ESMO ON AIR

ESMO VIRTUAL JOURNAL CLUB

Sylvie Lorenzen, Chair

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19 March 2025

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY

LEARNING OBJECTIVES

- To discuss and critically evaluate notable recent publications.
- To enhance the understanding and application of the latest research in the field.
- To assess the study's robustness, its significance to oncology practice, limitations, and its place within existing research.
- To identify and highlight any unclear aspects or unmet needs.

PROGRAMME AND SPEAKERS

19 March 2025

5 min	**Welcome and introduction** Sylvie Lorenzen
20 min	**Imlunestrant with or without Abemaciclib in Advanced Breast Cancer** Michael Ignatiadis
20 min	**Nivolumab plus Ipilimumab in Microsatellite-Instability–High Metastatic Colorectal Cancer** Claire Gallois
10 min	**Live Q&A and Discussion** All speakers

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Chair
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Department of Hematology and Oncology
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Michail Ignatiadis
Speaker
Institut Jules Bordet
Hôpital Universitaire de Bruxelles

Claire Gallois
Speaker
Hôpital européen Georges-Pompidou

ESMO ON AIR

Imlunestrant with or without Abemaciclib in Advanced Breast Cancer

Michail Ignatiadis MD, PhD

Director Breast Medical Oncology Clinic, Institut Jules Bordet, Hôpital Universitaire de Bruxelles, Belgium

Chair Breast Cancer Group, EORTC

19 March 2025

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Disclosures

- ✓ Consultant or advisory role (honoraria): Seattle Genetics, Daichi, AstraZeneca, Menarini/Stemline, Gilead Sciences, Rejuveron Senescence Therapeutics, and Novartis

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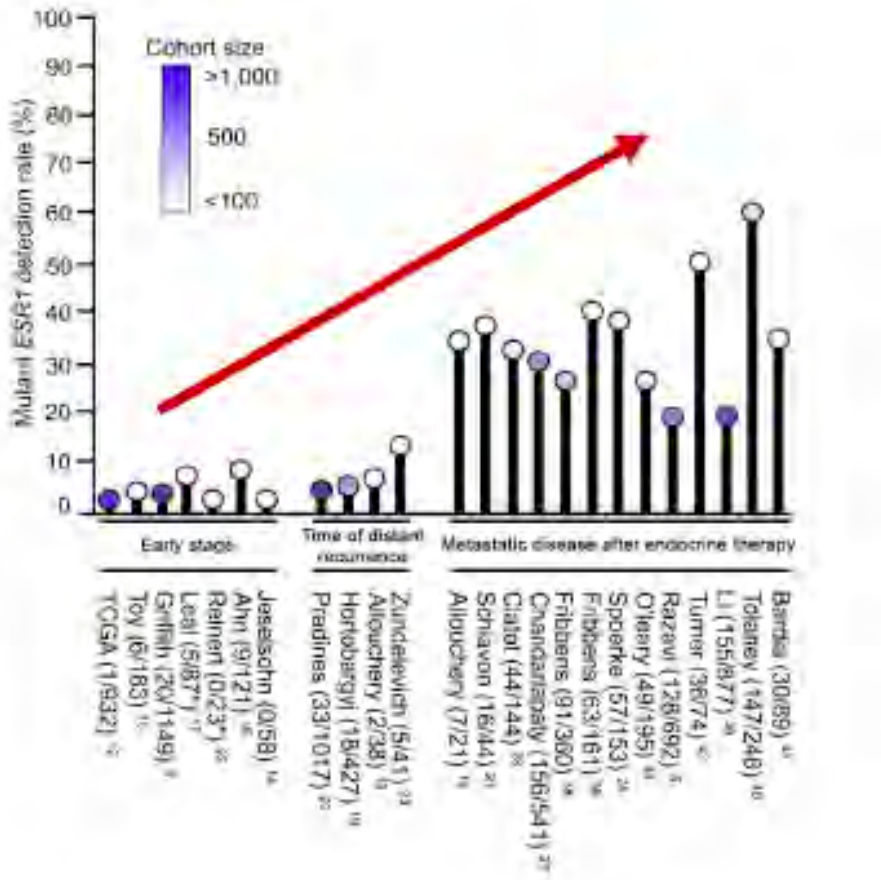
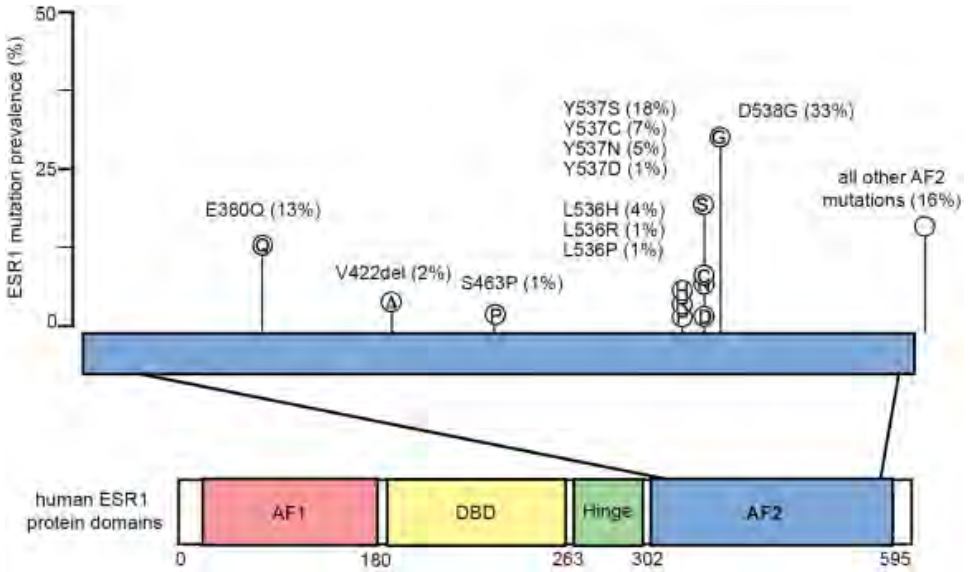
- ✓Stock ownership: None

- ✓Travel grants: Gilead, Roche, Astra Zeneca

ESR1 mutations





Ligand-binding domain

Constitutive ligand-independent ER activity

Enriched in metastatic disease

AI resistance

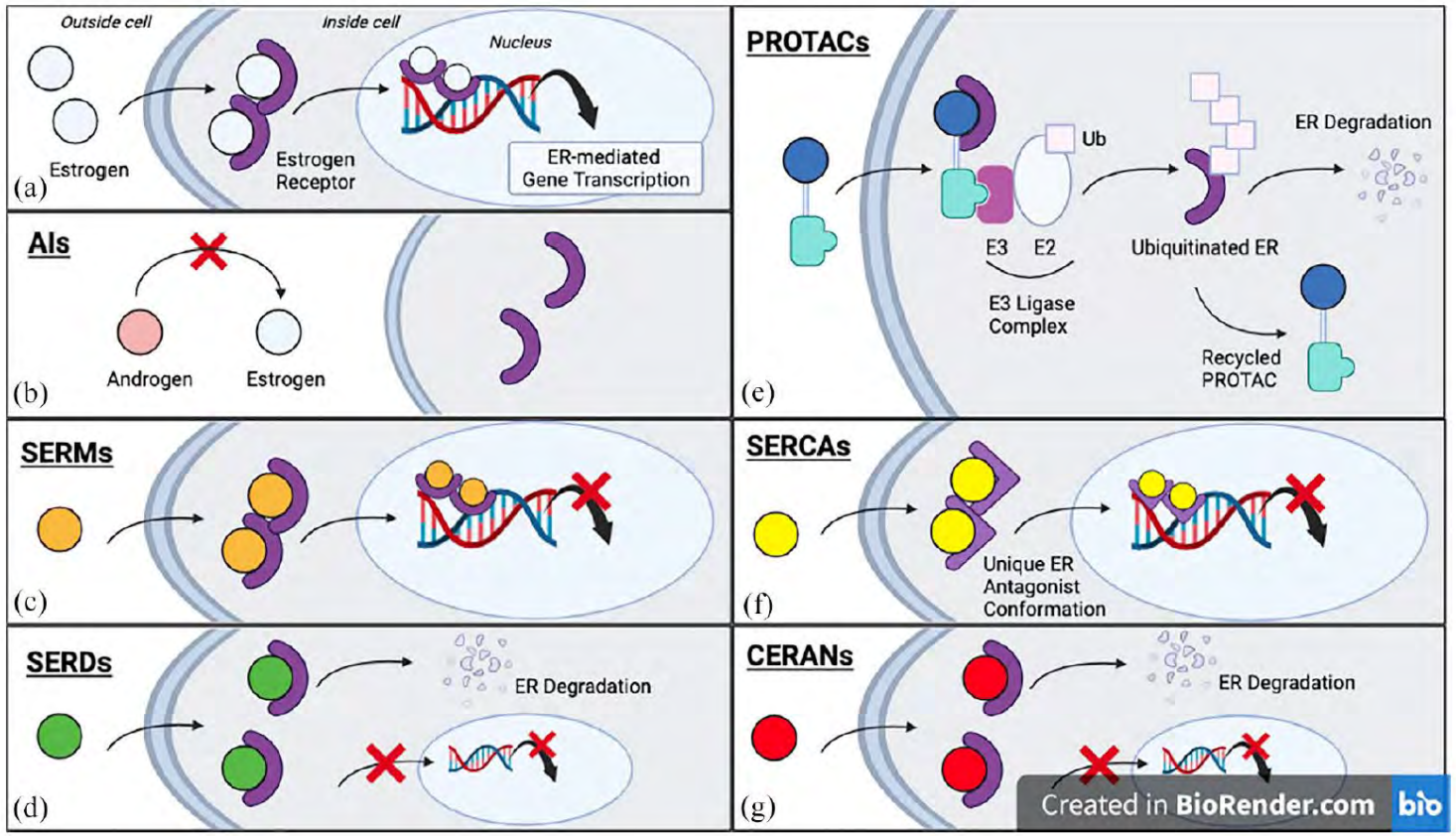
Decreased Fulvestrant affinity

A. Grinshpun, Heme Onc Clinics 2023; A. Grinshpun et al, BBA Rev on Cancer, 2023

Emerging ER targeting drugs

Selective ER Modulators
Tamoxifen
Lasoxifen

Selective ER Degraders
Elacestrant
Imlunestrant
Camizestrant
Giredestrant
….



Proteolysis Targeting Chimeras
Vepdegestrant

Selective ER Covalent Antagonist
H3B-6545

Complete ER antagonists
OP1250

Loyd MR et al, Ther Adv Med Oncol 2022

Trial design

ER+, HER2- ABC

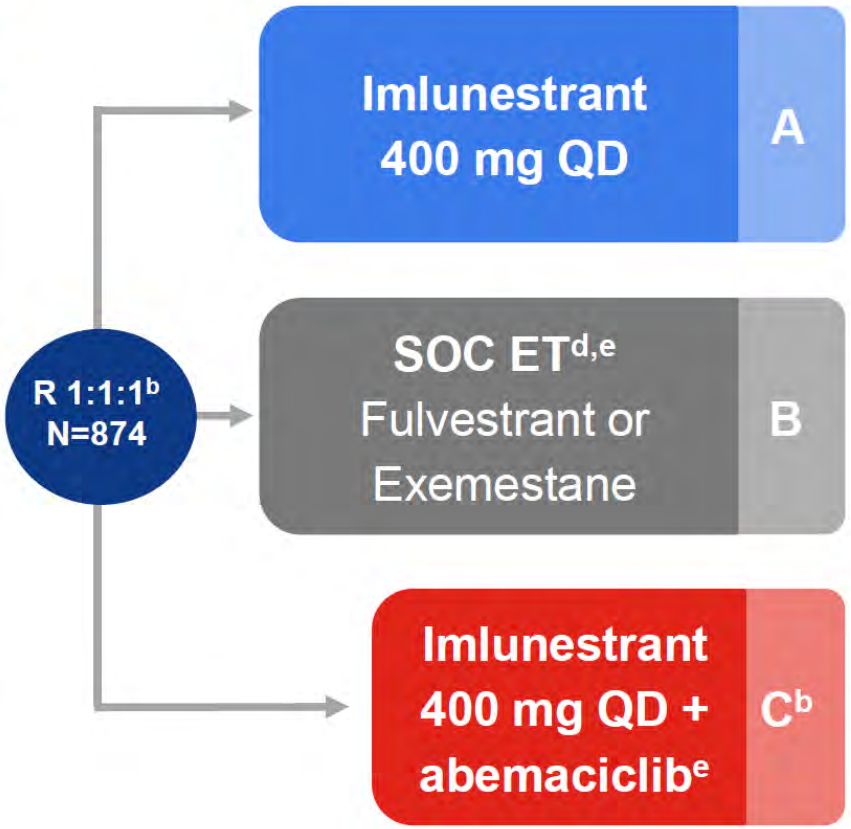
Men and Pre-[a]/Post-menopausal women

Prior therapy:

- **Adjuvant**: Recurrence on or within 12 months of completion of AI ± CDK4/6i
- **ABC:** Progression on first-line AI ± CDK4/6i
- No other therapy for ABC

Stratification Factors:

- Prior CDK4/6i therapy (Y/N)
- Visceral metastases (Y/N)
- Region[c]



Primary Endpoints

Investigator-assessed PFS for[f]:

- A vs B in patients with *ESR1*m[g]
- A vs B in all patients
- C vs A in all[h] patients

Key Secondary Endpoints

- OS, PFS by BICR, and ORR
- Safety

Exploratory Endpoints

- PFS and OS for C vs B in all[h] patients

ABC, advanced breast cancer; AI, aromatase inhibitor; BICR, blinded independent central review; CDK4/6i CDK4/6 inhibitor; ER, estrogen receptor; *ESR1*m, *ESR1* mutation; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QD, once daily; SOC ET, standard of care endocrine therapy. Patients were enrolled from October 2021 to November 2023 across 195 sites in 22 countries. [a] A GnRH agonist was required in men and premenopausal women; [b] Enrollment into Arm C started with Protocol Amendment A (at which point 122 patients had been randomized across Arms A and B); [c] East Asia vs United States/European Union vs others; [d] Investigator's choice; [e] Labeled dose; [f] Scans every 8 weeks for the first 12 months, then every 12 weeks; [g] *ESR1*m status was centrally determined in baseline plasma by the Guardant 360 ctDNA assay and OncoCompass Plus assay (Burning Rock Biotech) for patients from China; [h] Analysis conducted in all concurrently randomized patients.

