

The relevance of individual components in combination therapies

Regulatory aspects

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Why combinations?

- **The combination improves response in those with inadequate response to monotherapy, has a greater overall effect and/or is more rapidly effective;**
- **The combination improves safety due to one active substance counteracting the adverse drug reactions of another or by combining doses that are sub-therapeutic when used in monotherapy.**

Better efficacy / better safety

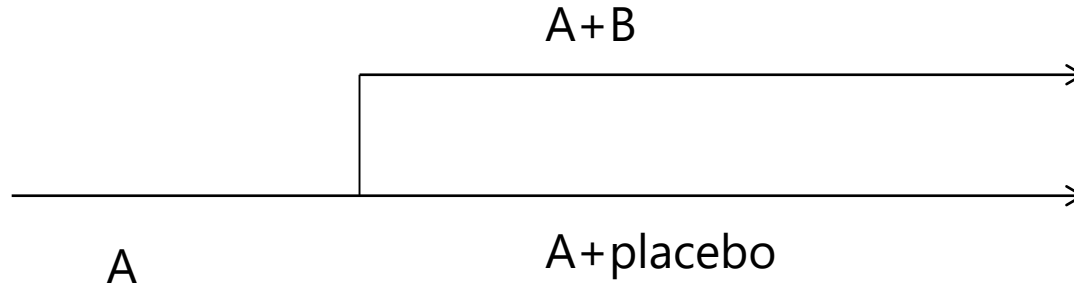
That's all, or not?

1. Justification of the pharmacological and medical ***rationale*** for the combination.
 2. Establishment of the ***evidence base*** for the:
 - a. relevant contribution of **all active substances** to the desired therapeutic effect (efficacy and/or safety);
 - b. positive benefit-risk for the combination in the targeted indication.
- Three therapeutic scenarios are foreseen: add-on treatment, substitution therapy and initial combination treatment requiring different types of evidence.
3. ***Demonstration*** that the ***evidence*** presented - if based on combined administration of separate active substances - ***is relevant to the fixed combination medicinal product*** for which the application is made.

“add-on indication”

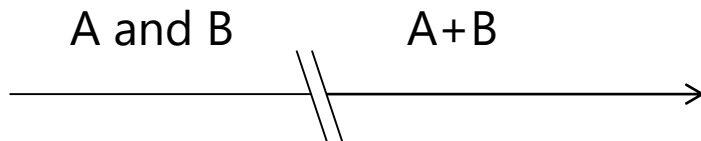
In this scenario, the usual approach is that patients insufficiently responding to A are randomised to receive B or placebo in addition to continued use of A, and vice-versa

...a comparison of AB against A or B only may also suffice, but this will result in an indication restricted to insufficient responders to A or B



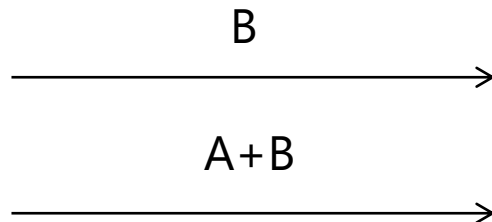
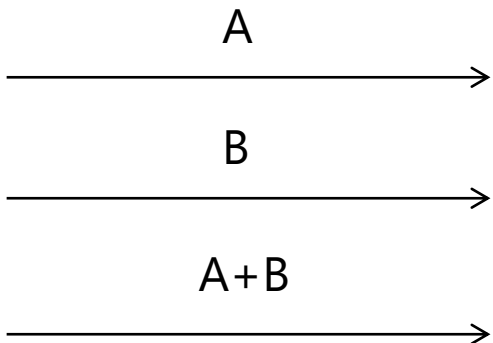
“substitution”

The fixed combination medicinal product is intended to be used in patients who are already stabilised on optimal doses of the combination of the same, but separately administered, active substances, taken at the same dose interval and time.

