Novinky z ASCO 2023

Celkové hodnocení

- 1. dominance imunoterapie a jejích kombinací napříč dg.
- 2. boom nových ADC a jejich posun do primární léčby
- 3. vakcinace v nových indikacích (CRC)
- 4. mnoho studií a prací FI a II
- 5. části věnované dostupnosti léčby, přístupu ke starším pac., genderové problematice

LBA 1

2023 ASCO ANNUAL MEETING

INDIGO: a Phase 3 global, randomized, double-blinded study of vorasidenib versus placebo in patients with residual or recurrent grade 2 glioma with an IDH1/2 mutation

Ingo K. Mellinghoff,[1] Martin J. van den Bent,[2] Deborah T. Blumenthal,[3] Mehdi Touat,[4] Katherine B. Peters,[5] Jennifer Clarke,[6] Joe Mendez,[7] Liam Welsh,[8] Warren P. Mason,[9] Andreas F. Hottinger,[10] Juan M. Sepulveda,[11] Wolfgang Wick,[12] Riccardo Soffietti,[13] Steven Schoenfeld,[14] Dan Zhao,[14] Susan Pandya,[14] Lori Steelman,[14] Islam Hassan,[14] Patrick Y. Wen,[15*] Timothy F. Cloughesy[16*]

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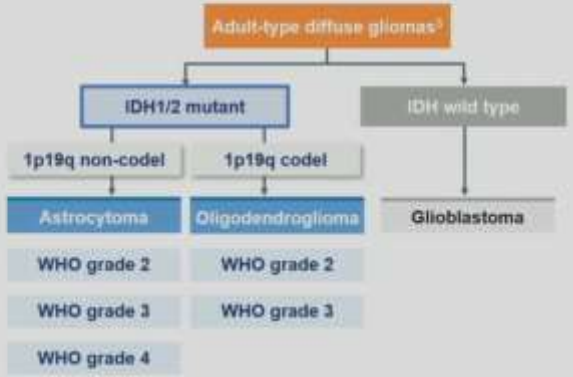
ClinicalTrials.gov identifier: NCT04164901. This study was sponsored by Servier

IDH1/2-mutant diffuse gliomas

- IDH1/2 mutations occur in most low-grade diffuse gliomas[1,2]
- Characteristic molecular and clinical features[3]
- Distinct disease entity in revised WHO classification (2021)[3]
- Median age ~40 years[4]



1. Yan H et al. *N Engl J Med* 2009;360:765–73; 2. Hartmann C et al. *Acta Neuropathol* 2009;118:469–74; 3. Louis DN et al. *Neuro Oncol* 2021;23:1231–51; 4. Ostrom QT et al. *Neuro Oncol* 2022;24:v1–v95.
codel, codeletion

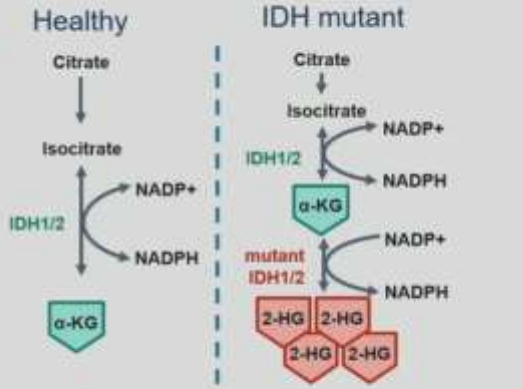
Current treatment approach to newly diagnosed IDH1/2-mutant glioma

No curative therapy

Figure modified from: Weller M et al. *Nat Rev Clin Oncol* 2021;18:170–86, with permission.
PCV, procarbazine, lomustine and vincristine; TMZ, temozolomide

Isocitrate dehydrogenase

- IDH1/2 hotspot mutations occur in various cancers, including diffuse gliomas[1]
- IDH1/2 mutations result in:[2]
  - Overproduction of R-2-hydroxyglutarate
  - Epigenetic dysregulation
  - Impaired cellular differentiation
  - Immunosuppressive tumor microenvironment

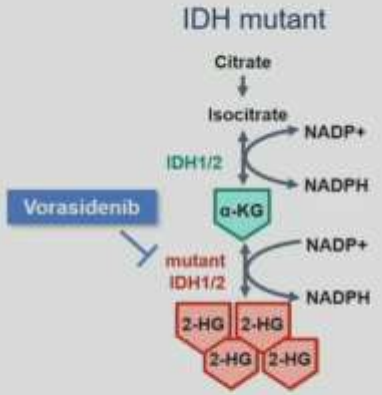


Competitive inhibition of α-KG-dependent enzymes

1. Dang L et al. *Nature* 2009;462:739–44; 2. Clark O et al. *Clin Cancer Res* 2016;22:1837–42.
IDH, isocitrate dehydrogenase; NADP(H), nicotinamide adenine dinucleotide phosphate; 2-HG, R-2-hydroxyglutarate; α-KG, alpha-ketoglutarate

Vorasidenib

- Oral inhibitor of mutant IDH1 and IDH2[1]
- Specifically designed for brain penetrance[1]
- Reduced tumor 2-HG by >90% in resected grade 2/3 non-enhancing diffuse glioma[1]
- 2-HG reduction associated with:[2]
  - Lower tumor cell proliferation
  - Reversal of IDH1/2 mutation-associated gene expression programs
  - Increased DNA 5-hydroxy-methylcytosine
  - Increased tumor infiltrating lymphocytes



Competitive inhibition of α-KG-dependent enzymes

1. Mellinghoff I et al. *Nat Med* 2023;29:615–22; 2. Liu M et al. Presented at the American Association for Cancer Research Virtual Annual Meeting II June 22–24, 2020; abstract 2046.

INvestigating vorasiDenIb in GliOma (NCT04164901)

Key eligibility criteria
- ≥12 years of age
- IDH1/2-mutated* grade 2 oligodendroglioma or astrocytoma per WHO 2016 guidelines
- Prior surgery only
- Measurable non-enhancing disease (≥1 target lesion measuring ≥1 cm × ≥1 cm), confirmed by blinded review
- Not in need of immediate chemotherapy or radiotherapy per investigator assessment

1:1 double-blind randomization (N=331)

Stratified by 1p19q status and baseline tumor size

Orally, once daily, 28-day cycles

Centrally confirmed progressive disease permitted unblinding and crossover†

- Vorasidenib 40 mg (N=168)
- Placebo (N=163)

IDMC regularly reviewed safety and other clinical data, as well as the efficacy data following prespecified interim analyses

*Centrally confirmed using an investigational clinical trial assay, based on the Oncomine Dx Target Test and developed in partnership with Thermo Fisher Scientific Inc.; †Real-time single BIRC reader.
IDMC, independent data monitoring committee

Endpoints and planned analyses

1 Primary endpoint

PFS: time from randomization to the first imaging-based disease progression as assessed by BIRC or death because of any cause
- MRI every 3 months for 3 years, then every 6 months

2 Key secondary endpoint

TTNI: time from randomization to the initiation of first subsequent anticancer therapy or death because of any cause

Three prespecified analyses*

IA1: futility (~55 PFS events) – Jan 2022

IA2: futility/superiority (~123 PFS events) – Sep 2022

Final analysis (~164 events) → no longer needed after IA2 superiority outcome

Other secondary/exploratory endpoints include: safety, tumor growth rate by volume, objective response rate, overall survival, HRQoL, seizure activity and neurocognitive function.
*With multiplicity adjustment and alpha spending.
HRQoL, health-related quality of life; IA, interim analysis; MRI, magnetic resonance imaging.

Patient disposition

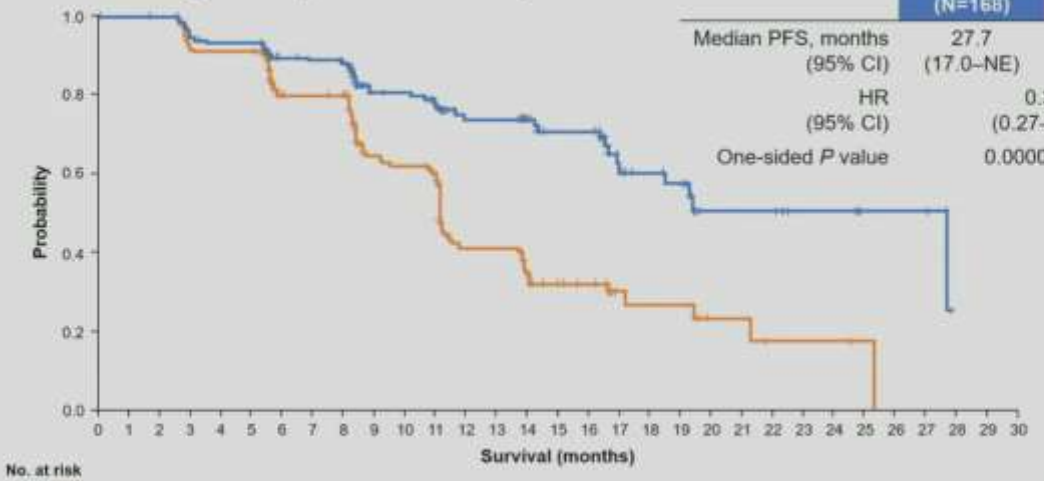
As of Sep 2022 data cutoff (IA2):
- Enrollment:
  - Jan 2020 to Feb 2022
- 77 centers across 10 countries
- Median follow-up:
  - 14.0 months with vorasidenib
  - 14.3 months with placebo
- No deaths
- No patients lost to follow-up for the primary outcome

	Vorasidenib	Placebo
Randomized to treatment – n (%)	168 (100)	163 (100)
Received treatment (safety set)	167 (99.4)*	163 (100)
Discontinued treatment – n (%)	36 (21.4)	68 (41.7)
Centrally confirmed disease progression†	24 (14.3)	59 (36.2)
Patient decision	5 (3.0)	5 (3.1)
Adverse event	6 (3.6)	2 (1.2)
Investigator decision	1 (0.6)	1 (0.6)
Clinical disease progression‡	0	1 (0.6)
Crossed over to vorasidenib – n (%)	–	52 (31.9)

Study unblinded in Mar 2023 following IDMC recommendation based on early demonstration of efficacy, after which the majority of patients randomized to placebo crossed over to vorasidenib

*One patient withdrew consent from study treatment and later withdrew consent from the study overall; †Real-time single BIRC reader; ‡In absence of imaging-based progression.

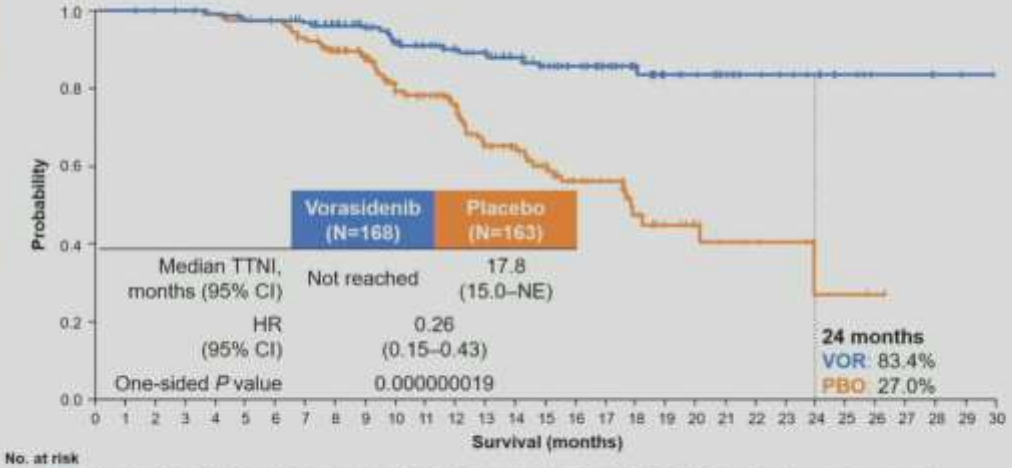
Primary endpoint: PFS per BIRC



	Vorasidenib (N=168)	Placebo (N=163)
Median PFS, months (95% CI)	27.7 (17.0–NE)	11.1 (11.0–13.7)
HR (95% CI)	0.39 (0.27–0.56)	
One-sided *P* value	0.000000067	

+ Censored.
P value is from one-sided stratified log-rank test.
NE, not estimable; PBO, placebo; VOR, vorasidenib.

Key secondary endpoint: TTNI



+ Censored
P value is from one-sided stratified log-rank test.

Safety: TEAEs

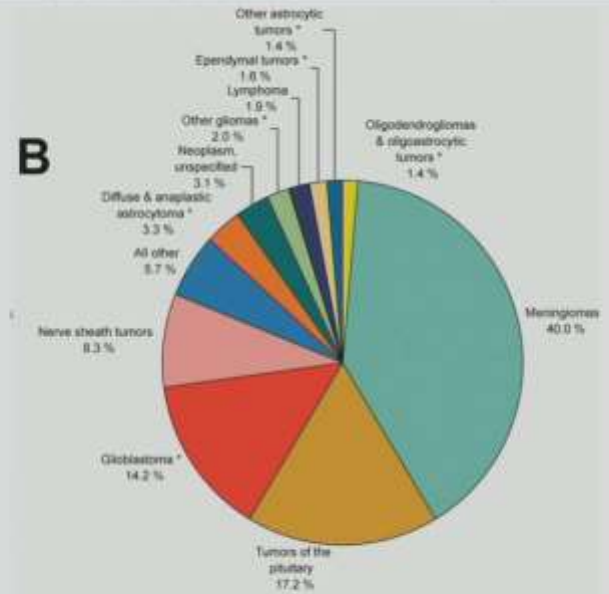
	Vorasidenib (N=167)	Placebo (N=163)
Any grade ≥3 AE – n (%)	38 (22.8)	22 (13.5)
Increased alanine aminotransferase	16 (9.6)	0
Increased aspartate aminotransferase	7 (4.2)	0
Seizure	7 (4.2)	4 (2.5)
Increased gamma-glutamyltransferase	5 (3.0)	2 (1.2)
Syncope	3 (1.8)	1 (0.6)
Hypertension	2 (1.2)	3 (1.8)
Decreased neutrophil count	2 (1.2)	0

- Treatment interruption due to TEAE
  - Vorasidenib 29.9% (n=50)
  - Placebo 22.7% (n=37)
- Dose reduction due to TEAE
  - Vorasidenib 10.8% (n=18)
  - Placebo 3.1% (n=5)
- Discontinuation due to TEAE
  - Vorasidenib 3.6% (n=6)
  - Placebo 1.2% (n=2)
- No fatal TEAE

The safety set included all the patients who received at least one dose of study treatment.
Preferred terms listed are those that occurred at Grade ≥3 in two or more patients in the vorasidenib group.
AE, adverse event; TEAE, treatment-emergent adverse event.

Summary

- Diffuse gliomas with IDH1/2 mutations are not curable with current therapies and infiltrate the brain in the absence of treatment
- Vorasidenib is an oral inhibitor of the mutant IDH1/2 enzymes with proven brain penetrance
- Treatment with vorasidenib significantly improved imaging-based PFS and TTNI with a manageable safety profile in patients who were not in need of immediate chemotherapy or radiotherapy



Ostrom QT, et al. Neuro Oncol. 2022;24(suppl_5):v1-v95.

2023 ASCO ANNUAL MEETING

LBA 2

Preoperative Chemotherapy with Selective Chemoradiation versus Chemoradiation for Locally Advanced Rectal Cancer:

The PROSPECT Trial (Alliance N1048)

D Schrag MD MPH Q Shi PhD MR Weiser MD MJ Gollub MD LB. Saltz MD BL Musher MD J. Goldberg MD T. Al Baghdadi MD KA Goodman MD RR McWilliams MD MSc JM Farma MD TJ George MD HF Kennecke MD A Shergill MD M Montemurro MD GD Nelson MS B Colgrove BS V Gordon MD AP Venook MD EM O'Reilly MD JA Meyerhardt MD MPH AC Dueck PhD E. Basch MD MSc GJ Chang MD HJ Mamon MD PhD

ClinicalTrials.gov Identifier: NCT01515787

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

NCI National Clinical Trials Network

PRESENTED BY: Deb Schrag MD MPH FASCO, Attending, Gastrointestinal Oncology Service, Memorial Sloan Kettering NY, NY USA

Background: Rectal Cancer

- Globally ~800,000 new rectal cancer diagnoses in 2023; about half with locally advanced rectal cancer[1]
- Pelvic chemoradiation with either 5FU or capecitabine reduces local pelvic recurrence-- a highly morbid outcome[2]
- Neoadjuvant pelvic chemoradiation has been standard treatment for the past two decades[3]

1. Morgan E et al. Gut 2023
2. Fisher et al JNCI 1988; Douglas NEJM 1986; Folkesson J JCO 2005
3. Sauer R et al NEJM 2004

Curative Intent Treatment for Locally Advanced Rectal Cancer when PROSPECT began:

PROSPECT Study Motivation

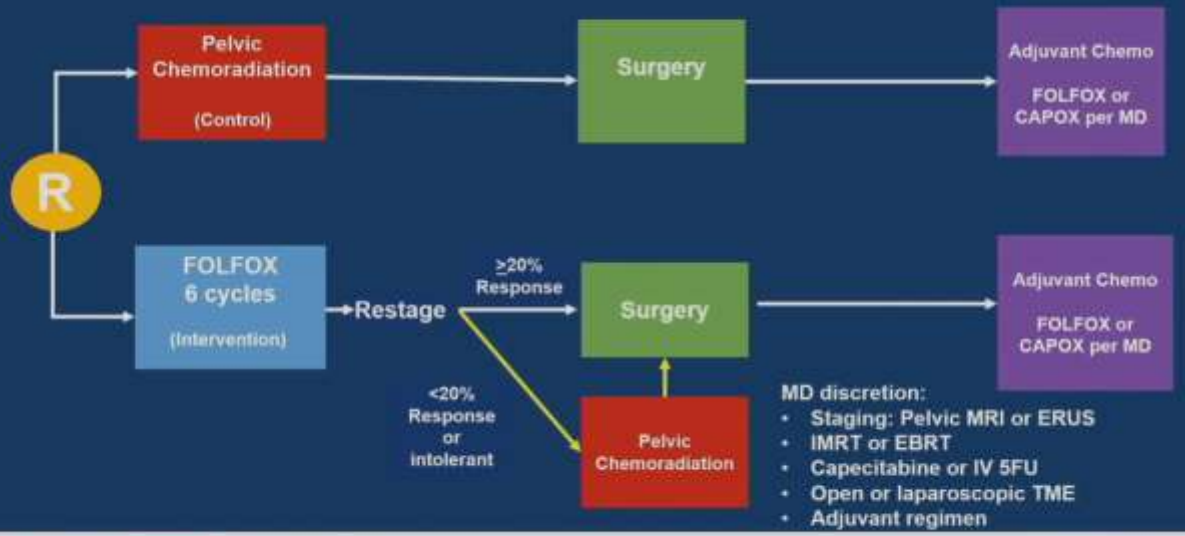
- Long term toxicity from pelvic chemoradiation:
  - Impaired bowel, bladder, and sexual function[1]
  - Increased risk of pelvic fracture and second malignancy[2]
  - Impaired marrow reserve[3]
  - Infertility and premature menopause[4]
    - Increasing diagnosis of rectal cancer before age 50[5]

1. Bruheim Int J Radiat Oncol Biol Phys 2010
2. Baxter N et al JAMA 2005
3. Chen MF et al Int J. Radiat. Oncol.Biol. Phys 2006
4. Ogilvy-Stuart AL Environ Health Perspect 1983
5. Meyer JE et al Cancer 2010 and Sinicrope F NEJM 2022

PROSPECT Trial Hypothesis (circa 2011):

- Neoadjuvant chemotherapy with FOLFOX and only *selective* use of pelvic chemoradiation will be noninferior to routine use of pelvic chemoradiation for locally advanced rectal cancer

PROSPECT Study Full Schema



PROSPECT Main Eligibility Criteria

Inclusion:

- Clinical Stage T2N+, T3N-, T3N+
- Chemoradiation is indicated
- Candidate for sphincter-sparing surgery

Exclusion:

- Tumor requiring an APR
- cT4 tumor
- ≥ 4 pelvic lymph nodes ≥ 1cm in short axis