K.L. Jhaveri et al SABCS 2024, K.L. Jhaveri et al NEJM 2024

Baseline Patient Characteristics

Characteristic		Imlunestrant n=331	SOC ET n=330	Imlunestrant + abemaciclib n=213
Median age, years (range)		61 (28-87)	62 (27-89)	62 (36-87)
Female, %		99	99	99
Post-menopausal, %		84	86	86
Race, %	White	56	58	52
	Asian	28	29	34
	Black or African American	3	2	4
Region, %	East Asia	25	26	31
	North America/ Western Europe	38	39	45
	Other	37	36	24
PR-positive, %		78	79	74
***ESR1* mutation, %[a]**		42	36	32
PI3K pathway mutations, %[b]		39	39	41

Characteristic		Imlunestrant n=331	SOC ET n=330	Imlunestrant + abemaciclib n=213
Site of metastases, %	Visceral	57	54	56
	Liver	32	30	27
	Bone-only	22	26	24
Endocrine resistance, %[c]	Primary	8	11	8
	Secondary	92	89	93
Most recent ET, %[d]	Adjuvant	32	34	30
	ABC	63	63	68
Previous CDK4/6i, %	Overall	59	57	65
	Adjuvant	4	5	3
	ABC	55	53	62
Previous CDK4/6i therapy, %[e]	Palbociclib	61	69	65
	Ribociclib	29	27	27
	Abemaciclib	10	4	7

Baseline characteristics were generally well balanced including in patients with *ESR1*m[f]

CDK4/6i, CDK4/6 inhibitor; *ESR1*m, *ESR1* mutation; ET, endocrine therapy; PR, progesterone receptor; SOC ET, standard of care endocrine therapy. [a] Samples were analyzed by Guardant360 CDx, except for patients from China where samples were analyzed by OncoCompass Target assay, Burning Rock Biotech; [b] Includes single nucleotide variants and insertions/deletions of *PIK3CA*, *AKT1* or *PTEN* analyzed by Guardant 360 ctDNA assay. This analysis excludes patients from China or with unknown *ESR1*m status; [c] Per ESO-ESMO International Consensus Guidelines for ABC (ABC 6 and 7); [d] Adjuvant ET = First-line; ABC = Second-line; [e] Percentages calculated based on the numbers of patients who received prior CDK4/6i therapy (imlunestrant, n=195; SOC ET, n=189; imlunestrant + abemaciclib, n=139); [f] Data available in the online supplementary slides.

K.L. Jhaveri et al SABCS 2024, K.L. Jhaveri et al NEJM 2024

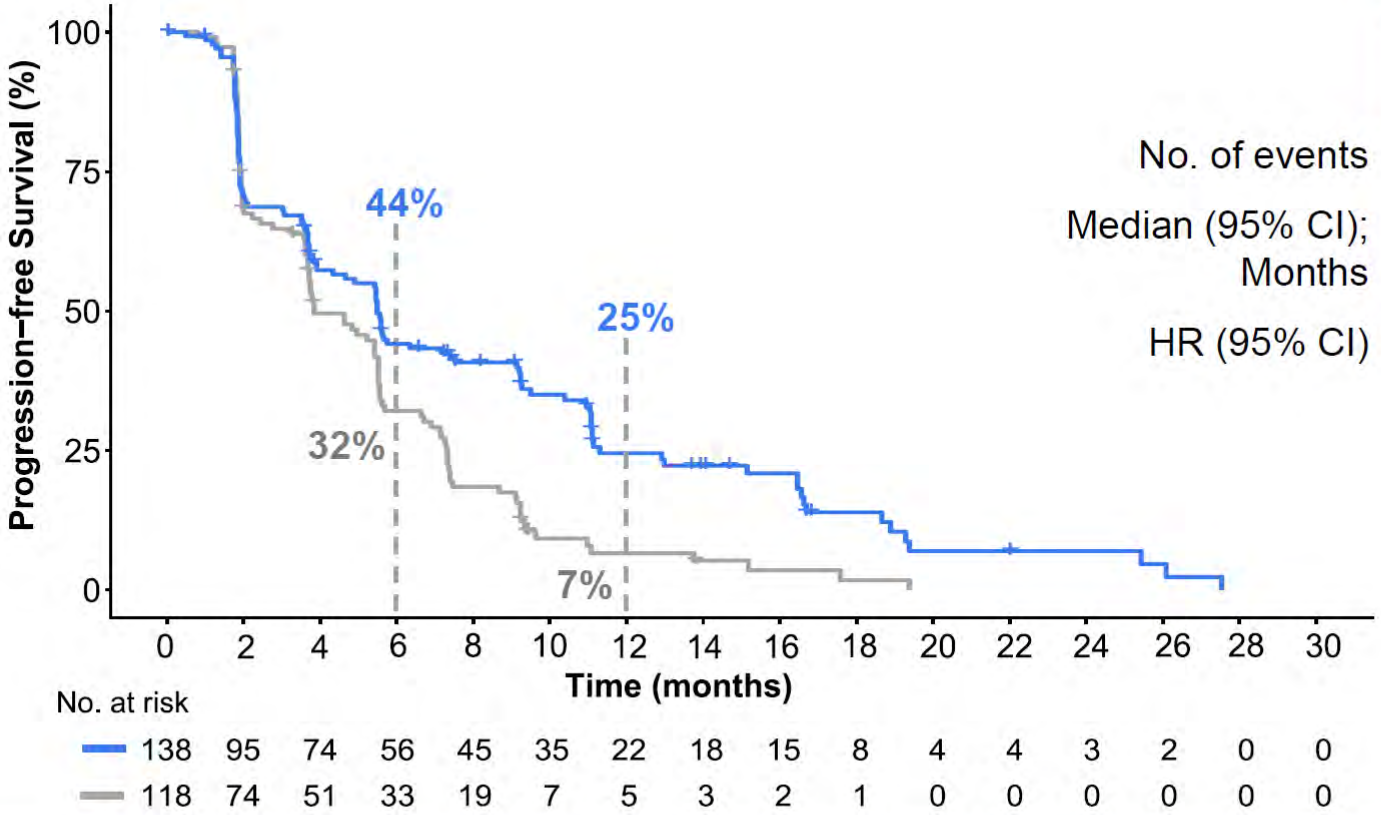
Statistical Considerations

- **A graphical approach was used to control the overall type I error rate at 1-sided 0.025**
- **Alpha was initially assigned to the first PFS analysis of imlunestrant vs SOC ET**
  - 0.02 alpha assigned to patients with *ESR1*m (192 PFS events, 97%[a] power to detect a HR of 0.57)
  - 0.005 alpha assigned to all patients (480 PFS events, 76%[a] and 91%[b] power to detect a HR of 0.74)
- **Analysis of imlunestrant + abemaciclib vs imlunestrant[c] was only tested if one of the imlunestrant vs SOC ET endpoints was significant**
  - 80%[b] power, with 248 PFS events, to detect a target HR of 0.7
- **OS was only tested if the corresponding PFS endpoint was significant**

*ESR1*m, *ESR1* mutation; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; SOC ET, standard of care endocrine therapy. [a] At initial alpha; [b] At full alpha after recycling; [c] Analysis conducted in all concurrently randomized patients.

K.L. Jhaveri et al SABCS 2024, K.L. Jhaveri et al NEJM 2024

Primary endpoint: Imlunestrant vs SOC ET
Investigator-assessed PFS in Patients with ESR1 mutations



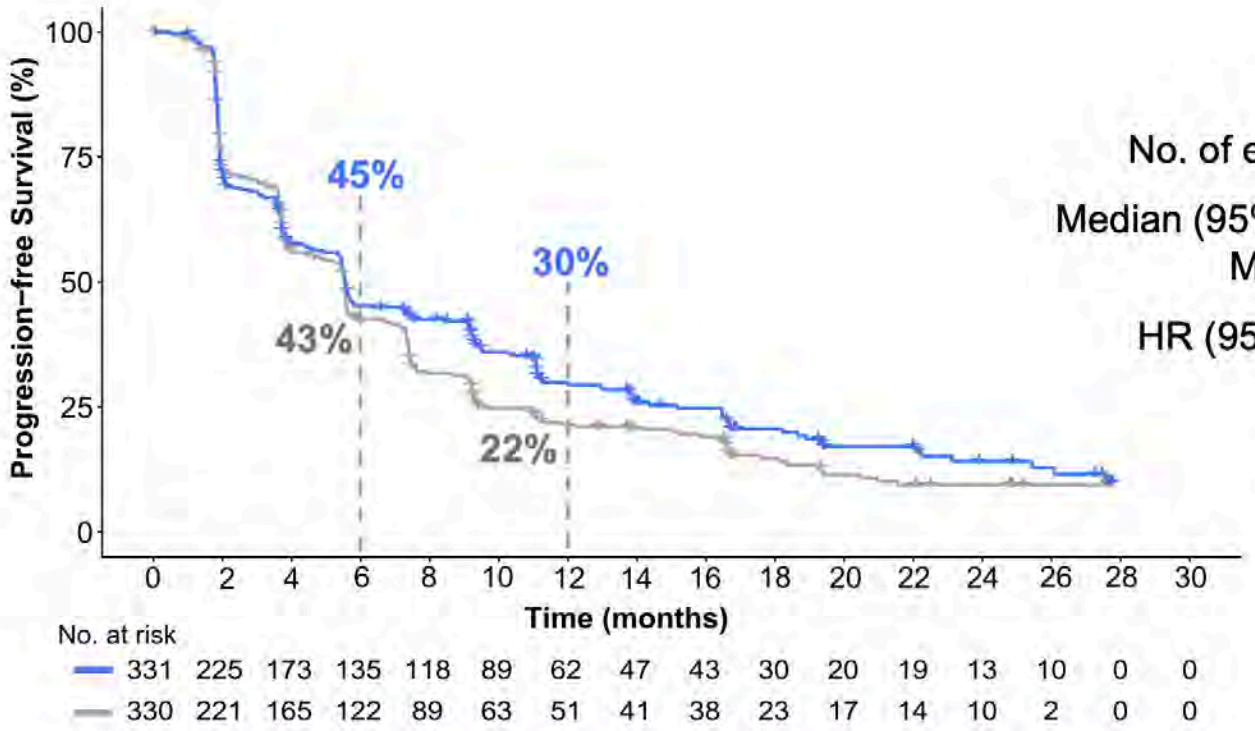
	Imlunestrant n=138	SOC ET n=118
No. of events	109	102
Median (95% CI); Months	**5.5** (3.9-7.4)	**3.8** (3.7-5.5)
HR (95% CI)	**0.62 (0.46-0.82)**[a] *p*-value<0.001	

Imlunestrant led to a 38% reduction in the risk of progression or death in patients with *ESR1*m

CI, confidence interval; *ESR1*m, *ESR1* mutation; HR, hazard ratio; RMST, restricted mean survival time; SOC ET, standard of care endocrine therapy. The median follow-up was 16.7 months in the imlunestrant arm and 13.8 months in the SOC ET arm.
[a] Due to evidence of non-proportional hazards, a sensitivity analysis of PFS using RMST was conducted. Estimated RSMT at 19.4 months was 7.9 months (95% CI 6.8-9.1) in the imlunestrant arm vs 5.4 months (95% CI 4.6-6.2) in the SOC ET arm [difference 2.6 months (1.2.-3.9)].

K.L. Jhaveri et al SABCS 2024, K.L. Jhaveri et al NEJM 2024

Primary endpoint: Imlunestrant vs SOC ET
Investigator-assessed PFS in All Patients



	Imlunestrant n=331	SOC ET n=330
No. of events	237	253
Median (95% CI); Months	**5.6** (5.3-7.3)	**5.5** (4.6-5.6)
HR (95% CI)	**0.87 (0.72-1.04)** *p*-value 0.12	

Prespecified Critical HR < 0.84[a]

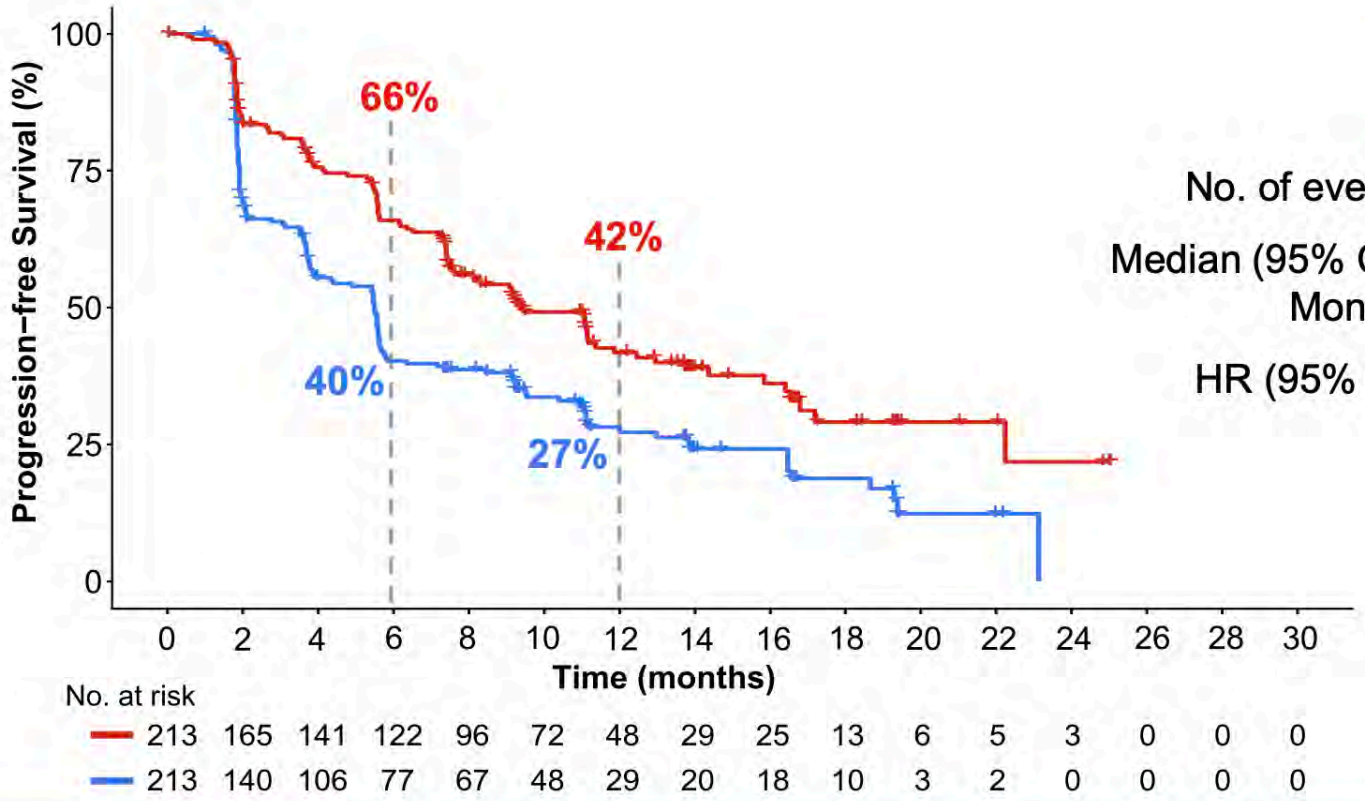
PFS difference of imlunestrant vs SOC ET in all patients did not reach significance

- The majority subgroup of patients without *ESR1*m showed no difference in PFS (HR=1.00; 95% CI, 0.79-1.27)[b]

CI, confidence interval; *ESR1*m, *ESR1* mutation; HR, hazard ratio; PFS, progression-free survival; SOC ET, standard of care endocrine therapy. The median follow-up was 16.6 months in the imlunestrant arm and 16.8 months in the SOC ET arm.
[a] At full alpha; [b] Data available in the online supplementary slides.

