Ente Ospedaliero Cantonale

Tumori di fegato e pancreas: regimi terapeutici nella pratica clinica

Sara De Dosso

24 ottobre 2019

Carcinoma del pancreas: nuove opzioni terapeutiche

- FOLFIRINOX adiuvante
- Gemcitabina con Nab-Paclitaxel in prima linea
- Irinotecan liposomiale (Nal-IRI)

FOLFIRINOX in setting adiuvante

The NEW ENGLAND JOURNAL of MEDICINE

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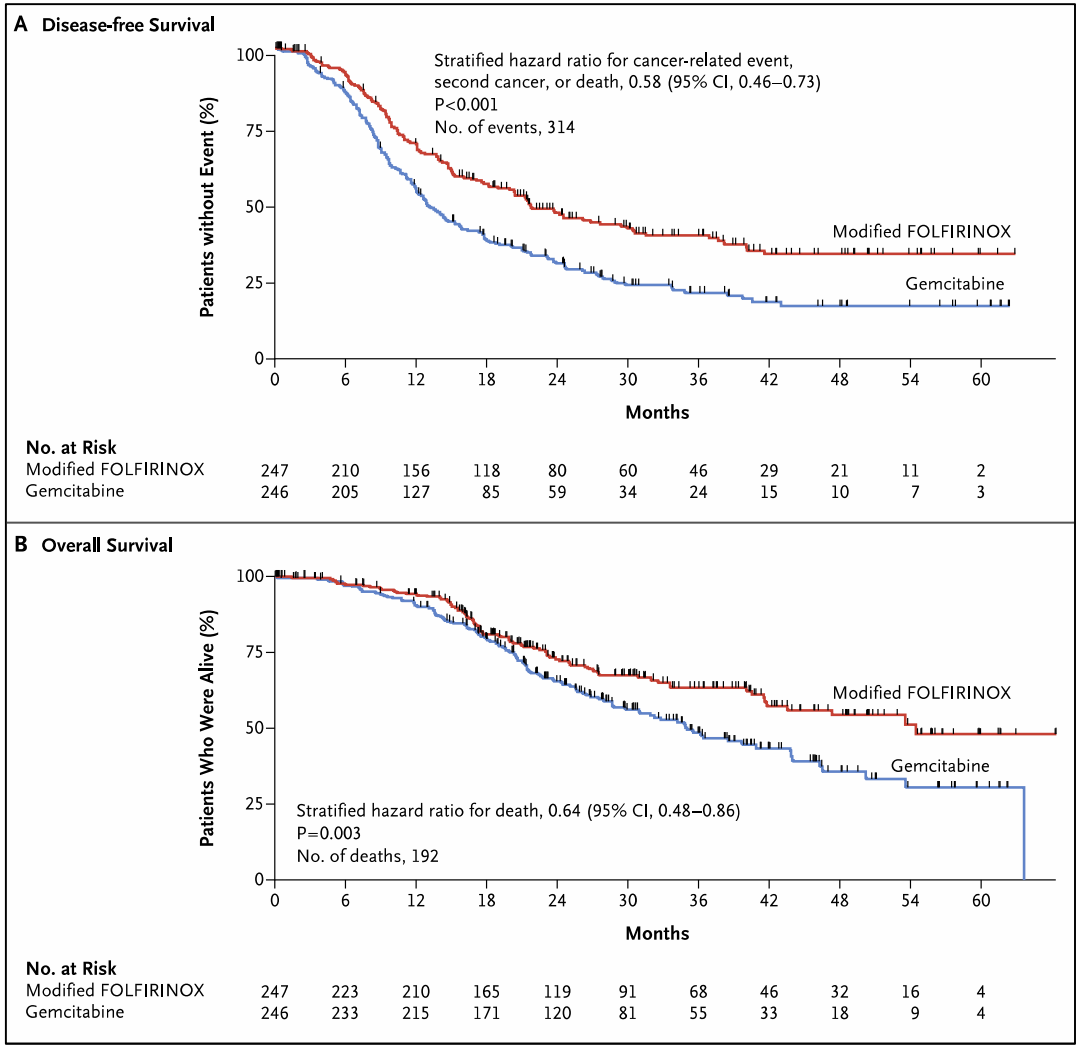
FOLFIRINOX or Gemcitabine as Adjuvant Therapy for Pancreatic Cancer

T. Conroy, P. Hammel, M. Hebbar, M. Ben Abdelghani, A.C. Wei, J.-L. Raoul, L. Choné, E. Francois, P. Artru, J.J. Biagi, T. Lecomte, E. Assenat, R. Faroux, M. Ychou, J. Volet, A. Sauvanet, G. Breysacher, F. Di Fiore, C. Cripps, P. Kavan, P. Texereau, K. Bouhier-Leporrier, F. Khemissa-Akouz, J.-L. Legoux, B. Juzyna, S. Gourgou, C.J. O'Callaghan, C. Jouffroy-Zeller, P. Rat, D. Malka, F. Castan, and J.-B. Bachet, for the Canadian Cancer Trials Group and the Unicancer-GI–PRODIGE Group*