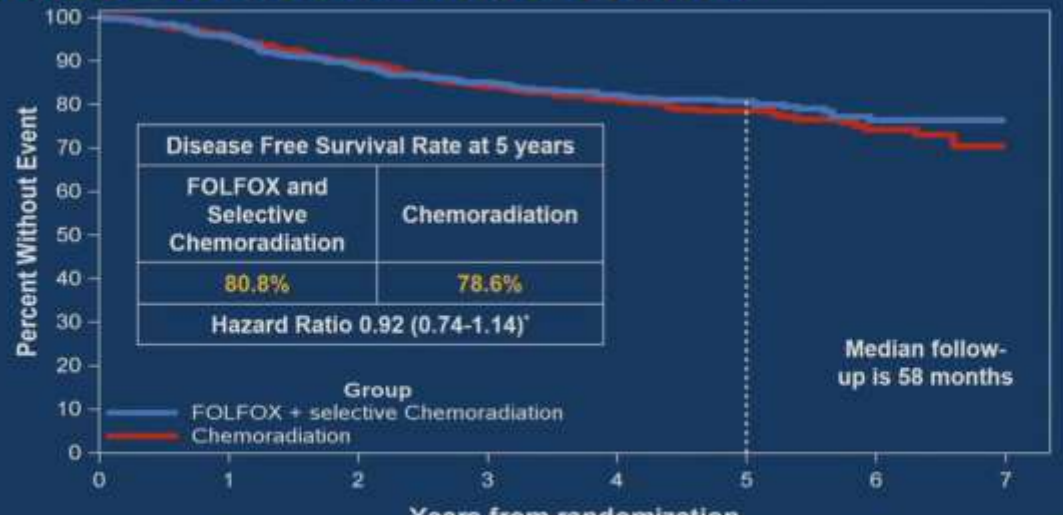
PROSPECT Study Endpoints

- Primary Endpoint:
  - Disease Free Survival
- Secondary Endpoints:
  - Local recurrence
  - Overall survival
  - Complete (R0) surgical resection
  - Complete pathologic response
  - Toxicity-CTCAE and PRO-CTCAE
  - Quality of Life

Characteristics of PROSPECT Participants

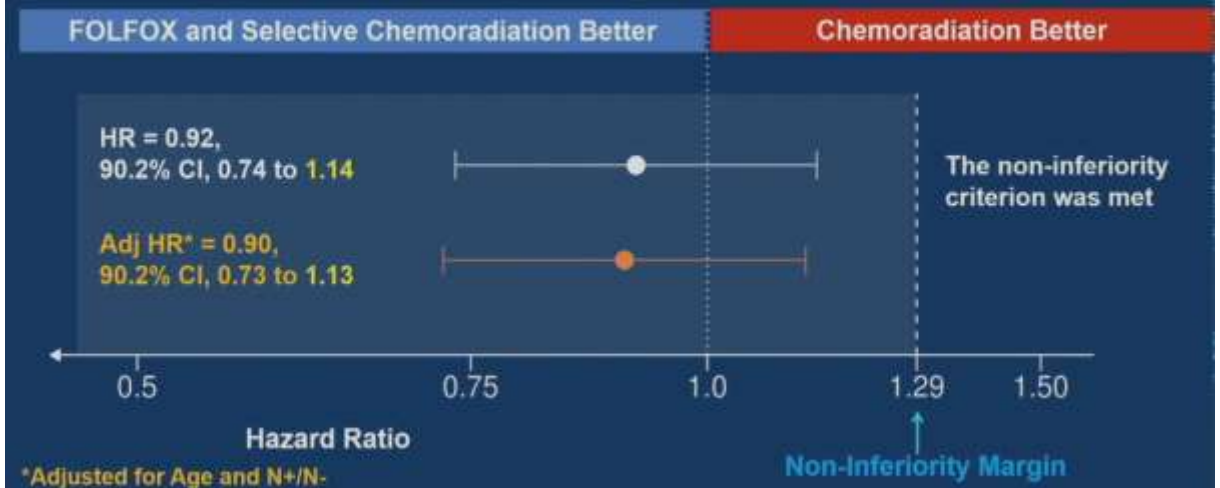
Recruitment: 264 Centers	FOLFOX and Selective Chemoradiation	Chemoradiation
N	585	543
Age Mean (SD)	57 (11)	57(11)
Sex		
Female	37%	32%
Male	63%	68%
Tumor location from the anal verge in cm (SD)	8 (3)	8 (3)
Baseline Staging Performed with MRI	84%	84%
Clinical Stage at Baseline		
cT2N+	11%	7%
cT3N-	39%	37%
cT3N+	50%	56%

PROSPECT: Disease Free Survival



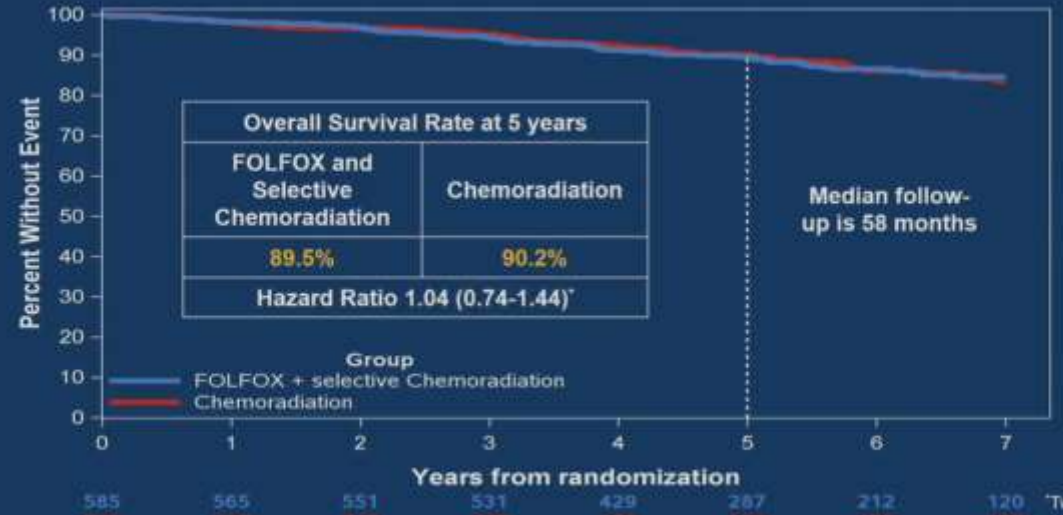
*Two-sided 90.2% confidence interval

PROSPECT: Disease Free Survival



*Adjusted for Age and N+/N-

PROSPECT: Overall Survival



*Two-sided 95% confidence interval

Use of Pelvic Chemoradiation in patients randomized to FOLFOX

9% (53/585) of participants randomized to FOLFOX received neoadjuvant chemoradiation either because:

Restaging demonstrated clinical response <20% or

They did not tolerate at least 5 cycles of FOLFOX

Patient-Reported Adverse Events During Neoadjuvant Treatment

% Reporting Severe PRO-CTCAE Scores	Neoadjuvant Treatment: FOLFOX and Selective Chemoradiation 12 weeks (22 weeks if also 5FUCRT)	Neoadjuvant Treatment: Chemoradiation 6 weeks
Anxiety	11%	6%
Appetite Loss	22%	9%
Constipation	27%	11%
Depression	10%	3%
Diarrhea	6%	20%
Dysphagia	12%	1%
Dyspnea	7%	1%
Edema	2%	2%
Fatigue	42%	20%
Mucositis	11%	2%
Nausea	21%	7%
Neuropathy	19%	5%
Pain	22%	18%
Vomiting	4%	2%

Values represent % with PRO-CTCAE composite scores ≥3 which were worse than each patient's baseline score (n=940).

Caveat: *While conducting this trial, new approaches have emerged*

- Shorter courses of adjuvant FOLFOX[1]
- Short course radiation[2]
- Total neoadjuvant therapy[3]
- Non-operative management[4]
- Immuno-ablative therapy for MSI-high patients[5]

1. Grothey A NEJM 2018
2. Bahdoer R Lancet 2001
3. Cercek A Jama Oncol 2022
4. Habr-Gama A, Dis Colon Rectum 1998
5. Cercek A, NEJM 2022

PROSPECT Trial Conclusion

Neoadjuvant FOLFOX, with only selective use of pelvic chemoradiation, is a safe and effective treatment option for patients with cT2N+, cT3N-, or cT3N+ rectal cancer

Glynne-Jones, Ann Oncol 2017

ESMO guidelines on rectal cancer

	EARLY	INTERMEDIATE	LOCALLY ADVANCED	ADVANCED
Disease stage	• cT1-2 OR • cT3a/b (middle or high) • cN0 (cN1 if high) • MRF clear • No EMVI	• cT3a/b (very low) • levators clear • MRF clear OR • cT3a/b (middle or high) • cN1-2 (not extranodal) • No EMVI	• > cT3b • *and/or* EMVI • *and/or* extranodal cN1-2 • All clear MRF and levators	• cT3 with either • MRF involved • levators threatened • lateral node+ OR • cT4
ESMO guidelines	TME without preoperative radiotherapy	TME alone SCRT/CRT if good quality TME cannot be assured	SCRT or CRT	CRT or TNT

TME: total mesorectal excision
SCRT: short course radiotherapy (5x5 Gy)
CRT: chemoradiotherapy

Deng, ASCO 2023, abs. 3505

Similar effects on long-term survival as in FOWARC study

	PROSPECT		FOWARC		
	6 x FOLFOX 9% CRT Surgery 6 x FOLFOX	5FU CRT Surgery 12x FOLFOX	4-6x FOLFOX Surgery 6-8x FOLFOX	5x 5FU + RT Surgery 7x 5-FU	5x FOLFOX+RT Surgery 7x FOLFOX
Overall survival	90%	90%	73%	66%	73%
Disease free Survival	81%	79%	64%	56%	63%
	5 yr results		*10 yr results*		

Deng, JCO 2019

Increase in pCR rate with CRT in FOWARC study

	PROSPECT		FOWARC		
	6 x FOLFOX 9% CRT Surgery 6 x FOLFOX	5FU CRT Surgery 12x FOLFOX	4-6x FOLFOX Surgery 6-8x FOLFOX	5x 5FU + RT Surgery 7x 5-FU	5x FOLFOX + RT Surgery 7x FOLFOX
pCR rate	22%	24%	7%	14%	28%
T4 stage	none			33%	
N2 stage	none			27%	
< 5cm	no APE			49%	

Conroy, ASCO 2023, LBA 3504

PRODIGE-23: Introduction of total neoadjuvant treatment

	PROSPECT		PRODIGE 23	
	6 x FOLFOX 9% CRT Surgery 6 x FOLFOX	5FU CRT Surgery 12x FOLFOX	**6 x FOLFIRINOX 100% CRT** Surgery 6 x FOLFOX	5FU CRT Surgery 12x FOLFOX
Overall survival	90%	90%	82%	76%
Disease free Survival	81%	79%	68%	63%
	5 yr results		*7 yr results*	

Conroy, Lancet Oncol 2021

Increase in pCR rate with TNT in PRODIGE trial

	PROSPECT		PRODIGE 23	
	6 x FOLFOX 9% CRT Surgery 6 x FOLFOX	5FU CRT Surgery 12x FOLFOX	6 x FOLFIRINOX 100% CRT Surgery 6 x FOLFOX	5FU CRT Surgery 12x FOLFOX
pCR rate	22%	24%	28%	12%
T4 stage	none		17%	
N2 stage	none		24%	
< 5cm	no APE		37%	

TNT: total neoadjuvant treatment

Take-Away: for early/intermediate mid/high rectal tumors

- FOLFOX followed by selective chemoradiotherapy can replace standard neoadjuvant chemoradiotherapy
- Largest benefit is less long-term radiotherapy-related toxicity
- Shared decision making advised in all cases!

2023 ASCO ANNUAL MEETING

LBA 3

Overall survival analysis from the ADAURA trial of adjuvant osimertinib in patients with resected EGFR-mutated (EGFRm) stage IB–IIIA non-small cell lung cancer (NSCLC)

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PRESENTED BY: Roy S. Herbst

ADAURA overall survival: summary and impact

The ADAURA study has demonstrated a statistically significant and clinically meaningful OS benefit with adjuvant osimertinib vs placebo in patients with resected EGFRm stage IB–IIIA NSCLC

>2 million
new cases of lung cancer worldwide annually[1]

NSCLC represents **~80%** of all diagnoses[1]

Approximately **30%** of patients have resectable disease[2–4]

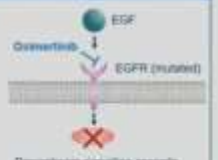
EGFR mutation prevalence ranges from **10–50%** in patients with NSCLC[5–9]

ADAURA

Surgery → Adjuvant Therapy

Osimertinib vs placebo

Adjuvant osimertinib



Osimertinib is the first EGFR-TKI to show significant OS benefit in a Phase III adjuvant study

Reinforces osimertinib as standard of care

EGFR mutation testing | **Best treatments early** | **New era for targeted treatment in early-stage disease**

PRESENTED BY: Roy S. Herbst

Survival outcomes in resectable NSCLC need to be improved

- Lung cancer is the leading cause of cancer death, accounting for almost 1.8 million deaths annually[1]
- NSCLC represents approximately 80% of all lung cancer diagnoses,[2] with an estimated 30% of patients presenting with resectable disease at diagnosis[3–5]

Global 5-year overall survival* rates in patients with resectable NSCLC[6–8]

PRESENTED BY: Roy S. Herbst

ADAURA Phase III study design

Patients with completely resected stage* IB, II, IIIA NSCLC, with or without adjuvant chemotherapy†

Key inclusion criteria:
- ≥18 years (Japan / Taiwan: ≥20)
- WHO performance status 0 / 1
- Confirmed primary non-squamous NSCLC Ex19del / L858R‡
- Brain imaging, if not completed pre-operatively
- Complete resection with negative margins§
- Maximum interval between surgery and randomization:
  - 10 weeks without adjuvant chemotherapy
  - 26 weeks with adjuvant chemotherapy

Stratification by:
Stage (IB vs II vs IIIA)
EGFRm (Ex19del vs L858R)
Race (Asian vs non-Asian)

Randomization 1:1 (N=682)

- **Osimertinib 80 mg, once daily**
- **Placebo, once daily**

Planned treatment duration: 3 years

Treatment continued until:
- Disease recurrence
- Treatment completion
- Discontinuation criterion met

Follow-up:
- Until recurrence: Week 12 and 24, then every 24 weeks to 5 years, then yearly
- After recurrence: every 24 weeks for 5 years, then yearly

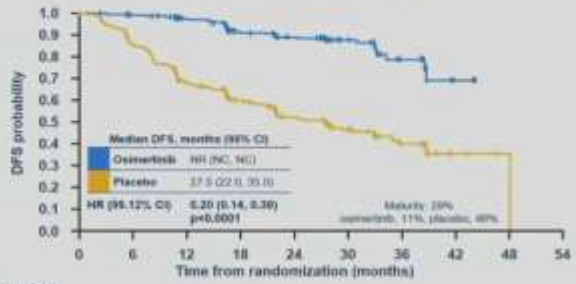
Endpoints
- **Primary endpoint:** DFS by investigator assessment in stage II–IIIA patients
- **Key secondary endpoints:** DFS in the overall population (stage IB–IIIA), landmark DFS rates, OS, safety, health-related quality of life

PRESENTED BY: Roy S. Herbst

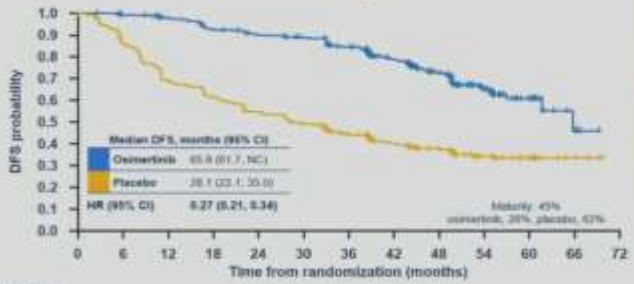
Adjuvant osimertinib has significantly improved DFS

- Adjuvant osimertinib demonstrated highly statistically significant[1,2] and clinically meaningful improvement in DFS in completely resected EGFRm NSCLC vs placebo in both the primary (stage II–IIIA) and overall (IB–IIIA) populations, along with a tolerable safety profile[1–4]

ADAURA primary DFS analysis[1,2] (stage IB–IIIA)*
NEJM October 2020



ADAURA updated DFS analysis[3,4] (stage IB–IIIA)†
JCO January 2023



PRESENTED BY: Roy S. Herbst

Adjuvant osimertinib has significantly improved CNS DFS

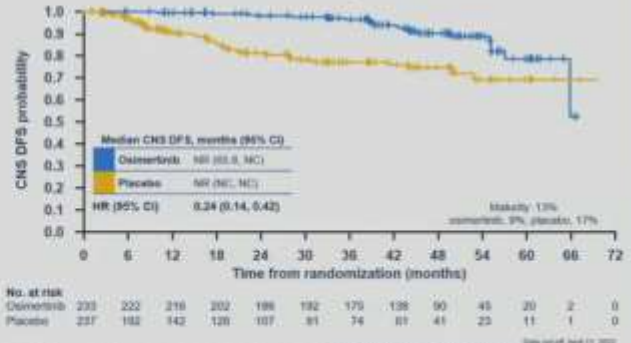
- CNS metastases are a poor prognostic factor among patients with NSCLC, and are associated with deterioration in quality of life[1]

Improved CNS efficacy with osimertinib treatment

- Osimertinib has shown greater penetration of the blood-brain barrier and higher exposure in the brain compared with other EGFR-TKIs[2–4]
- Adjuvant osimertinib demonstrated CNS DFS* benefit vs placebo in both the stage II–IIIA and IB–IIIA populations[5,6]

ADAURA updated CNS DFS analysis[5,6] (stage II–IIIA)

JCO January 2023



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DFS benefit with adjuvant EGFR-TKIs in resected EGFRm NSCLC

Phase III EGFR-TKI studies in resected EGFRm NSCLC

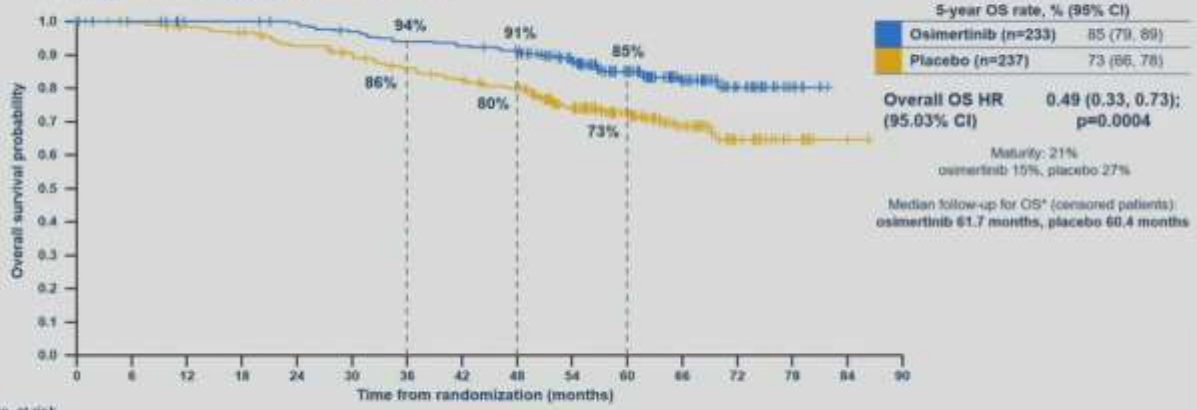
Date	Adjuvant treatment	Phase III study	Key results	Conclusion
2015	Erlotinib vs placebo	RADIANT[1] (stage IB–IIIA)	EGFRm subgroup: DFS HR 0.75 (95% CI: 0.48, 1.16); p=0.1906	**Non-significant DFS improvement**
2020	Gefitinib vs chemotherapy	ADJUVANT / CTONG1104[2,3] (stage II–IIIA)	Updated DFS HR 0.56 (95% CI: 0.40, 0.79); p=0.001; OS HR, 0.92 (95% CI: 0.62, 1.36); p=0.674	**Significant DFS benefit, but no OS benefit**
2020	Osimertinib vs placebo	ADAURA[4,5] (stage IB–IIIA)	DFS HR, 0.20 (99.12% CI: 0.14, 0.30); p<0.0001	**Highly significant DFS benefit**
2021	Gefitinib vs chemotherapy	IMPACT[9] (stage II–III)	DFS HR, 0.92 (95% CI: 0.67, 1.28); p=0.63 OS HR, 1.03 (95% CI: 0.65, 1.65); p=0.89	**No significant DFS or OS benefit**

To date, no EGFR-TKI in a Phase III study has demonstrated translation of DFS benefit to significant OS benefit[7]

2023 ASCO ANNUAL MEETING #ASCO23 presented by: Roy S. Herbst

Overall survival: patients with stage II / IIIA disease

- Adjuvant osimertinib demonstrated a statistically and clinically significant improvement in OS vs placebo in the primary population of stage II–IIIA disease



5-year OS rate, % (95% CI)	
Osimertinib (n=233)	85 (79, 89)
Placebo (n=237)	73 (66, 78)
Overall OS HR (95.03% CI)	0.49 (0.33, 0.73); p=0.0004

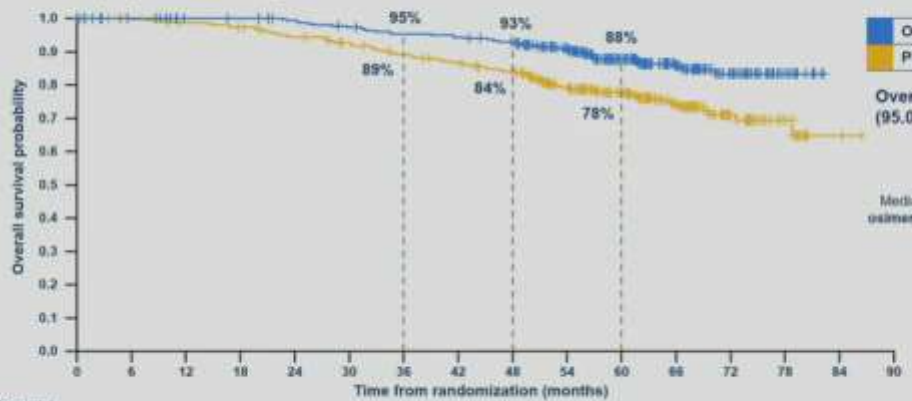
Maturity: 21%
osimertinib 15%, placebo 27%

