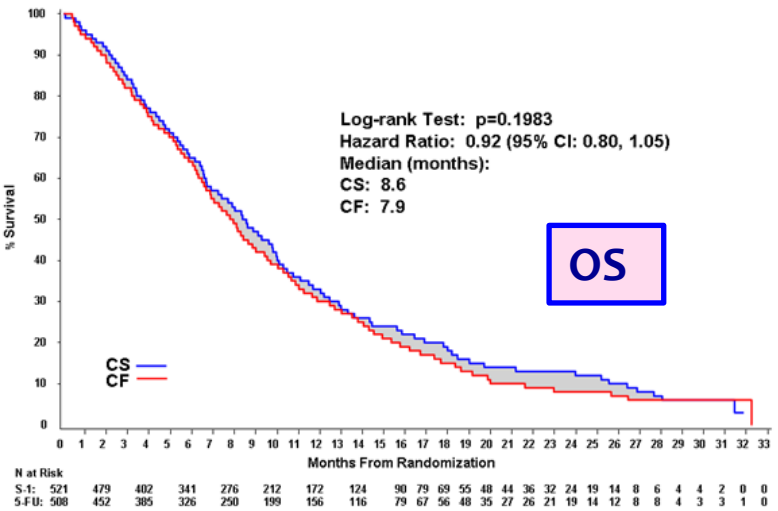


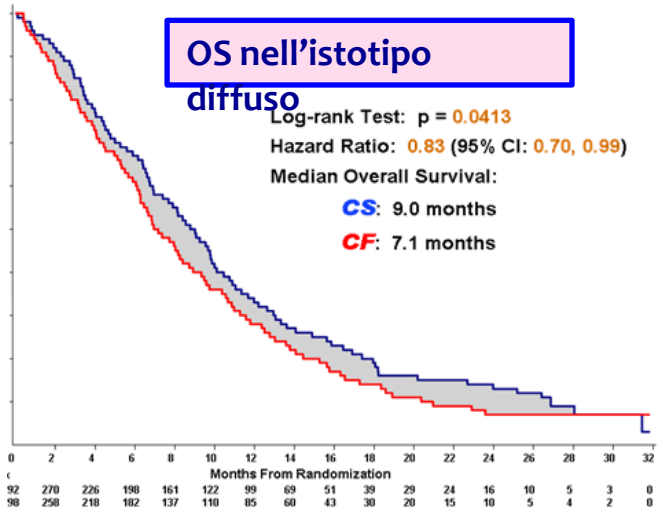


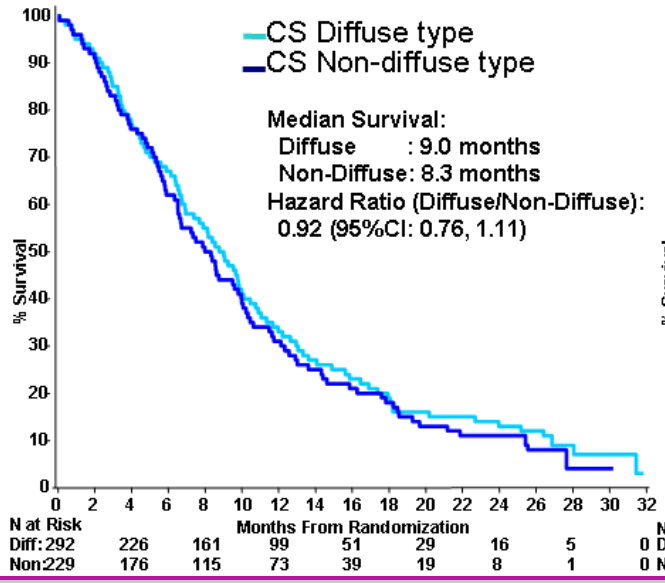


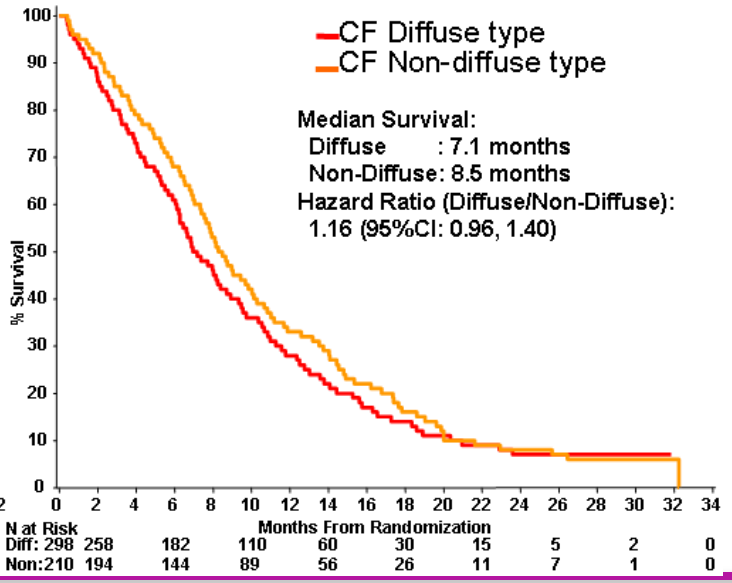

# S1 nel 2015

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original article

*Annals of Oncology* 00: 1–5, 2015
doi:10.1093/annonc/mdv316

**Comparison of two different S-1 plus cisplatin dosing schedules as first-line chemotherapy for metastatic and/or recurrent gastric cancer: a multicenter ra**

M.-H
B.-Y
S. R

**Phase II/III study of a comparing iri plus irinotecan in adv factory to first-line**

No seconda linea con CPT-11
sì in prima linea con oxaliplatino

*Annals of Oncology* 26: 141–148, 2015
doi:10.1093/annonc/mdu472
Published online 14 October 2014