Obiettivo primario: DFS



Mediana: 21.6 versus 12.8 mesi

3-years DFS rate: 39.7 versus 21.4%

Mediana: 54 versus 35.6 mesi

3-years OS rate: 63.4 versus 48.6%

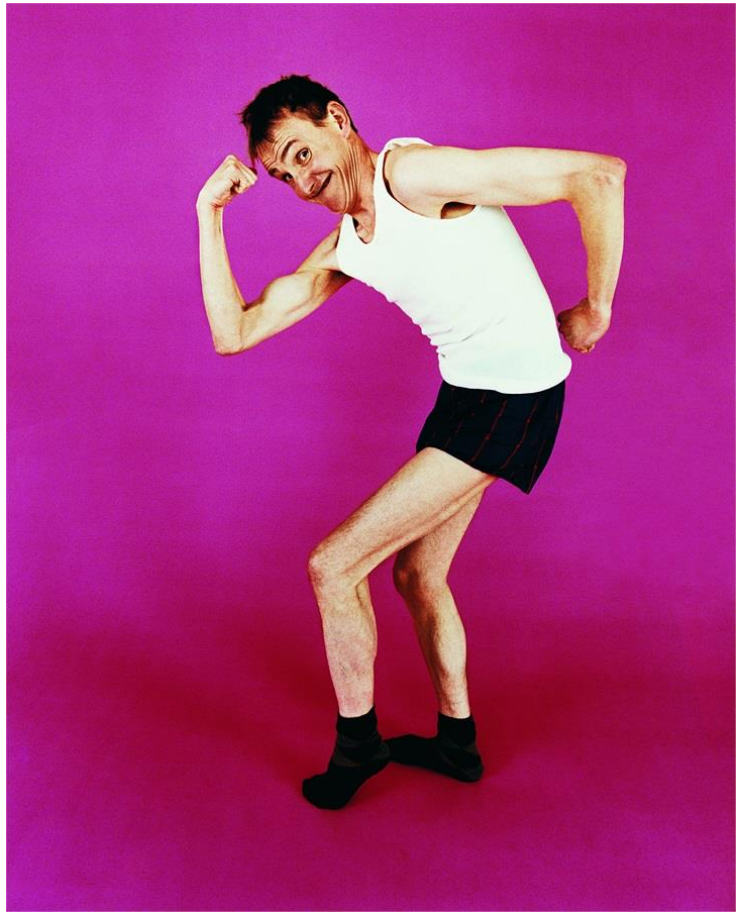
Conroy T et al. N Engl J Med 2018

Tossicità

G3-4 AEs:
76 versus 53%

Event	Modified FOLFIRINOX (N=238)			Gemcitabine (N=243)			P Value
	Any Grade	Grade 3 or 4	Grade 4	Any Grade	Grade 3 or 4	Grade 4	
	number of patients with event (percent)						
Hematologic event†							
Low hemoglobin level	200 (84.7)	8 (3.4)	0	216 (89.3)	6 (2.5)	0	0.56
Neutropenia	157 (66.5)	67 (28.4)	14 (5.9)	154 (63.6)	63 (26.0)	14 (5.8)	0.56
Febrile neutropenia	7 (3.0)	7 (3.0)	2 (0.8)	10 (4.1)	9 (3.7)	1 (0.4)	0.64
Hyperleukocytosis	110 (46.6)	11 (4.7)	2 (0.8)	134 (55.4)	17 (7.0)	1 (0.4)	0.27
Thrombocytopenia	111 (47.0)	3 (1.3)	0	122 (50.4)	11 (4.5)	3 (1.2)	0.03
Lymphopenia	87 (36.9)	3 (1.3)	0	117 (48.3)	7 (2.9)	1 (0.4)	0.34
Nonhematologic event‡							
Fatigue	199 (84.0)	26 (11.0)	0	187 (77.6)	11 (4.6)	0	0.009
Diarrhea	200 (84.4)	44 (18.6)	3 (1.3)	118 (49.0)	9 (3.7)	0	<0.001
Nausea	187 (78.9)	13 (5.5)	0	133 (55.2)	2 (0.8)	0	0.004
Abdominal pain	111 (46.8)	8 (3.4)	0	114 (47.3)	1 (0.4)	0	0.02
Vomiting	108 (45.6)	12 (5.1)	0	70 (29.0)	3 (1.2)	0	0.02
Anorexia	106 (44.7)	6 (2.5)	0	60 (24.9)	3 (1.2)	0	0.34
Sensory peripheral neuropathy	145 (61.2)	22 (9.3)	2 (0.8)	21 (8.7)	0	0	<0.001
Paresthesia	136 (57.4)	30 (12.7)	0	13 (5.4)	0	0	<0.001
Weight loss	90 (38.0)	3 (1.3)	0	49 (20.3)	1 (0.4)	0	0.37
Fever	39 (16.5)	1 (0.4)	0	78 (32.4)	1 (0.4)	0	1.00
Mucositis	80 (33.8)	6 (2.5)	0	36 (14.9)	0	0	0.01
Alopecia§	64 (27.0)	0	—	47 (19.5)	0	—	—
Hand–foot syndrome	12 (5.1)	1 (0.4)	0	2 (0.8)	0	0	0.50
Thrombosis or embolism	14 (5.9)	6 (2.5)	0	19 (7.9)	1 (0.4)	0	0.07
Constipation	49 (20.7)	0	0	52 (21.6)	0	0	—
Biochemical event¶							
Increased alanine aminotransferase level	151 (64.0)	10 (4.2)	0	178 (73.6)	12 (5.0)	0	0.71
Increased aspartate aminotransferase level	158 (66.9)	9 (3.8)	1 (0.4)	167 (69.0)	8 (3.3)	0	0.76
Increased alkaline phosphatase level	173 (73.6)	5 (2.1)	0	111 (45.9)	5 (2.1)	0	1.00
Increased γ-glutamyltransferase level	150 (65.2)	42 (18.3)	6 (2.6)	110 (46.0)	20 (8.4)	3 (1.3)	0.002
Hyperglycemia	59 (24.9)	7 (3.0)	0	59 (24.4)	5 (2.1)	0	0.53