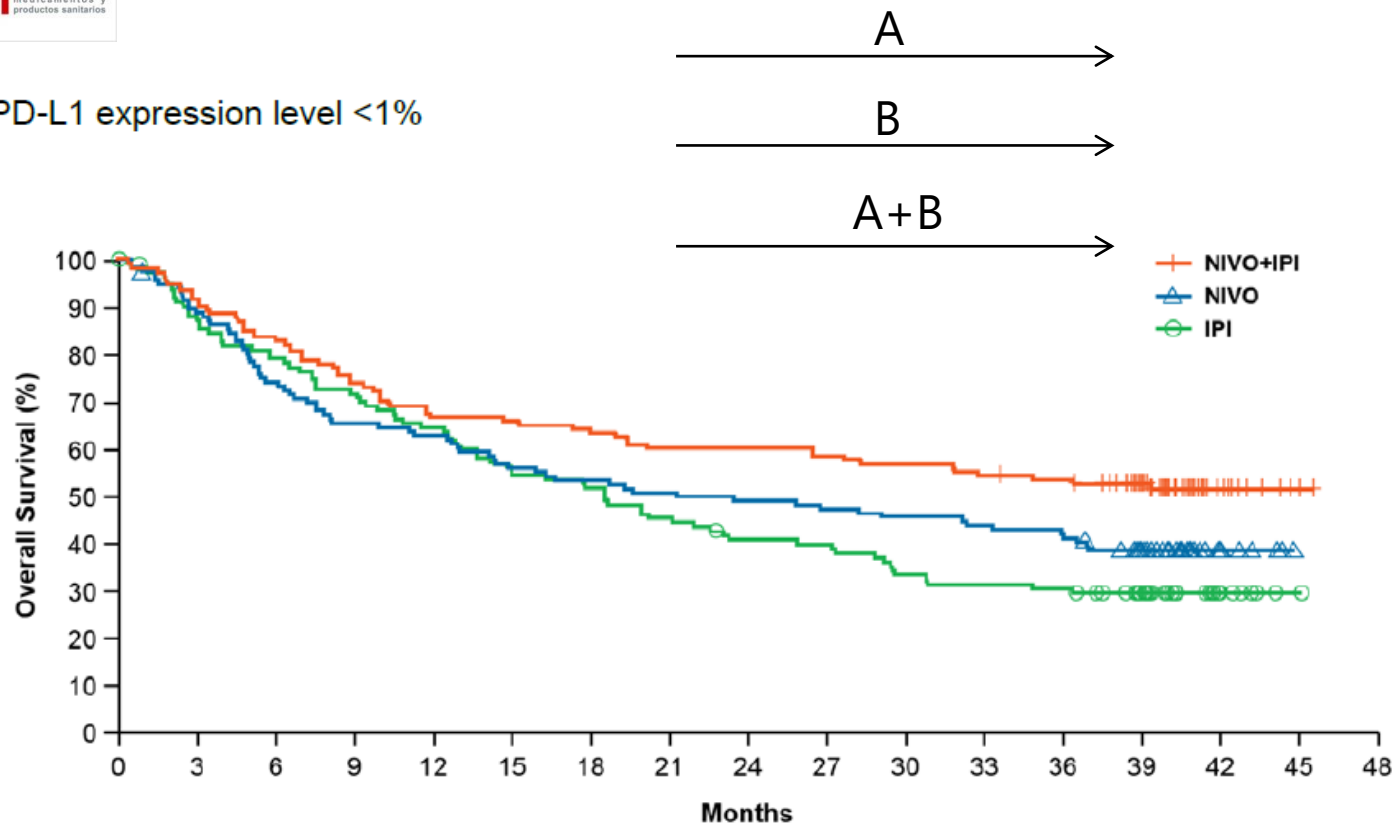


“Initial combination treatment”

1. Two (or more) active substances that each have established efficacy in the targeted indication.



(D) PD-L1 expression level <1%

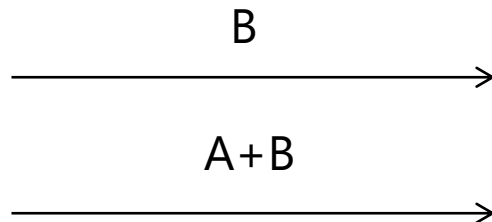
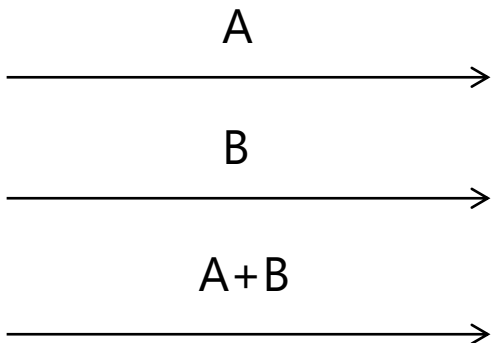


Patients at risk:

NIVO+IPI	123	113	102	91	82	82	79	74	74	72	70	67	65	50	11	2	0
NIVO	117	103	86	76	73	65	62	59	57	55	53	51	49	37	7	0	0
IPI	113	96	87	79	71	61	57	50	44	43	36	34	33	24	8	1	0

“Initial combination treatment”