Median follow-up for OS* (censored patients):
osimertinib 61.7 months, placebo 60.4 months

2023 ASCO ANNUAL MEETING #ASCO23 presented by: Roy S. Herbst

Overall survival: patients with stage IB / II / IIIA disease

- Adjuvant osimertinib demonstrated a statistically and clinically significant improvement in OS vs placebo in the overall population of stage IB–IIIA disease



5-year OS rate, % (95% CI)	
Osimertinib (n=339)	88 (83, 91)
Placebo (n=343)	78 (73, 82)
Overall OS HR (95.03% CI)	0.49 (0.34, 0.70); p<0.0001

Maturity: 18%
osimertinib 12%, placebo 24%

Median follow-up for OS* (censored patients):
osimertinib 61.5 months, placebo 61.5 months

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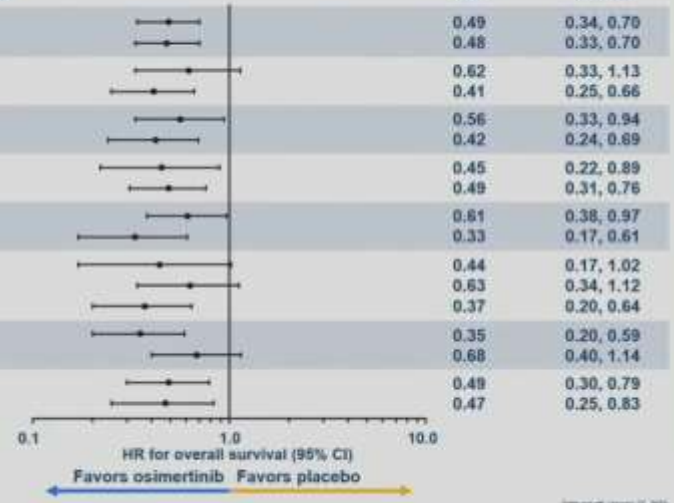
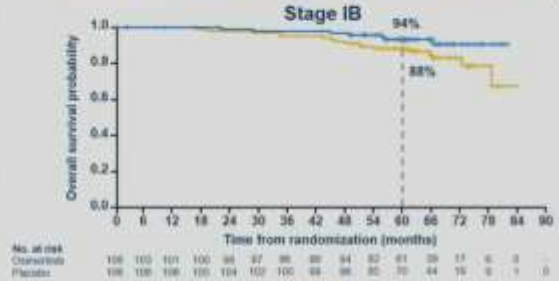
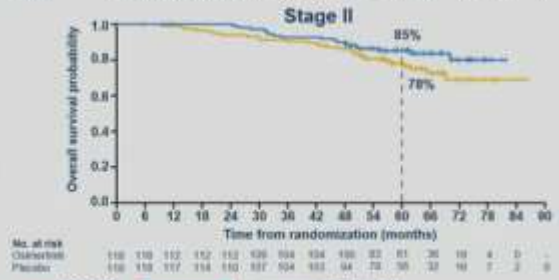
OS across subgroups: patients with stage IB / II / IIIA disease

Subgroup		No. of events / patients	HR	95% CI
Overall (N=682)	Stratified log-rank	124 / 682	0.49	0.34, 0.70
	Unadjusted Cox PH	124 / 682	0.48	0.33, 0.70
Sex	Male	42 / 204	0.62	0.33, 1.13
	Female	82 / 478	0.41	0.25, 0.66
Age	<65 years	60 / 380	0.56	0.33, 0.94
	≥65 years	64 / 302	0.42	0.24, 0.69
Smoking history	Yes	34 / 194	0.45	0.22, 0.89
	No	90 / 488	0.49	0.31, 0.76
Race	Asian	73 / 434	0.61	0.38, 0.97
	Non-Asian	51 / 248	0.33	0.17, 0.61
Stage*	IB	24 / 212	0.44	0.17, 1.02
	II	46 / 236	0.63	0.34, 1.12
	IIIA	54 / 234	0.37	0.20, 0.64
EGFR mutation	Ex19del	65 / 378	0.35	0.20, 0.59
	L858R	59 / 304	0.68	0.40, 1.14
Adjuvant chemotherapy	Yes	74 / 410	0.49	0.30, 0.79
	No	50 / 272	0.47	0.25, 0.83

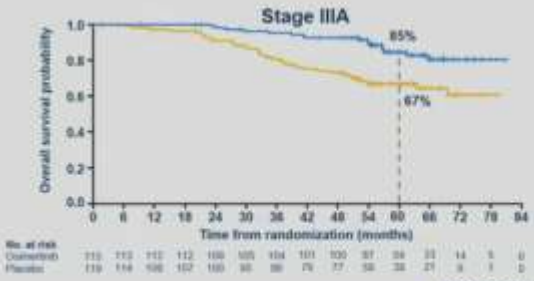


Overall survival by disease stage





5 year OS rate, % (95% CI)	Stage IB	Stage II	Stage IIIA
Osimertinib	94 (86, 97)	85 (77, 91)	85 (76, 91)
Placebo	88 (80, 93)	78 (69, 85)	67 (57, 75)
Overall HR (95% CI)	0.44 (0.17, 1.02)	0.63 (0.34, 1.12)	0.37 (0.20, 0.64)



Safety summary

- At the final DFS analysis (data cut-off: April 11, 2022), all patients had completed or discontinued study treatment; the safety profile of adjuvant osimertinib with extended follow-up[1,2] was consistent with the ADAURA primary analysis[3]

AE, any cause*, n (%)	Osimertinib (n=337)	Placebo (n=343)
Any AE	330 (98)	309 (90)
Any AE Grade ≥3	79 (23)	48 (14)
Any AE leading to death	1 (<1)	2 (1)
Any serious AE	68 (20)	47 (14)
Any AE leading to discontinuation	43 (13)	9 (3)
Any AE leading to dose reduction	42 (12)	3 (1)
Any AE leading to dose interruption	91 (27)	43 (13)
AE, possibly causally related*†, n (%)		
Any AE	308 (91)	199 (58)
Any AE Grade ≥3	36 (11)	7 (2)
Any AE leading to death	0	0
Any serious AE	10 (3)	2 (1)

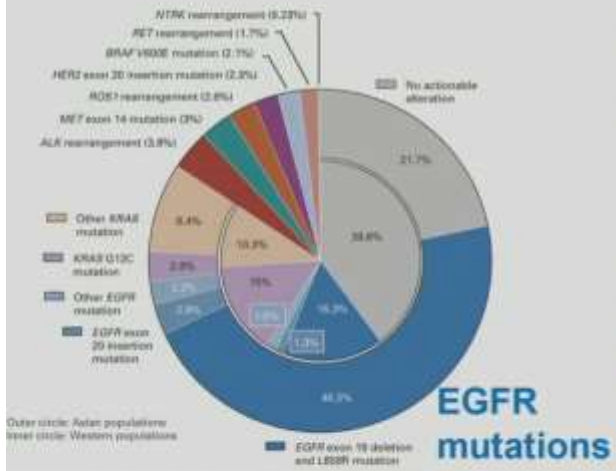
- At the time of the current data cut-off for OS (January 27, 2023), one additional serious AE (COVID-19 pneumonia) had been reported, which occurred >28 days after treatment discontinuation; the investigator determined that this was not treatment related and the patient made a full recovery

Conclusions

- In the ADAURA primary analysis, adjuvant osimertinib demonstrated a statistically significant[1] and clinically meaningful DFS benefit vs placebo in resected EGFRm stage IB–IIIA NSCLC, along with improved CNS DFS and a tolerable safety profile[1,2]
- **DFS benefit in ADAURA has translated into a statistically significant OS benefit with adjuvant osimertinib vs placebo**
  - **Primary (stage II–IIIA) population, OS HR 0.49; 95.03% CI 0.33, 0.73; p=0.0004**
  - **Overall (stage IB–IIIA) population, OS HR 0.49; 95.03% CI 0.34, 0.70; p<0.0001**
- OS benefit with adjuvant osimertinib vs placebo was generally consistent across subgroups, including by disease stage (IB / II / IIIA) and prior adjuvant chemotherapy use (yes / no)

ADAURA is the first global Phase III study to demonstrate statistically significant and clinically meaningful OS benefit with targeted treatment in this patient population, reinforcing adjuvant osimertinib as the standard of care for patients with resected EGFRm stage IB–IIIA NSCLC

Epidermal Growth Factor Receptor (*EGFR*) mutations in NSCLC



EGFR mutations are found in 15-40% of tumors from patients with advanced NSCLC – similar frequency in early-stage disease.

EGFR mutations

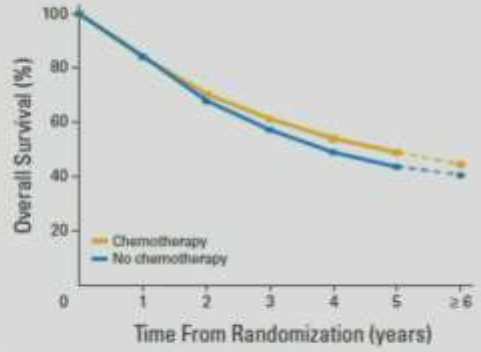
Third Generation EGFR Tyrosine Kinase Inhibitor (TKI) osimertinib improved survival compared to first generation TKIs *eg* gefitinib or erlotinib

Tan JCO 2022; Soo ASCO 2023

Poor outcomes in early-stage NSCLC

High recurrence rates and poor survival in patients undergoing potentially curative resections for early-stage NSCLC.

Absolute improvement in survival with **adjuvant cisplatin-based chemotherapy** of **5.4% at 5 years**



LACE meta-analysis

Pignon JCO 2008

Phase III studies of adjuvant (first gen) EGFR TKIs vs chemotherapy in resected *EGFR* mutation positive NSCLC

	AJUVANT/ CTONG 1104	EVIDENCE	IMPACT
Design	**Gefitinib** 2 years v Chemotherapy Phase 3, n=222	**Icontinib** 2 years v Chemotherapy Phase 3, n=322	**Gefitinib** 2 years v Chemotherapy Phase 3, n=232
Disease Free Survival	mDFS: 28.7 v 18.0M (HR, 0.60; p=0.0054) ✓	mDFS 47 v 22M (HR 0.36, p<0.01) ✓	mDFS: 35.9 vs 25.1 M (HR, 0.92; p=0.63) ✗
Overall Survival	mOS: 75.5 vs 62.8 mo (HR 0.92; p=0.674) ✗	NR ?	mOS: NR vs NR (HR, 1.03; p=0.89) ✗

✗

Zhong Lancet Oncology 2018; Zhong JCO 2021; He Lancet Respir Med 2021;Tada JCO 2022

2023 ASCO ANNUAL MEETING

LBA 4

SWOG S1826, a Randomized Study of Nivolumab(N)-AVD Versus Brentuximab Vedotin(Bv)-AVD in Advanced Stage Classic Hodgkin Lymphoma (cHL)

Alex F. Herrera, MD[1], Michael L. LeBlanc, PhD[2], Sharon M. Castellino, MD, MSc[3], Hongli Li, MS[2], Sarah C. Rutherford, MD[4], Andrew M Evens, DO, MSc[5], Kelly Davison, MD[6], Angela Punnett, MD[7], David C. Hodgson, MD, MPH, FRCPC[8], Susan K Parsons, MD, MRP[9], Sairah Ahmed, MD[10], Carla Casulo, MD[11], Nancy L. Bartlett, MD[12], Joo Y. Song, MD[13], Richard F. Little[14], Brad S. Kahl, MD[12], John P. Leonard, MD[4], Sonali M. Smith, MD[15], Kara M. Kelly, MD[16], and Jonathan W. Friedberg, MD, MSSc[11]

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S1826 Main Findings

- At planned 2nd interim analysis (50% of total PFS events), the SWOG Data and Safety Monitoring Committee recommended to report the primary S1826 results because the primary PFS endpoint crossed the protocol-specified conservative statistical boundary
- N-AVD improved progression-free survival (PFS) compared to Bv-AVD as initial treatment of advanced stage cHL
- N-AVD was well-tolerated
  - Few immune-related adverse events
  - < 1% of patients received radiation therapy (RT)
- Key step towards harmonizing pediatric and adult therapy of cHL
- **N-AVD is poised to be a new standard for treatment of advanced stage cHL**

Treatment Landscape for Advanced Stage cHL (pre-2018)

Pediatric approach

ABVE-PC +/- Radiation

Adult approaches

ABVD

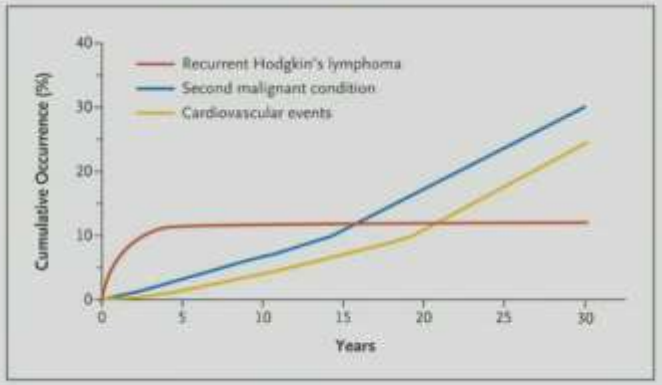
BEACOPP

- PET-adapted combination chemotherapy has been the standard for cHL[1,2,3]
- Global, adult, and pediatric approaches differ
  - Consolidative radiation therapy (RT) is still delivered to 55-60% of pediatric patients
- Second-line treatment: high-dose chemo/autologous stem cell transplant

1. Stephens DM et al. Blood 2019. 2. Borchmann P. et al. Lancet 2017 3. Friedman DL et al. JCO 2014

Late Effects of Treatment in cHL

- Long-term morbidity and mortality related to treatment remains significant for a largely young patient population[4]



4. Armitage JO. N Engl J Med 2010;362:943-44

Rationale for PD-1 blockade in cHL

- PD-1 ligand genetic alterations (chr 9p24.1) central to cHL pathogenesis[7]
  - More 9p24.1 genetic alteration in advanced stage cHL[7]
  - ↑ 9p24.1 alteration → poorer outcome with standard frontline therapy[7]
- Nivolumab highly effective in relapsed or refractory cHL (ORR ~70%)[8,9]

7. Roemer MGM et al. JCO 2016. 8. Armand P et al. JCO 2018. 9. Younes A et al. Lancet Oncol 2016.

S1826 Study Design

Newly diagnosed Stage III-IV Hodgkin lymphoma

RANDOMIZE 1:1

N-AVD x 6 cycles
Nivolumab 240mg days 1,15[a]
Doxorubicin, Vinblastine, Dacarbazine days 1,15[b]
*G-CSF optional
470 pts

Bv-AVD x 6 cycles
Bv 1.2mg/kg days 1,15
Doxorubicin, Vinblastine, Dacarbazine days 1,15[b]
*G-CSF required
470 pts

EOT RT (residual FDG-avid lesions)

Stratification:
- Age (12-17/18-60/>60)
- IPS (0-3/4-7)
- EOT RT intended (Y/N)

- Primary endpoint: PFS
- Assume 84% 2-year PFS for BV-AVD, 90% 2-year PFS in N-AVD, final analysis @ 179 events

[a]Nivolumab 3mg/kg for ages ≤ 17, max 240mg
[b]Conventional doses of AVD; Stephens DM et al Blood 2019; Ansell SM et al NEJM 2022

S1826 Eligibility Criteria (abbreviated)

Newly diagnosed Stage III-IV cHL

RANDOMIZE 1:1

N-AVD x 6
*G-CSF optional

Bv-AVD x 6
*G-CSF required

EOT RT

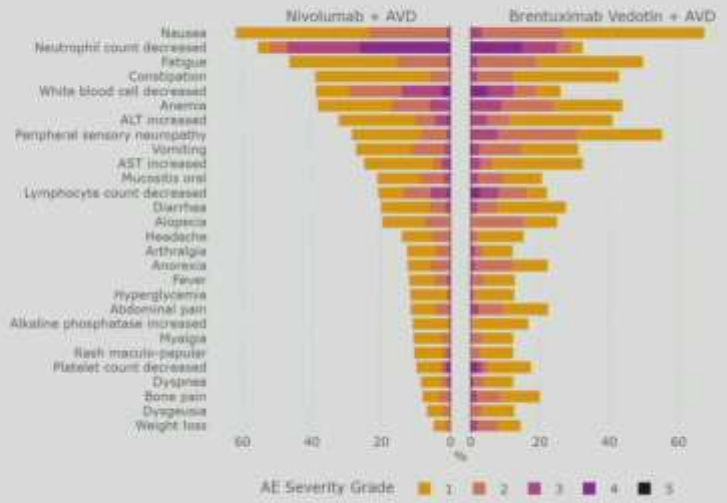
Key Inclusion

- Age ≥ 12 years old
- HIV+ eligible, if controlled
- Zubrod PS 0-2 (Peds: Lansky)
- LVEF ≥ 50% (or SF ≥ 27%)
- CrCl ≥ 30 mL/min (Peds: CrCl/GFR ≥ 70, SCr ≤ 1.5 ULN)
- Tbili ≤ 2 x ULN and AST/ ALT ≤ 3 x ULN

Key Exclusion

- Interstitial lung disease or pneumonitis
- Peripheral neuropathy ≥ Gr2
- Active autoimmune disease

Adverse Events in ≥ 10% patients by Arm

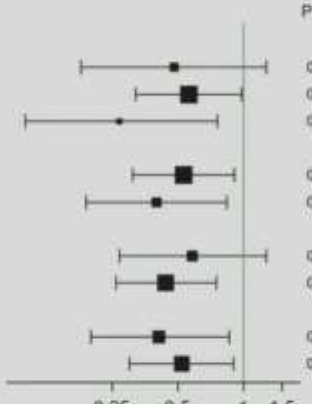


N-AVD improves PFS compared to Bv-AVD

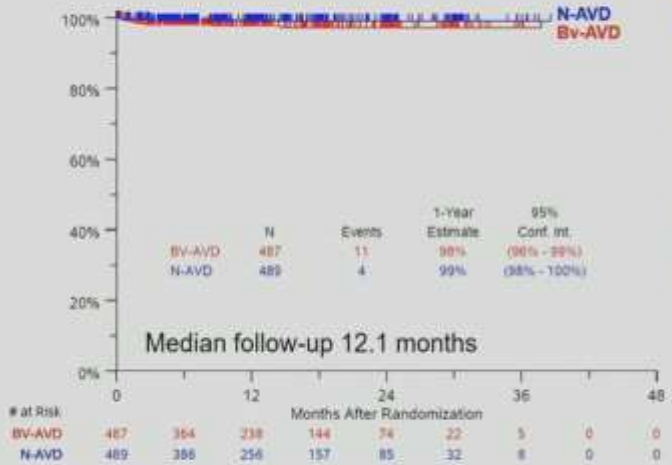
1-year PFS
N-AVD 94%
Bv-AVD 86%

PFS benefit consistent across subgroups

Subgroup	N + AVD Events/N (%)	BV + AVD Events/N (%)	HR (95% CI)	P Value
Age				
12 - 17 y	6/120 (5.0)	12/117 (10.3)	0.48 (0.18, 1.27)	0.140
18 - 60 y	19/323 (5.9)	32/323 (9.9)	0.56 (0.32, 0.98)	0.042
> 60 y	5/46 (10.9)	14/47 (29.8)	0.27 (0.10, 0.78)	0.013
IPS				
0 - 3	20/331 (6.0)	36/330 (10.9)	0.53 (0.31, 0.91)	0.023
4 - 7	10/158 (6.3)	22/157 (14.0)	0.40 (0.19, 0.84)	0.015
Stage				
III	11/187 (5.9)	15/167 (9.0)	0.58 (0.27, 1.27)	0.176
IV	19/301 (6.3)	43/317 (13.6)	0.44 (0.26, 0.75)	0.003
Symptoms				
A	10/202 (5.0)	24/210 (11.4)	0.41 (0.20, 0.86)	0.017
B	20/286 (7.0)	34/274 (12.4)	0.52 (0.30, 0.90)	0.020



Overall Survival



Cause of death	N-AVD	Bv-AVD
Infection	2	4
Sepsis	1	2*
Cardiac arrest	0	1
Pneumonitis	0	1
Dehydration, vomiting, cHL	0	1
cHL	1**	0
Unknown	1	2
Total OS events	**4**	**11**

* 1 death from COVID-19/sepsis
** never received treatment, ineligible on C1D1

S1826 Conclusions

- **N-AVD improved PFS compared to Bv-AVD in advanced stage cHL**
  - N-AVD improved EFS versus Bv-AVD
- N-AVD was well-tolerated
  - Few immune-related adverse events
- < 1% of patients received consolidative RT
  - May reduce late effects
- Follow-up ongoing to confirm durability of PFS, assess long-term safety, OS, and PROs
- Key step towards harmonizing pediatric and adult therapy of cHL
- **N-AVD is poised to be a new standard therapy for advanced stage cHL**