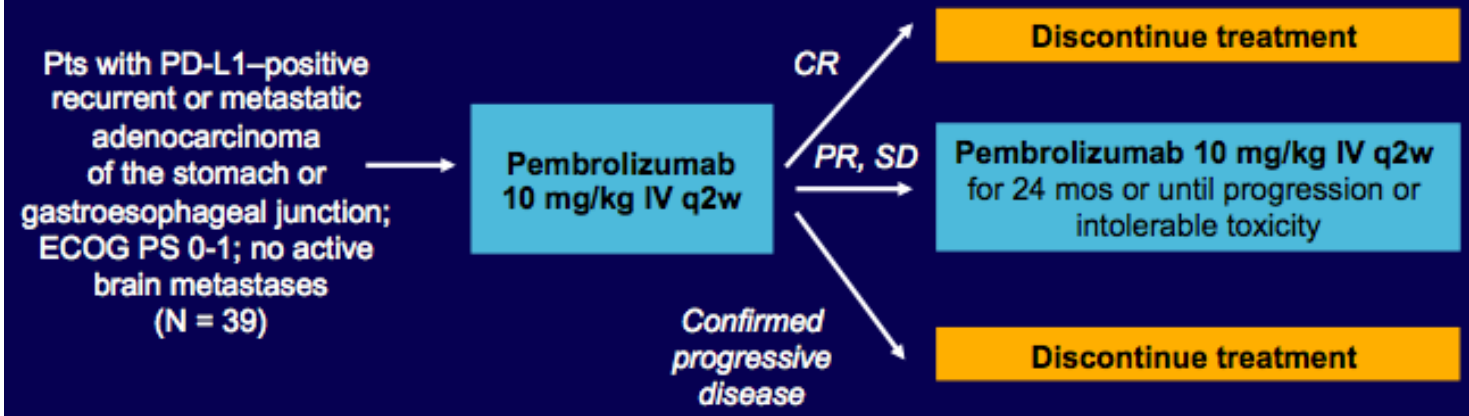
**Phase III study comparing oxaliplatin plus S-1 with cisplatin plus S-1 in chemotherapy-naïve patients with advanced gastric cancer**

Y. Yamada[1*], K. Higuchi[2], K. Nishikawa[3], M. Gotoh[4], N. Fuse[5], N. Sugimoto[6], T. Nishina[7], K. Amagai[8], K. Chin[9], Y. Niwa[10], A. Tsuji[11], H. Imamura[12], M. Tsuda[13], H. Yasui[14], H. Fujii[15], K. Yamaguchi[16], H. Yasui[17], S. Hironaka[18], K. Shimada[19], H. Miwa[20], C. Hamada[21] & I. Hyodo[22]

# KEYNOTE-012: Gastric Cancer Cohort



- Multicenter, multicohort open-label phase Ib trial




- Endpoints: Association of clinical response with PD-L1 expression
  - Assessment of response every 8 wks by RECIST v.1
  - Assessment of PD-L1 expression by immunohistochemistry