1. Two (or more) active substances that each have established efficacy in the targeted indication.



A Overall Survival

ORIGINAL ARTICLE

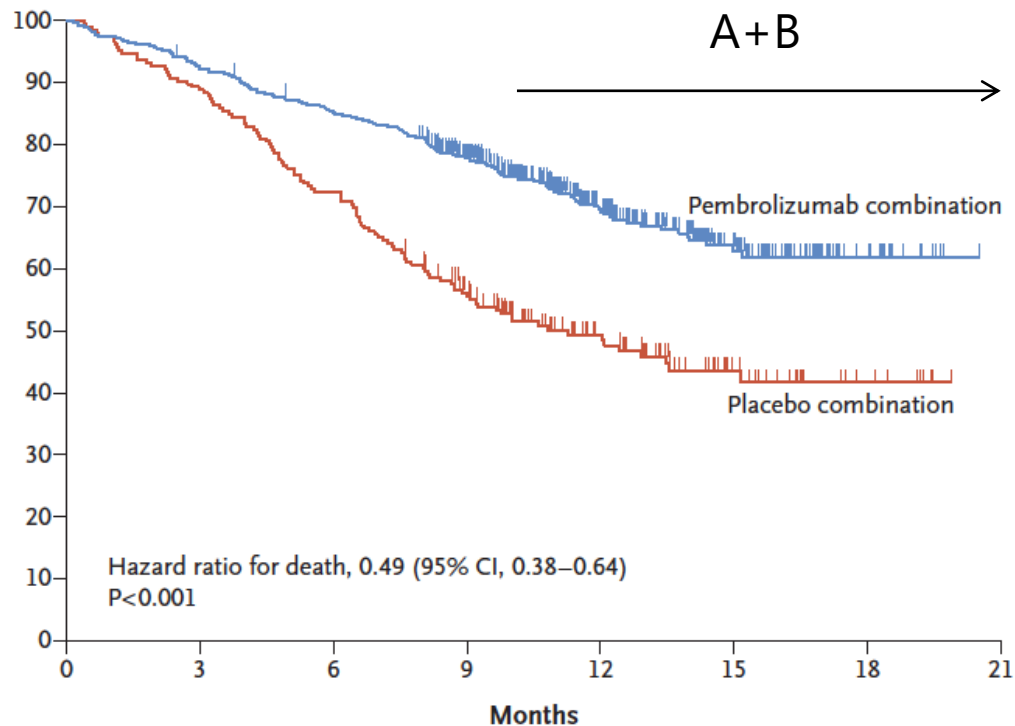
Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer

L. Gandhi, D. Rodríguez-Abreu, S. Gadgeel, E. Esteban, E. Felip,

No. at Risk

Pembrolizumab combination
Placebo combination

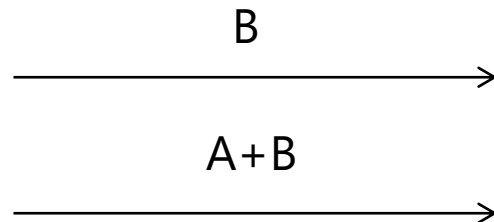
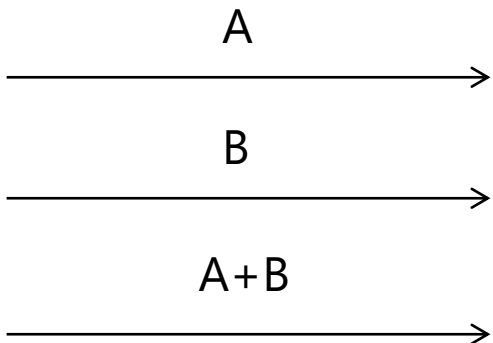
Patients Who Survived (%)



410	377	347	278	163	71	18	0
206	183	149	104	59	25	8	0

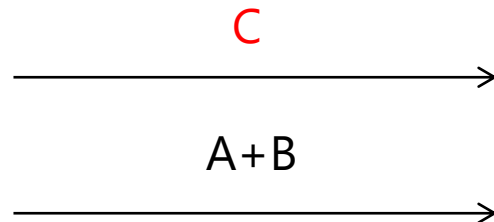
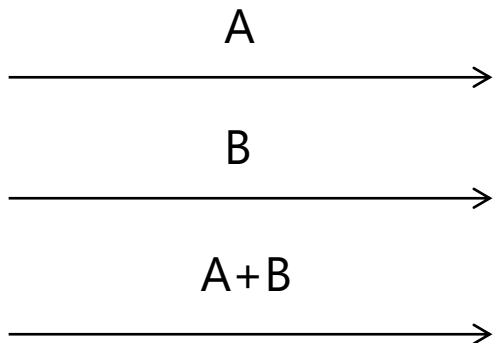
“Initial combination treatment”