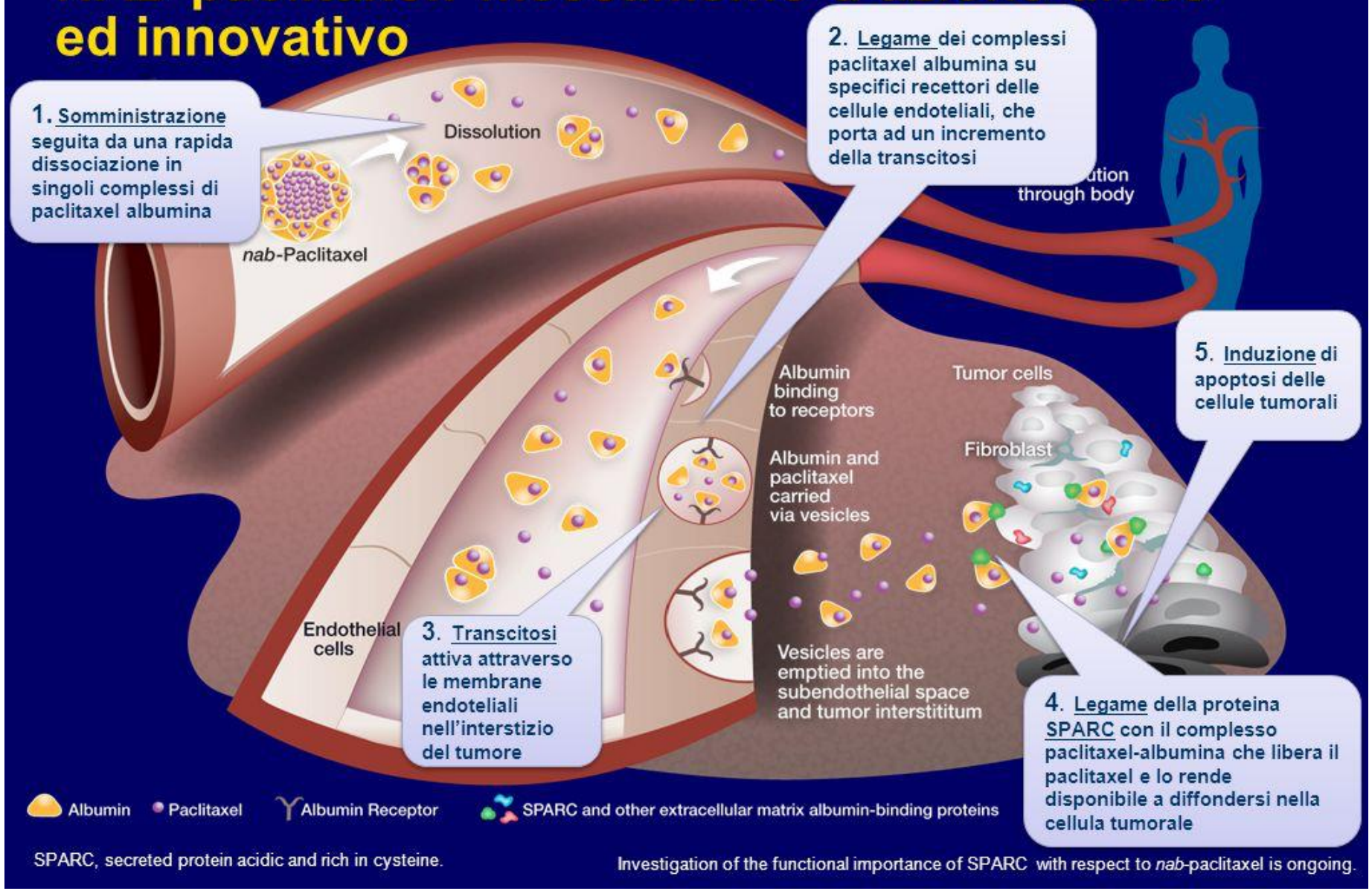
Conroy T et al. N Engl J Med 2018



Nab-paclitaxel in prima linea

- Paclitaxel racchiuso in un guscio di albumina in nano particelle (Nab)
- La tecnologia unica di nanoparticelle legate all’albumina permette al chemioterapico di raggiungere più facilmente la sede del tumore perché migliora:
  - la capacità di uscire dal flusso sanguigno
  - la sua capacità di raggiungere la sede del tumore
  - la sua captazione da parte delle cellule tumorali

NAB-paclitaxel: meccanismo d'azione unico ed innovativo



SPARC, secreted protein acidic and rich in cysteine.

Investigation of the functional importance of SPARC with respect to *nab*-paclitaxel is ongoing.