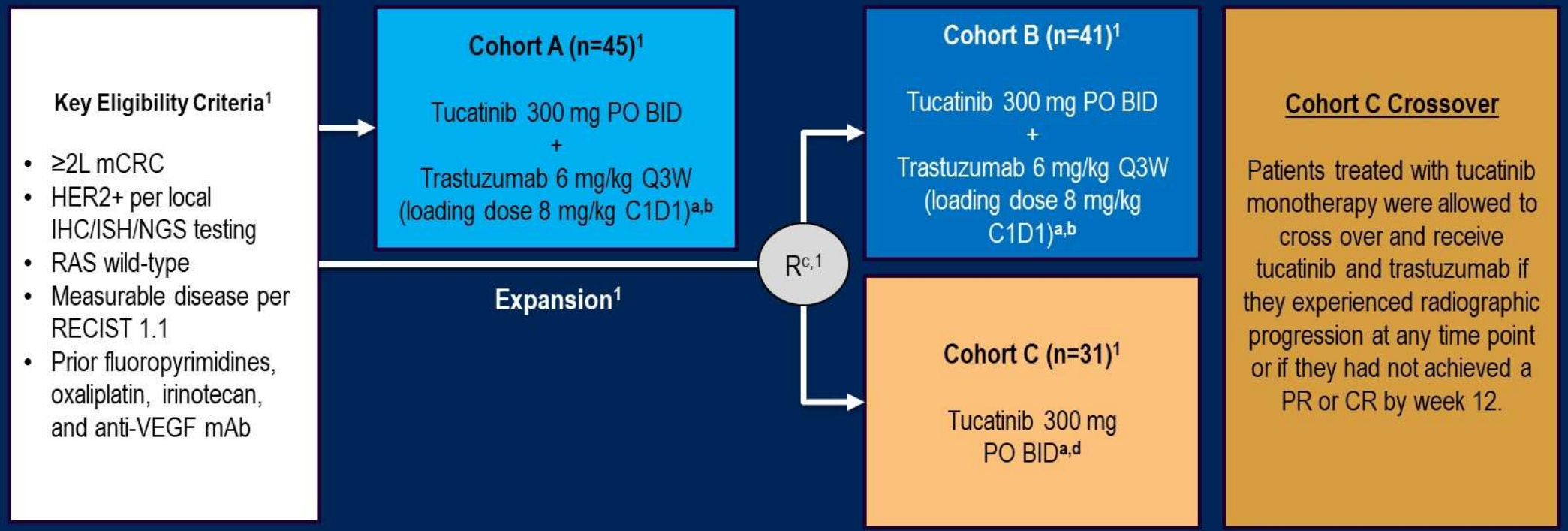
Kolorektum

Conclusions/Take-Away

- All metastatic colorectal cancer should have NGS testing
- Patients with KRAS/BRAF wild-type tumors should have HER2 amplification testing
- Upcoming trials targeting KRAS G12C mutation, and more common KRAS mutations

Targets	Drug
EGFR (RAS/RAF wild-type)	• Cetuximab • Panitumumab
VEGF	• Bevacizumab • Ziv-aflibercept • Ramucirumab • Regorafenib
PDL-1 (dMMR or MSI-H)	• Pembrolizumab • Nivolumab +/- ipilumumab • Dostarlimab
BRAF V600E mutation	• Encorafenib + anti-EGFR
ERBB2 (HER2) amplification (+RAS/RAF wild-type)	• Trastuzumab + Tucatinib Pertuzumab Lapatinib • Trastuzumab deruxtecan
TRK fusion	• Larotrectinib • Entrectanib
RET fusion	• Selpercatinib

MOUNTAINEER: Global, Open-label, Phase 2 Trial



Endpoints: ORR by 12 weeks of treatment (RECIST 1.1 per BICR) for cohort C (pre-crossover), cORR per BICR in post-crossover patients, and DCR per BICR and safety for both pre- and post-crossover patients

Data cut-off for current analysis, March 28, 2022

a Each treatment cycle is 21 days; b Patients remained on therapy until evidence of radiographic or clinical progression, unacceptable toxicity, withdrawal of consent, or study closure; c Stratification: Left sided tumour primary vs other ≥2L, second line and later; BICR, blinded independent central review; BID, twice a day; C1D1, cycle 1 day 1; cORR, confirmed objective response rate; CR, complete response; DCR, disease control rate; DOR, duration of response; HER2, human epidermal growth receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; mAb, monoclonal antibody; mCRC, metastatic colorectal cancer; NGS, next-generation sequencing; ORR, objective response rate; PO, orally; Q3W, every 3 weeks; PR, partial response; R, randomisation; RAS, rat sarcoma virus; RECIST, Response Evaluation Criteria in Solid Tumours; US, United States; VEGF, vascular endothelial growth factor.

1. Strickler et al. ESMO-World GI 2022. Oral presentation no. LBA-2.

MOUNTAINEER- Efficacy Outcomes

Responses		Tucatinib + Trastuzumab Cohorts A+B n=84[1]	Tucatinib Monotherapy Cohort C n=30	Tucatinib + Trastuzumab Post-Crossover n=28
Best overall response per BICR[a], n (%)	CR	3 (4%)	0	0
	PR	29 (35%)	1 (3.3)	5 (17.9)
	SD[b]	28 (33%)	23 (76.7)	18 (64.3)
	PD	22 (26%)	4 (13.3)	5 (17.9)
	Not available[c]	2 (2%)	2 (6.7)	0
ORR per BICR, % (95% CI)[d]		38.1 (27.7-49.3)[f]	3.3 (0.1-17.2)[g]	17.9 (6.1-36.9)[f]
DCR[e] per BICR, n (%)		60 (71.4)	24 (80.0)	23 (82.1)

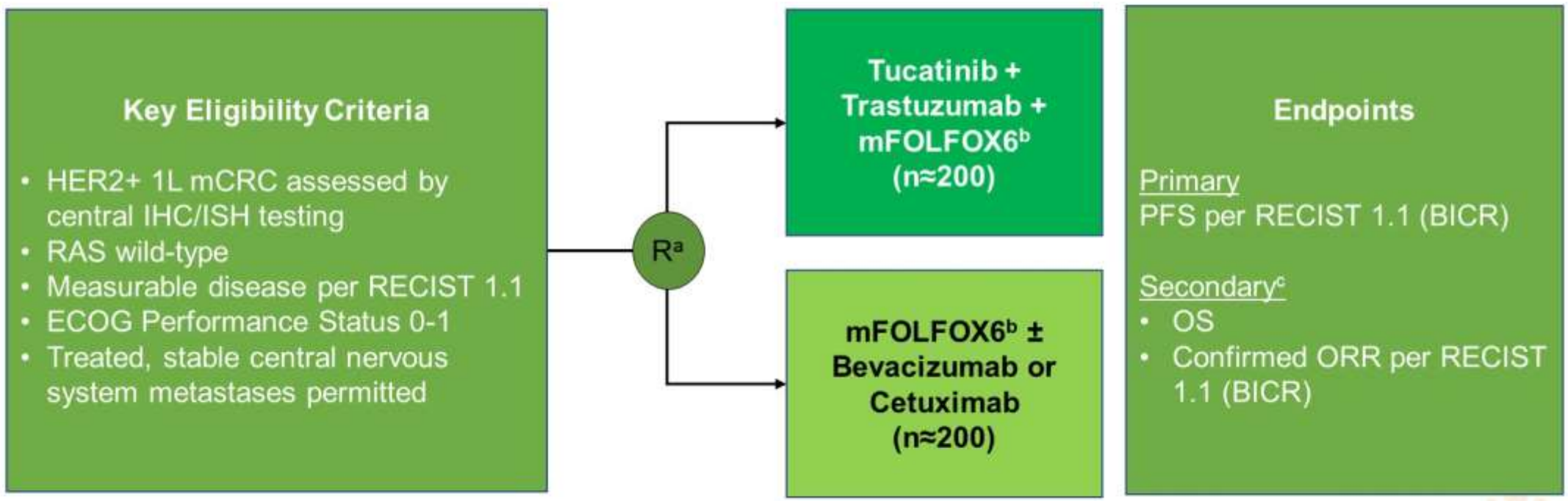
a Confirmed best overall response assessed per RECIST 1.1; b Includes SD and non-CR/non-PD; c Includes patients with no post-baseline response assessment and patients whose disease assessments are not evaluable; d Two-sided 95% exact confidence interval, computed using the Clopper-Pearson method (1934); e Defined as sum of CR, PR, and SD; f cORR; g ORR by 12 weeks of treatment

BICR, blinded independent central review; cORR, confirmed objective response rate; CR, complete response; DCR, disease control rate; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; SD, stable disease.

Data cutoff: 28 Mar 2022

1. Strickler et al. ESMO-World GI 2022. Oral presentation no. LBA-2.

MOUNTAINEER-03:
Global, Randomised, Open-Label, Phase 3 Trial



Conclusions/Take-Away

- Aberrant DNA damage response is present in 15%-20% of CRC tumors, and offers an attractive therapeutic target
- Previous studies have been associated with unimpressive outcomes, due to poor molecular selection and/or combination regimen
- Emerging innovative combinations with PARP inhibitors (such as EGFRi) appear promising, and could improve the current treatment landscape

Does it matter?
Genetic alterations in mCRC

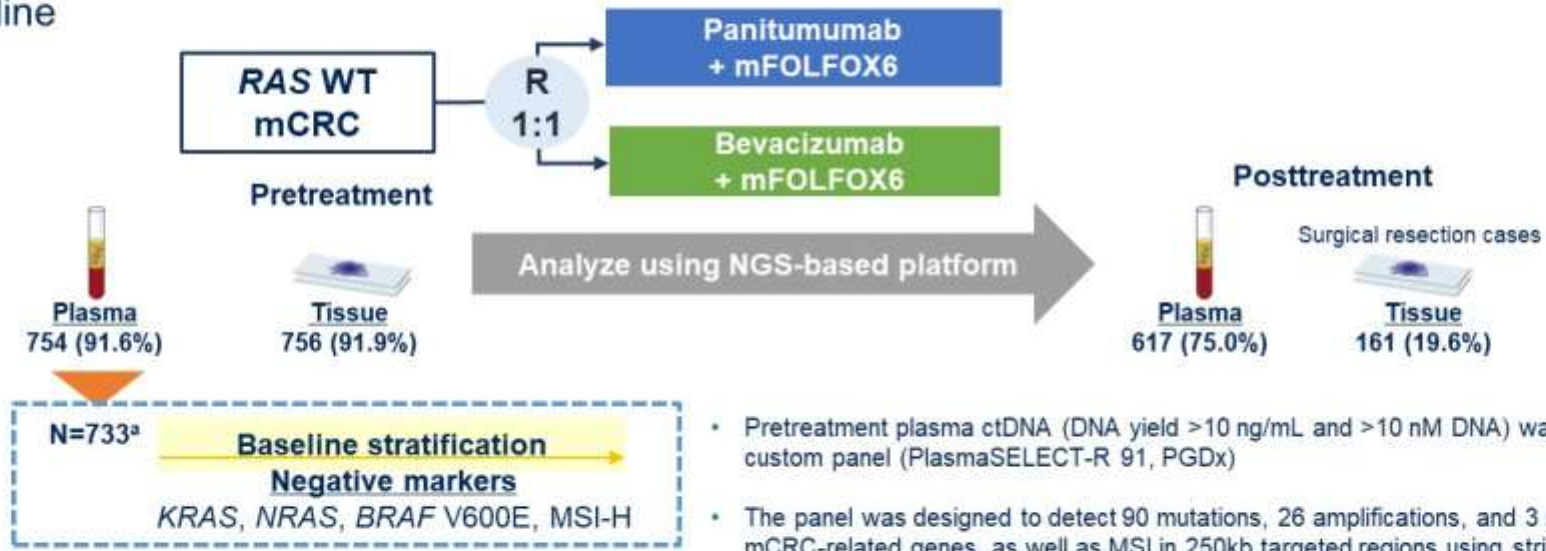
Abstract	Disease	Trial
3508	RAS/BRAF WT mCRC	PARADIGM
3501	HER2+ mCRC	DESTINY-CRC02

Sequencing therapies in early stage CRC

Abstract	Disease	Trial
LBA3504	T3-T4 rectal cancer	PRODIGE23
LBA3503	T3-T4 colon cancer	NEOCOL

PARADIGM biomarker study

- The PARADIGM biomarker study (NCT02394834) was designed to investigate molecular biomarkers of primary and secondary resistance to each therapy based on testing of tumor tissue and ctDNA
- Based on current guideline recommendations regarding clinically relevant biomarkers for first-line mCRC,[1,2] we report clinical outcomes for patients with MSS or MSI-L and *RAS* (*KRAS*/*NRAS*)/*BRAF* V600E WT in ctDNA at baseline

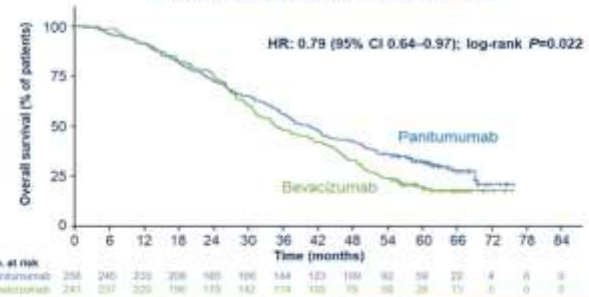


- Pretreatment plasma ctDNA (DNA yield >10 ng/mL and >10 nM DNA) was sequenced using a custom panel (PlasmaSELECT-R 91, PGDx)
- The panel was designed to detect 90 mutations, 26 amplifications, and 3 rearrangements in mCRC-related genes, as well as MSI in 250kb targeted regions using stringent quality criteria
- Efficacy (OS, PFS, RR, R0 rate, and depth of response) by treatment group was evaluated according to *RAS (KRAS/NRAS)*, *BRAF* V600E, and MSI status and primary tumor location

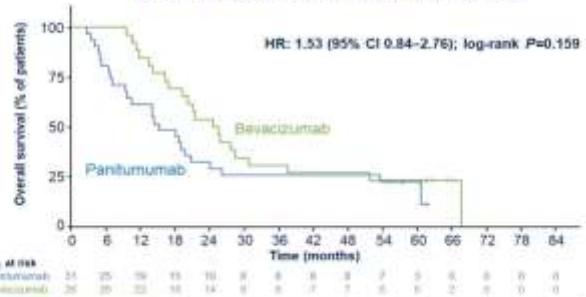
ctDNA, circulating tumor DNA; MSI, microsatellite instability; MSI-H, microsattelite instability-high; MSI-L, microsatellite instability-low; MSS, microsatellite stable; NGS, next-generation sequencing.
[a]Patients with available ctDNA among those included in efficacy analysis set in the PARADIGM study
1. Morris VK, et al. J Clin Oncol. 2023;41:678–700; 2. Cervantes A, et al. Ann Oncol. 2022;34:10–32.

Overall survival by MSS/MSI and *RAS/BRAF* status in left-sided mCRC

MSS/MSI-L and *RAS/BRAF* WT



MSI-H and/or *RAS/BRAF* mutation

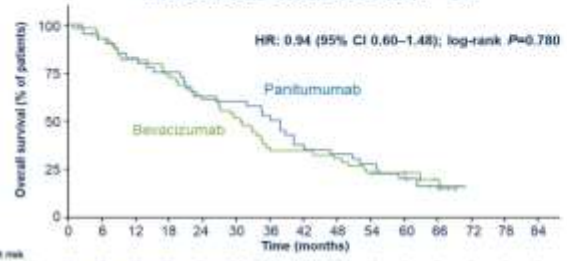


	Panitumumab		Bevacizumab				
	n	mOS, months (95% CI)	n	mOS, months (95% CI)	HR (95% CI)	*P*-value for interaction
All	287	37.7 (34.1–42.5)	267	34.1 (30.8–38.8)	0.83 (0.69–1.01)	0.089
MSS/MSI-L and *RAS/BRAF* WT	256	40.6 (36.3–44.4)	241	34.8 (31.3–41.2)	0.79 (0.64–0.97)	
MSI-H and/or *RAS/BRAF* mutation	31	15.4 (9.6–20.9)	26	25.2 (17.0–30.9)	1.53 (0.84–2.76)	

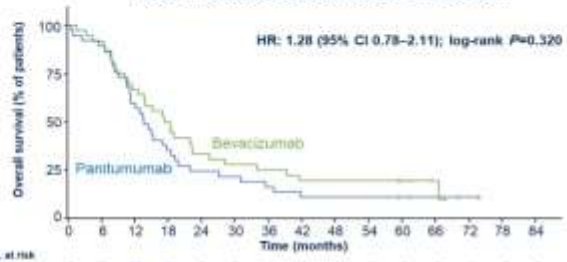
0.5 1.0 3.0 5.0
Panitumumab better | Bevacizumab better

Overall survival by MSS/MSI and *RAS/BRAF* status in right-sided mCRC

MSS/MSI-L and *RAS/BRAF* WT



MSI-H and/or *RAS/BRAF* mutation

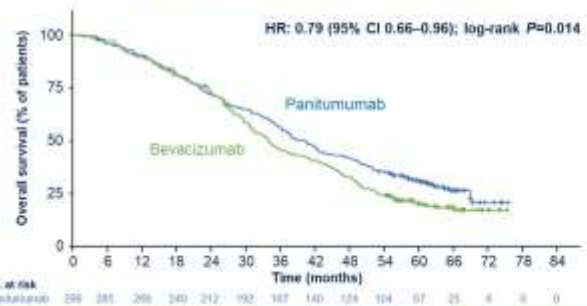


	Panitumumab		Bevacizumab			
	n	mOS, months (95% CI)	n	mOS, months (95% CI)	HR (95% CI)	*P*-value for interaction
All	78	20.8 (15.1–32.0)	91	25.5 (19.1–31.3)	1.12 (0.80–1.56)	0.327
MSS/MSI-L and *RAS/BRAF* WT	41	37.9 (22.0–42.2)	55	30.8 (23.2–35.4)	0.94 (0.60–1.48)	
MSI-H and/or *RAS/BRAF* mutation	37	13.7 (11.3–18.7)	36	17.9 (11.6–22.4)	1.28 (0.78–2.11)	

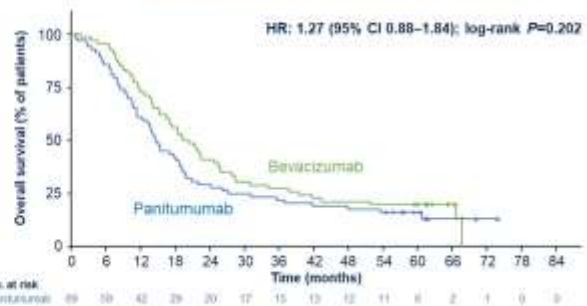
0.5 1.0 3.0 5.0
Panitumumab better | Bevacizumab better

Overall survival by MSS/MSI and *RAS/BRAF* status in the overall population

MSS/MSI-L and *RAS/BRAF* WT



MSI-H and/or *RAS/BRAF* mutation



	Panitumumab		Bevacizumab			
	n	mOS, months (95% CI)	n	mOS, months (95% CI)	HR (95% CI)	*P*-value for interaction
All	368	35.6 (31.1–38.9)	365	31.6 (28.3–34.5)	0.87 (0.73–1.02)	0.027
MSS/MSI-L and *RAS/BRAF* WT	299	39.0 (36.3–43.3)	299	34.1 (31.1–37.6)	0.79 (0.66–0.96)	
MSI-H and/or *RAS/BRAF* mutation	69	14.6 (11.3–18.8)	66	19.8 (15.3–25.5)	1.27 (0.88–1.84)	

0.5 1.0 3.0 5.0
Panitumumab better | Bevacizumab better

Conclusions/Take Home Points

- Clinically relevant? Yes
- Immediately practice changing? No
- Impact on value/cost of care, long-/short-term side effects, etc.? Anti-EGFR mAb should only be considered in first line treatment in those with left-sided disease

2023 ASCO ANNUAL MEETING

T-DXd in Patients With HER2-Overexpressing/Amplified (HER2+) Metastatic Colorectal Cancer (mCRC): Primary Results From the Multicenter, Randomized, Phase 2 DESTINY-CRC02 Study