1. Two (or more) active substances that each have established efficacy in the targeted indication.

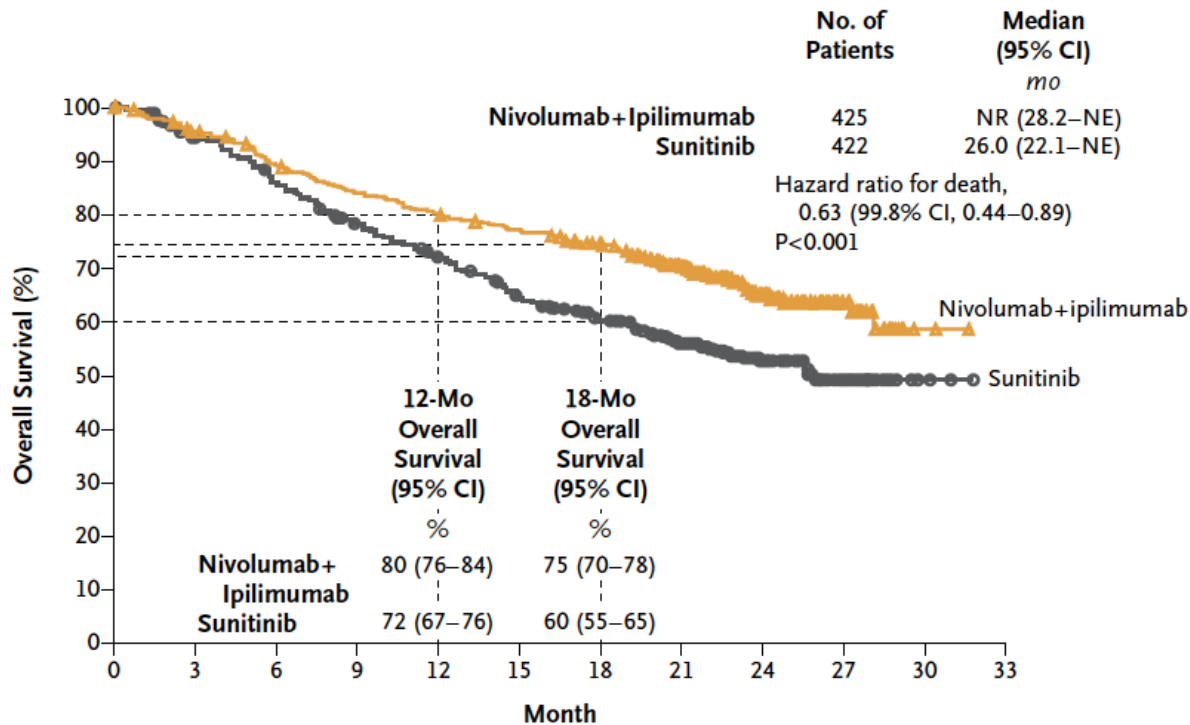


“Initial combination treatment”

1. Two (or more) active substances that each have established efficacy in the targeted indication.



A Overall Survival



No. at Risk

Nivolumab+ipilimumab	425	399	372	348	332	318	300	241	119	44	2	0
Sunitinib	422	387	352	315	288	253	225	179	89	34	3	0

C

A+B

Refusal of a change to the marketing authorisations for Opdivo (nivolumab) and Yervoy (ipilimumab)

On 26 July 2018, the Committee for Medicinal Products for Human Use (CHMP) adopted a **negative opinion**, recommending the refusal of a change to the marketing authorisations for the medicinal products Opdivo and Yervoy. The change concerned adding the use of both medicines in combination for the treatment of renal cell carcinoma (kidney cancer).

The company that applied for the change to the authorisation is Bristol-Myers Squibb Pharma EEIG. It may request a re-examination of the opinion within 15 days of receipt of notification of this negative opinion.

What were the CHMP's main concerns that led to the refusal of the change to the marketing authorisation?

Although improvements in survival were seen in previously untreated patients given the combination of Opdivo and Yervoy compared with sunitinib, **there was no evidence showing if Yervoy contributed to these results and if so, how much.** It is known that Opdivo alone produces benefit in previously treated patients with renal cell carcinoma. This means that the CHMP had no way to know if the addition of Yervoy to Opdivo treatment produced additional benefit. At the same time it was clear that combination with Yervoy resulted in more side effects than are seen with Opdivo alone.