Gemcitabina e Nab-paclitaxel in prima linea

The NEW ENGLAND JOURNAL of MEDICINE

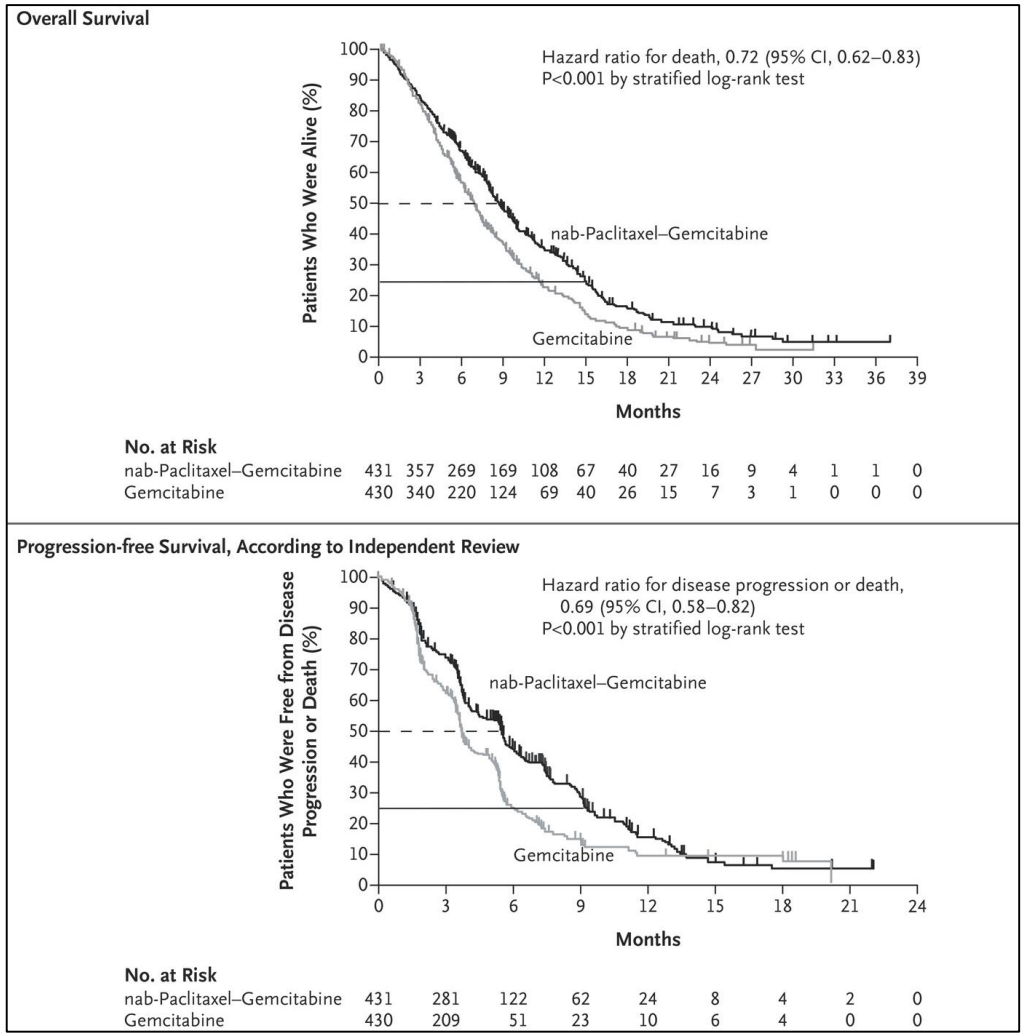
2013

ORIGINAL ARTICLE

Increased Survival in Pancreatic Cancer with nab-Paclitaxel plus Gemcitabine

Daniel D. Von Hoff, M.D., Thomas Ervin, M.D., Francis P. Arena, M.D., E. Gabriela Chiorean, M.D., Jeffrey Infante, M.D., Malcolm Moore, M.D., Thomas Seay, M.D., Sergei A. Tjulandin, M.D., Wen Wee Ma, M.D., Mansoor N. Saleh, M.D., Marion Harris, M.D., Michele Reni, M.D., Scot Dowden, M.D., Daniel Laheru, M.D., Nathan Bahary, M.D., Ramesh K. Ramanathan, M.D., Josep Tabernero, M.D., Manuel Hidalgo, M.D., Ph.D., David Goldstein, M.D., Eric Van Cutsem, M.D., Xinyu Wei, Ph.D., Jose Iglesias, M.D., and Markus F. Renschler, M.D.

Obiettivo primario: OS



Mediana: 8.5 versus 6.7 mesi

1-year OS rate: 35 versus 22%
2-years OS rate: 9 versus 4%

Mediana: 5.5 versus 3.7 versus

Von Hoff DD et al. N Engl J Med 2013

Tossicità

Table 3. Common Adverse Events of Grade 3 or Higher and Growth-Factor Use.*

Event	nab-Paclitaxel plus Gemcitabine (N=421)	Gemcitabine Alone (N=402)
Adverse event leading to death — no. (%)	18 (4)	18 (4)
Grade ≥3 hematologic adverse event — no./total no. (%)†		
Neutropenia	153/405 (38)	103/388 (27)
Leukopenia	124/405 (31)	63/388 (16)
Thrombocytopenia	52/405 (13)	36/388 (9)
Anemia	53/405 (13)	48/388 (12)
Receipt of growth factors — no./total no. (%)	110/431 (26)	63/431 (15)
Febrile neutropenia — no. (%)‡	14 (3)	6 (1)
Grade ≥3 nonhematologic adverse event occurring in >5% of patients — no. (%)‡		
Fatigue	70 (17)	27 (7)
Peripheral neuropathy§	70 (17)	3 (1)
Diarrhea	24 (6)	3 (1)
Grade ≥3 peripheral neuropathy		
Median time to onset — days	140	113
Median time to improvement by one grade — days	21	29
Median time to improvement to grade ≤1 — days	29	NR
Use of nab-paclitaxel resumed — no./total no. (%)	31/70 (44)	NA

Von Hoff DD et al. N Engl J Med 2013

Irinotecan liposomiale in seconda linea

- Irinotecan incapsulato in particelle nanoliposomiali
- Migliore biodisponibilità, migliore penetrazione nelle cellule tumorali

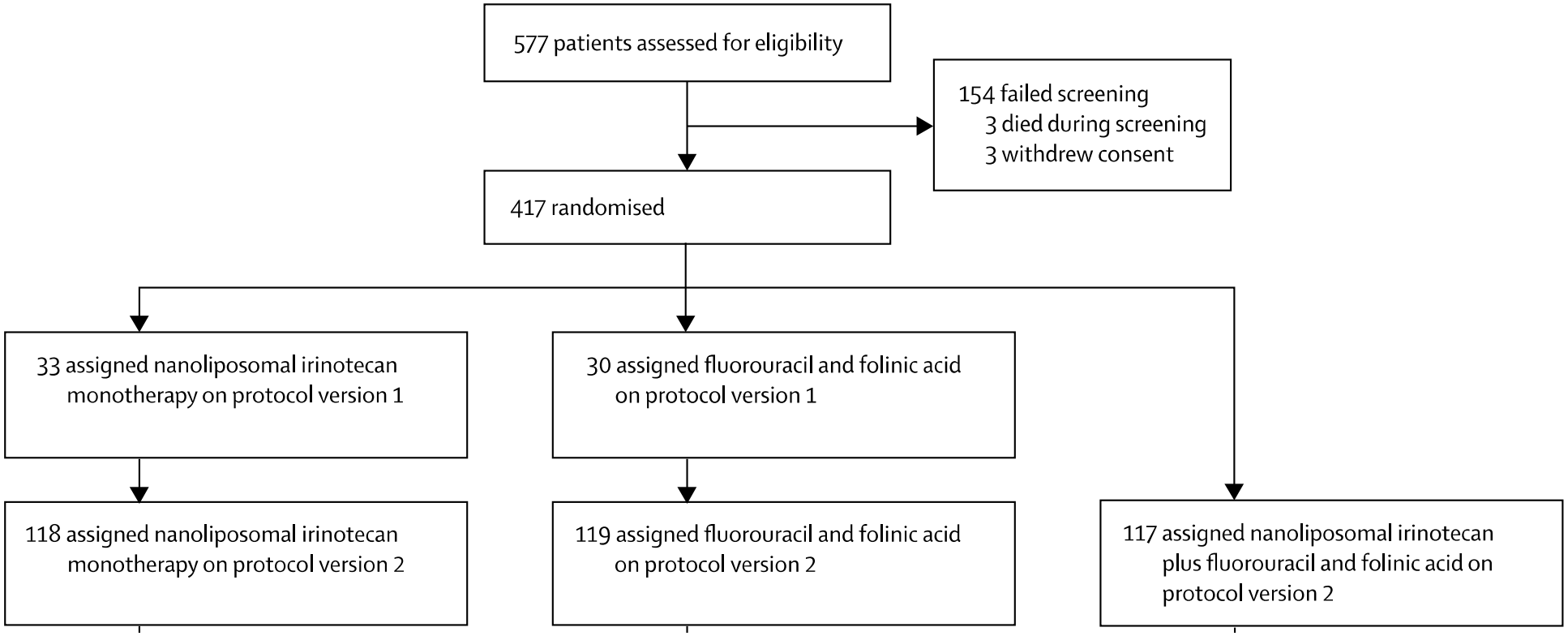
Nal-irinotecan con 5-FU in seconda linea

Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial

Andrea Wang-Gillam, Chung-Pin Li, György Bodoky, Andrew Dean, Yan-Shen Shan, Gayle Jameson, Teresa Macarulla, Kyung-Hun Lee, David Cunningham, Jean F Blanc, Richard A Hubner, Chang-Fang Chiu, Gilberto Schwartsmann, Jens T Siveke, Fadi Braiteh, Victor Moyo, Bruce Belanger, Navreet Dhindsa, Eliel Bayever, Daniel D Von Hoff*, Li-Tzong Chen*, for the NAPOLI-1 Study Group†*

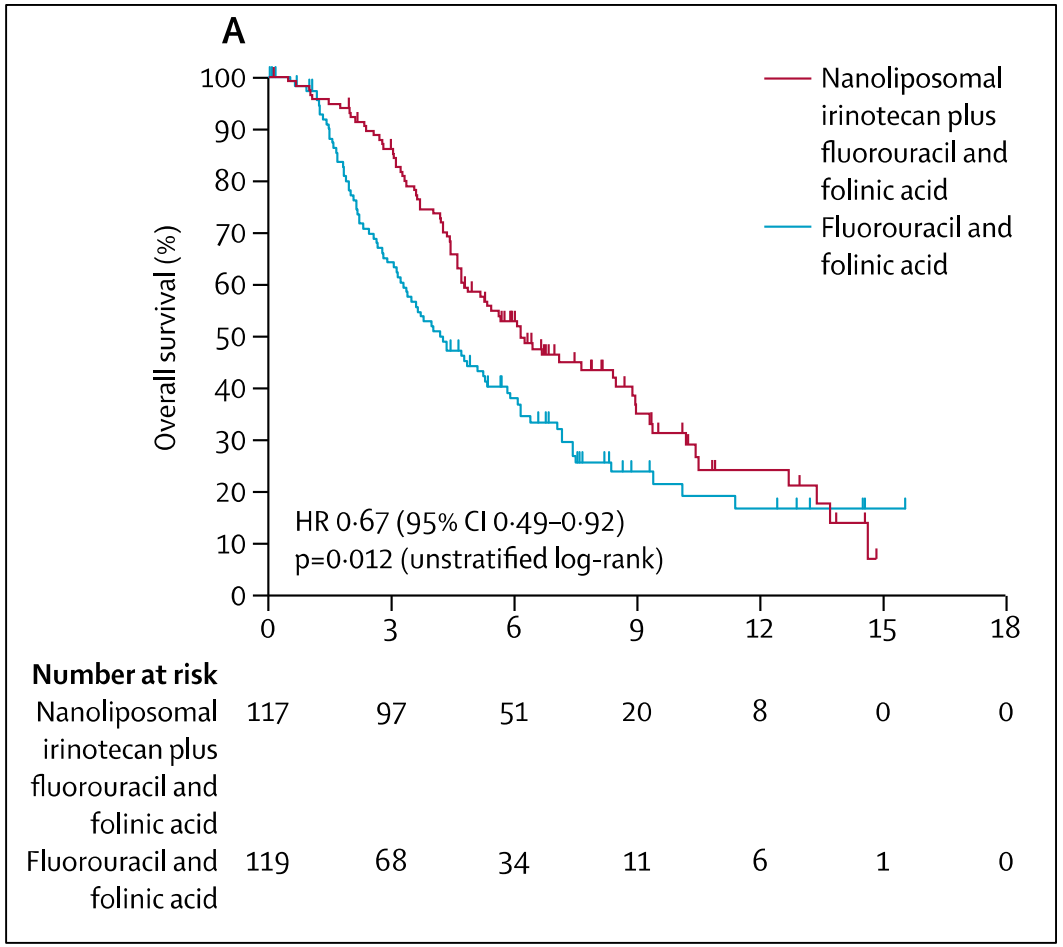
Lancet 2016; 387: 545–57

Disegno dello studio



Wang-Gillam A et al. Lancet 2016

Obiettivo primario: OS



Mediana: 6.1 versus 4.2 mesi

Wang-Gillam A et al. Lancet 2016

Tossicità

	Nanoliposomal irinotecan plus fluorouracil and folinic acid combination therapy (n=117)		Fluorouracil and folinic acid control (n=134)	
	Any grade	Grades 3–4	Any grade	Grades 3–4
Diarrhoea	69 (59%)	15 (13%)	35 (26%)	6 (4%)
Vomiting	61 (52%)	13 (11%)	35 (26%)	4 (3%)
Nausea	60 (51%)	9 (8%)	46 (34%)	4 (3%)
Decreased appetite	52 (44%)	5 (4%)	43 (32%)	3 (2%)
Fatigue	47 (40%)	16 (14%)	37 (28%)	5 (4%)
Neutropenia*	46 (39%)	32 (27%)	7 (5%)	2 (1%)
Anaemia	44 (38%)	11 (9%)	31 (23%)	9 (7%)
Hypokalaemia	14 (12%)	4 (3%)	12 (9%)	3 (2%)

Wang-Gillam A et al. Lancet 2016

Stretegia terapeutica

- Selezione dei pazienti
- Modulazione delle dosi
- Lavoro di squadra
  - Oncologo
  - Infermiere (curante, al domicilio)
  - Medico curante
  - Medico palliativista
  - Dietista, fisioterapista

Epatocarcinoma: nuove opzioni terapeutiche

- Sorafenib e lenvatinib in prima linea
- In seconda linea:
  - Regorafenib, Cabozantinib
  - Ramucirumab
  - Nivolumab o Pembrolizumab