K.L. Jhaveri et al SABCS 2024, K.L. Jhaveri et al NEJM 2024

Primary endpoint Imlunestrant + Abemaciclib vs Imnulestrant Investigator-assessed PFS in All Patients



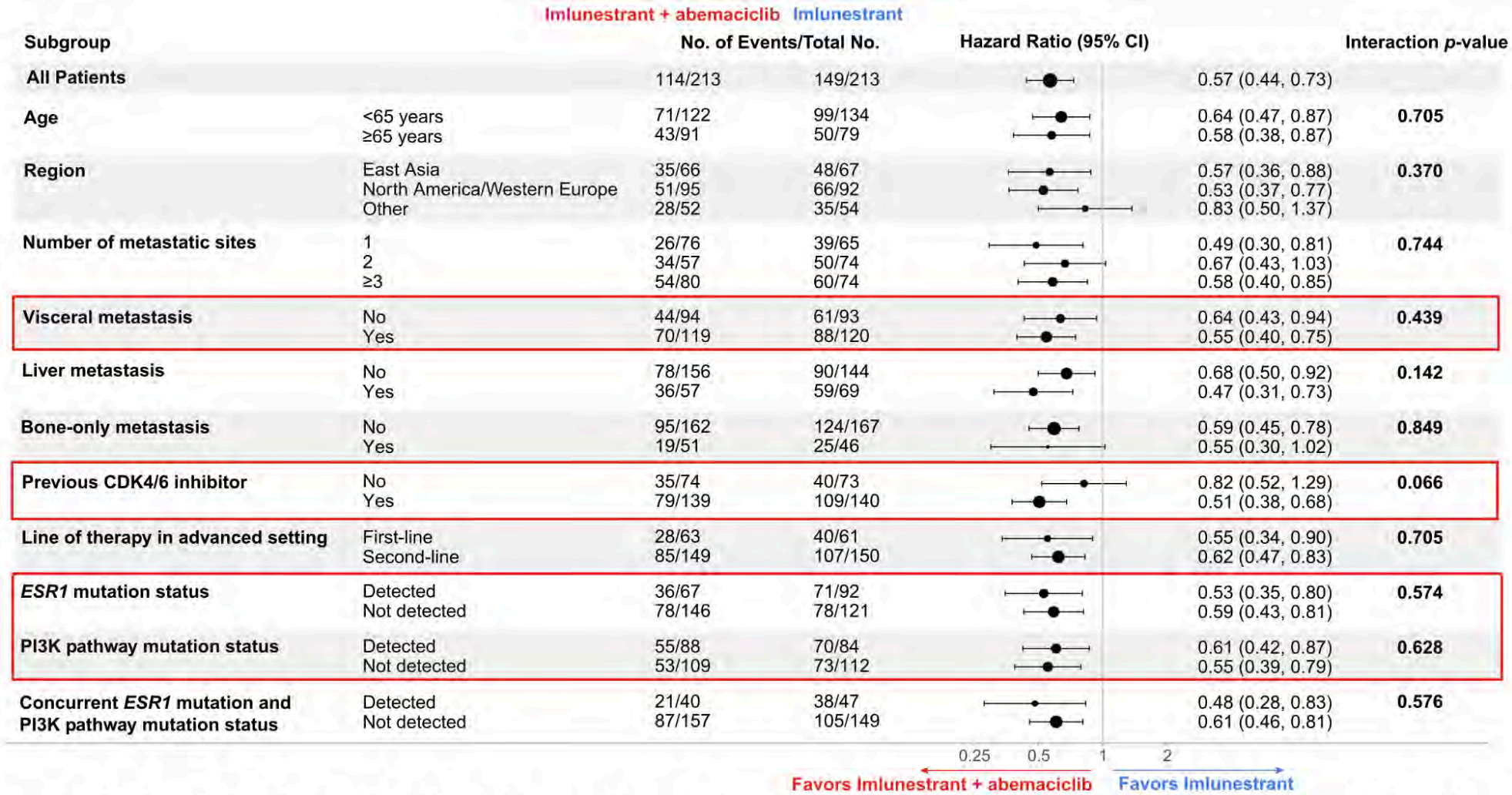
	Imlunestrant + abemaciclib n=213	Imlunestrant n=213[a]
No. of events	114	149
Median (95% CI); Months	**9.4** (7.5-11.9)	**5.5** (3.8-5.6)
HR (95% CI)	**0.57 (0.44-0.73)** *p*-value <0.001	

Imlunestrant + abemaciclib led to a 43% reduction in the risk of progression or death over imlunestrant alone in all patients

CI, confidence interval; HR, hazard ratio. [a] Efficacy analyses confined to the imlunestrant population concurrently randomized to imlunestrant + abemaciclib treatment arm. The median follow-up was 13.5 months in the imlunestrant + abemaciclib arm and 13.7 months in the imlunestrant arm.

K.L. Jhaveri et al SABCS 2024, K.L. Jhaveri et al NEJM 2024

Investigator-assessed PFS by subgroup: Consistent benefit of Imlunestrant + Abemaciclib



Subgroup		No. of Events/Total No.		Hazard Ratio (95% CI)	Interaction *p*-value
All Patients		114/213	149/213	0.57 (0.44, 0.73)	
Age	<65 years	71/122	99/134	0.64 (0.47, 0.87)	**0.705**
	≥65 years	43/91	50/79	0.58 (0.38, 0.87)	
Region	East Asia	35/66	48/67	0.57 (0.36, 0.88)	**0.370**
	North America/Western Europe	51/95	66/92	0.53 (0.37, 0.77)	
	Other	28/52	35/54	0.83 (0.50, 1.37)	
Number of metastatic sites	1	26/76	39/65	0.49 (0.30, 0.81)	**0.744**
	2	34/57	50/74	0.67 (0.43, 1.03)	
	≥3	54/80	60/74	0.58 (0.40, 0.85)	
Visceral metastasis	No	44/94	61/93	0.64 (0.43, 0.94)	**0.439**
	Yes	70/119	88/120	0.55 (0.40, 0.75)	
Liver metastasis	No	78/156	90/144	0.68 (0.50, 0.92)	**0.142**
	Yes	36/57	59/69	0.47 (0.31, 0.73)	
Bone-only metastasis	No	95/162	124/167	0.59 (0.45, 0.78)	**0.849**
	Yes	19/51	25/46	0.55 (0.30, 1.02)	
Previous CDK4/6 inhibitor	No	35/74	40/73	0.82 (0.52, 1.29)	**0.066**
	Yes	79/139	109/140	0.51 (0.38, 0.68)	
Line of therapy in advanced setting	First-line	28/63	40/61	0.55 (0.34, 0.90)	**0.705**
	Second-line	85/149	107/150	0.62 (0.47, 0.83)	
***ESR1* mutation status**	Detected	36/67	71/92	0.53 (0.35, 0.80)	**0.574**
	Not detected	78/146	78/121	0.59 (0.43, 0.81)	
PI3K pathway mutation status	Detected	55/88	70/84	0.61 (0.42, 0.87)	**0.628**
	Not detected	53/109	73/112	0.55 (0.39, 0.79)	
Concurrent *ESR1* mutation and PI3K pathway mutation status	Detected	21/40	38/47	0.48 (0.28, 0.83)	**0.576**
	Not detected	87/157	105/149	0.61 (0.46, 0.81)	

CI, confidence interval. First-line: most recent ET was adjuvant; Second-line: most recent ET was ABC. The total number of patients may not add up due to missing data in certain subgroups. Patients without *ESR1*m include 8 with unknown *ESR1*m status (imlunestrant + abemaciclib, n=1; Imlunestrant, n=7).

K.L. Jhaveri et al SABCS 2024, K.L. Jhaveri et al NEJM 2024

Safety

TEAEs in ≥ 10% of Patients, %	Imlunestrant n=327		SOC ET n=324	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Patients with ≥ 1 TEAE	83	17	84	21
Fatigue[a]	23	<1	13	1
Diarrhea	21	<1	12	0
Nausea	17	<1	13	0
Arthralgia	14	1	14	<1
AST increased	13	1	13	1
Back pain	11	1	7	<1
ALT increased	10	<1	10	1
Anemia[a]	10	2	13	3
Constipation	10	0	6	<1

Patients with ≥ 1 SAE, %		10	12
Dose reductions due to AE, %		2	0
Discontinuations due to AE, %		4	1
Deaths due to AE on study, %		2	1
Injection Site Reaction[a]	TEAE, n/N (%)[b]	NA	27/292 (9%)
	PRO-CTCAE, n/N (%)[c]	NA	201/278 (72%)

Generally favorable safety profile

TEAEs in ≥ 20% of Patients, %	Imlunestrant + abemaciclib n=208	
	Any Grade	Grade ≥3
Patients with ≥ 1 TEAE	98	49
Diarrhea	86	8
Nausea	49	2
Neutropenia[a]	48	20
Anemia[a]	44	8
Fatigue[a]	39	5
Vomiting	31	1
Leukopenia[a]	26	4
Hypercreatinemia[a]	22	1
Abdominal pain[a]	20	2
Decreased appetite	20	1

Patients with ≥ 1 SAE, %	17
Dose reductions due to AE, %[d]	39
Discontinuations due to AE, %	6
Deaths due to AE on study, %	1

Safety consistent with the known abemaciclib profile

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NA, not applicable; PRO-CTAE, Patient Reported Outcomes-Common Terminology Criteria for AEs; SAE, serious AEs; TEAE, treatment-emergent AE. [a] Consolidated term; [b] N is the number of evaluable patients who received fulvestrant; [c] N is the number of evaluable patients who completed the PRO-CTCAE survey (answered "yes" or "no" to injection site pain, swelling, or redness).

[d] Dose reduction of imlunestrant alone: 2%; abemaciclib alone: 23%; both drugs: 14%

K.L. Jhaveri et al SABCS 2024, K.L. Jhaveri et al NEJM 2024

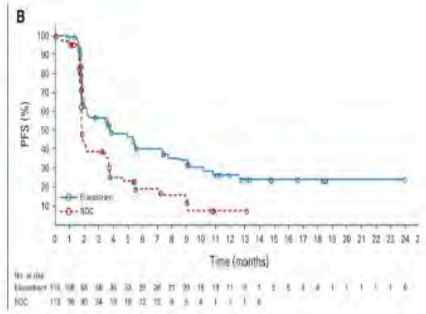
SERDs monotherapy efficacy according to ESR1 mutations

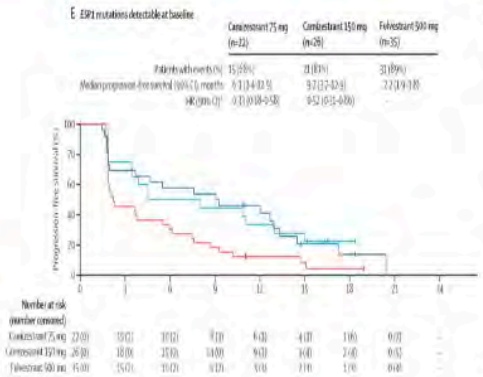
EMERALD
SOC vs Elacestrant

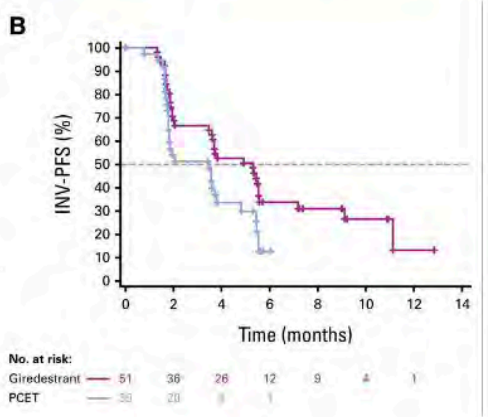
SERENA-2
Fulv vs Camizestrant

acelERA
PCET vs Giredestrant

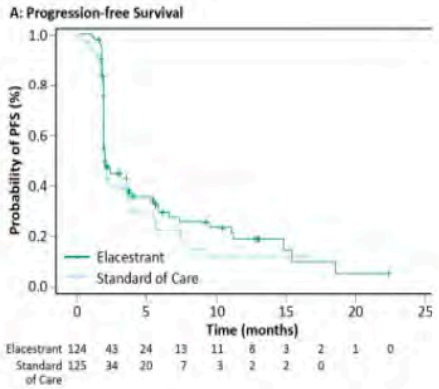
***ESR1* mut**

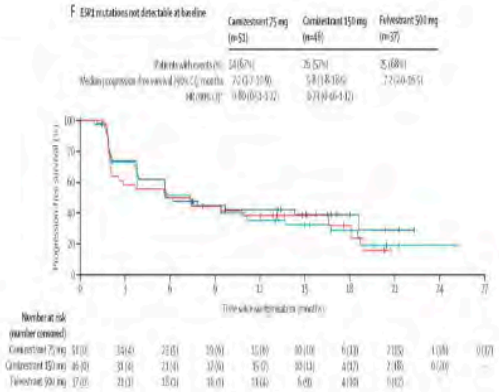


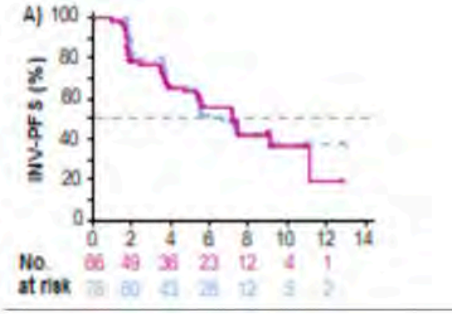




***ESR1* wt**







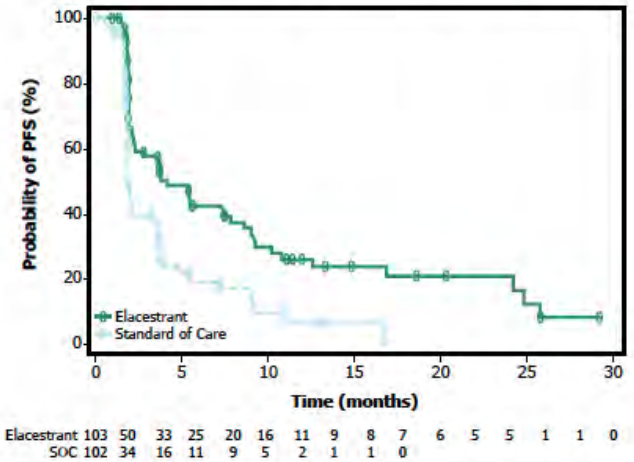
Bidard, FC et al.
J Clin Oncol 2022;40:3246