Bang YJ et al. ASCO 2015

# KEYNOTE-012: response rate



- Pembrolizumab therapy associated with PR in 13 of 39 pts by investigator review and 8 of 36 pts by central review
  - 53% of pts had decrease in lesion size
  - Median time to response: 8 wks
  - 4 of 8 responses ongoing at time of data cutoff
  - Median response duration: 40 wks (range: 20+ to 48+)

| Outcomes | | |
|---|---|---|
| Response | Investigator Review (n = 39) | Central Review (n = 36) |
| ORR, % (95% CI) | 33 (19-50) | 22 (10-39) |
| Best response, n (%) | | |
| ▪ CR | 0 | 0 |
| ▪ PR | 13 (33) | 8 (22) |
| ▪ SD | 3 (8) | 5 (14) |
| ▪ PD | 23 (59) | 19 (53) |
| ▪ No assessment | 0 | 1 (3) |
| ▪ Not determined | 0 | 3 (8) |

Bang YJ et al. ASCO 2015

# KEYNOTE-012: PFS and OS

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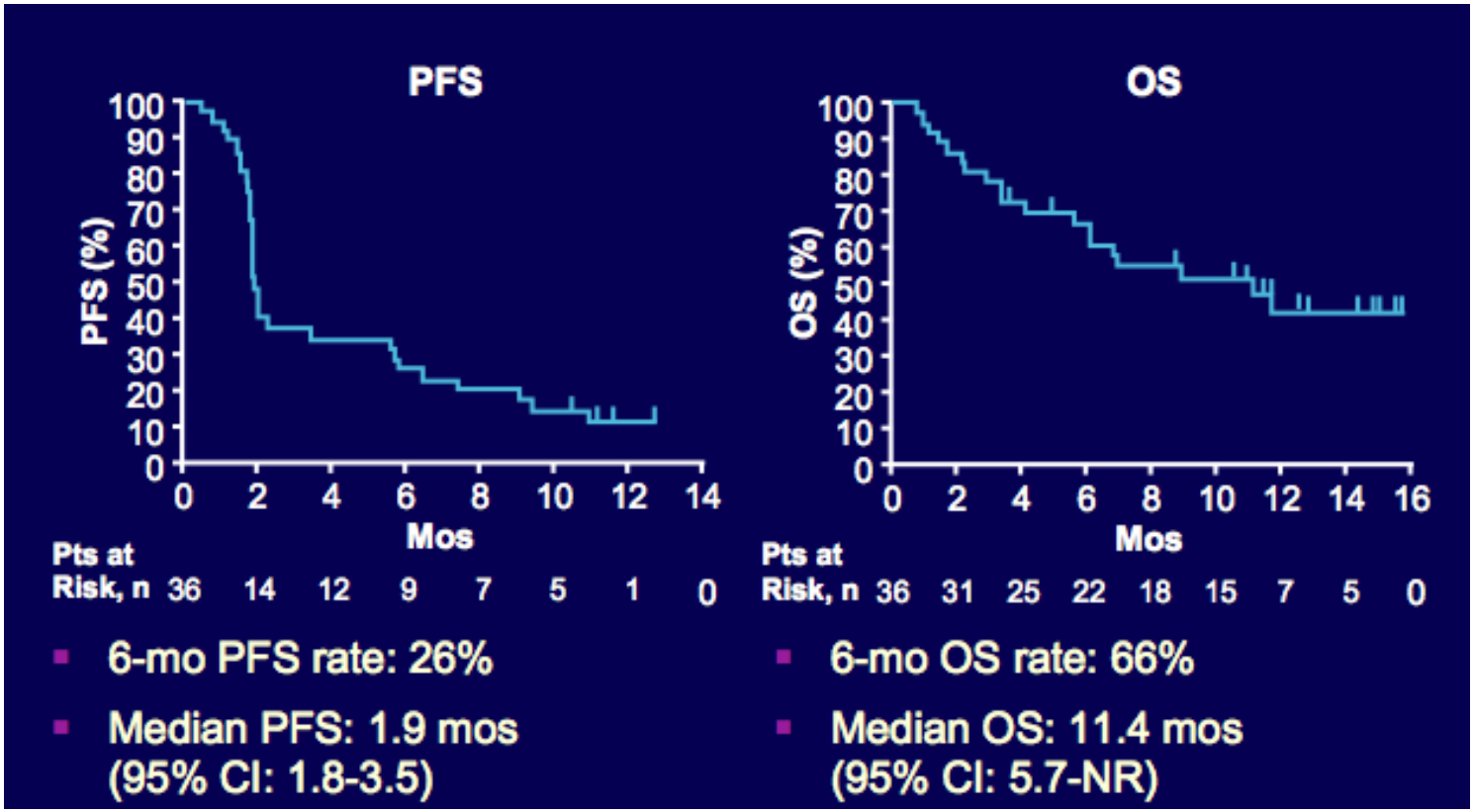