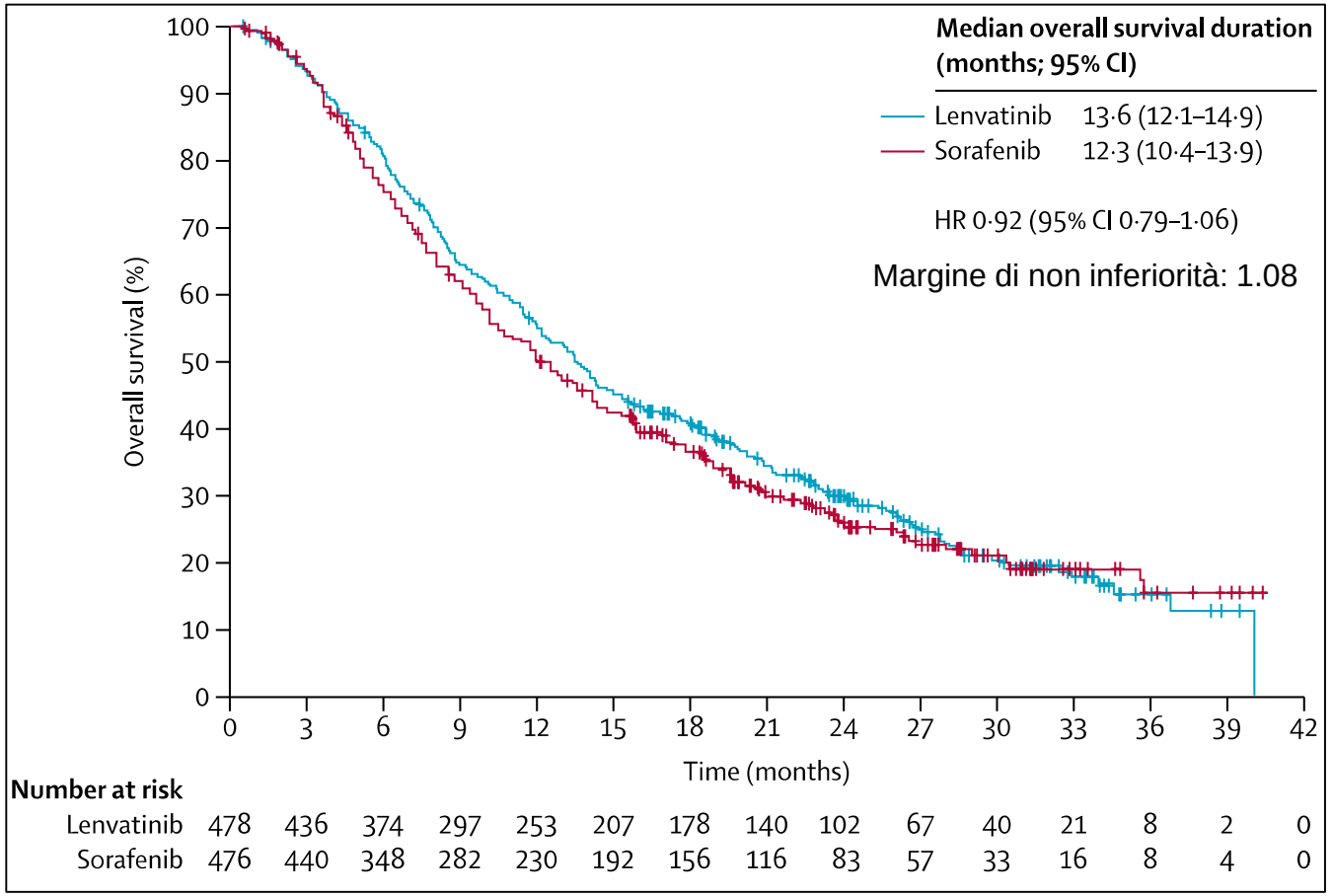
Sorafenib e lenvatinib in prima linea

Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial

Masatoshi Kudo, Richard S Finn, Shukui Qin, Kwang-Hyub Han, Kenji Ikeda, Fabio Piscaglia, Ari Baron, Joong-Won Park*, Guohong Han*, Jacek Jassem, Jean Frederic Blanc, Arndt Vogel, Dmitry Komov, T R Jeffry Evans, Carlos Lopez, Corina Dutcus, Matthew Guo, Kenichi Saito, Silvija Kraljevic, Toshiyuki Tamai, Min Ren, Ann-Lii Cheng*

Lancet 2018; 391: 1163–73

Obiettivo primario: OS (non inferiorità)



Kudo M et al. Lancet 2018

Tossicità

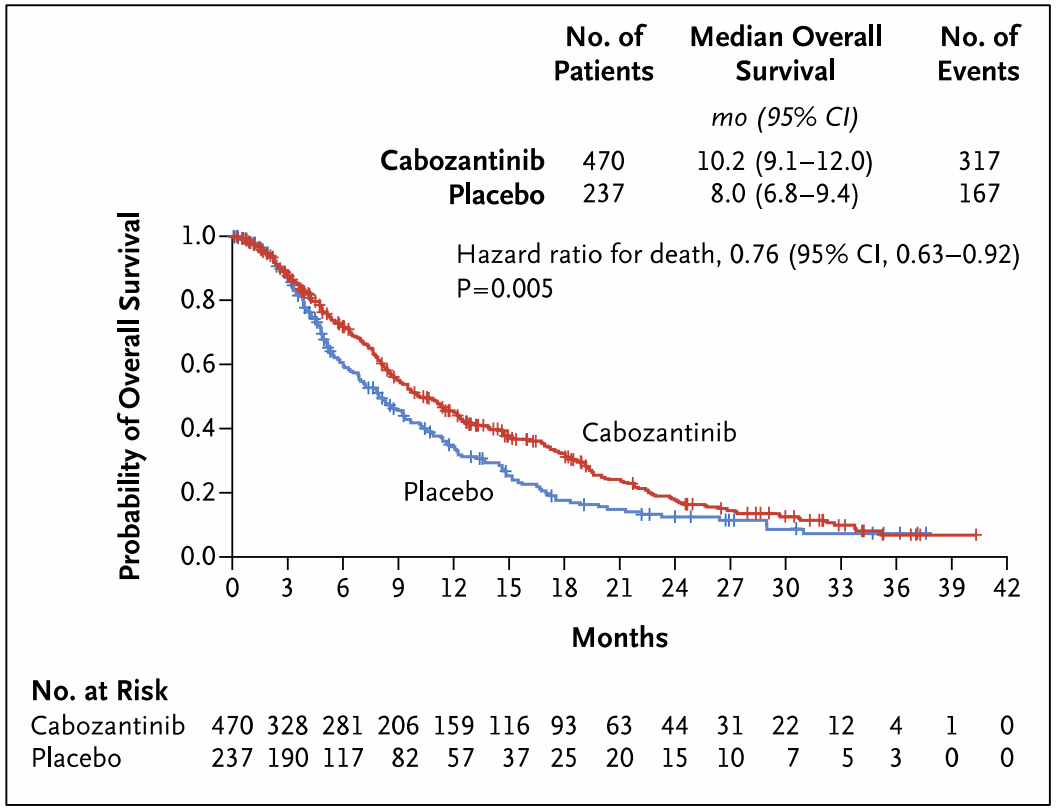
- Lenvatinib: ipertensione (42%), diarrea (39%), inappetenza (34%), calo ponderale (31%)
- Sorafenib: eritrodisestesia palmo-plantare (52%), diarrea (46%, ipertensione (30%), inappetenza (27%)
- AEs grado ≥3: lenvatinib 57%, sorafenib 49%