Oliveira M, et al.
Lancet Oncol 2024;25:1424

Martin M, et al.
J Clin Oncol 2024;42:2149

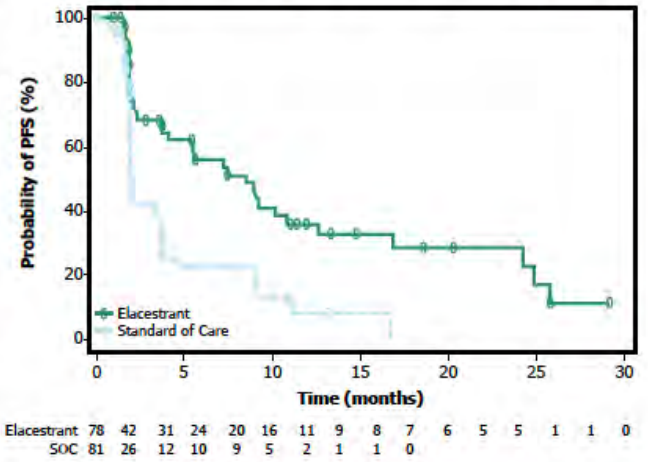
Patients with *ESR1*-mut Tumors: PFS by Duration of CDK4/6i

At least 6 mo CDK4/6i



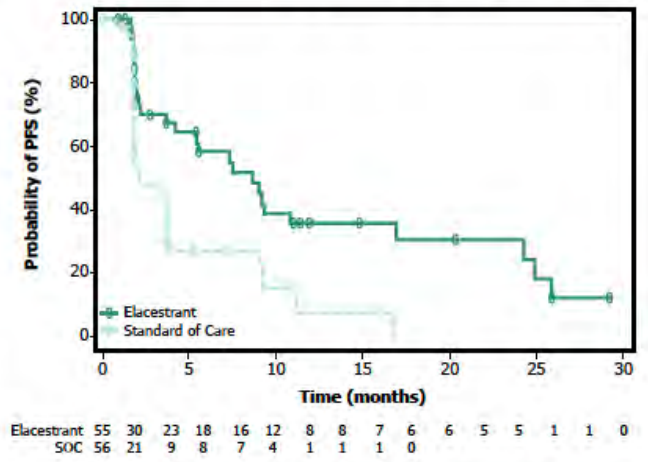
	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**4.14** (2.20 - 7.79)	**1.87** (1.87 - 3.29)
PFS rate at 12 months, % (95% CI)	26.02 (15.12 - 36.92)	6.45 (0.00 - 13.65)
Hazard ratio (95% CI)	**0.517** (0.361 - 0.738)	

At least 12 mo CDK4/6i



	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**8.61** (4.14 - 10.84)	**1.91** (1.87 - 3.68)
PFS rate at 12 months, % (95% CI)	35.81 (21.84 - 49.78)	8.39 (0.00 - 17.66)
Hazard ratio (95% CI)	**0.410** (0.262 - 0.634)	

At least 18 mo CDK4/6i



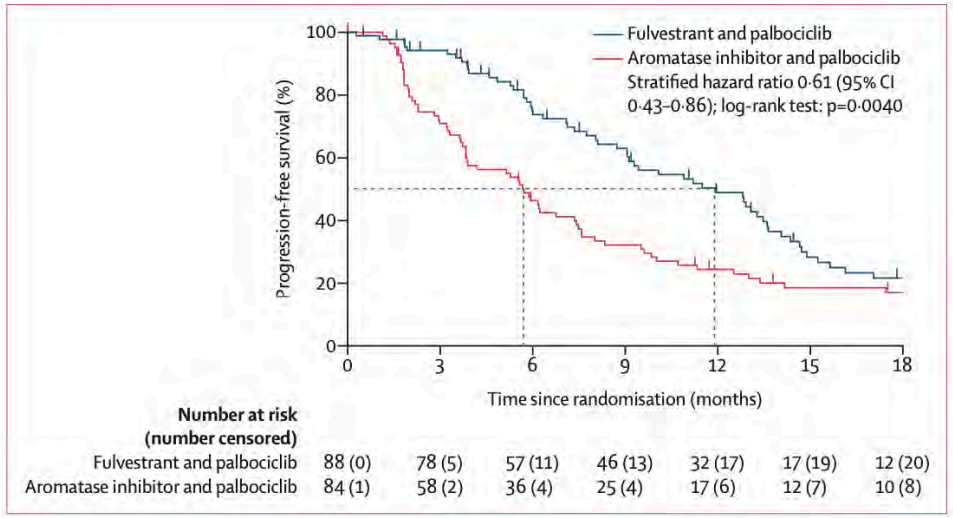
	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**8.61** (5.45 - 16.89)	**2.10** (1.87 - 3.75)
PFS rate at 12 months, % (95% CI)	35.79 (19.54 - 52.05)	7.73 (0.00 - 20.20)
Hazard ratio (95% CI)	**0.466** (0.270 - 0.791)	

FDA & EMA approved in ESR1mut ER+ MBC with progression after at least 1 ET

A. Bardia et al, Clin Cancer Res 2024

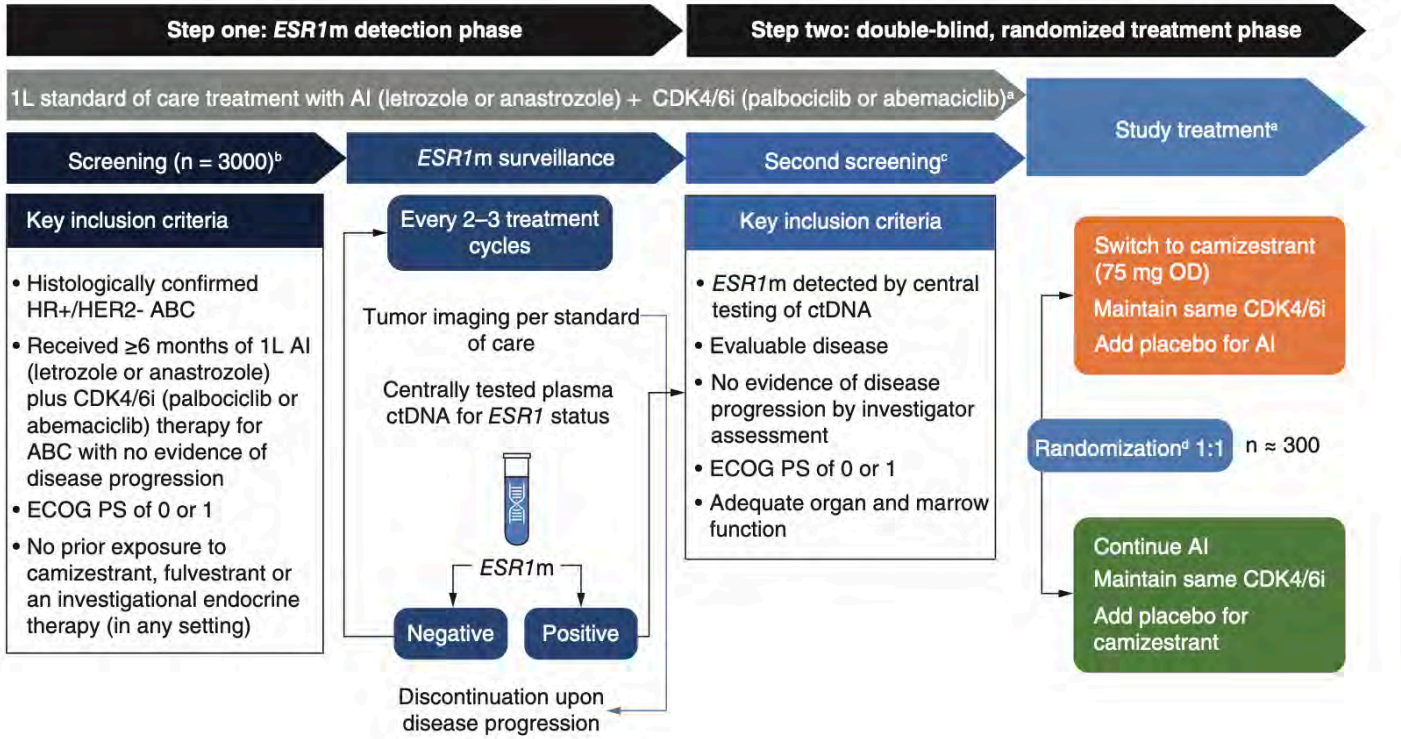
Early switch based on ESR1 mutations

PADA1



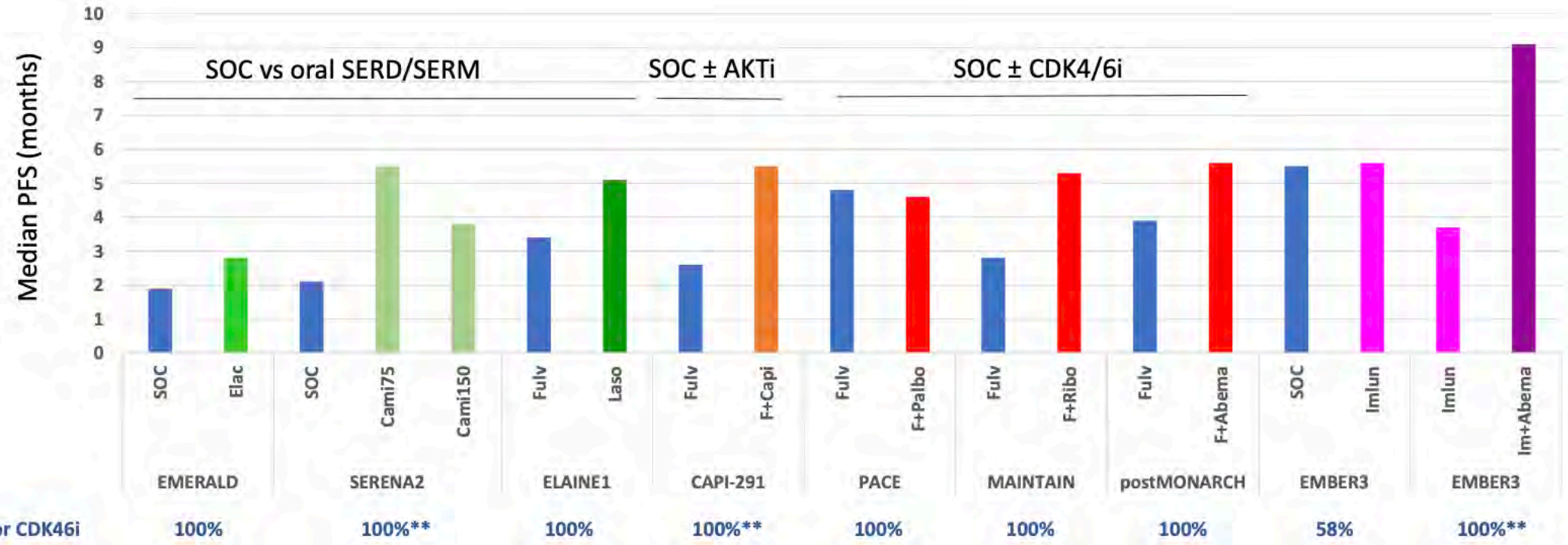
F.C. Bidard et al, Lancet Oncol 2022

SERENA 6



N. Turner et al, Future Oncol 2023

Median Progression Free Survival in Recent Randomized Trials of Endocrine Therapy:
*Outcomes among patients with prior CDK4/6 inhibitor treatment**



*there are a lot of problems with cross study comparisons, especially in unplanned subset analyses:
extent/types of prior therapy, variable tumor genomics/biomarker profile,
SOC options, sample size, exposure vs resistance, investigator vs BICR, etc.