Positive opinion on the change to the marketing authorisation for Opdivo (nivolumab) and Yervoy (ipilimumab)

Outcome of re-examination

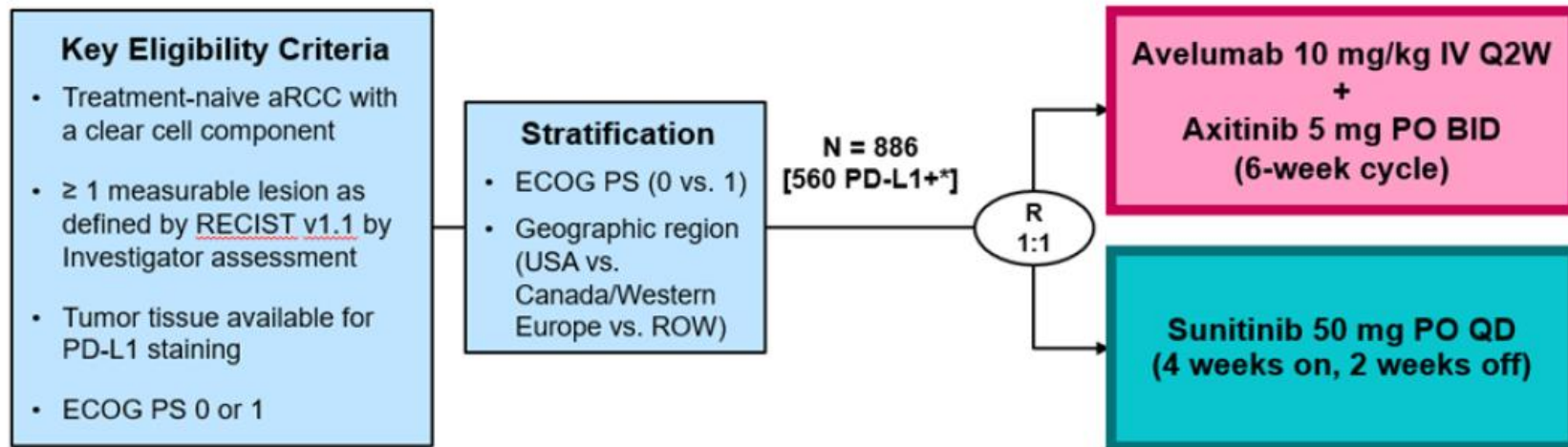
What happened during the re-examination?

During the re-examination, the CHMP looked again at all the data and consulted a group of cancer experts and patients with cancer. The CHMP also discussed the possibility to request that further data be collected following the authorisation of the combination.

What were the conclusions of the CHMP following the re-examination?