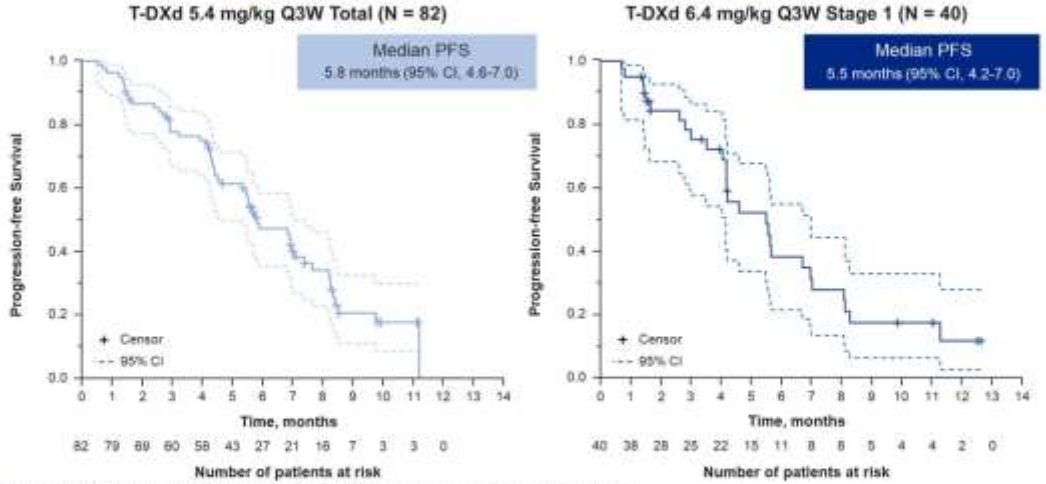
Kanwal Raghav

The University of Texas MD Anderson Cancer Center, Houston, TX, USA

June 4, 2023

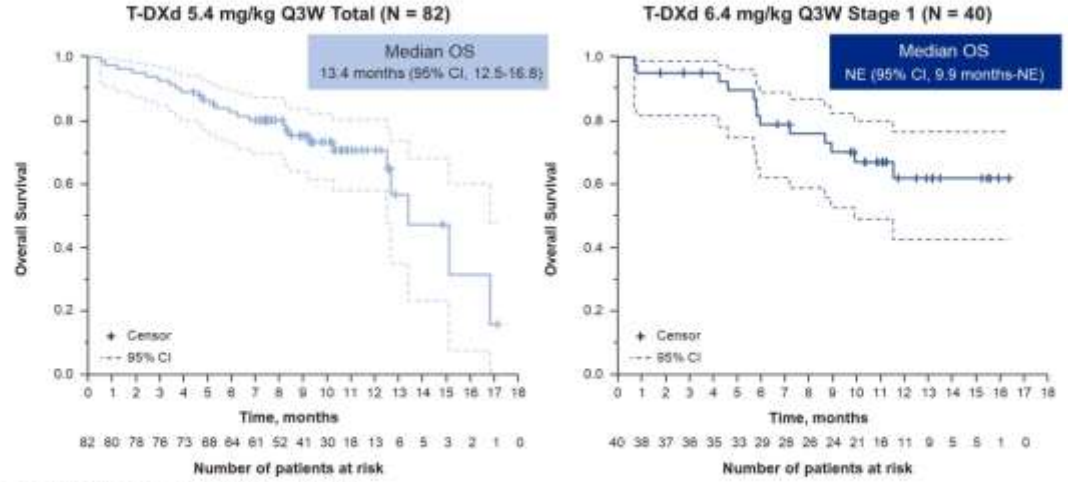
Additional authors: Salvatore Siena, Atsuo Takashima, Takeshi Kato, Marc Van Den Eynde, Maria Di Bartolomeo, Yoshito Komatsu, Hisato Kawakami, Marc Peeters, Thierry Andre, Sara Lonardi, Kensei Yamaguchi, Jeanne Tie, Christina Gravalos Castro, John Strickler, Daniel Barrios, Qi Yan, Takahiro Kamio, Kojiro Kobayashi, Takayuki Yoshino

Median Progression-Free Survival by BICR



BICR, blinded independent central review; PFS, progression-free survival; Q3W, every 3 weeks; T-DXd, trastuzumab deruxtecan.

Median Overall Survival



NE, not evaluable; Q3W, every 3 weeks; T-DXd, trastuzumab deruxtecan.

Conclusions/Take Home Points

- Clinically relevant? Yes
- Immediately practice changing? Yes
- Impact on value/cost of care, long-/short-term side effects, etc.?
  - Another targeted therapy for HER2+ mCRC
  - 5.4mg/kg preferred dose
  - *Optimal* sequencing of HER2 therapies?

Total neoadjuvant therapy with mFOLFIRINOX versus preoperative chemoradiation in patients with locally advanced rectal cancer: 7-year results of PRODIGE 23 phase III trial, a UNICANCER GI trial.

T. Conroy, P-L. Etienne, E. Rio, L. Evesque, N. Mesgouez-Nebout, V. Vendrely, X. Artignan, O. Bouché, A. Boilève, M. Delaye, D. Gargot, V. Boige, N. Bonichon-Lamichhane, C. Louvet, C. de la Fouchardière, C. Morand, V. Pezzella, E. Rullier, F. Castan, and C. Borg

PRODIGE 23 trial: trial design

MRI staging
Randomisation: 1/1
Stratification:
- center
- cT3 vs cT4
- cN0 vs cN+
- T extramural extension (≥5 vs. <5 mm)
- tumor location (cm from anal verge)

461 patients included

RANDOMIZE

SoC arm

Radiotherapy 50.4 Gy /5wks + capecitabine 1600 mg/m²/d 5 days/7 → 7 weeks → **TME** → mFOLFOX6, 12 cycles or capecitabine, 8 cycles*(6 months)

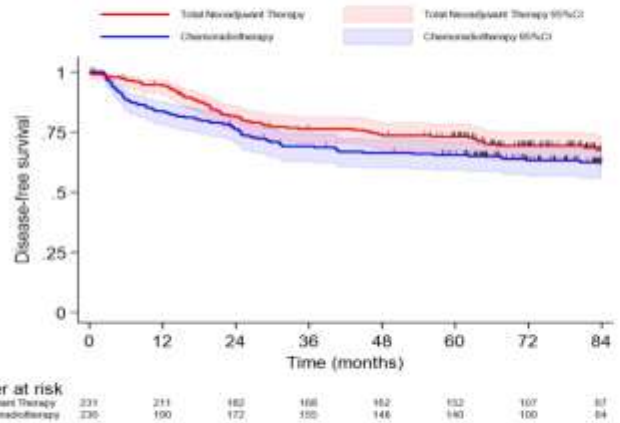
TNT arm

mFOLFIRINOX** 6 cycles, 3 months → Radiotherapy 50.4 Gy /5 wks + capecitabine 1600 mg/m²/d 5 days/7 → 7 weeks → **TME** → mFOLFOX6, 6 cycles or capecitabine, 4 cycles* (3 months)

**mFOLFIRINOX: At d1, Oxaliplatin 85 mg/m², Leucovorin 400 mg/m², Irinotecan 180 mg/m²; Fluorouracil continuous IV infusion 2.4 g/m² over 46 hours (no bolus Fluorouracil)

*according to center choice throughout the study; adjuvant chemotherapy was mandatory in both arms regardless of ypTNM stage.

Disease-Free Survival



155 events

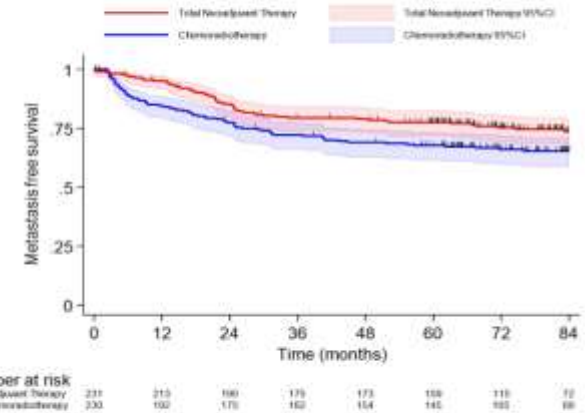
7-yr DFS rate:
- 67.6% [95%CI: 60.7-73.6] TNT arm
- 62.5% [95%CI: 55.6-68.6] SoC arm

5-yr DFS rate:
- 73.1% [95%CI: 66.8-78.4] TNT arm
- 65.5% [95%CI: 58.9-71.3] SoC arm

RMST (7-yr), months:
5.73 [0.05-11.41] DFS benefit for TNT arm
p=0.048

Metastasis-free Survival

At 5 years, the cumulative incidence of developing metastatic recurrences was 18.4% in the TNT arm vs 26.6% in the SoC arm.



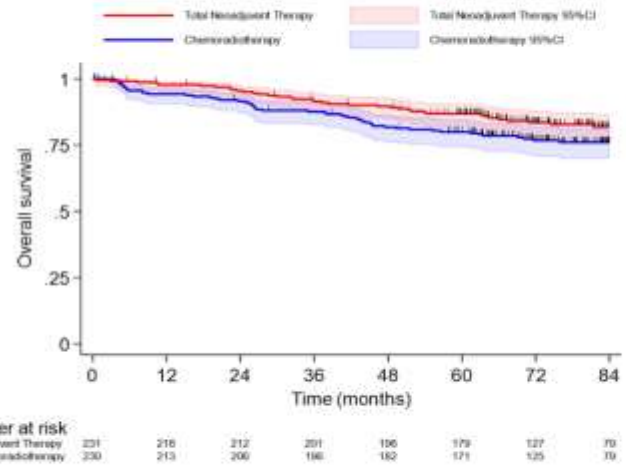
138 events

7-yr MFS:
- 73.6% [95%CI: 67.0-79.2] TNT arm
- 65.4% [95%CI: 58.7-71.3] SoC arm

5-yr MFS:
- 77.6% [95%CI: 71.5-82.5] TNT arm
- 67.7% [95%CI: 61.2-73.4] SoC arm

RMST (7-yr), months:
7.1 [1.65-12.63] MFS benefit for TNT arm
p=0.011

Overall Survival



98 events.

7-yr OS:
- 81.9% [95%CI: 75.8-86.7] TNT arm
- 76.1% [95%CI: 69.8-81.3] SoC arm

5-yr OS:
- 86.9% [95%CI: 81.6-90.7] TNT arm
- 80.0% [95%CI: 74.1-84.6] SoC arm

RMST (7-yr), months:
4.37 [0.35-8.38] benefit for TNT arm
p=0.033

Conclusions/Take Home Points

- Clinically relevant? Yes
- Immediately practice changing? Yes
- Impact on value/cost of care, long-/short-term side effects, etc.?
  Improvement in MFS, DFS and OS
  Understanding the disease biology

2023 ASCO ANNUAL MEETING

Phase III randomized clinical trial comparing the efficacy of neoadjuvant chemotherapy and standard treatment in patients with locally advanced colon cancer

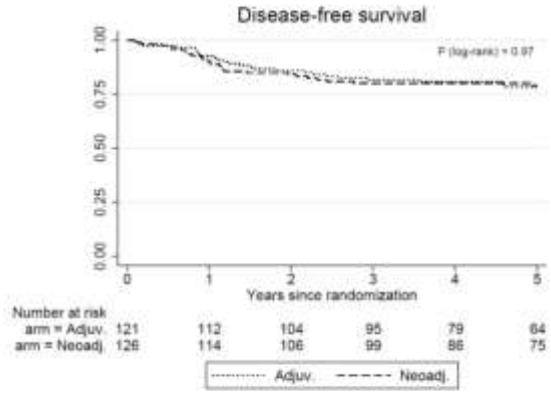
The Scandinavian **NeoCol** trial

Lars Henrik Jensen MD PhD

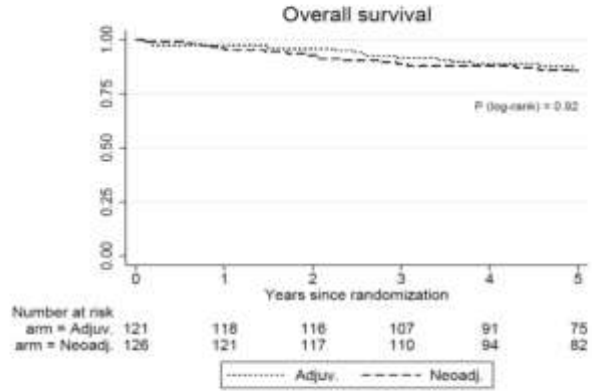
Treatment

- Arm A standard upfront surgery
- Arm B neoadjuvant chemotherapy before surgery
  - 3 cycles of CAPOX (3-week cycle, oxaliplatin 130 mg/m^2 and capecitabine 1000 mg/m^2 twice daily for 14 days, *or*
  - 4 cycles of FOLFOX (2-week cycle, oxaliplatin 85 mg/m^2, 5FU 400 mg/m^2 bolus and 2400 mg/m^2 over 46 hours)
- Adjuvant chemotherapy in both arms was chosen based on the pathological stage of the cancer according to guidelines

Efficacy outcomes - Disease-free survival (DFS)



Efficacy outcomes - Overall survival (OS)



Conclusions/Take Home Points

- Clinically relevant? Yes
- Immediately practice changing? No
- Impact on value/cost of care, long-/short-term side effects, etc.?
  - Upfront surgery *remains* gold standard

Karcinom prsu

ABSTRACTS

- Hormone receptor positive breast cancer
  - LBA500 – NATALEE, Slamon et al
  - Abst 503 – EBCTCG ovarian suppression or ablation, Gray et al
- HER2 positive breast cancer
  - LBA506 – PHERGain, Cortés et al
  - LBA637 – Short HER, Conte et al

2023 ASCO ANNUAL MEETING

Ribociclib and endocrine therapy as adjuvant treatment in patients with HR+/HER2− early breast cancer: primary results from the Phase III NATALEE trial

Dennis Slamon,[1] Daniil Stroyakovskiy,[2] Denise A. Yardley,[3] Chiun-Sheng Huang,[4] Peter A. Fasching,[5] John Crown,[6] Aditya Bardia,[7] Stephen Chia,[8] Seock-Ah Im,[9] Miguel Martin,[10] Sherene Loi,[11] Binghe Xu,[12] Sara Hurvitz,[13] Carlos Barrios,[14] Michael Untch,[15] Rebecca Moroose,[16] Frances Visco,[17] Rodrigo Fresco[18] Tetiana Taran,[19] Gabriel N. Hortobagyi[20]

[1]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [2]Moscow City Oncology Hospital #62 of Moscow Healthcare Department, Moscow Oblast, Russia; [3]Sarah Cannon Research Institute, Tennessee Oncology, Nashville, TN, USA; [4]National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei City, Taiwan; [5]University Hospital Erlangen Comprehensive Cancer Center Erlangen-EMN, Friedrich-Alexander University Erlangen-Nuremberg, Erlangen, Germany; [6]St. Vincents Hospital, Dublin, Ireland; [7]Mass General Cancer Center, Harvard Medical School, Boston, MA, USA; [8]British Columbia Cancer Agency, Vancouver, BC, Canada; [9]Cancer Research Institute, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea; [10]Instituto de Investigación Sanitaria Gregorio Marañon, Centro de Investigación Biomédica en Red de Cáncer, Grupo Español de Investigación en Cáncer de Mama, Universidad Complutense, Madrid, Spain; [11]Peter MacCallum Cancer Centre, Melbourne, Australia; [12]Department of Medical Oncology Cancer Hospital, Chinese Academy of Medical Sciences (CAMS), and Peking Union Medical College (PUMC), Beijing, China; [13]University of California, Los Angeles Jonsson Comprehensive Cancer Center, Los Angeles, CA, USA; [14]Latin American Cooperative Oncology Group (LACOG), Porto Alegre, 16 Brazil; [15]Interdisciplinary Breast Cancer Center, Helios Klinikum Berlin-Buch, Germany; [16]Orlando Health Cancer Institute, Orlando, FL, USA; [17]National Breast Cancer Coalition (NBCC), Washington DC, USA; [18]TRIO - Translational Research in Oncology, Montevideo, Uruguay; [19]Novartis Pharma AG, Basel, Switzerland; [20]Department of Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA.

NATALEE study design

- Adult patients with HR+/HER2– EBC
- Prior ET allowed up to 12 mo
- **Anatomic stage IIA[a]**
  - **N0** with:
    - Grade 2 and evidence of high risk:
      - Ki-67 ≥ 20%;
      - Oncotype DX Breast Recurrence Score ≥ 26; OR
      - High risk via genomic risk profiling
    - Grade 3
  - **N1**
- **Anatomic stage IIB[a] & III**
  - Stage IIB: N0 or N1
  - Stage III: N0, N1, N2, or N3

N=5101[b]

R 1:1[c]

Ribociclib
400 mg/day
3 weeks on/1 week off
for 3y

NSAI
Letrozole or anastrozole[d] for ≥5y
+ goserelin in premenopausal women and men

NSAI
Letrozole or anastrozole[d] for ≥5y
+ goserelin in premenopausal women and men

Primary Endpoint
- iDFS using STEEP criteria

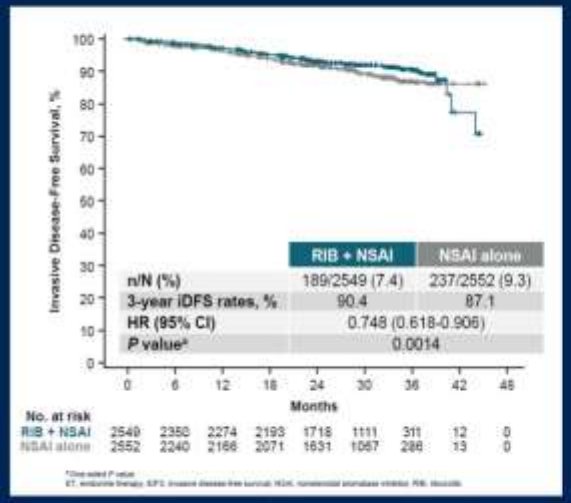
Secondary Endpoints
- Recurrence-free survival
- Distant disease-free survival
- OS
- PROs
- Safety and tolerability
- PK

Exploratory Endpoints
- Loco-regional recurrence-free survival
- Gene expression and alterations in tumor ctDNA/ctRNA samples

Randomization stratification
Anatomic stage: II vs III
Menopausal status: Premenopausal women & men vs postmenopausal women
Receipt of prior (neo)adjuvant chemotherapy: yes/no
Geographic location: North America/Western Europe/Oceania vs Rest of world

Slamon et al, Abstract LBA500

NATALEE: Invasive DFS (iDFS) Results

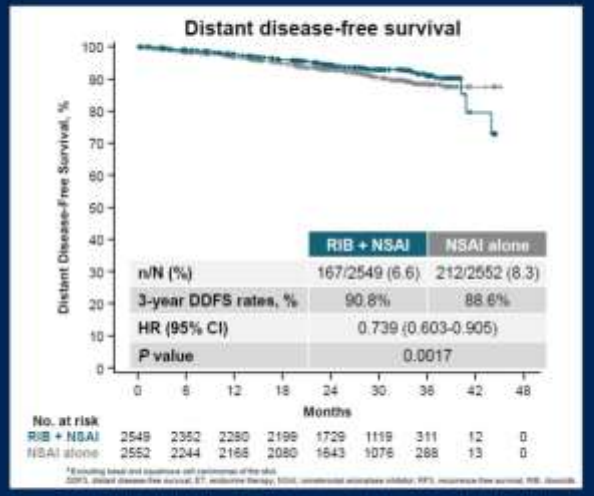


	RIB + NSAI	NSAI alone
n/N (%)	189/2549 (7.4)	237/2552 (9.3)
3-year iDFS rates, %	90.4	87.1
HR (95% CI)	0.748 (0.618-0.906)	
P value[a]	0.0014	

- Median follow-up 27.7 mo
- Absolute iDFS benefit 3.3% at 3 years, HR 0.748
- Consistent across key pre-specified subgroups

Slamon et al, Abstract LBA500

NATALEE: Distant DFS (DDFS) Results



	RIB + NSAI	NSAI alone
n/N (%)	167/2549 (6.6)	212/2552 (8.3)
3-year DDFS rates, %	90.8%	88.6%
HR (95% CI)	0.739 (0.603-0.905)	
P value	0.0017	

- Absolute DDFS benefit 2.2% at 3 years, HR 0.739

Slamon et al, Abstract LBA500

NATALEE: Key Considerations

- Used a lower dose of ribociclib (400 mg QD) than was used in trials of metastatic disease
  - Well-tolerated: toxicity primarily neutropenia and hepatobiliary
- Compared to the MonarchE trial:
  - Included patients with node negative disease
  - Ribociclib treatment duration was 3 years

Slamon et al, Abstract LBA500

NATALEE - Monday Morning

- The US FDA has approved abemaciclib for treatment of patients with high risk ER+, HER2-, LN+ disease
  - Absolute improvements 3 year iDFS 5.4% (HR 0.70), DDFS 4.2% (HR 0.69)
- With additional follow-up, will determine if ribociclib yields similar benefits to abemaciclib
  - Ribociclib has a different toxicity profile
- Need to determine whether benefit outweighs cost (QOL, financial)

Slamon et al, Abstract LBA500

Meta-analysis of Ovarian Ablation/Suppression in BC: Methods

- Study focused on premenopausal women <55 yr of age at randomization with ER-positive or ER-unknown early-stage breast cancer
- Analysis included patient-level data from 25 randomized trials (N = 14,999) that compared ovarian ablation/suppression with no ovarian ablation/suppression; other treatments were the same across groups
  - Trials grouped by use of chemotherapy (5 trials contributed to 2 categories)
    - No chemotherapy (12 trials; n = 3934)
    - Chemotherapy administered prior to randomization; premenopausal status confirmed afterward (2 trials; n = 3279)
    - Chemotherapy administered after randomization, which can induce menopause (14 trials; n = 7786)
- Primary outcomes: recurrence and cause-specific mortality
- Standard log-rank methods used to estimate ER-weighted annual event rate ratios

Gray. ASCO 2023. Abstr 503.