** Denotes subset of larger study cohort

H.J. Burstein SABCS 2024,

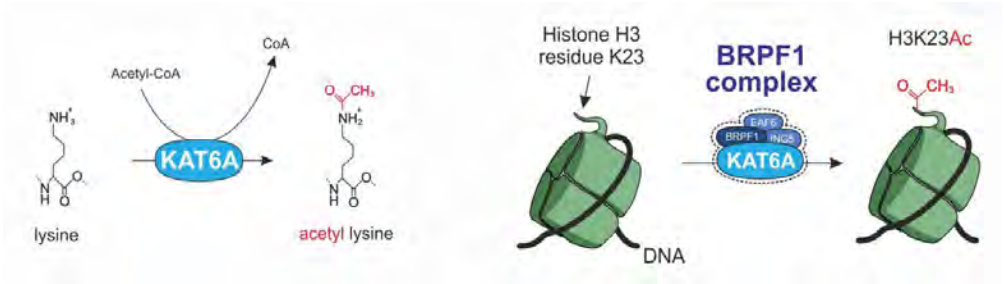
Toxicities of PI3K/AKT inhibitors

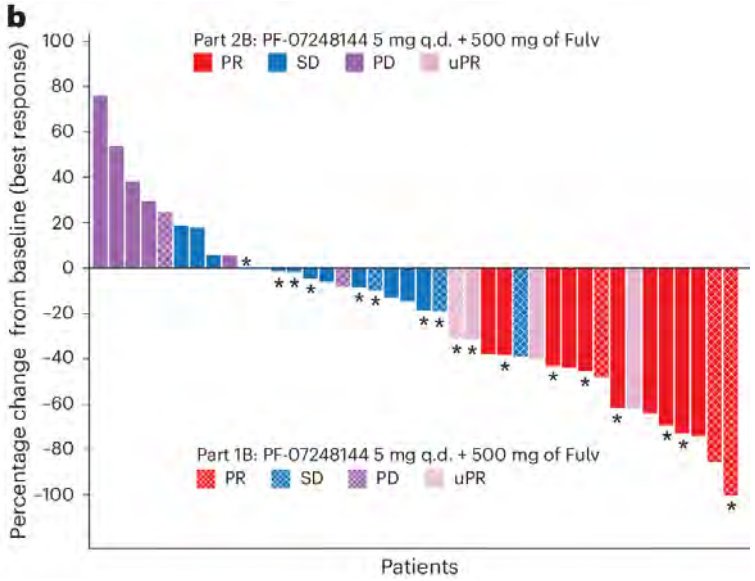
Toxicity	Alpelisib		Capivasertib		Inavolisib	
	All grades %	Grade 3+ %	All grades %	Grade 3+%	All grades %	Grade 3+%
Diarrhea	59.5	7	**72.4**	**9.3**	48	4
Rash	**36.3**	**10**	**38**	**12**	25	NA
Hyperglycemia	**64.8**	**37**	16.2	2.3	**59**	**6**
Stomatitis	25	2.5	14.6	2	**51**	**6**
Treatment discontinuation due to adverse events	**25%**		**13%**		**6.8%**	

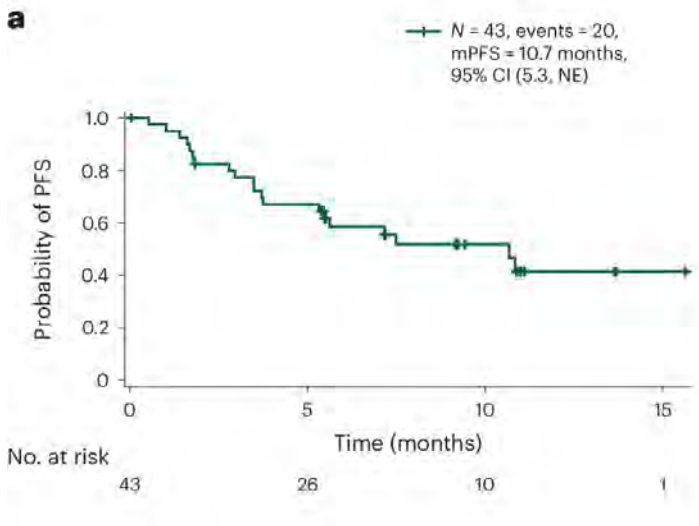
Adapted from Fanucci et al, ESMO Open 2024

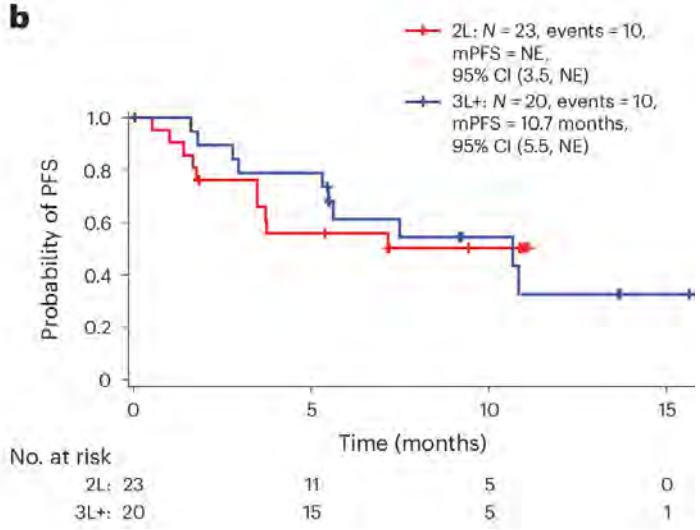
New epigenetic regulators

PF- 07248144 (KAT6 inhibitor) + fulvestrant









ORR 21.7%, CBR 43.5%, mPFS 10.7 mo, response in 3/5 patinets who had prior fulvestrant

Mukohara T et al, Nature Med 2024

Limitations

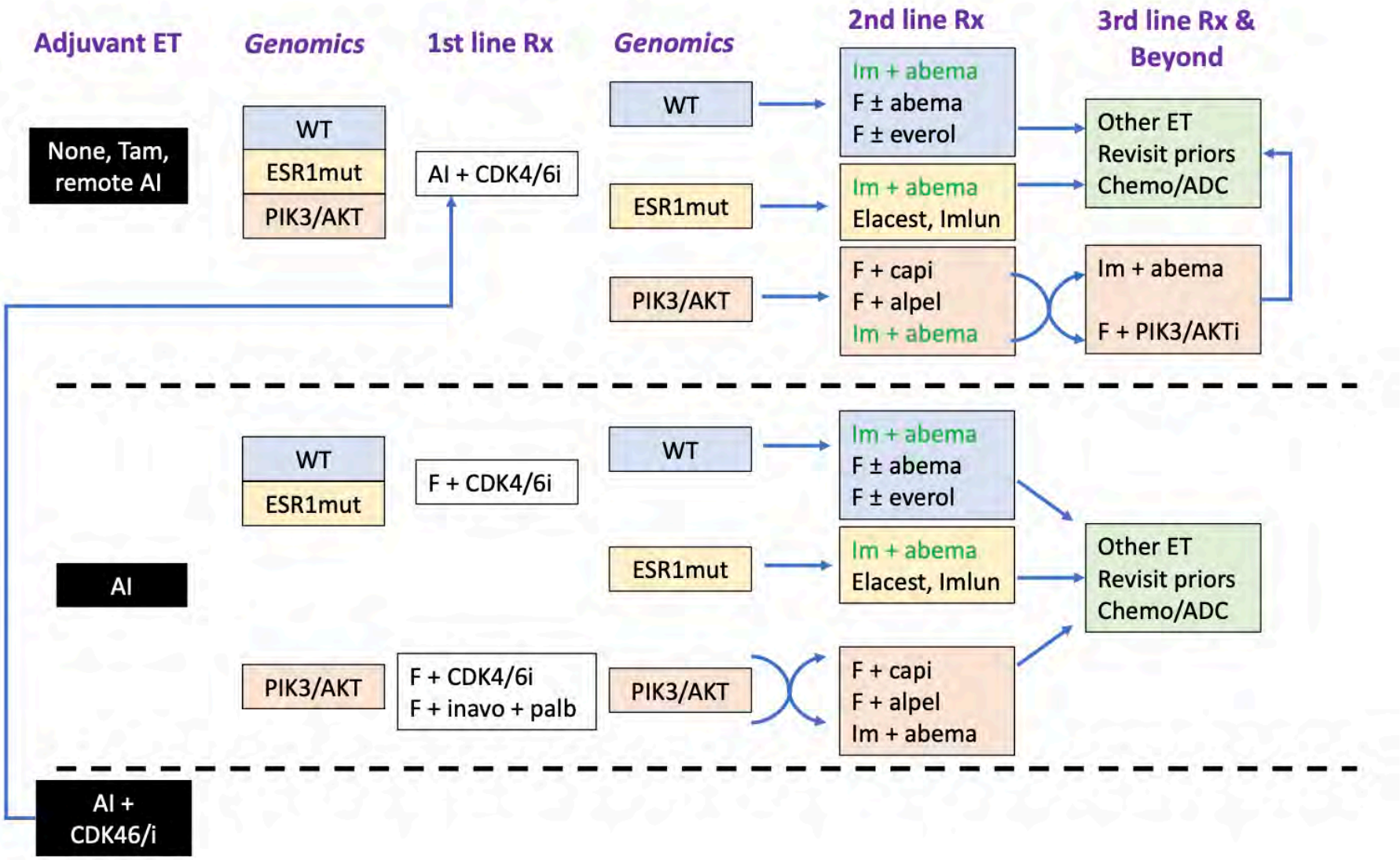
- ✓ Suboptimal control arm: How imlunestrant+abemaciclib compares with fulvestrant+ abemaciclib, fulvestrant+alpelisib, fulvestrant+ capivasertib?
- ✓ 60% of patients received prior CDK4/6inhibitor: Subgroup analysis according to prior CDK4/6inhibitor reassuring
- ✓ 60% of prior CDK4/6inhibitor was palbociclib: Not SOC any more

Strengths - messages

- ✓ Well conducted, international, phase 3 trial
- ✓ Imlunestant is a well tolerated oral SERD that is better than fulvestrant in ESR1 mutant tumors
- ✓ First study to suggest that post CDK4/6i an oral SERD (imlunestrant) can be used irrespective of ESR1 mutations when combined with abemaciclib
- ✓ Imlunestrant + abemaciclib can be a treatment option for patients with PIK3CA pathway mutated tumors

Open Questions

- ✓ Will there be an improvement in Overall Survival in EMBER3 with longer follow-up?
- ✓ What will be the optimal strategy in patients that have received abemaciclib/ribociclib in the adjuvant or in the 1st line metastatic setting?
- ✓ Will oral SERDs be better than SOC ET in the 1st line metastatic and adjuvant setting where ESR1 mutations are rare?



H.J. Burstein SABCS 2024,

ESMO ON AIR

Nivolumab plus Ipilimumab in Microsatellite-Instability–High Metastatic Colorectal Cancer

Claire Gallois

Digestive Oncology Department
Hôpital Européen Gorges Pompidou, Paris, France

March 19, 2025

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY

Meeting Abstract: 2024 ASCO Gastrointestinal Cancers Symposium

FREE ACCESS | Colorectal Cancer | January 22, 2024

Nivolumab (NIVO) plus ipilimumab (IPI) vs chemotherapy (chemo) as first-line (1L) treatment for microsatellite instability-high/mismatch repair-deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC): First results of the CheckMate 8HW study.

Authors: Thierry Andre, Elena Elez, Eric Van Cutsem, Lars Henrik Jensen, Jaafar Bennouna, Guillermo Mendez, Michael Schenker, ... SHOW ALL ..., and Sara Lonardi AUTHORS INFO & AFFILIATIONS

André et al. ASCO GI 2024

Meeting Abstract: 2024 ASCO Annual Meeting I

FREE ACCESS | Gastrointestinal Cancer—Colorectal and Anal | May 29, 2024

Nivolumab (NIVO) plus ipilimumab (IPI) vs chemotherapy (chemo) as first-line (1L) treatment for microsatellite instability-high/mismatch repair-deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC): Expanded efficacy analysis from CheckMate 8HW.

Authors: Heinz-Josef Lenz, Sara Lonardi, Elena Elez, Eric Van Cutsem, Lars Henrik Jensen, Jaafar Bennouna, Guillermo Mendez, ... SHOW ALL ..., and Thierry Andre AUTHORS INFO & AFFILIATIONS

Lenz et al. ASCO 2024

Meeting Abstract: 2025 ASCO Gastrointestinal Cancers Symposium

FREE ACCESS | Colorectal Cancer | January 27, 2025

First results of nivolumab (NIVO) plus ipilimumab (IPI) vs NIVO monotherapy for microsatellite instability-high/ mismatch repair-deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC) from CheckMate 8HW.

Authors: Thierry Andre, Elena Elez, Heinz-Josef Lenz, Lars Henrik Jensen, Yann Touchefeu, Eric Van Cutsem, Rocio Garcia-Carbonero, ... SHOW ALL ..., and Sara Lonardi AUTHORS INFO & AFFILIATIONS

André et al. ASCO GI 2025

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab plus Ipilimumab in Microsatellite-Instability–High Metastatic Colorectal Cancer

T. André, E. Elez, E. Van Cutsem, L.H. Jensen, J. Bennouna, G. Mendez, M. Schenker, C. de la Fouchardiere, M.L. Limon, T. Yoshino, J. Li, H.-J. Lenz, J.L. Manzano Mozo, G. Tortora, R. Garcia-Carbonero, L. Dahan, M. Chalabi, R. Joshi, E. Goekkurt, M.I. Braghiroli, T. Cil, E. Cela, T. Chen, M. Lei, M. Dixon, S. Abdullaev, and S. Lonardi, for the CheckMate 8HW Investigators*

André et al. NEJM 2024

Nivolumab plus ipilimumab versus nivolumab in microsatellite instability-high metastatic colorectal cancer (CheckMate 8HW): a randomised, open-label, phase 3 trial

Thierry André, Elena Elez, Heinz-Josef Lenz, Lars Henrik Jensen, Yann Touchefeu, Eric Van Cutsem, Rocio Garcia-Carbonero, David Tougeron, Guillermo Ariel Mendez, Michael Schenker, Christelle de la Fouchardiere, Maria Luisa Limon, Takayuki Yoshino, Jin Li, Jose Luis Manzano Mozo, Laetitia Dahan, Giampaolo Tortora, Myriam Chalabi, Eray Goekkurt, Maria Ignez Braghiroli, Rohit Joshi, Timucin Cil, Francine Aubin, Elvis Cela, Tian Chen, Ming Lei, Lixian Jin, Steven I Blum, Sara Lonardi

André et al. Lancet 2025

Rationale

- **MSI-high/dMMR: 5%** of mCRC and associated with poor outcomes with chemotherapy +/- targeted therapies

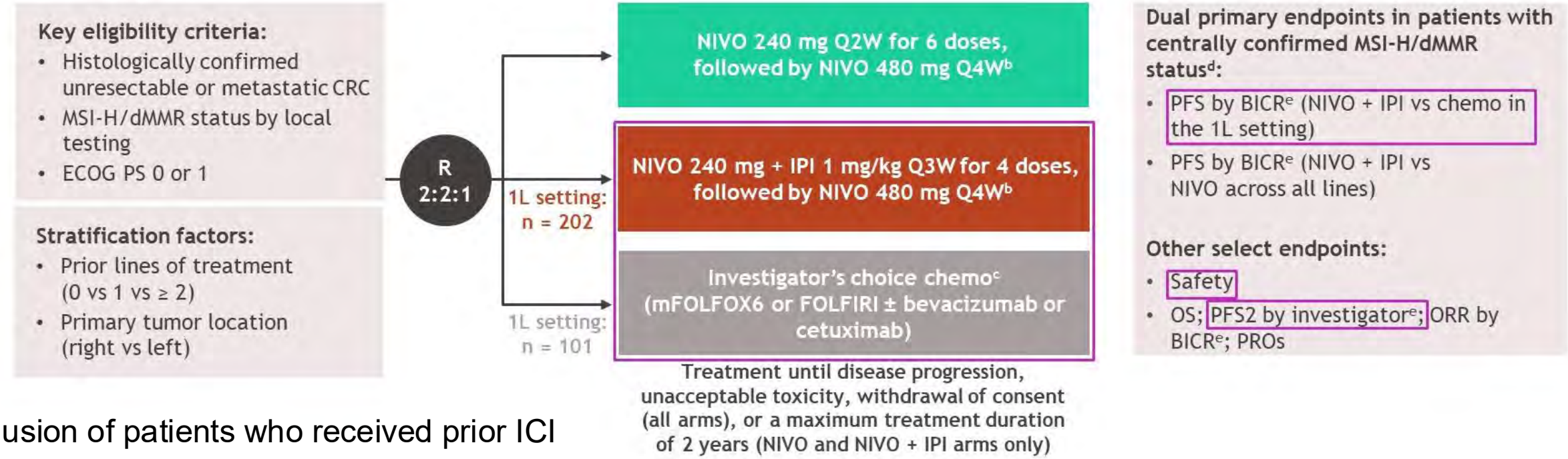
- Keynote-177: **Pembrolizumab monotherapy** showed improved PFS vs chemo in the **1L setting**
  BUT **primary progression: 29%** of cases
  and for long-term outcomes →**5-year PFS rate: 34%**