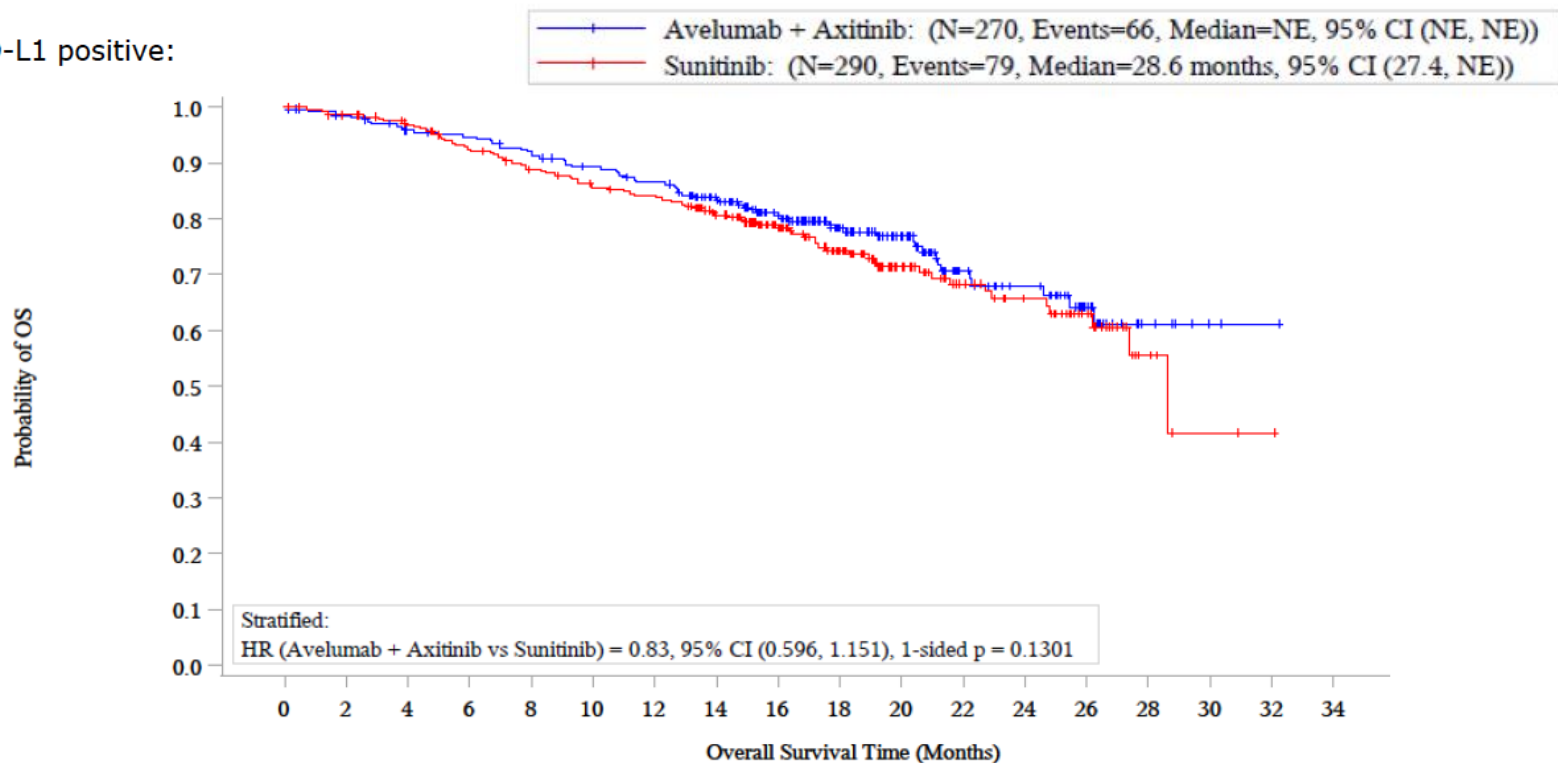
The CHMP considered that the results from the main study comparing Opdivo and Yervoy with sunitinib showed a clinically important increase in patients' survival with the combination, and side effects were considered acceptable. Although the precise contribution of Yervoy was not clear, the CHMP re-assessed data from other non-clinical and clinical studies, including studies with the combination in

Pivotal study B9991003 (JAVELIN Renal 101)



Primary Endpoints	• PFS by BICR in the PD-L1+ Population • OS in the PD-L1+ Population
Key Secondary Endpoints	• PFS by BICR in the Overall Population • OS in the Overall Population
Other Secondary	• PFS by Investigator in the PD-L1+ and Overall Population • OR by BICR and by Investigator in the PD-L1+ Population • OR by BICR and by Investigator in the Overall Population • Safety

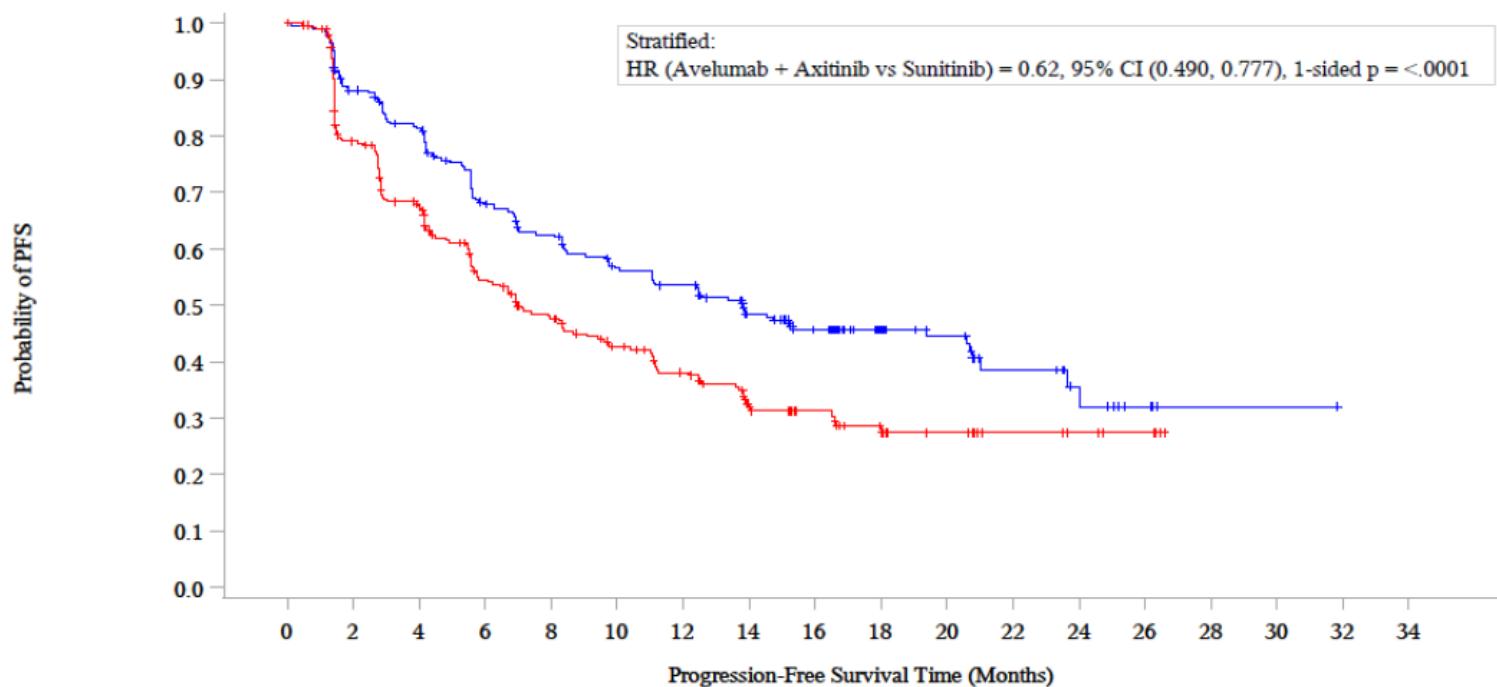
PD-L1 positive:



No. at risk

Avelumab + Axitinib:	270	262	251	247	239	229	221	197	159	118	89	53	43	25	9	4	1	0
Sunitinib:	290	281	271	256	243	232	227	197	148	115	81	61	48	30	8	2	1	0

PD-L1 positive:



No. at risk

Avelumab + Axitinib:	270	225	203	165	149	131	123	93	75	50	36	19	10	5	1	1	0
Sunitinib:	290	209	171	130	109	89	74	51	36	24	14	9	6	4	0		

1. Guideline on clinical development of fixed combination medicinal products EMA/CHMP/158268/2017

- Two (or more) active substances that **each have established efficacy in the targeted indication.**
 - Avelumab has not shown (PFS/OS) benefit in RCC

2. OS benefit overcomes the need of knowledge of activity of monocomponents

- There is no superiority in OS

	Study B9991003		Study EMR100070-001	Study A4061051	
	Avelumab + Axitinib (N=442)		Avelumab (N=62)	Axitinib (N=192)	
	BICR	Investigator	Investigator	BICR	Investigator
Progression-Free Survival					
Subjects with event, n (%)	180 (40.7)	188 (42.5)	10 (16.1)	111 (57.8)	117 (60.9)
Kaplan-Meier estimates of Time to Event (months) Quartiles (95% CI)[1]					
Median	13.8 (11.1, NE)	12.5 (11.1, 15.2)	8.28 (5.52, 9.53)	10.1 (7.2, 12.1)	11.1 (8.3, 13.6)
Confirmed Best Overall Response n (%)					
Complete response (CR)	15 (3.4)	14 (3.2)	1 (1.6)	0	0
Partial response (PR)	212 (48.0)	233 (52.7)	9 (14.5)	62 (32.3)	72 (37.5)
Stable disease (SD)	131 (29.6)	127 (28.7)	38 (61.3)	83 (43.2)	86 (44.8)
Non-CR/Non-PD	8 (1.8)	1 (0.2)	0	0	0
Progressive disease (PD)	51 (11.5)	38 (8.6)	11 (17.7)	20 (10.4)	21 (10.9)
Not evaluable (NE) [2]	25 (5.7)	29 (6.6)	3 (4.8)	11 (5.7)	13 (6.8)
Objective Response (CR+PR), n (%)	227 (51.4)	247 (55.9)	10 (16.1)	62 (32.3)	72 (37.5)
95% CI [3]	46.6, 56.1	51.1, 60.6	8.0, 27.7	25.7, 39.4	30.6, 44.8

3.3. Uncertainties and limitations about favourable effects

The PFS in patients with PD-L1 negative tumours had a HR of 0.87 (0.62; 1.22). However, the study is not powered to show effect in the PD-L1 negative subgroup (which comprises 36.8% of the trial population) and does not lead to a restriction of the indication.