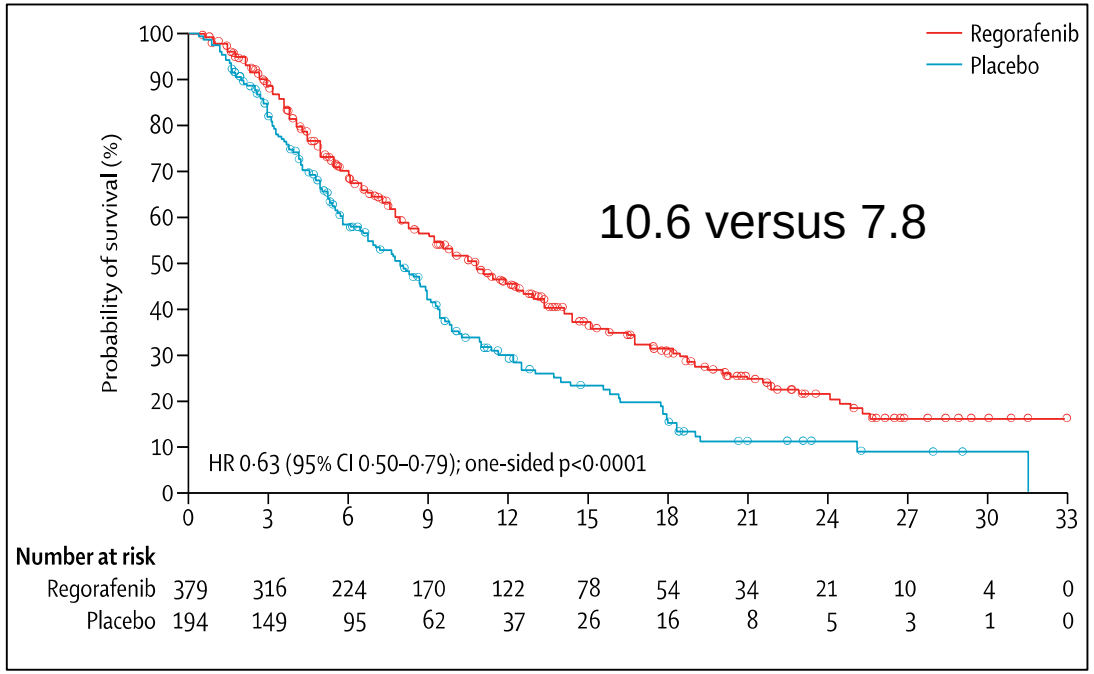
Kudo M et al. Lancet 2018

Seconda linea TKI: Cabozantinib e regorafenib

- Cabozantinib: VEGFR 1, 2 e 3, MET e AXL
- Regorafenib: angiogenesi tumorale (VEGFR1, -2, -3, TIE2), oncogenesi (KIT, REG, RAF-1, BRAF, BRAFV600E), e microambiente tumorale (PDGFR, FGFR)

Obiettivo primario: OS





G.K Abou-Alfa et al. N Engl J Med 2018

J. Bruix et al. Lancet 2017

Tossicità Grado 3-4

- Cabozantinib (68%): sindrome mano-piede (17%), ipertensione (16%), transaminite (12%), fatigue (10%), diarrhea (10%)
- Regorafenib (67%): ipertensione (15%), sindrome mano-piede (13%), fatigue (9%), diarrea (3%).