- Phase II CheckMate-142 indirect comparisons suggested that Nivolumab + Ipilimumab provided better outcomes than Nivolumab monotherapy

CheckMate 8HW study design

Phase III trial

Randomized, mulicenter, open-label



Exclusion of patients who received prior ICI

- **Patients in 1st line or 2nd line** randomly assigned, in a 2:2:1 ratio, to receive **nivo + ipi, nivo alone, or chemotherapy**
- Patients in **3rd line or more** randomly assigned in a 1:1 ratio, to receive **nivo + ipilimumab, or nivo alone**

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In the chemo group: cross-over permitted with nivo + ipi

André et al. ASCO GI 2024
Lenz et al. ASCO 2024
André et al. NEJM 2024

CheckMate 8HW
Nivolumab + Ipilimumab vs chemotherapy in 1st Line

Characteristic (1L all randomized patients)	Category	NIVO + IPI (n = 202)	Chemo (n = 101)
Age	Median (range), years	62 (21-86)	65 (26-87)
	< 65 years	117 (58)	46 (46)
Sex	Male	95 (47)	45 (45)
Region	US/Canada/Europe	133 (66)	71 (70)
	Asia	19 (9)	11 (11)
	Rest of world	50 (25)	19 (19)
ECOG PS	0	111 (55)	52 (51)
Disease stage at initial diagnosis[a]	Stage IV	85 (42)	49 (49)
Tumor sidedness	Right	138 (68)	68 (67)
Sites of metastases[b,c,d]	Liver	76 (38)	42 (42)
	Lung	44 (22)	25 (25)
	Peritoneum	84 (42)	43 (43)
Centrally confirmed MSI-H/dMMR status	Yes	171 (85)	84 (83)
	No	31 (15)	17 (17)
Tumor cell PD-L1 expression[e,f]	< 1%	145 (72)	80 (79)
	≥ 1%	43 (21)	12 (12)
BRAF, *KRAS*, *NRAS* mutation status[f,g]	*BRAF*/*KRAS*/*NRAS* wild-type	47 (23)	23 (23)
	BRAF mutant	52 (26)	24 (24)
	KRAS or *NRAS* mutant	43 (21)	21 (21)
	Unknown	55 (27)	31 (31)
Clinical history of Lynch syndrome[f,h]	Yes	22 (11)	17 (17)
	No	135 (67)	49 (49)
	Reported as unknown	44 (22)	30 (30)

André et al. ASCO GI 2024; Lenz et al. ASCO 2024; André et al. NEJM 2024

CheckMate 8HW
Nivolumab + Ipilimumab vs chemotherapy in 1st Line

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	Lung	44 (22)	25 (25)
Centrally confirmed MSI-H/dMMR status			
Tumor cell PD-L1 expression[e,f]			
BRAF, *KRAS*, *NRAS* mutation status[f,g]			
Clinical history of Lynch syndrome[f,h]			

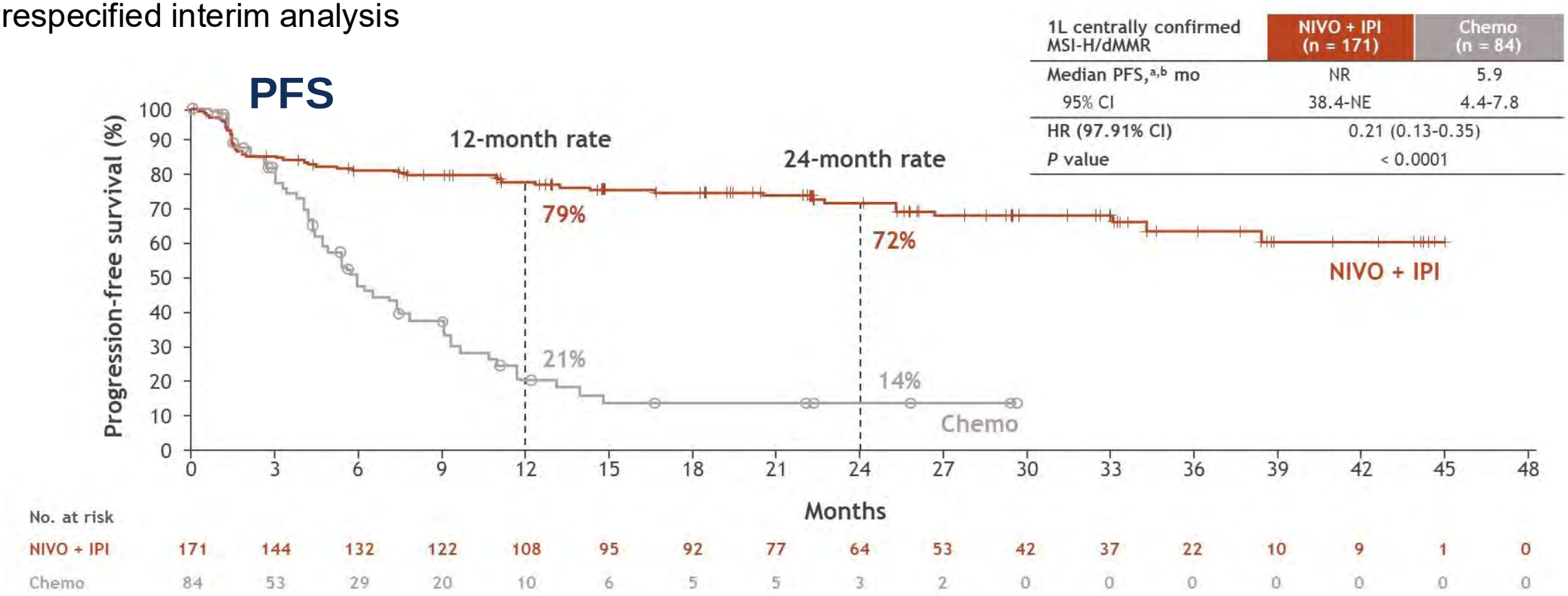
	NIVO + IPI (n=202)	Chemo (n=101)
Previous systemic therapy	**67 (33%)**	**32 (32%)**
Neoadjuvant	7/67 (10%)	5/32 (16%)
Adjuvant	60/67 (90%)	27/32 (84%)
Metastatic	2/67 (3%)	2/32 (6%)

André et al. ASCO GI 2024; Lenz et al. ASCO 2024; André et al. NEJM 2024

CheckMate 8HW
Nivolumab + Ipilimumab vs chemotherapy in 1st Line

At data cutoff: median follow- up was 31.5 months (range 6.1-48.4)

Prespecified interim analysis



1L centrally confirmed MSI-H/dMMR	NIVO + IPI (n = 171)	Chemo (n = 84)
Median PFS,[a,b] mo	NR	5.9
95% CI	38.4-NE	4.4-7.8
HR (97.91% CI)	0.21 (0.13-0.35)	
P value	< 0.0001	

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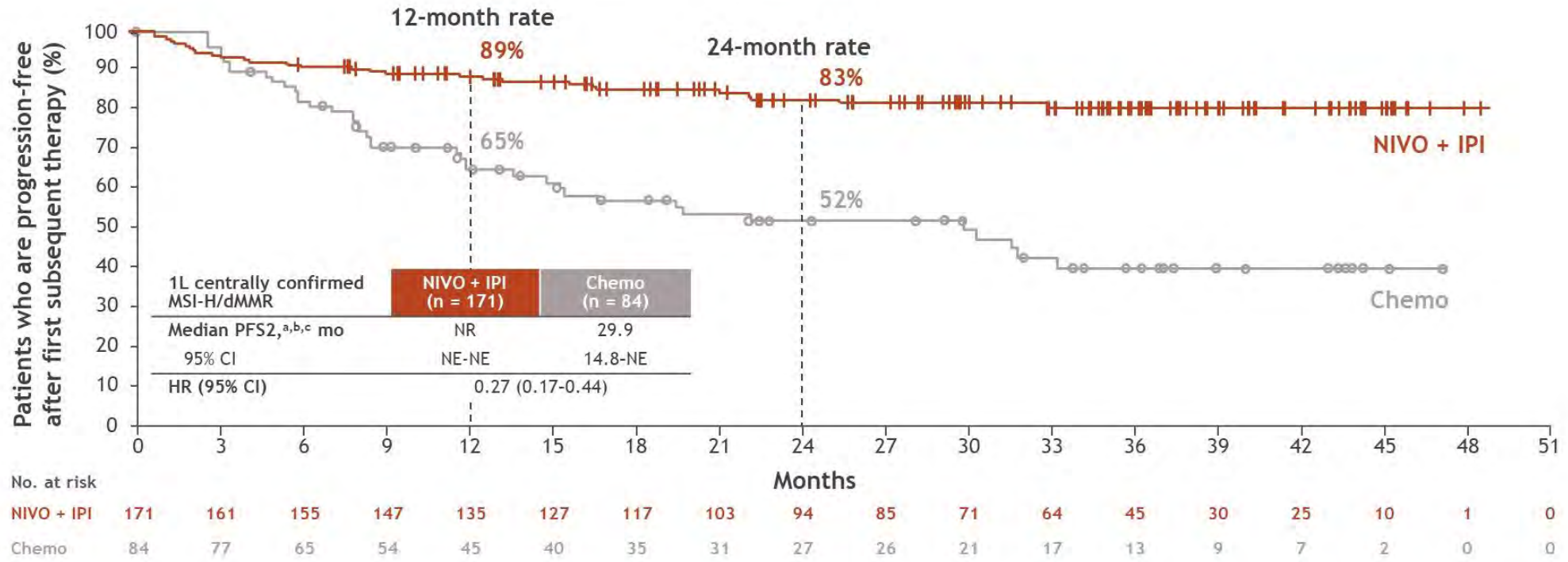
CheckMate 8HW
Nivolumab + Ipilimumab vs chemotherapy in 1st Line

68% of patients of chemo group received ICI as subsequent treatment

PFS2 = time from randomization to progression after subsequent systemic treatment, initiation of systemic subsequent treatment or death



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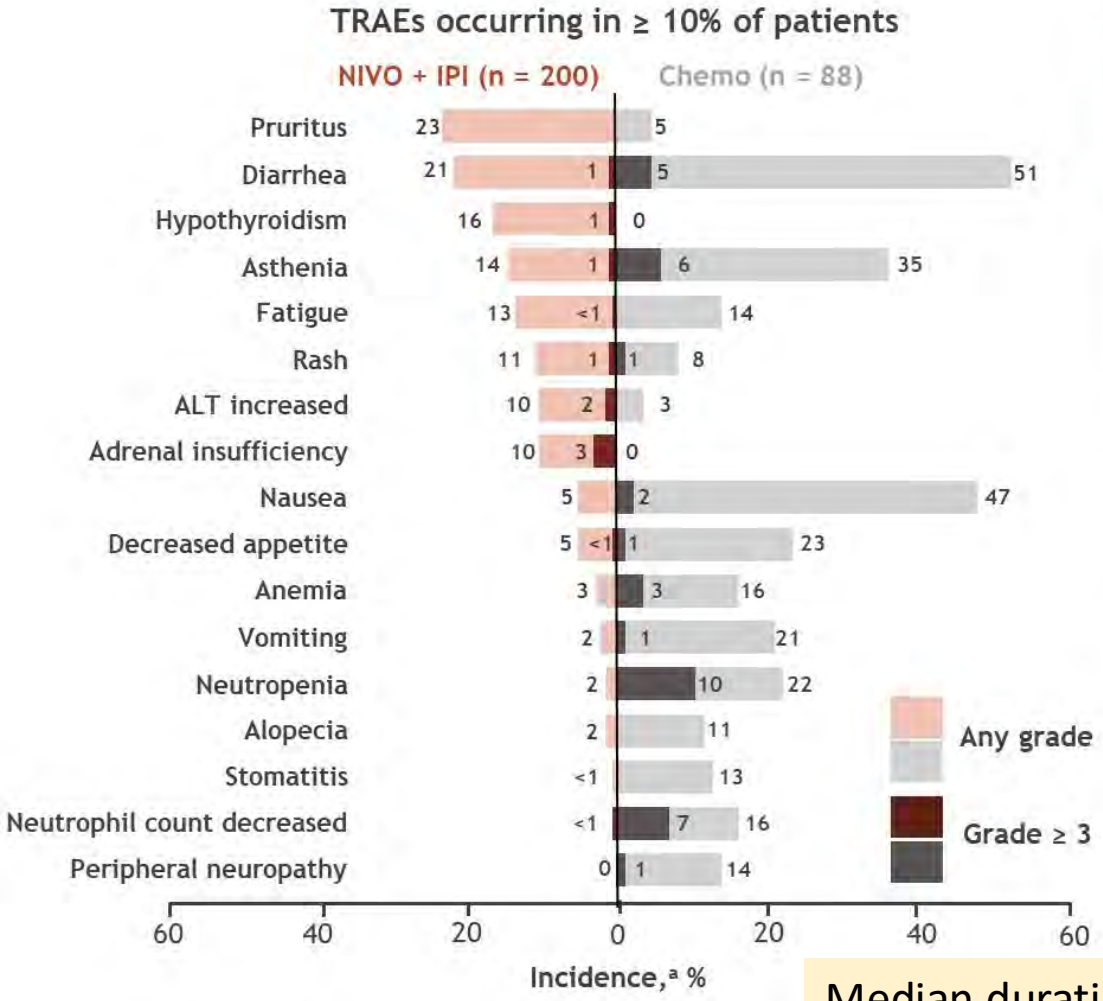
Lenz et al. ASCO 2024

CheckMate 8HW
Nivolumab + Ipilimumab vs chemotherapy in 1st Line

Treatment-related adverse events



1L all treated patients	NIVO + IPI (n = 200)		Chemo (n = 88)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
TRAEs,[a] n (%)				
Any TRAEs	160 (80)	46 (23)	83 (94)	42 (48)
Serious TRAEs	38 (19)	32 (16)	17 (19)	14 (16)
TRAEs leading to discontinuation	33 (17)	23 (12)	28 (32)	9 (10)
Treatment-related deaths, n (%)	2 (1)[b]		0 (0)[c]	