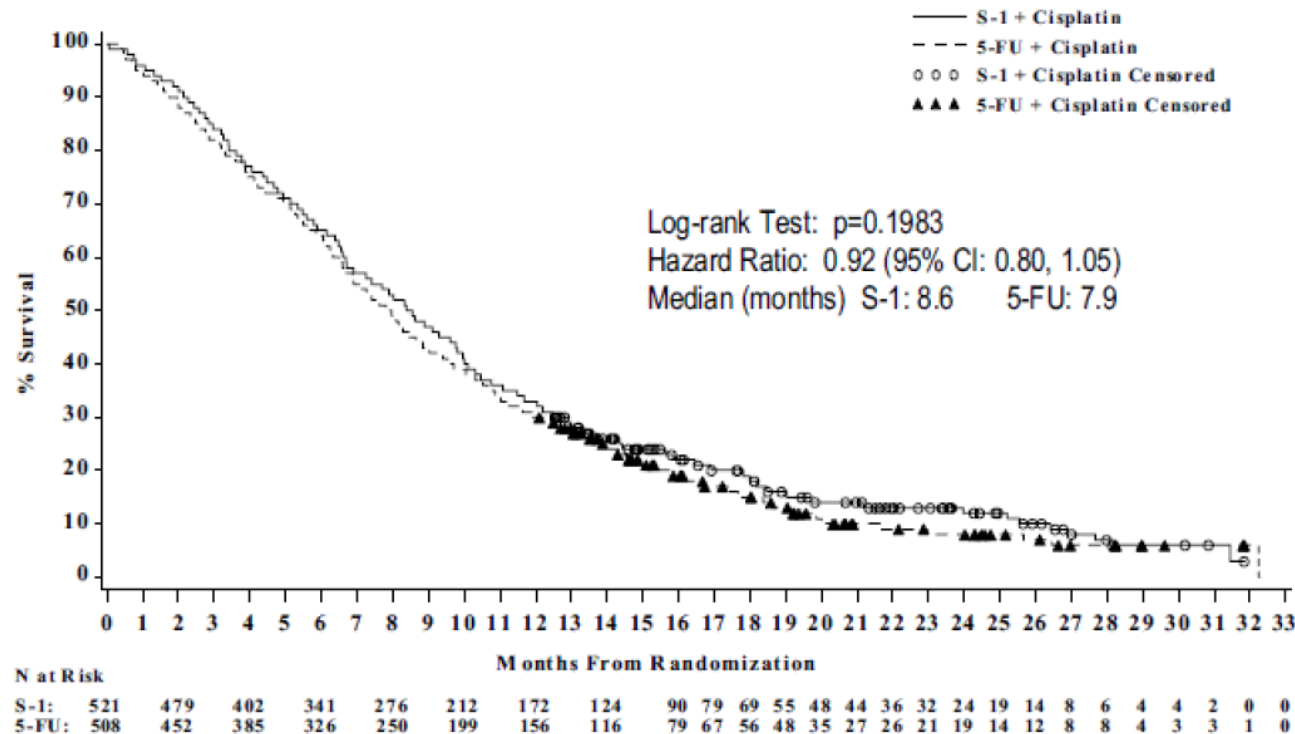
OS point estimates favour avelumab in combination with axitinib compared to sunitinib. However, the OS results are immature (irrespective of PD-L1 expression, the OS maturity by arm was 20% for the experimental arm and 24% for the control arm in January 2019) and statistical significance has not been reached. The uncertainty concerning the maturity of OS is noted. However, a detrimental effect on OS is shown to be unlikely.

While the additive effect of axitinib and avelumab have been shown based on a substantial increase in ORR over the individual agents, this is based on cross study comparisons. Thus, the additive effect has been shown in a qualitative sense, but there is no precise quantification of the contribution of each agent. However, available data are considered sufficient to justify the contribution of each agent to the overall activity of the proposed regimen..

“Initial combination treatment”

2. A PK enhancer with one (or more) active substance(s) with established efficacy in the targeted indication

... if appropriately justified based on in vitro, preclinical and/or PK and PD data, a comparator arm with the PK enhancing active substance alone is not required in the clinical studies



Teysono (S-1), a fixed dose combination (tegafur, prodrug of 5-FU; gimeracil, to prevent degradation of 5-FU by the body; and, oteracil, an inhibitor that decreases the activity of 5-FU in normal gastrointestinal mucosa.

“Initial combination treatment”

3. One (or more) active substance has no individual efficacy in the targeted indication

... preclinical and human PD data may be sufficient to support a claim of improved efficacy of the fixed combination medicinal product instead of (stepwise) up-titration or addition of those active substances in a clinical efficacy/safety study

Summary

- The contribution of each agent to the overall activity can be justified based on cross study comparison (same disease and setting) in terms of PD activity (ORR)
- Important increase in patients' survival along with MoA and non-clinical data can justify a new combination
- SA is always recommendable

Thank you!



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