Bang YJ et al. ASCO 2015

# KEYNOTE-012: Conclusions



- Pembrolizumab shows durable efficacy in treatment-experienced pts with advanced PD-L1–positive gastric cancer
  - In this preselected pt population, association noted between PD-L1 expression and efficacy
  - ORR: 22% (central review)
  - Median duration of response: 40 wks
  - Median OS: 11 mos
- Safety and efficacy similar with pembrolizumab in other tumor types
  - Manageable toxicity with no new events observed
- Other phase I and II trials ongoing in pts with advanced gastric cancer

Bang YJ et al. ASCO 2015

# Carcinoma gastrico…malattia eterogenea!

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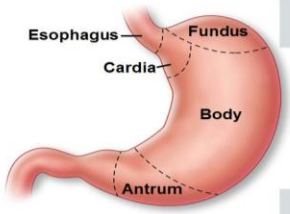
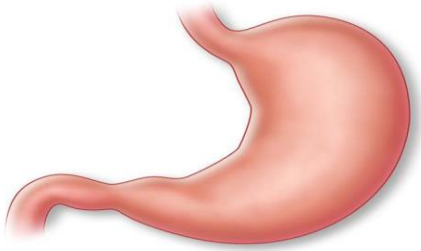



| Distinct Histology | Distinct Anatomy | Different Prognosis, Different Risk Factors |
|---|---|---|
| **Squamous cell cancer** | Esophagus | Tobacco<br>Alcohol<br>GERD<br>*Helicobacter pylori* infection |
| **Adenocarcinoma 1.1% (ranked #18)** | GEJ | |
| | First 5 cm stomach *Extending in GEJ* | |
| **Adenocarcinoma 1.9% (ranked #16)** Poorly cohesive cells Intestinal type | Stomach | *(CDH1)* mutation<br>Ethnicity<br>*Helicobacter pylori* infection |

Same trials!

- Distal esophagus, GEJ, cardia
  - Increasing dramatically in West; reflux, smoking, obesity
- Subcardial intestinal-type (well differentiated)
  - High incidence in Asia, Russia, parts of Europe; decreasing in West; *Helicobacter pylori;* better prognosis
- Subcardial diffuse-type (undifferentiated)
  - No discrete mass; decreasing gradually; inactivated *CDH1*

**SAME TRIALS!!**



| Anatomical → | Gene Expression → | Molecular Driver |
|---|---|---|
| Stomach | | HER2 |
| | | VEGFR |
| | | EGFR, HER2 |
| | | *KRAS*, MEK |
| | | EGFR |
| | | PI3K, PTEN, mTOR |
| | | cMET |
| | GEJ type | HH-PTCH1-SMO |
| | Diffuse type | FGFR |
| | Intestinal type | PD-1, PDL-1 |

Shah MA, et al. *Clin Cancer Res*. 2011;17:2693-2701.[4]

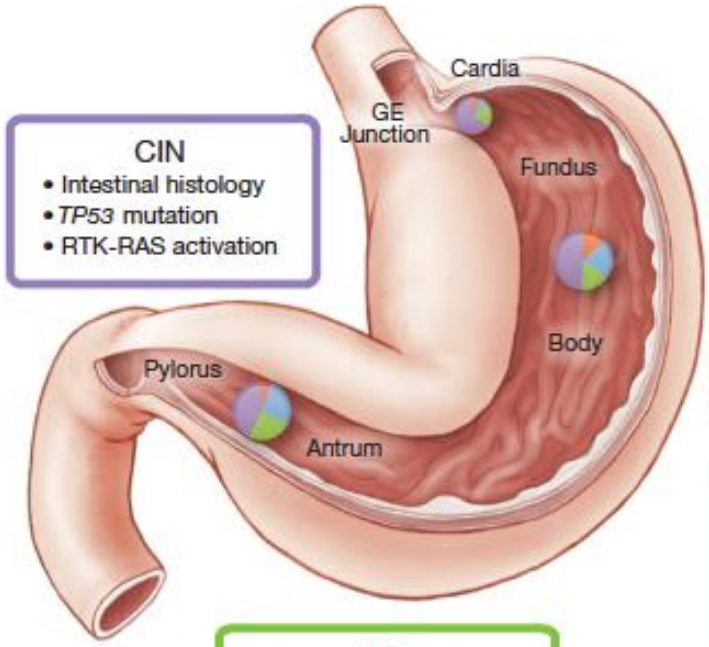
# Anche gli adenocarcinomi gastrici non sono tutti uguali…