Meta-analysis of Ovarian Ablation/Suppression in BC: Mortality

Outcomes for Women Who Received No CT or Premenopausal After CT (N = 7213)	Mortality Rate at 20 Yr, %		RR (95% CI)	*P* Value	20-Yr Gain, %
	Ovarian Ablation/Suppression	Control			
Breast cancer mortality	23.8	34.7	0.71 (0.62-0.81)	<.00001	10.9
Death without recurrence	9.3	11.5	0.89 (0.68-1.15)	.36	2.2
All-cause mortality	30.4	42.0	0.75 (0.66-0.84)	<.00001	11.6

Meta-analysis of Ovarian Ablation/Suppression in BC: Investigators' Conclusions

- Meta-analysis of individual patient-level data indicates that premenopausal women with ER-positive breast cancer derive substantial benefit from ovarian ablation/suppression with regard to:
  - Reduced breast cancer recurrence
  - Reduced cause-specific mortality
- Benefits similar for women who received prior chemotherapy and remained premenopausal thereafter vs women who received no chemotherapy
- May be more benefit for women who received no tamoxifen vs tamoxifen

2023 ASCO ANNUAL MEETING

3-year invasive disease-free survival (iDFS) of the strategy-based, randomized phase II PHERGain trial evaluating chemotherapy (CT) de-escalation in human epidermal growth factor receptor 2-positive (HER2[+]) early breast cancer (EBC)

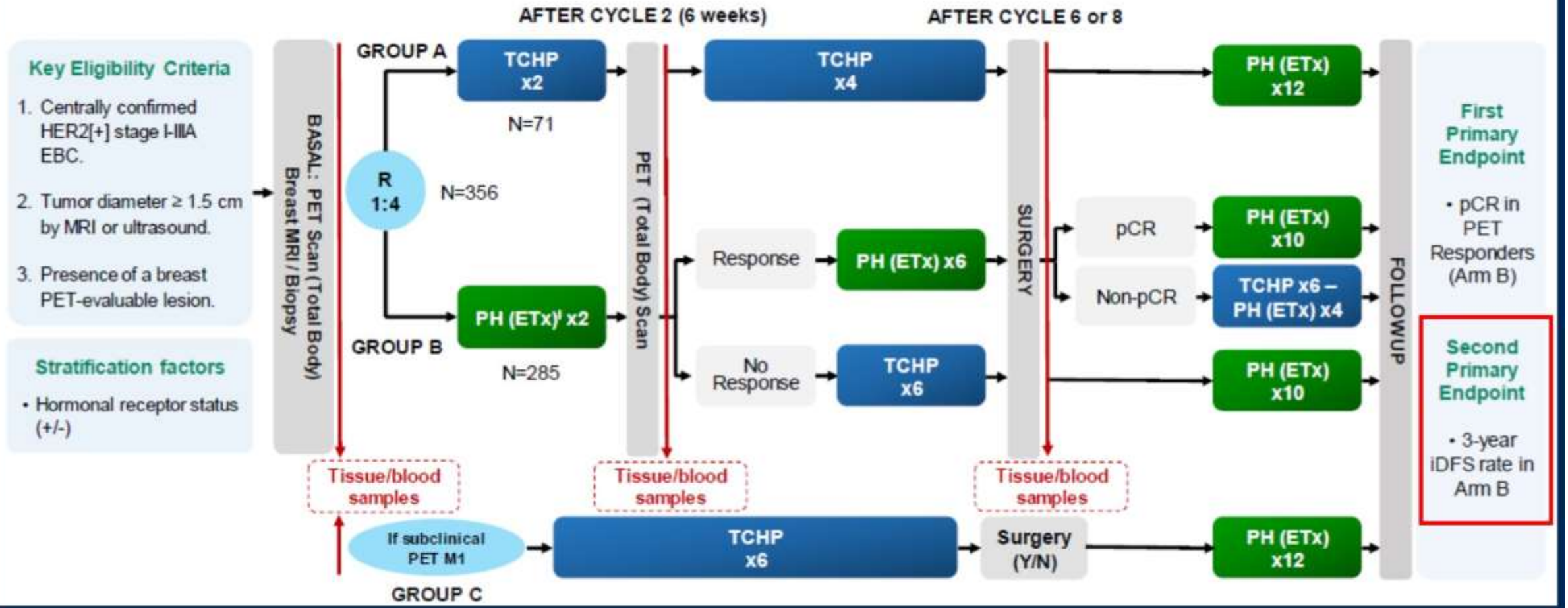
Javier Cortés[1,2,3], José Manuel Pérez-García[1,2], Manuel Ruiz-Borrego[4], Agostina Stradella[5], Begoña Bermejo[6], Santiago Escrivá-de-Romaní[7], Lourdes Calvo Martínez[8], Nuria Ribelles[9], Alfonso Cortés[10], Cinta Albacar[11], Marco Colleoni[12], Geraldine Gebhart[13], Aleix Prat[14], Kerrou Khaldoun[15], Peter Schmid[16], Serena Di Cosimo[17], Crina Popa[2], Daniel Alcalá-López[2], Miguel Sampayo-Cordero[2], Antonio Llombart-Cussac[2,18]

1.) International Breast Cancer Center (IBCC), Pangaea Oncology, Quiron Group, Barcelona, Spain; 2.) Medica Scientia Innovation Research (MedSIR), Barcelona, Spain and Ridgewood, New Jersey, US; 3.) Universidad Europea de Madrid, Faculty of Biomedical and Health Sciences, Department of Medicine, Madrid, Spain; 4.) University Hospital Virgen del Rocío, Sevilla, Spain; 5.) Medical Oncology Department, Institut Català D'Oncologia, L'HospitaletdeLlobregat, Barcelona, Spain; 6.) Medical Oncology, Hospital Clínico Universitario de Valencia, Biomedical Research Institute INCLIVA, Valencia; Medicine Department, Universidad de Valencia, Oncology Biomedical Research National Network (CIBERONC-ISCIII), Madrid.; 7.) Medical Oncology Department, Breast Cancer Group, Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; 8.) Hospital Universitario A Coruña, A Coruña, Spain; 9.) UGC Oncología Intercentros. Hospitales Universitarios Regional y Virgen de la Victoria de Málaga. Instituto de Investigaciones Biomédicas de Málaga (IBIMA), Málaga, Spain; 10.) University Hospital Ramón y Cajal, Madrid, Spain; 11.) Hospital Universitari Sant Joan de Reus, Reus, Spain; 12.) European Institute of Oncology IRCCS, Milan, Italy; 13.) Institut Jules Bordet–Université Libre de Bruxelles, Brussels, Belgium; 14.) Department of Medical Oncology, Hospital Clinic of Barcelona, Barcelona, Spain, Translational Genomics and Targeted Therapies Group, IDIBAPS, Barcelona, Spain, Department of Medicine, University of Barcelona, Barcelona, Spain; 15.) APHP, Tenon Hospital IUC-UPMC, Nuclear Medicine and PET Center Department, Sorbonne University, Paris, France; 16.) Barts Experimental Cancer Medicine Centre, Barts Cancer Institute, Queen Mary University of London, UK; Barts Hospital NHS Trust, London, UK; 17.) Department of Advanced Diagnostics, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano; 18.) Arnau de Vilanova Hospital; Universidad Católica de Valencia, Valencia, Spain.

PRESENTED BY: Dr. JAVIER CORTÉS MD PhD

phergain

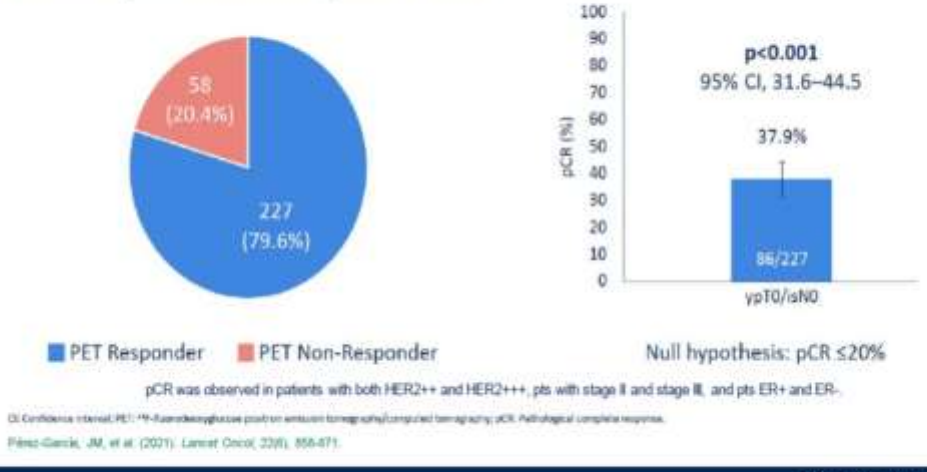
PHERGain Study Design



Cortes et al, Abstract LBA506

PRESENTED BY: N. Lynn Henry, MD, PhD/University of Michigan

Primary Endpoint: pCR IN ^{18}F-FDG-PET responders in group B



pCR was observed in patients with both HER2++ and HER2+++, pts with stage II and stage III, and pts ER+ and ER-.

CI: Confidence interval; PET: ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography; pCR: Pathological complete response.

Pérez-García, JM, et al. (2021). Lancet Oncol; 23(6): 859-871.

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Cortes et al, Abstract LBA506

Primary Endpoint: 3-year iDFS rate in group B

ITT population

Cortes et al, Abstract LBA506

PHERGain Conclusions

- Trial met its 2nd primary endpoint (3 yr iDFS in grp B)
- Results are in line with those seen with chemotherapy plus anti-HER2 therapy regimens for similar patient populations
- Strategy identifies about 1 in 3 patients with HER2+ EDC who can omit chemotherapy, less toxicity risk

Cortes et al, Abstract LBA506

2023 ASCO ANNUAL MEETING

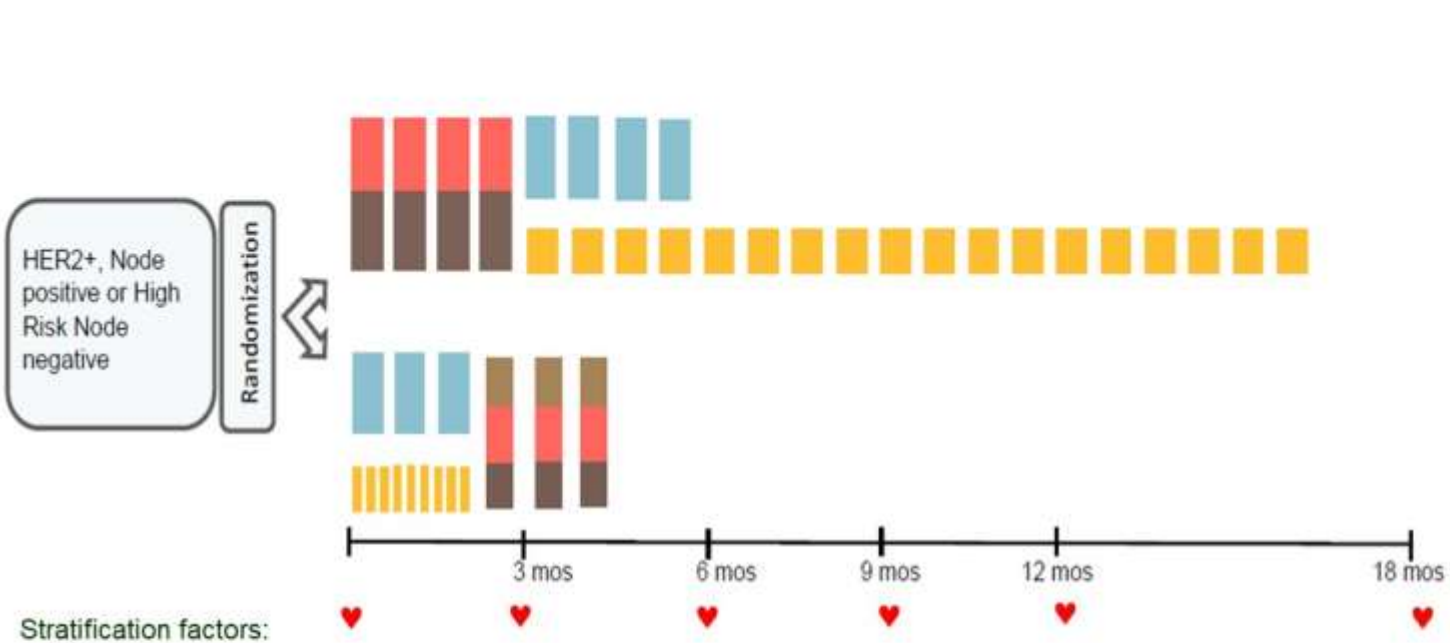
Nine weeks versus one-year trastuzumab for early HER2+ breast cancer: 10-year update of the Short-HER phase III randomised trial

PF Conte, G Bisagni, F Piacentini, S Sarti, S Minichillo, E Anselmi, M Aieta, V Gebbia, A Schirone, A Musolino, O Garrone, A Beano, A Rimanti, F Giotta, A Turletti, MV Dieci, R Vicini, S Balduzzi, R D'Amico, V Guarneri.

S Camillo Hospital IRCCS, Istituto Oncologico Veneto IRCCS, University of Padova
on behalf of the ShortHER study team

Short-HER: Study Design

EUDRACT number: 2007-004326-25
NCI ClinicalTrials.gov number: NCT00629278



Stratification factors:
- HR status
- Nodal status
- Radiotherapy and hormonal therapy at the completion of ChemoRx, when indicated

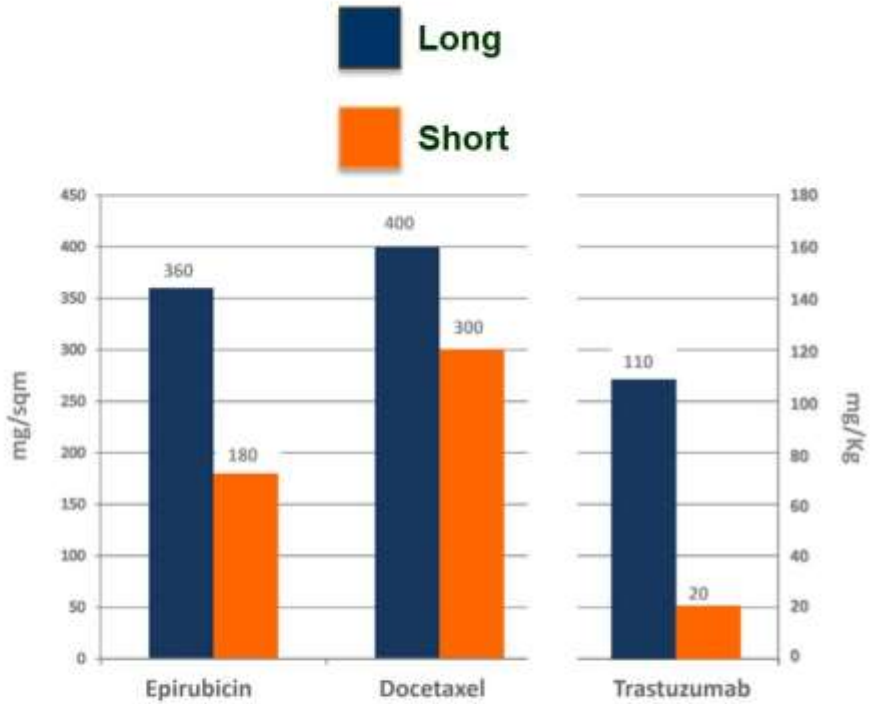
AC60/600 or EC90/600 q3w

FEC60 q3w

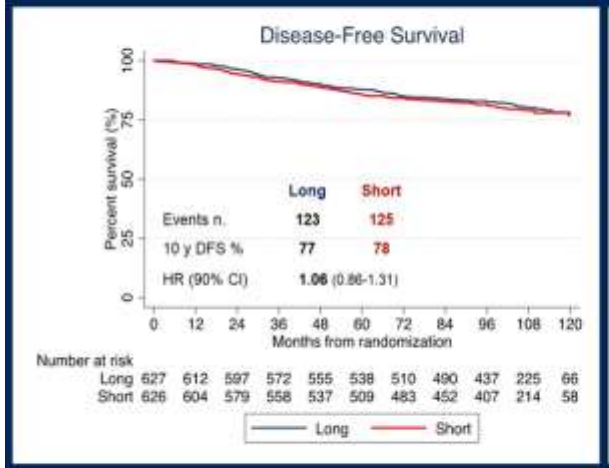
Docetaxel 100 q3w

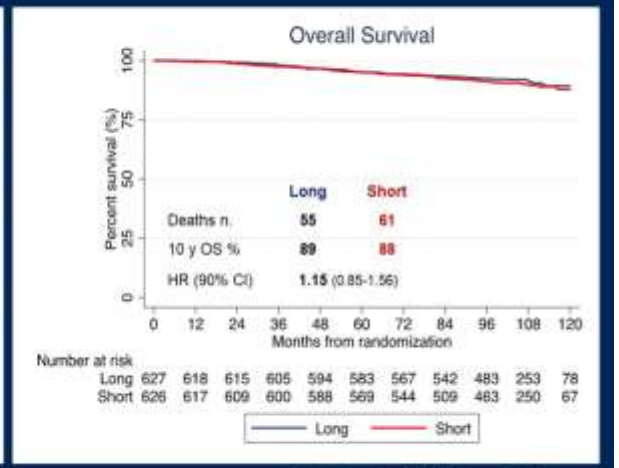
H 8 mg/kg load. → 6 mg/kg q 3 wks

H 4 mg/kg load. → 2 mg/kg wkly



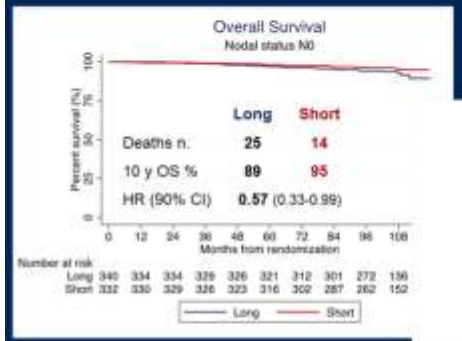
Short HER – 10 year DFS and OS





Conte et al, Abstract 637

Short HER – 10 year OS by Nodal Status



Conte et al, Abstract 637

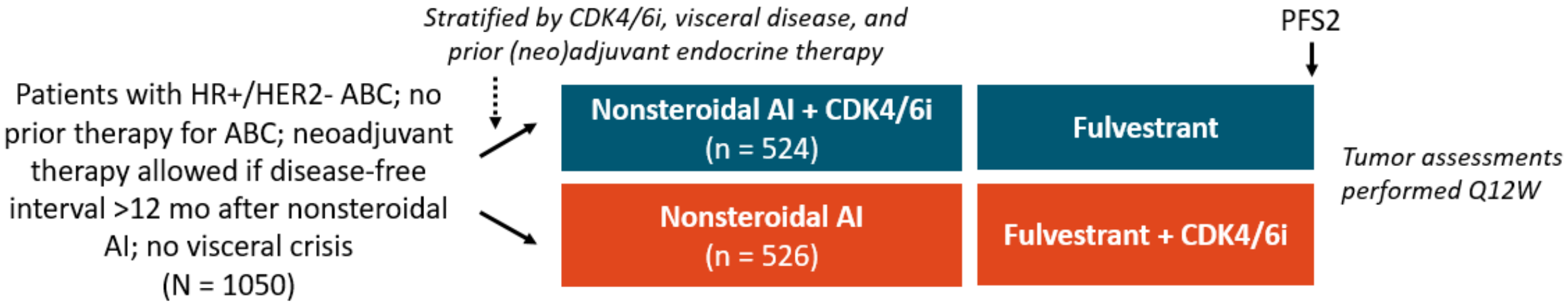
Short HER – Conclusions from the Authors

- Numerically 10-year DFS and OS of long vs short trastuzumab are quite close
- Patients with 4+ nodes have an advantage with one-year of trastuzumab (additional chemo was also given)
- **Non-inferiority cannot be claimed and one-year trastuzumab remains standard of care**
- Nine weeks of trastuzumab might represent an affordable and effective option for low/intermediate HER2+ eBC patients living in low/middle income countries not covered by NHS

Conte et al, Abstract 637

SONIA: Study Design

- Investigator-initiated, randomized phase III trial

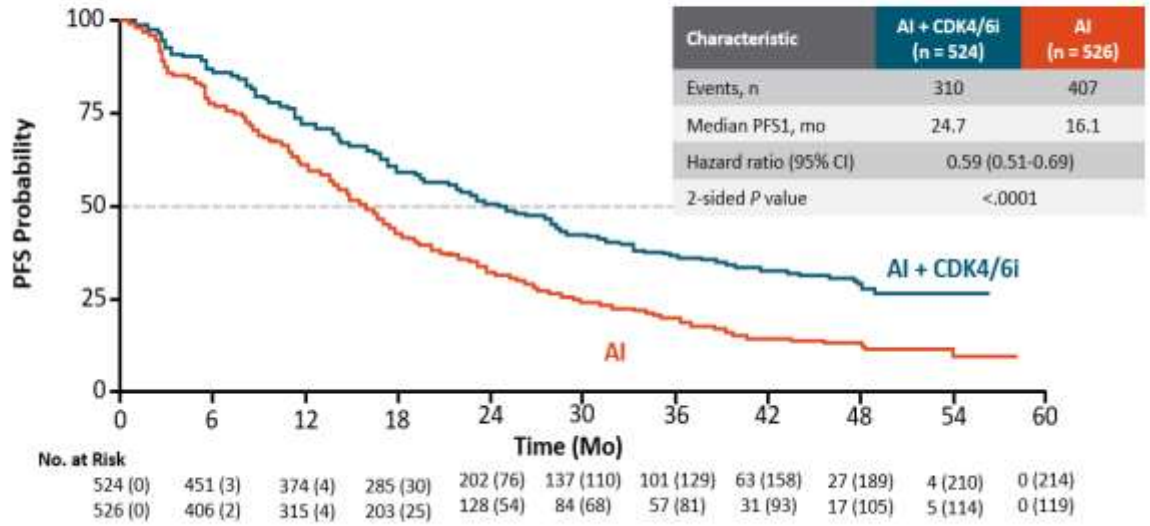


- **Primary endpoint:** PFS2 (time from randomization to second disease progression or death) per RECIST V1.1
  - Planned primary analysis after 574 PFS2 events; 89% power to detect superiority with 2-sided $\alpha = 5\%$
- **Secondary endpoints:** OS, QoL, cost-effectiveness

Sonke. ASCO 2023. Abstr LBA1000.