- Any-grade and grade 3/4 TRAEs were less frequent in the NIVO + IPI arm than in chemo arm
- The most common any-grade TRAEs occurring in ≥ 10% of patients were:
  - NIVO + IPI: pruritis (23%), diarrhea (21%), and hypothyroidism (16%)
  - Chemo: diarrhea (51%), nausea (47%), and asthenia (35%)

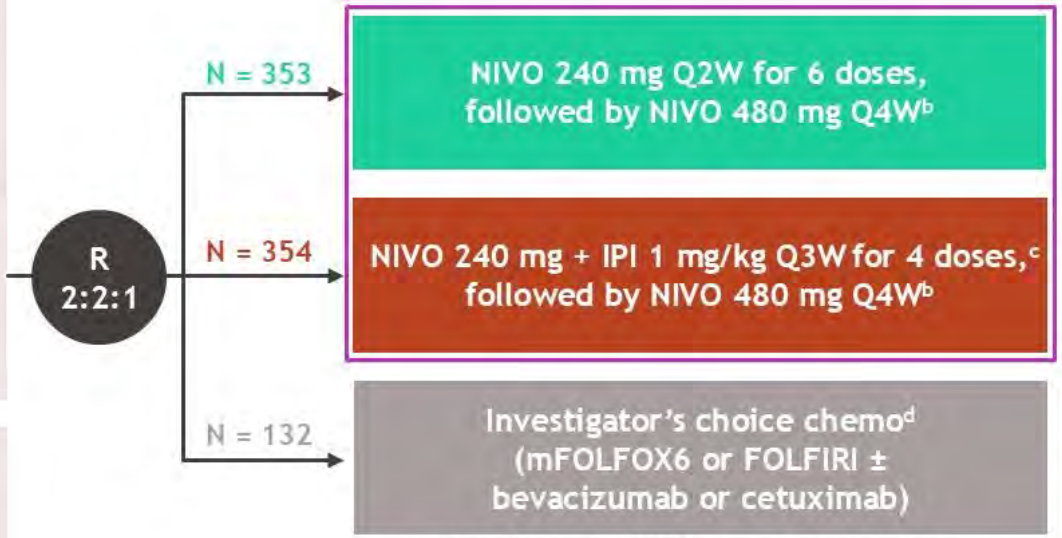
Median duration of treatment: 13.5 months (nivo+ipi) vs 4 months (chemo)

André et al. ASCO GI 2024; Lenz et al. ASCO 2024; André et al. NEJM 2024

CheckMate 8HW
Nivolumab + Ipilimumab vs Nivolumab across all lines

Key eligibility criteria:
- Histologically confirmed unresectable or metastatic CRC
- MSI-H/dMMR status by local testing
- Immunotherapy-naive
- ECOG PS 0 or 1

Stratification factors:
- Prior lines of treatment (0 vs 1 vs ≥ 2)
- Primary tumor location (right vs left)



Treatment until disease progression, unacceptable toxicity, withdrawal of consent (all arms), or a maximum treatment duration of 2 years (NIVO and NIVO + IPI arms only)

Dual primary endpoints in patients with centrally confirmed MSI-H/dMMR status[e]:
- PFS by BICR[f] (NIVO + IPI vs chemo in the 1L setting)
- PFS by BICR[f] (NIVO + IPI vs NIVO across all lines)

Other select endpoints:
- Safety
- ORR by BICR[f] (NIVO + IPI vs NIVO across all lines)
- HRQoL
- OS

André et al. ASCO GI 2025; André et al. Lancet 2025

CheckMate 8HW
Nivolumab + Ipilimumab vs Nivolumab across all lines

Characteristic (all randomized patients)	Category	NIVO + IPI (n = 354)	NIVO (n = 353)
Age	Median (range), years	62 (21-86)	63 (20-87)
Sex	Female	192 (54)	163 (46)
	Male	162 (46)	190 (54)
Region	US/Canada/Europe	251 (71)	246 (70)
	Asia	26 (7)	33 (9)
	Rest of world	77 (22)	74 (21)
ECOG PS	0	192 (54)	183 (52)
Disease stage at initial diagnosis[a]	Stage IV	152 (43)	158 (45)
Number of prior lines of therapy per IRT	0	202 (57)	201 (57)
	1	67 (19)	67 (19)
	≥ 2	85 (24)	85 (24)
Tumor sidedness	Right	244 (69)	244 (69)
Sites of metastases[b-d]	Liver	140 (40)	149 (42)
	Peritoneum	143 (40)	126 (36)
Centrally confirmed MSI-H/dMMR status	Yes	296 (84)	286 (81)
	No	58 (16)	67 (19)
	MSS and pMMR	41 (12)	40 (11)
	MSS or pMMR[e]	8 (2)	10 (3)
	Not available[f]	9 (3)	17 (5)
Tumor cell PD-L1[g,h]	< 1%	255 (72)	264 (75)
	≥ 1%	74 (21)	63 (18)
BRAF, *KRAS*, *NRAS* mutation status[g,i]	*BRAF*/*KRAS*/*NRAS* all wild type	83 (23)	103 (29)
	BRAF mutant	106 (30)	85 (24)
	KRAS or *NRAS* mutant	83 (23)	89 (25)
	Unknown	73 (21)	74 (21)
Clinical history of Lynch syndrome[g,j]	Yes	48 (14)	49 (14)
	No	217 (61)	207 (59)
	Reported as unknown	86 (24)	91 (26)

André et al. ASCO GI 2025; André et al. Lancet 2025

CheckMate 8HW
Nivolumab + Ipilimumab vs Nivolumab across all lines

Centrally confirmed MSI-H/dMMR	NIVO + IPI (n = 296)	NIVO (n = 286)
ORR,[a] % (95% CI)	**71 (65-76)**	**58 (52-64)**
Difference in ORR,[b] % (95% CI)	13 (5-21)	
P value[c]	0.0011	
Best overall response,[a,d] %		
Complete response	30	28
Partial response	40	30
Stable disease	14	19
Progressive disease	10	19
Median TTR (range),[a,e] mo	2.8 (1.2-44.5)	2.8 (1.2-29.5)
Median DOR (95% CI),[a,e] mo	NR (NE)	NR (NE)

André et al. ASCO GI 2025; André et al. Lancet 2025

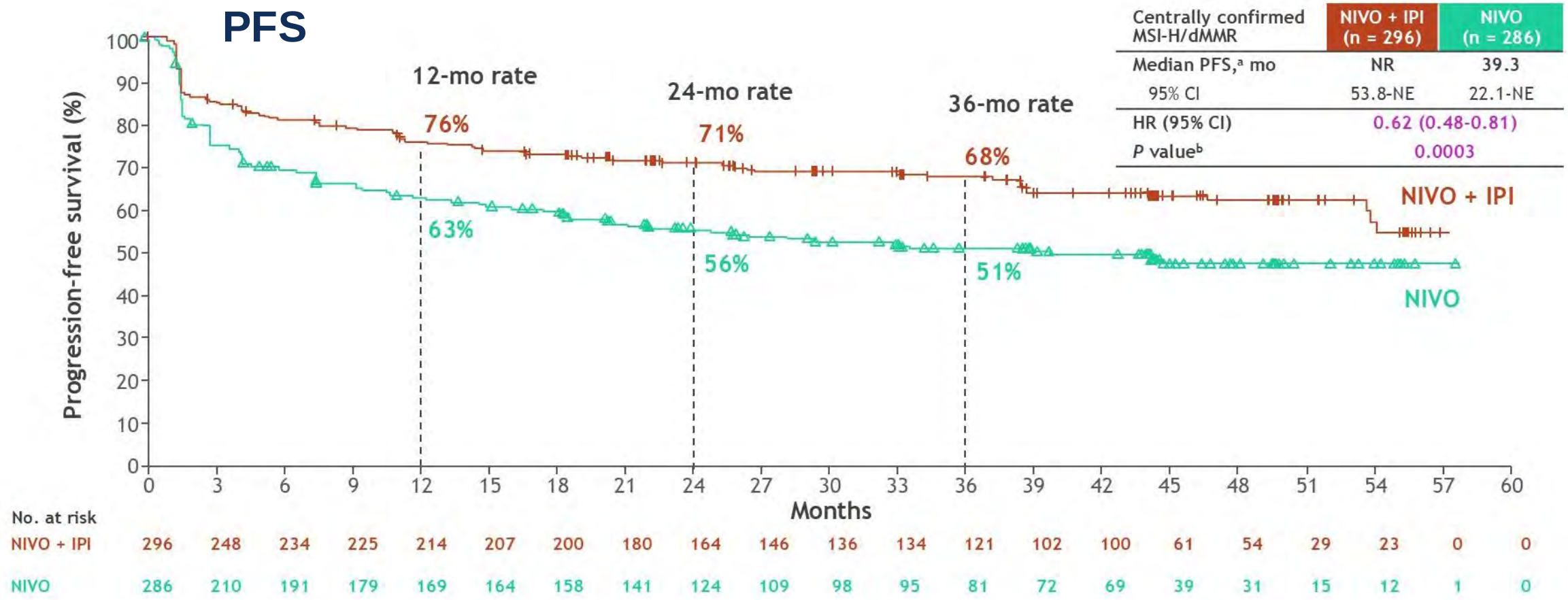
CheckMate 8HW
Nivolumab + Ipilimumab vs Nivolumab across all lines

Disposition	NIVO + IPI	NIVO
All randomized patients, n	354	353
All treated patients, n	352	351
Ongoing treatment,[a] n (%)	20 (6)	13 (4)
Completed treatment,[a,b] n (%)	159 (45)	137 (39)
Discontinued treatment,[a] n (%)	173 (49)	201 (57)
Disease progression	82 (23)	137 (39)
AE related to treatment	48 (14)	28 (8)
AE not related to treatment	22 (6)	28 (8)
Other[c]	21 (6)	8 (2)
Median duration of treatment (range),[d] mo	20.5 (0-35.9)[e]	16.4 (0-36.0)
Median number of doses (range)[d]	NIVO: 23 (1-41) IPI: 4 (1-4)	NIVO: 21 (1-43)
Received all 4 doses of IPI,[a] n (%)	288 (82)	-
Death,[a] n (%)	103 (29)	149 (42)
Disease progression	74 (21)	122 (35)
Other[f]	29 (8)	27 (8)

André et al. ASCO GI 2025; André et al. Lancet 2025

CheckMate 8HW
Nivolumab + Ipilimumab vs Nivolumab across all lines

Prespecified interim analysis



Centrally confirmed MSI-H/dMMR	NIVO + IPI (n = 296)	NIVO (n = 286)
Median PFS,[a] mo	NR	39.3
95% CI	53.8-NE	22.1-NE
HR (95% CI)	0.62 (0.48-0.81)	
P value[b]	0.0003	

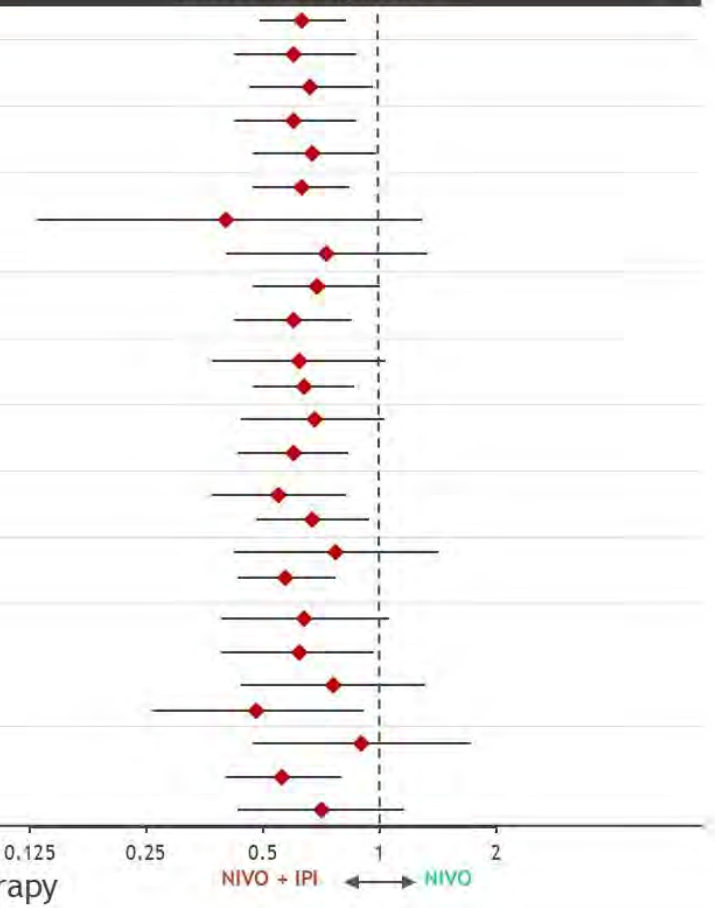
median follow-up: 47 months (range 16.7 – 60.5)

André et al. ASCO GI 2025; André et al. Lancet 2025

CheckMate 8HW
Nivolumab + Ipilimumab vs Nivolumab across all lines

PFS subgroup analysis

Category (centrally confirmed MSI-H/dMMR)	Subgroup	Median PFS,[a] mo		Unstratified HR
		NIVO + IPI	NIVO	
Overall (N = 582)		NR	39.3	0.63
Age, years	< 65 (n = 321)	NR	NR	0.60
	≥ 65 (n = 261)	NR	29.4	0.66
Sex	Male (n = 284)	NR	28.2	0.60
	Female (n = 298)	NR	NR	0.67
Region	US/Canada/Europe (n = 415)	NR	29.4	0.63
	Asia (n = 52)	NR	NR	0.40
	Rest of world (n = 115)	NR	NR	0.73
ECOG PS	0 (n = 313)	54.1	NR	0.69
	1 (n = 269)	NR	18.2	0.60
Tumor sidedness	Left (n = 152)	NR	NR	0.62
	Right (n = 430)	NR	33.2	0.64
Liver metastases[a,b]	Yes (n = 210)	NR	NR	0.68
	No (n = 368)	NR	33.2	0.60
Peritoneal metastases[a,b]	Yes (n = 226)	54.1	24.8	0.55
	No (n = 352)	NR	NR	0.67
Tumor cell PD-L1 expression	≥ 1% (n = 133)	NR	NR	0.77
	< 1% (n = 427)	NR	24.8	0.57
BRAF/KRAS/NRAS mutation status	*BRAF/KRAS/NRAS* all wild type (n = 156)	NR	44.3	0.64
	BRAF mutant (n = 179)	NR	25.9	0.62
	KRAS or *NRAS* mutant (n = 125)	NR	NR	0.76
	Unknown (n = 114)	54.1	38.1	0.48
Clinical history of Lynch syndrome	Yes (n = 83)	53.8	38.1	0.90
	No (n = 334)	NR	44.3	0.56
	Unknown (n = 156)	NR	33.2	0.71