G.K Abou-Alfa N Engl J Med 2018
J. Bruix et al. Lancet 2017

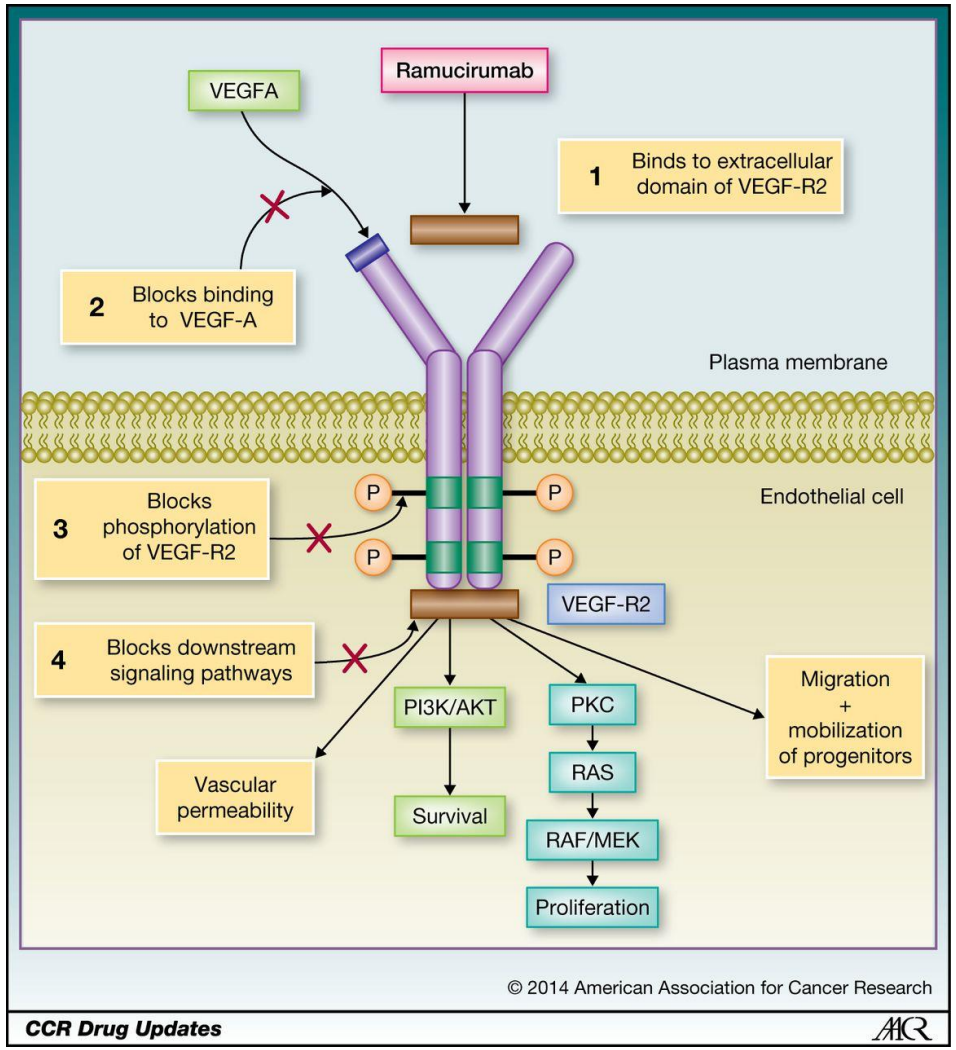
Tossicità dei TKI

Ramucirumab

Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial

*Andrew X Zhu, Yoon-Koo Kang, Chia-Jui Yen, Richard S Finn, Peter R Galle, Josep M Llovet, Eric Assenat, Giovanni Brandi, Marc Pracht, Ho Yeong Lim, Kun-Ming Rau, Kenta Motomura, Izumi Ohno, Philippe Merle, Bruno Daniele, Dong Bok Shin, Guido Gerken, Christophe Borg, Jean-Baptiste Hiriart, Takuji Okusaka, Manabu Morimoto, Yanzhi Hsu, Paolo B Abada, Masatoshi Kudo, for the REACH-2 study investigators**

Ramucirumab



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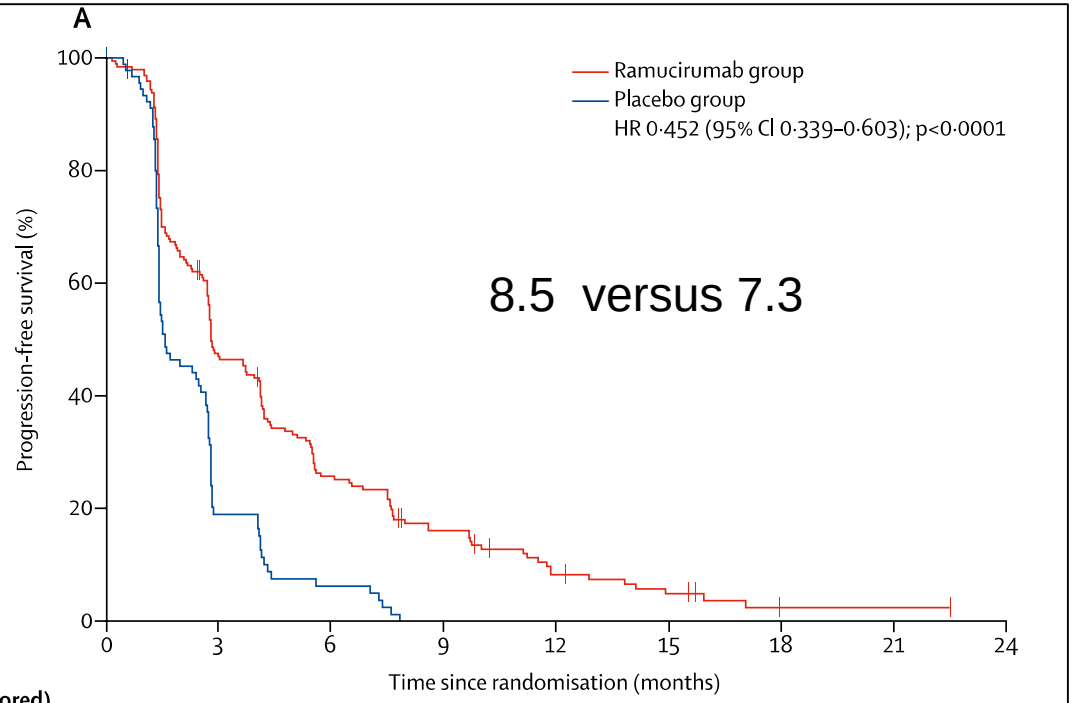

Number at risk (number censored)

Ramucirumab group	197 (0)	87 (10)	44 (14)	25 (17)	11 (20)	6 (21)	1 (24)	1 (24)	0 (25)
Placebo group	95 (0)	15 (9)	5 (9)	0 (9)	0 (9)	0 (9)	0 (9)	0 (9)	0 (9)

A.X. Zhu et al. Lancet Oncology 2019

Tossicità Grado 3-4

- Ipertensione (13%) iponatriemia (6 %) e transaminite (5%)

A.X. Zhu et al. Lancet Oncology 2019

Conclusioni

- Tante novità, nanotecnologie, farmaci orali
- Percorso terapeutico possibile
- Tossicità non trascurabili
- Malattie a cattiva prognosi, pazienti fragili
- Multidisciplinarietà

Grazie per l’attenzione!