Slide credit: clinicaloptions.com

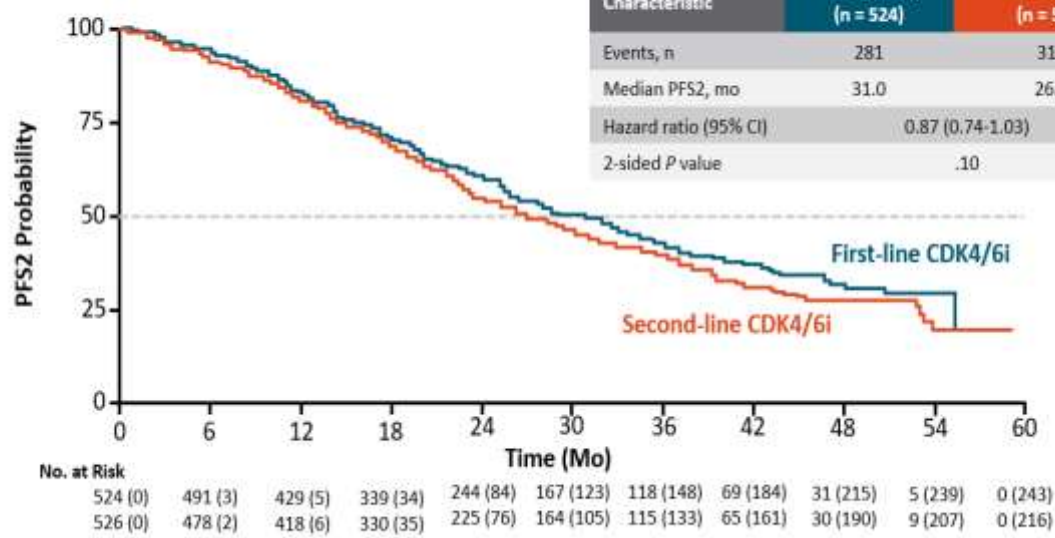
SONIA: PFS1



Characteristic	AI + CDK4/6i (n = 524)	AI (n = 526)
Events, n	310	407
Median PFS1, mo	24.7	16.1
Hazard ratio (95% CI)	0.59 (0.51-0.69)	
2-sided *P* value	<.0001	

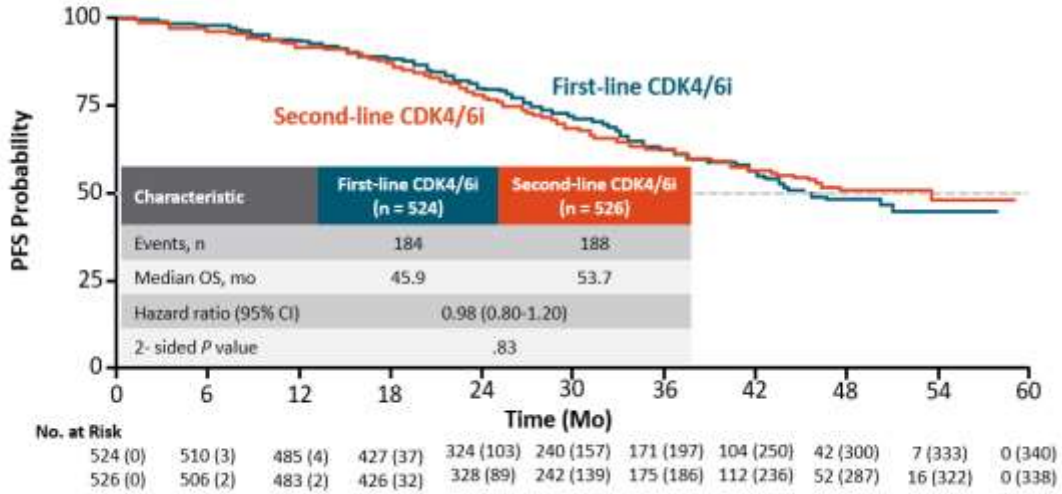
Median follow up: 37.3 mo

SONIA: PFS2 (Primary Endpoint)



Characteristic	First-line CDK4/6i (n = 524)	Second-line CDK4/6i (n = 526)
Events, n	281	310
Median PFS2, mo	31.0	26.8
Hazard ratio (95% CI)	0.87 (0.74-1.03)	
2-sided *P* value	.10	

SONIA: Overall Survival



Characteristic	First-line CDK4/6i (n = 524)	Second-line CDK4/6i (n = 526)
Events, n	184	188
Median OS, mo	45.9	53.7
Hazard ratio (95% CI)	0.98 (0.80-1.20)	
2- sided *P* value	.83	

SONIA: Investigators' Conclusions

- In the phase III investigator-initiated SONIA trial, there was no PFS2 or OS benefit to adding CDK4/6i to endocrine therapy in the first-line vs second-line setting for women with HR+/HER2- advanced breast cancer
  - Addition of first-line CDK4/6i prolongs time on CDK4/6i and increases toxicity
- Investigators concluded that first-line endocrine monotherapy continues to be an excellent option, and therefore, second-line use of CDK4/6i may be preferred for most patients

Onkogynekologie

2023 ASCO ANNUAL MEETING

Phase III MIRASOL (GOG 3045/ENGOT-ov55) Study: Mirvetuximab Soravtansine vs. Investigator's Choice of Chemotherapy in Platinum-Resistant, Advanced High-Grade Epithelial Ovarian, Primary Peritoneal or Fallopian Tube Cancers with High Folate Receptor-Alpha (FRα) Expression

Kathleen N. Moore[1], Antoine Angelergues[2], Gottfried E. Konecny[3], Susana Banerjee[4], Sandro Pignata[5], Nicoletta Colombo[6], John Moroney[7], Casey Cosgrove[8], Jung-Yun Lee[9], Andrzej Roszak[10], Shani Breuer[11], Jacqueline Tromp[12], Diana Bello Roufai[13], Lucy Gilbert[14], Rowan Miller[15], Tashanna Myers[16], Yuemei Wang[17], Anna Berkenblit[17], Domenica Lorusso[18], Toon Van Gorp[19]

[1]Stephenson Cancer Center University of Oklahoma College of Medicine, Oklahoma City, OK, USA; [2]Groupe Hospitalier Diaconesses Croix Saint Simon, Paris, France; [3]UCLA Jonsson Comprehensive Cancer Center, Los Angeles, CA, USA; [4]The Royal Marsden NHS Foundation Trust - Royal Marsden Hospital, London, UK; [5]Istituto Nazionale Tumori- G. Pascale, Naples, Italy; [6]European Institute of Oncology IRCCS, Milan, Italy and University of Milan-Bicocca, Milan, Italy; [7]The University of Chicago, Chicago, IL, USA; [8]The Ohio State University, Columbus, OH, USA; [9]Severance Hospital, Seoul, South Korea; [10]Wielkopolskie Centrum Onkologii, Poznan, Poland; [11]Hadassah Ein Kerem – Sharett, Jerusalem, Israel; [12]Amsterdam UMC, Amsterdam, The Netherlands; [13]Hopital Rene Huguenin, Institut Curie, Saint-Cloud, France; [14]McGill University Health Centre, Montreal, Canada; [15]University College London Hospital, London, UK; [16]Baystate Medical Center, Springfield, MA, USA; [17] ImmunoGen, Inc., Waltham, MA, USA; [18]Fondazione Policlinico Universitario A. Gemelli, IRCCS and Catholic University of Sacred Heart, Rome, Italy; [19]University Hospital Leuven Leuven Cancer Institute, Leuven, Belgium

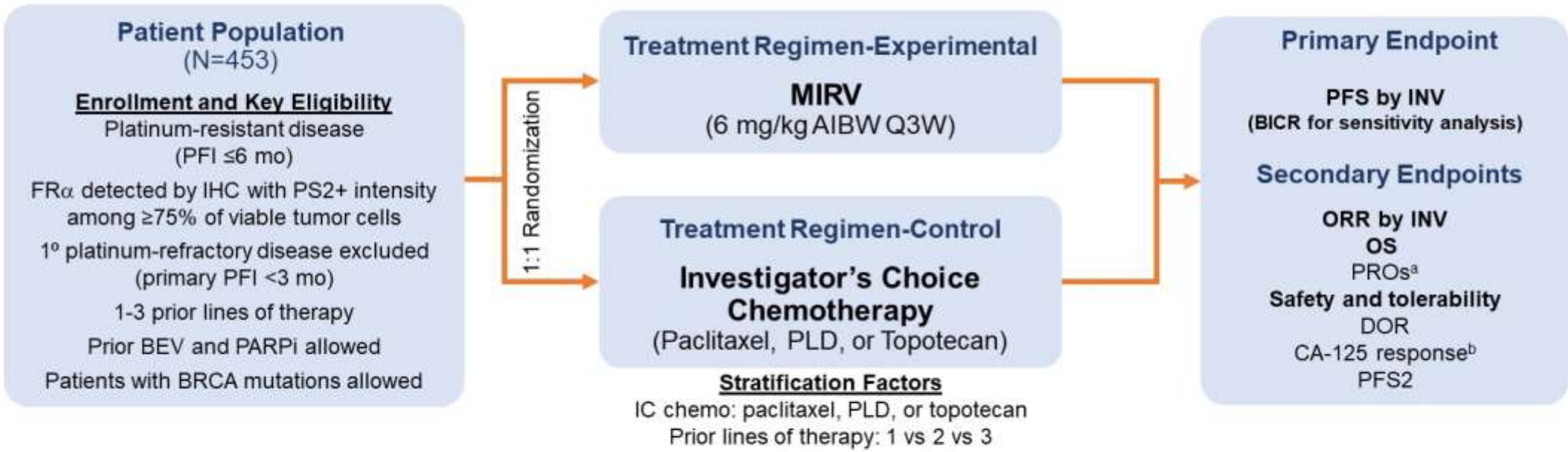
ENGOT European Network of Gynaecological Oncological Trial groups

GOG FOUNDATION® Transforming the standard of care™

PRESENTED BY: Kathleen Moore, Associate Director of Clinical Research, Stephenson Cancer Center University of Oklahoma College of Medicine

MIRASOL (NCT04209855) – Study Design[1,2]

An open-label, phase 3 randomized trial of MIRV vs investigator's choice chemotherapy in patients with FRα-high platinum-resistant ovarian cancer

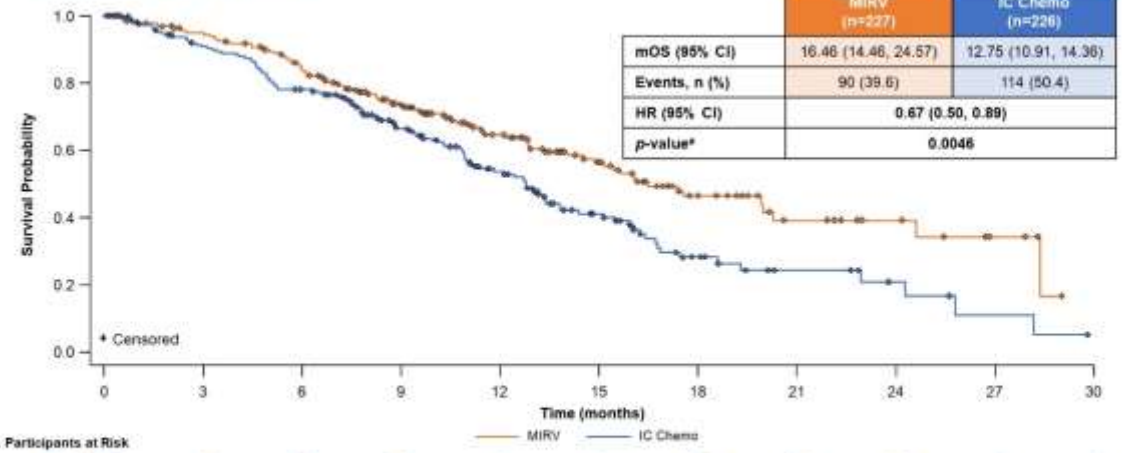


AIBW, adjusted ideal body weight; BEV, bevacizumab; BICR, blinded independent central review; BRCA, BReast CAncer gene; CA-125, cancer antigen 125; chemo, chemotherapy; DOR, duration of response; FRα, folate receptor alpha; IC, investigator's choice; IHC, immunohistochemistry; INV, investigator; MIRV, mirvetuximab soravtansine; ORR, objective response rate; OS, overall survival; PARPi, poly (ADP-ribose) polymerase inhibitors; PFI, platinum-free interval; PFS, progression-free survival; PFS2, time from randomization until second disease progression; PLD, pegylated liposomal doxorubicin; PROs, patient-reported outcomes; PS2+, positive staining intensity ≥2; Q3W, every 3 weeks.
[a]PROs will be measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, 28-item Ovarian Cancer Module (OV28) study instrument.
[b]Gynecological Cancer InterGroup (GCIG) criteria.

1. ClinicalTrials.gov identifier: NCT04209855. Updated June 16, 2022. Accessed October 5, 2022. https://clinicaltrials.gov/ct2/show/NCT04209855
2. Moore K, et al. Presented at: 2020 American Society of Clinical Oncology Annual Meeting; May 29-31, 2020; Virtual. Abstract TPS6103.

PRESENTED BY: Kathleen Moore, Associate Director of Clinical Research, Stephenson Cancer Center University of Oklahoma College of Medicine

Overall Survival



	MIRV (n=227)	IC Chemo (n=226)
mOS (95% CI)	16.46 (14.46, 24.57)	12.75 (10.91, 14.36)
Events, n (%)	90 (39.6)	114 (50.4)
HR (95% CI)	0.67 (0.50, 0.89)	
p-value*	0.0046	

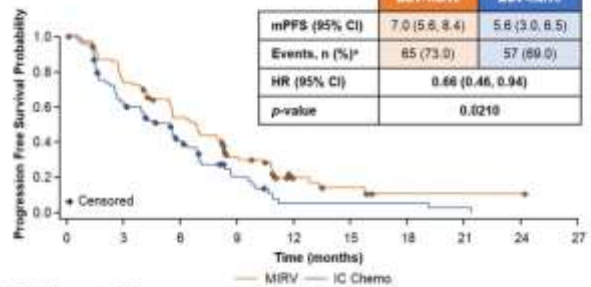
No. Participants at Risk											
MIRV	227	204	175	129	82	53	28	15	9	4	0
IC Chemo	226	185	157	107	68	39	18	9	5	2	0

Data cutoff: March 6, 2023
MIRV, mirvetuximab soravtansine; IC Chemo, investigator choice chemotherapy; mOS, median overall survival; CI, confidence interval; HR, hazard ratio.
*Overall survival is statistically significant based on pre-specified boundary p-value at interim analysis = 0.01313

Presented by: Kathleen Moore, Associate Director of Clinical Research, Stephenson Cancer Center University of Oklahoma College of Medicine

Progression-Free Survival in Bevacizumab Naïve and Prior Bevacizumab Subsets by Investigator

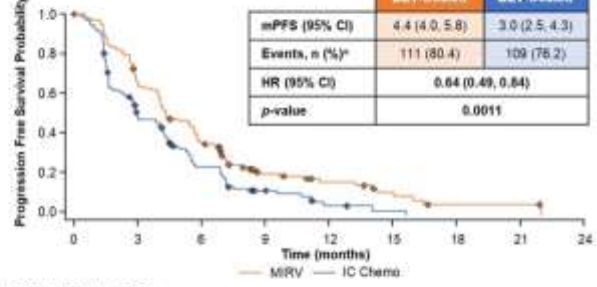
BEV-naïve



	MIRV BEV-naïve	IC Chemo BEV-naïve
mPFS (95% CI)	7.0 (5.6, 8.4)	5.6 (3.0, 6.5)
Events, n (%)*	65 (73.0)	57 (69.0)
HR (95% CI)	0.66 (0.46, 0.94)	
p-value	0.0210	

No. Participants at Risk											
MIRV	89	63	42	21	7	4	1	1	1	0	
IC Chemo	83	42	23	9	2	2	2	1	0		

BEV-treated



	MIRV BEV-treated	IC Chemo BEV-treated
mPFS (95% CI)	4.4 (4.0, 5.8)	3.0 (2.5, 4.3)
Events, n (%)*	111 (80.4)	109 (76.2)
HR (95% CI)	0.64 (0.49, 0.84)	
p-value	0.0011	

No. Participants at Risk											
MIRV	138	88	47	17	11	6	2	2	0		
IC Chemo	143	56	25	10	3	1	0				

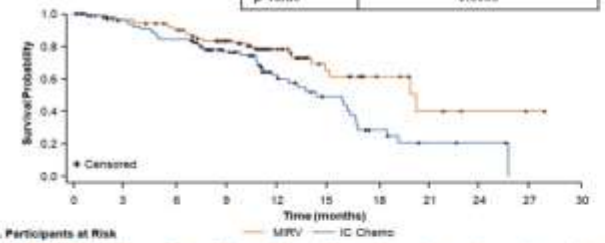
Data cutoff: March 6, 2023
BEV, bevacizumab; HR, hazard ratio; CI, confidence interval; mPFS, median progression-free survival; MIRV, mirvetuximab soravtansine; IC Chemo, investigator's choice of chemotherapy
Patients were not stratified for prior BEV.
*Percentage of PFS events was calculated out of the total number of patients in each treatment arm: n=227 for MIRV and n=226 for IC Chemo.

Presented by: Kathleen Moore, Associate Director of Clinical Research, Stephenson Cancer Center University of Oklahoma College of Medicine

Overall Survival in Bevacizumab Naïve and Prior Bevacizumab Subsets by Investigator

BEV-naïve

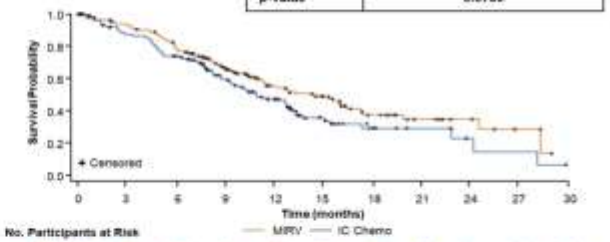
	MIRV BEV-naïve	IC Chemo BEV-naïve
mOS (95% CI)	20.2 (14.8, NE)	14.4 (11.8, 16.7)
Events, n (%)*	23 (25.8)	39 (47.0)
HR (95% CI)	0.51 (0.31, 0.86)	
p-value	0.0099	



No. Participants at Risk											
MIRV	89	79	71	57	35	17	8	4	2	1	0
IC Chemo	83	72	63	44	28	17	8	3	2	1	

BEV-treated

	MIRV BEV-treated	IC Chemo BEV-treated
mOS (95% CI)	15.4 (11.3, 17.5)	10.9 (9.4, 13.3)
Events, n (%)*	67 (48.6)	75 (52.4)
HR (95% CI)	0.74 (0.54, 1.04)	
p-value	0.0789	



No. Participants at Risk											
MIRV	138	125	104	71	47	26	20	11	7	3	0
IC Chemo	143	113	94	63	42	22	10	6	3	2	0

Data cutoff: March 6, 2023
BEV, bevacizumab; HR, hazard ratio; CI, confidence interval; NE, not estimable; mOS, median overall survival; MIRV, mirvetuximab soravtansine; IC Chemo, investigator's choice of chemotherapy
*Percentage of OS events was calculated out of the total number of patients in each treatment arm: n=227 for MIRV and n=226 for IC Chemo.