- STATO DELL'ARTE
- NOVITA' 2015
- GUARDANDO AL FUTURO
- TAKE HOME MESSAGE

## Comprehensive molecular characterization of gastric adenocarcinoma

The Cancer Genome Atlas Research Network*

11 SEPTEMBER 2014 | VOL 513 | NATURE | 203




**CIN**
- Intestinal histology
- *TP53* mutation
- RTK-RAS activation

**EBV**
- *PIK3CA* mutation
- *PD-L1/2* overexpression
- EBV-CIMP
- *CDKN2A* silencing
- Immune cell signalling

**MSI**
- Hypermutation
- Gastric-CIMP
- *MLH1* silencing
- Mitotic pathways

**GS**
- Diffuse histology
- *CDH1, RHOA* mutations
- *CLDN18–ARHGAP* fusion
- Cell adhesion

**Analysis on 295 untreated primary gastric adenocarcinoma**

1. EBV +ve
2. MSI
3. Genomically Stable (GS)
4. Chromosomal instability (CIN)

## An Initial Comparison of Somatic Copy-Number of Eastern and Western Gastric Cancer

- Combined together ~700 fresh frozen gastric cancers which had been profiled on Affymetrix SNP6 arrays
  - Uniformly reprocessed at Broad Institute
- Samples from TCGA, collection of Italian GC, published collection from Singapore, and new collection from Korea
- In addition to using ethnic identifiers to annotate them, we used additional genomic data to ensure proper classification into E vs. W cohorts.

Schumacher et al, in preparation

# Revisiting the East/West Discussion

- We've been arguing if gastric cancer is a different disease in the East vs. West
- But there are quite biologic distinct classes of gastric cancer.....
- Imagine if we were discussing breast cancer between Eastern and Western populations
  - Probably the first thing we would do is to control for how many patients in each group were ER+, HER2+, triple negative....

# TAKE HOME MESSAGE

- STATO DELL'ARTE
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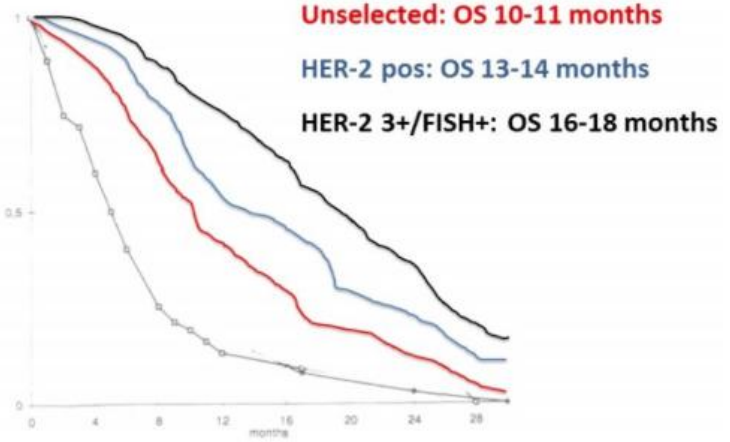
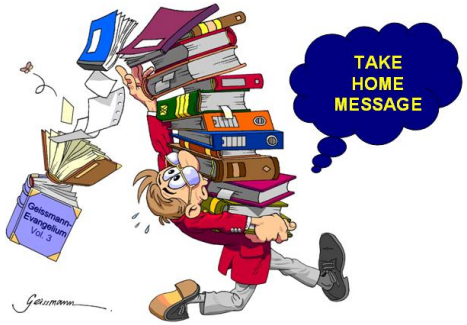
**Qualche miglioramento c'è stato…**




**Gli studi clinici spesso accomunano malattie biologicamente diverse e ancora non conosciamo la migliore classificazione biomolecolare**

**Tra i "nuovi" chemioterapici è disponibile anche in Italia S1**

**I farmaci anti-EGFR non hanno un'attività significativa nei tumori gastrici "unselected"**




**Tra gli agenti target solo il RAMUCIRUMAB ha mostrato finora un'efficacia significativa**

**Immunoterapia e regorafenib nel futuro?**

# TAKE HOME MESSAGE

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