- PFS consistently favored NIVO + IPI vs NIVO in prespecified subgroups across all lines of therapy

André et al. ASCO GI 2025; André et al. Lancet 2025

CheckMate 8HW
Nivolumab + Ipilimumab vs Nivolumab across all lines

Immune-related Adverse Events

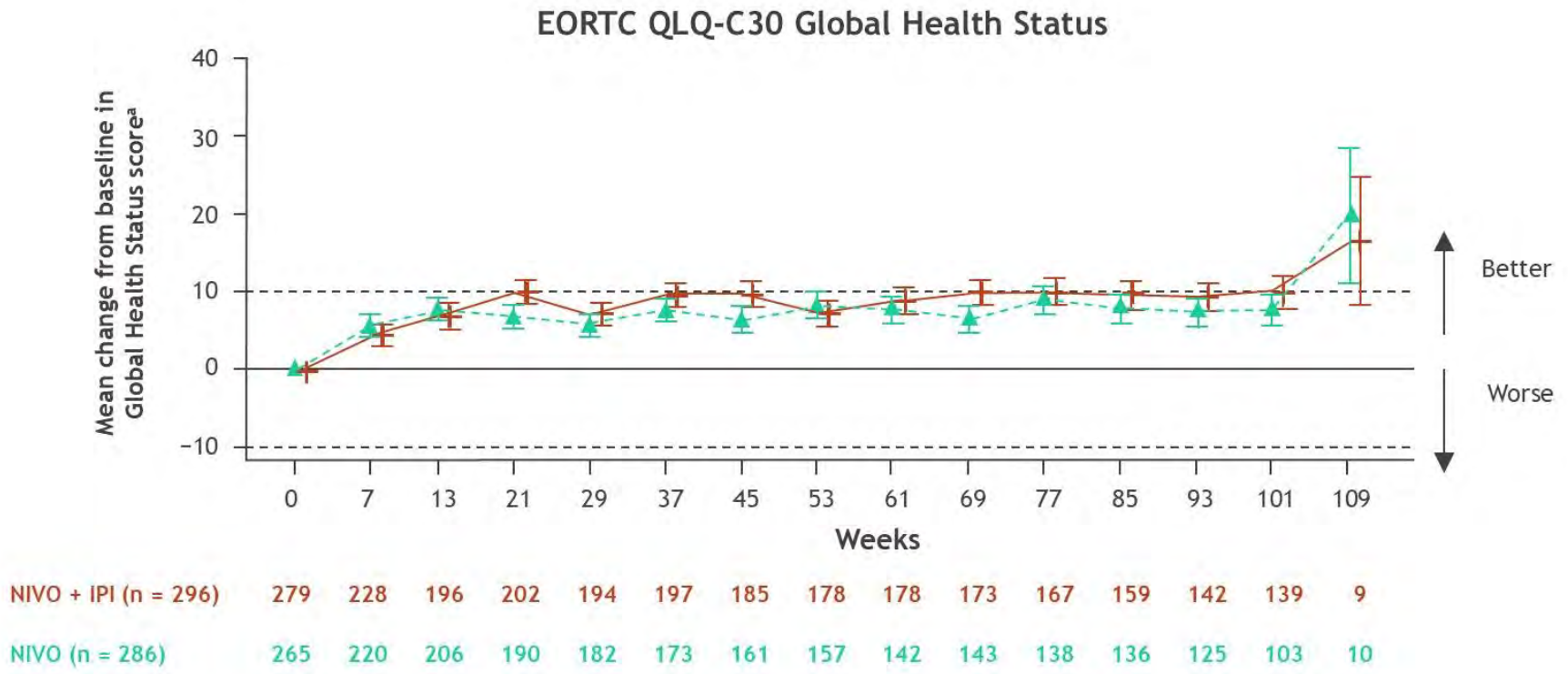
IMAEs[a] (all treated patients), n (%)	NIVO + IPI (n = 352)		NIVO (n = 351)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Non-endocrine events				
Rash	23 (7)	5 (1)	20 (6)	3 (< 1)
Diarrhea/colitis	21 (6)	12 (3)	13 (4)	8 (2)
Hepatitis	13 (4)	6 (2)	4 (1)	3 (< 1)
Pneumonitis	7 (2)	4 (1)	7 (2)	4 (1)
Nephritis and renal dysfunction	6 (2)	2 (< 1)	1 (< 1)	1 (< 1)
Hypersensitivity	0	0	3 (< 1)	0
Endocrine events				
Hypothyroidism/thyroiditis	62 (18)	3 (< 1)	33 (9)	0
Hyperthyroidism	42 (12)	0	16 (5)	0
Adrenal insufficiency	35 (10)	10 (3)	12 (3)	3 (< 1)
Hypophysitis	23 (7)	11 (3)	4 (1)	4 (1)
Diabetes mellitus	4 (1)	2 (< 1)	2 (< 1)	1 (< 1)

Treatment-related deaths: N= 2 in Nivo +Ipi group (myocarditis + pneumonitis) and N= 1 ni Nivo group (pneumonitis)

André et al. ASCO GI 2025; André et al. Lancet 2025

CheckMate 8HW
Nivolumab + Ipilimumab vs Nivolumab across all lines

Health-related Quality Of Life



André et al. ASCO GI 2025; André et al. Lancet 2025

Summary CheckMate 8HW
Nivo + Ipi vs Nivo

Positive phase III trial

- **Nivo + Ipi** demonstrated **statistically significant and clinically meaningful improvement in PFS vs Nivo** monotherapy in patients with **centrally confirmed MSI-H/dMMR mCRC across all lines of therapy** (HR: 0.62, p=0.0003)

- **Consistent PFS benefit across subgroups**

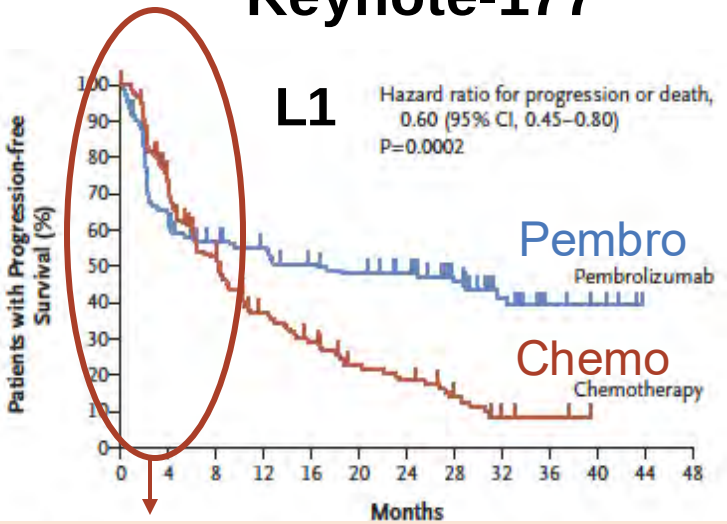
- **Better ORR** with **Nivo + Ipi** vs Nivolumab (71% vs 58%, p=0.001)

Primary resistance in only 10% of pts with Nivolumab +Ipilimumab vs 19% in Nivolumab group

- Limits:
  - Efficacy by line of therapy unknown →the outcomes might be driven by patients in 1st Line (57% in both arms)
  - No data on OS (immature data)

Nivolumab + Ipilimumab or Pembrolizumab/Nivolumab monotherapy?

Keynote-177



- Truly primary resistant pts
- + MSI misdiagnosed pts (%age? 13% in CM 8HW)

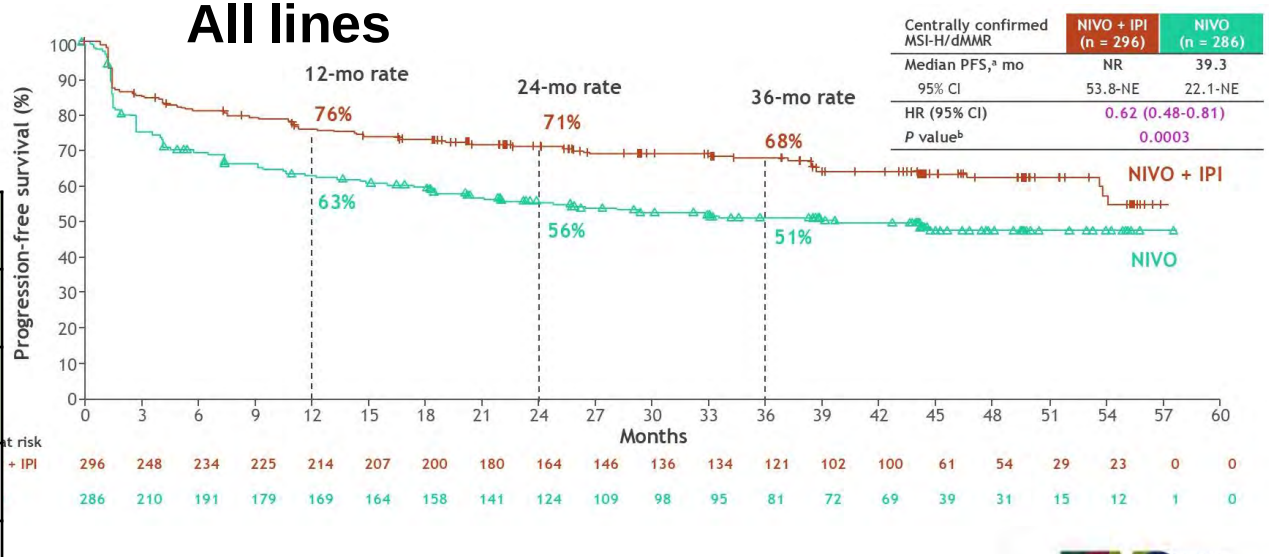
MSI local testing

- +/-pseudoprogression

CheckMate 8HW

Centrally confirmed MSI status

All lines



	Keynote-177	CheckMate 8HW		
	MSI local testing	Centrally confirmed MSI status		
	Pembro 1L	Nivo + Ipi 1L	Nivo all lines	Nivo + Ipi all lines
Primary progression	29%	-	19%	**10%**
24-month PFS	55%	72%	56%	**71%**

André et al. NEJM 2020; André et al. NEJM 2024; André et al. Lancet 2025

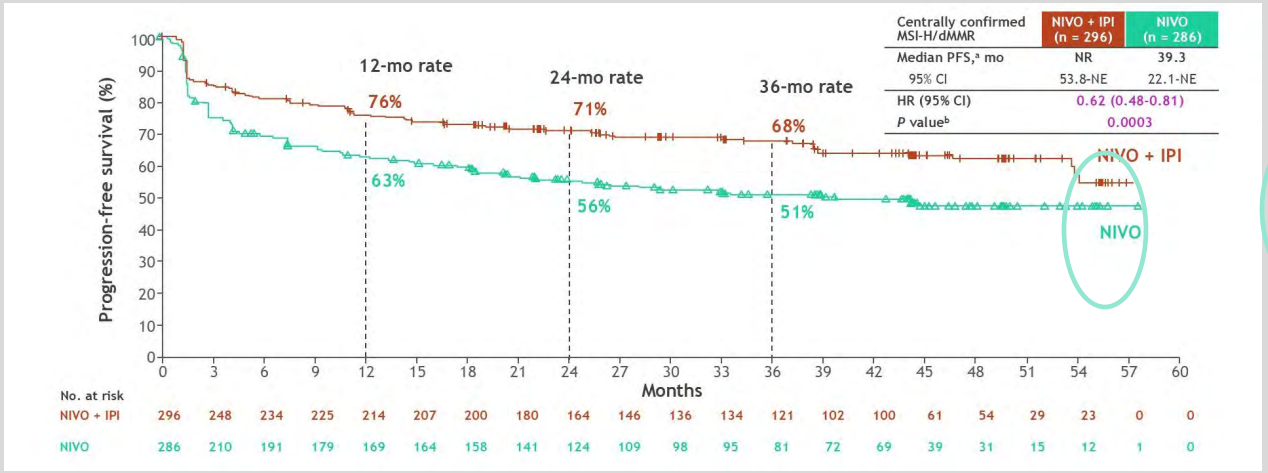
Nivolumab + Ipilimumab or Pembrolizumab/Nivolumab monotherapy?

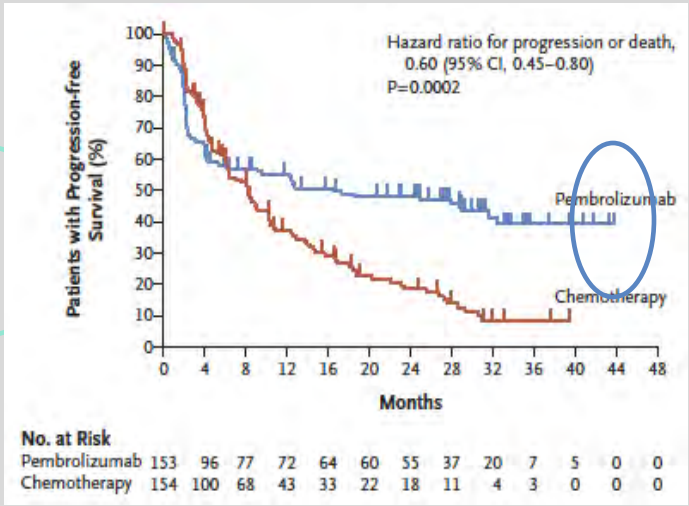
Combotherapy a little bit more toxic (G3/4 AEs 22% vs 14% with Nivo)

- Higher rates of **endocrine AEs**
  →7% hypophysitis, 10% adrenal insuffisency, 18% hypothyroidism, 12% hyperthyroidism
but **very rarely grade 3-4** and presumably **manageable** with hormonal supplementation
- **without impacting QoL**
- Higher rate of discontinuation of ttt related to AEs, although pts were able to continue with nivo alone

BUT

≃ 35-50% of patients: long-term responders to nivo/pembro and possibly already « cured »





ESMO ON AIR

André et al. NEJM 2024; André et al. Lancet 2025

Nivolumab + Ipilimumab or Pembrolizumab/Nivolumab monotherapy?

Nivolumab + Ipilimumab
Potential new standard of care in MSI-high patients

Perspectives:

Select the patient subgroups who truly benefit from the intensification of immunotherapy and are therefore exposed to more toxicities (study of the tumor microenvironment, transcriptomic data, etc...)