Presented by: Kathleen Moore, Associate Director of Clinical Research, Stephenson Cancer Center University of Oklahoma College of Medicine

MIRASOL Conclusions

- MIRV demonstrated statistically significant and clinically meaningful improvements in **PFS**, **ORR**, and **OS** compared to IC chemotherapy
- MIRV is the FIRST:
  - Treatment to demonstrate an OS benefit in a phase III trial in PROC
  - FDA-approved ADC for PROC with efficacy confirmed, regardless of prior BEV use in MIRASOL
  - Biomarker-directed therapy for ovarian cancer since PARPi
- With a safety database of more than 1000 patients, MIRV continues to demonstrate a differentiated safety profile consisting predominantly of low-grade ocular, gastrointestinal, and neuropathy events
  - No new safety signals were identified in MIRASOL
- Compared to IC chemotherapy, MIRV was associated with lower rates of:
  - Grade 3 or greater treatment-emergent adverse events (TEAEs) (42% vs 54%)
  - Serious adverse events (24% vs 33%)
  - TEAEs leading to discontinuation of study drug (9% vs 16%)
- These efficacy data, along with the well-characterized safety profile, are practice-changing and position MIRV as a new standard of care for patients with FRα-positive PROC

MIRV, mirvetuximab soravtansine; PFS, progression-free survival; ORR, objective response rate; OS, overall survival; IC, investigator choice; PROC, platinum-resistant ovarian cancer; FDA, Food and Drug Administration; ADC, antibody-drug conjugate; PARPi, poly (adenosine diphosphate [ADP]-ribose) polymerase inhibitor; TEAEs, treatment-emergent adverse events; FRα, folate receptor alpha.
1. Pujade-Lauraine et al. J Clin Oncol. 2014;32(13):1302-1308. 2. Richardson et al. JAMA Oncol. 2023;10.1001/jamaoncol.2023.0197.

Presented by: Kathleen Moore, Associate Director of Clinical Research, Stephenson Cancer Center University of Oklahoma College of Medicine

ORL

2023 ASCO ANNUAL MEETING

LBA6002
PD-1 blockade with Sintilimab plus induction chemotherapy (IC) and concurrent chemoradiotherapy (CCRT) versus IC and CCRT in locoregionally-advanced nasopharyngeal carcinoma (LANPC): a multicenter, phase 3, randomized controlled trial (CONTINUUM)

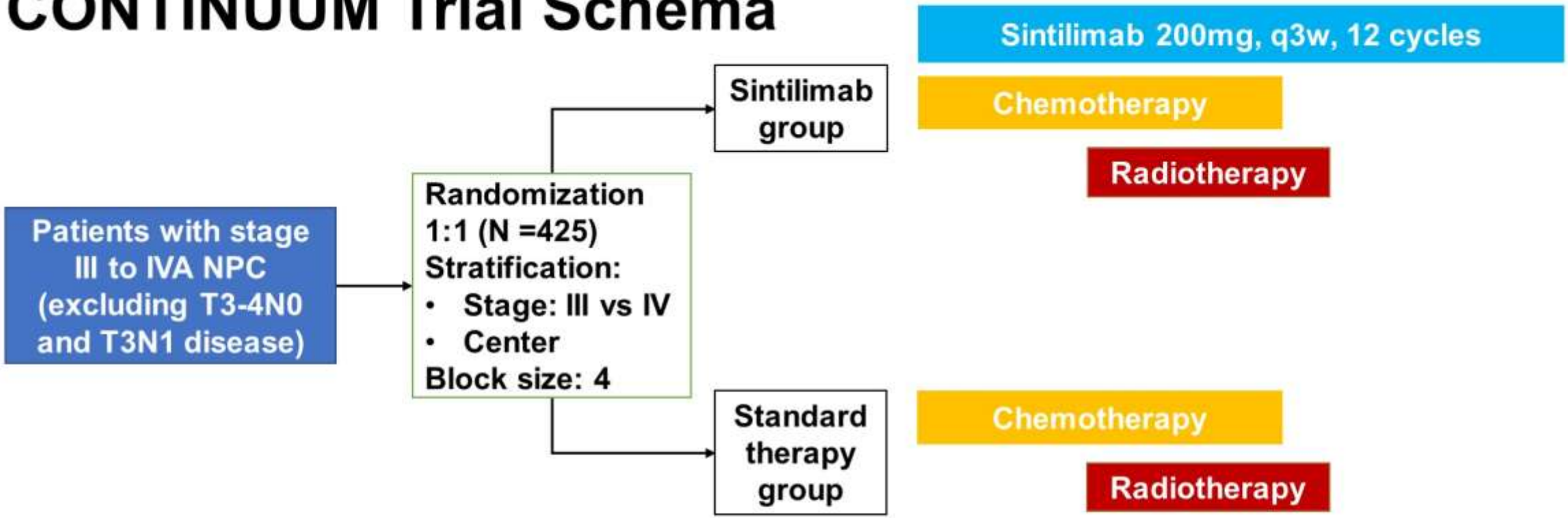
Jun Ma, Professor, M.D.; MSC; Vice President

Sun Yat-sen University Cancer Center

Jun 5, 2023

majun2@sysu.edu.cn

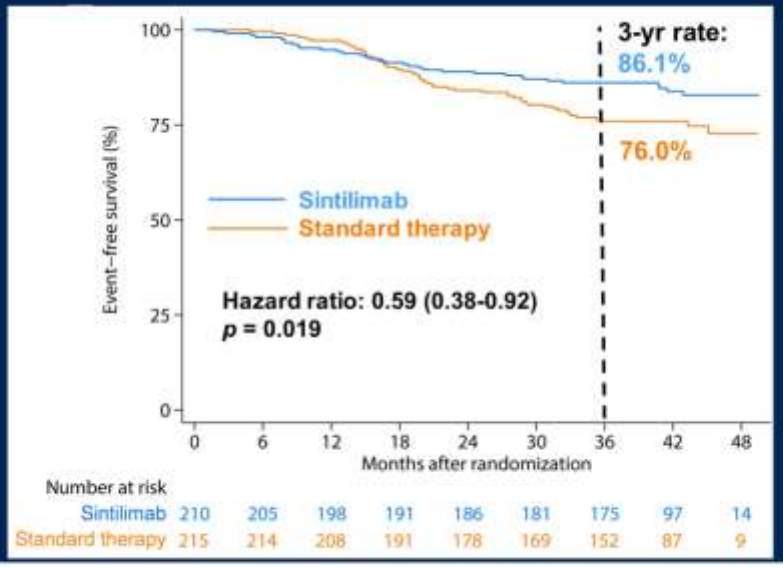
CONTINUUM Trial Schema



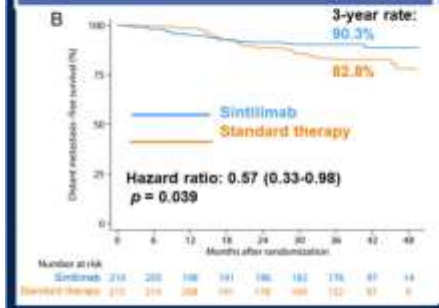
= GP IC, q3w * 3 cycles (Gemcitabine 1g/m2, d1 & 8; DDP 80mg/m2, d1) + CCRT (DDP 100mg/m2, d1 q3w * 2 cycles)

= Intensity modulated radiotherapy, 70Gy in 33 fractions

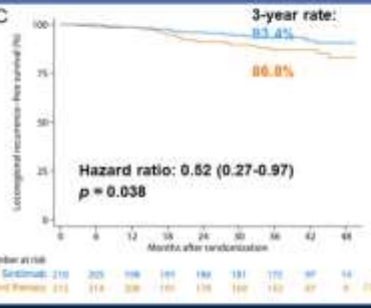
Primary endpoint: Event-free survival



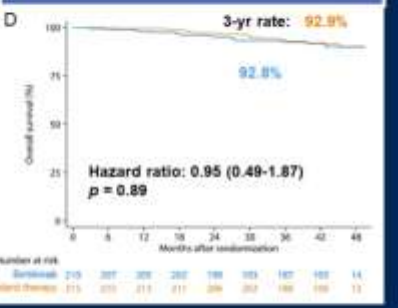
Distant metastasis-free survival



Locoregional recurrence-free survival

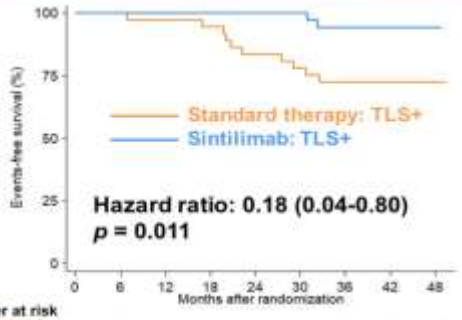


Overall survival

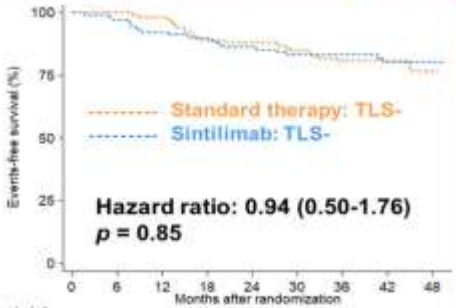


Paitents with TLS benefited addition of sintilimab (N=272)

Tertiary lymphoid structure positive



Tertiary lymphoid structure negative



Conclusions

- Addition of PD-1 inhibitor to induction chemotherapy and chemoradiation in predominantly EBV-associated NPC improves EFS at 3 years
- Completion of CRT was reduced
- OS data are not mature
  - Change to standard of care should wait on mature survival data
  - Longer exposure to immune checkpoint inhibition before definitive therapy with ablation of regional nodes merits study in non-NPC HNSCC

2023 ASCO ANNUAL MEETING

Concurrent chemoradiotherapy followed by adjuvant cisplatin-gemcitabine versus cisplatin-5-fluorouracil chemotherapy for N2-3 nasopharyngeal carcinoma: a multicentre, open-label, randomised, controlled, phase 3 trial

Presenter: Lin-Quan Tang, MD, PhD

Department of nasopharyngeal carcinoma

Sun Yat-sen University Cancer Center

Guangzhou, China

Study Design

Participants

- Aged 18-65
- Histologically confirmed as WHO II/III NPC
- T1-4N2-3M0 (AJCC 7th)
- ECOG score: 0-1
- Adequate hematological, renal, hepatic function

R
1:1

PF arm

CCRT : RT* + DDP 100 mg/m^2, D1, Q3W, 3 Cycles

Adjuvant Therapy: DDP 80 mg/m^2 D1+ fluorouracil 4 g/m^2 by 96-h infusion q 4 weeks X 3 Cycles after the end of RT

Stratified by

- Treatment Center
- Nodal (N) Category (N2 or N3)

GP arm

CCRT : RT* + DDP 100 mg/m^2, D1, Q3W, 3 Cycles

Adjuvant Therapy: DDP 80 mg/m^2, D1 + gemcitabine (1 g/m^2) D1 and D8, every 3 weeks, 3 Cycles after the end of RT

Interval between CCRT and AC is 4 weeks

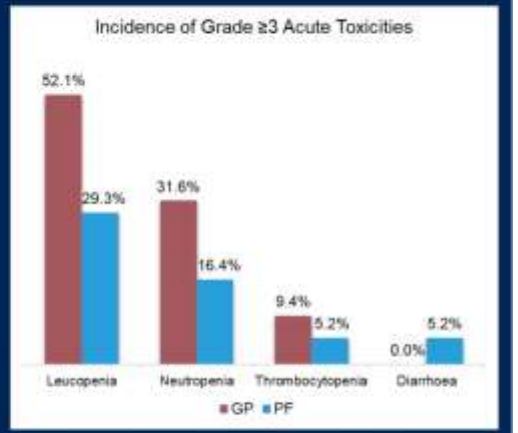
PRESENTED BY: Barbara Burtness, MD

CRT Response and Toxicity

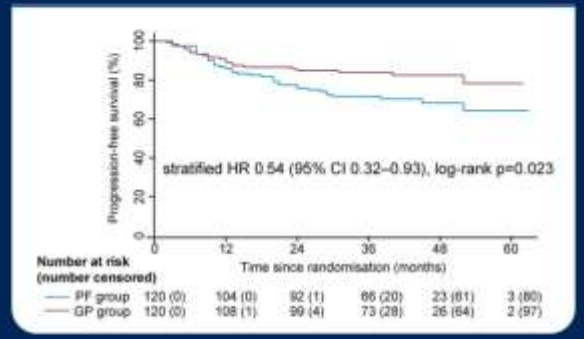
	PF group (n=120)	GP group (n=120)
Response rate†		
Complete response	111 (92.5%)	114 (95.0%)
Partial response	6 (5.0%)	2 (1.7%)
Overall response	**117 (97.5%)**	**116 (96.7%)**
Unassessable#	3 (2.5%)	4 (3.3%)
Plasma EBV DNA prior to AC		
= 0 copies/mL	89 (92.7%)	91 (94.8%)
> 0 copies/mL	**7 (7.3%)**	**5 (5.2%)**

† The first evaluation of tumor response was performed 16 weeks after completion of RT according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1

Patients who did not undergo the imaging measurements at the 16 weeks after RT



3-year PFS for ITT analysis



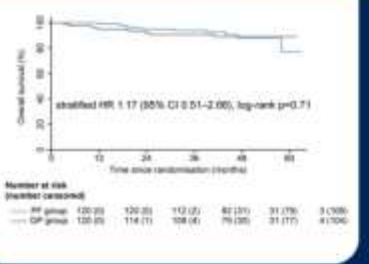
Group	Intention-to-treat population		
	3-year PFS	95% CI	$P_{log\text{-}rank}$
PF	**71.5%**	62.5-78.7 %	
GP	**83.9%**	75.9-89.4 %	**0.023**

Control arm PFS comparable to data from meta-analysis

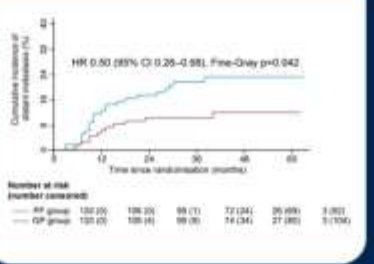
OS, LRFS, DMFS for ITT analysis

GP group reduced risk of LRFS and DMFS, but has no effect on 3-year OS

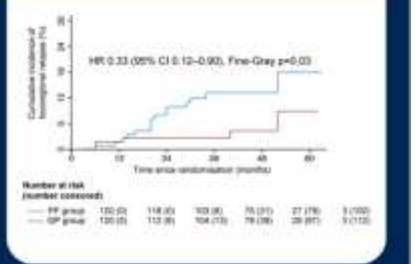
Overall Survival



Distant Metastases



Locoregional Relapse



* OS = overall survival; LRFS = locoregional relapse-free survival; DMFS = distant metastasis-free Survival

Conclusions

- Recurrence risk 20-30% in Stage III/IV$_{a,b}$ patients with clearance of EBV DNA
  - NRG HN001 ongoing study to evaluate omission of chemotherapy in patients who have cleared EBV DNA
- Despite lower use of adjuvant chemotherapy, significant PFS benefit for use of gemcitabine over 5FU adjuvant therapy
  - Comparable DFS with GP induction
  - Toxicity increased relative to PF adjuvant therapy
  - OS data not mature
  - Majority of patients will receive GP induction chemotherapy
  - Does not immediately impact SOC

2023 ASCO ANNUAL MEETING

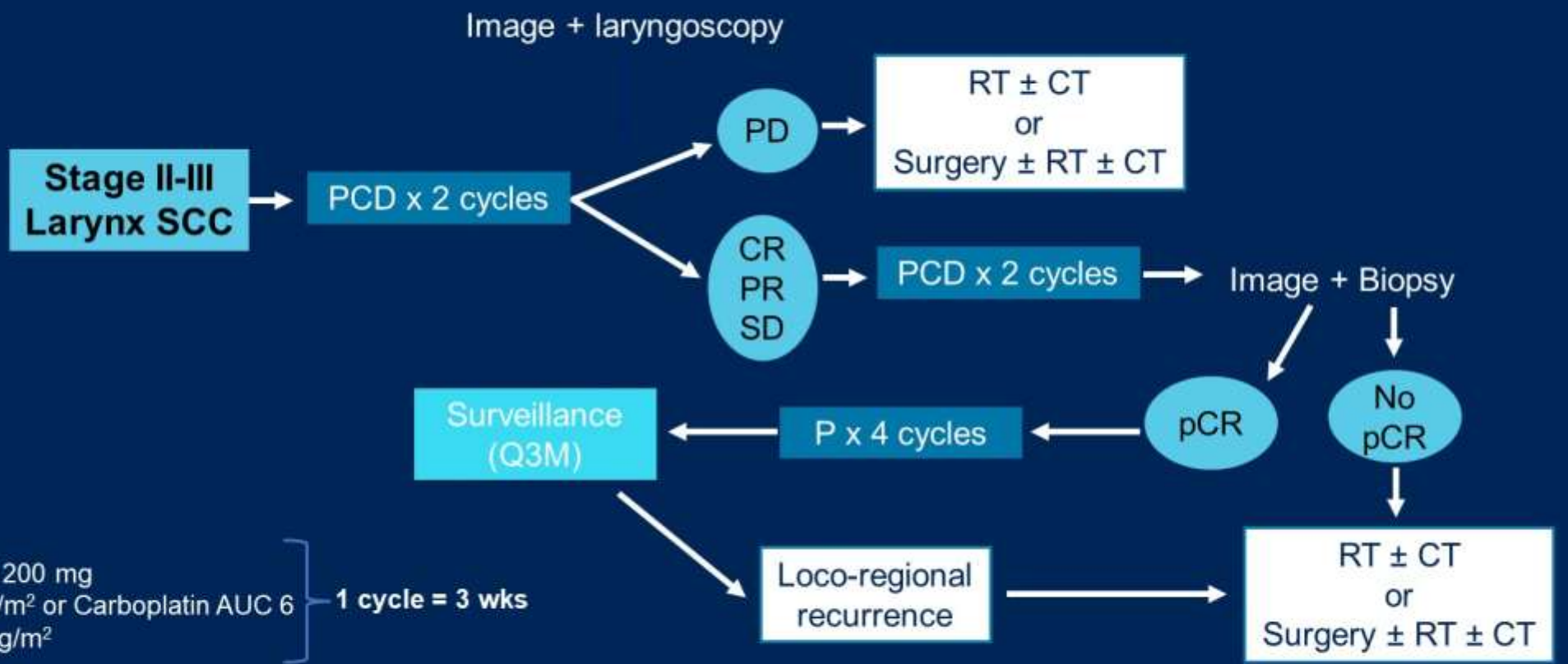
Immuno-Chemotherapy as single treatment modality for Larynx Preservation (ICoLP)

Co-primary endpoints and safety results

Renata Ferrarotto, Faye M Johnson, Kate Hutcheson, Dawen Sui, Jason J Johnson, Barbara Ebersole, Frank Mott, Carol Lewis, Flavia Bonini, Camilla O Hoff, Yoshitsugu Mitani, Maria Angelica Cortez, Diana Bell, Adel El Naggar, Brandon Gunn, Dave Fuller, Jeff Myers, J Jack Lee, David Rosenthal, Ed Diaz.

The University of Texas MD Anderson Cancer Center

ICoLP Trial Schema



P: Pembrolizumab 200 mg
C: Cisplatin 75 mg/m^2 or Carboplatin AUC 6
D: Docetaxel 75 mg/m^2

1 cycle = 3 wks

PD: progression of disease, CR: complete response, SD: stable disease
RT: photon radiotherapy, CT: concurrent chemotherapy (weekly cisplatin or carboplatin)
pCR: pathologic complete response in the biopsy specimen

Conclusions

- No early progression events precluded definitive treatment of larynx cancer when immunochemotherapy was initial therapy
- Durable response to systemic therapy only with immunochemotherapy can be achieved in larynx cancer
  - Majority of recurrences in patients with pCR occur early
- However, loss to follow up or intercurrent medical complications might preclude salvage for LP or cure
- Better methods of assessing risk of recurrence are required
- Given small sample size, this is not standard of care without further study

Uroonkologie

2023 ASCO ANNUAL MEETING

Adjuvant nivolumab plus ipilimumab vs placebo for patients with localized renal cell carcinoma at high risk of relapse after nephrectomy: subgroup analyses from the phase 3 CheckMate 914 (Part A) trial

Robert J. Motzer,[1] Paul Russo,[1] Viktor Grünwald,[2] Yoshihiko Tomita,[3] Philippe Barthélémy,[4] Jeffrey C. Goh,[5] Hernan Javier Cutuli,[6] Steven Blum,[7] Sai Vikram Vemula,[7] Burcin Simsek,[7] Julia Spiridigliozzi,[7] Aleksander Chudnovsky,[7] Axel Bex[8,9]

[1]Memorial Sloan Kettering Cancer Center, New York, NY; [2]Clinic for Internal Medicine (Tumor Research) and Clinic for Urology, West-German Cancer Center Essen, University Hospital Essen, Essen, Germany; [3]Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan; [4]Institut de Cancérologie Strasbourg Europe, Strasbourg, France; [5]ICON Research, South Brisbane, QLD, Australia; [6]Hospital Sirio Libanes, Buenos Aires, Argentina; [7]Bristol Myers Squibb, Princeton, NJ; [8]Netherlands Cancer Institute, Amsterdam, the Netherlands; [9]University College London, London, UK

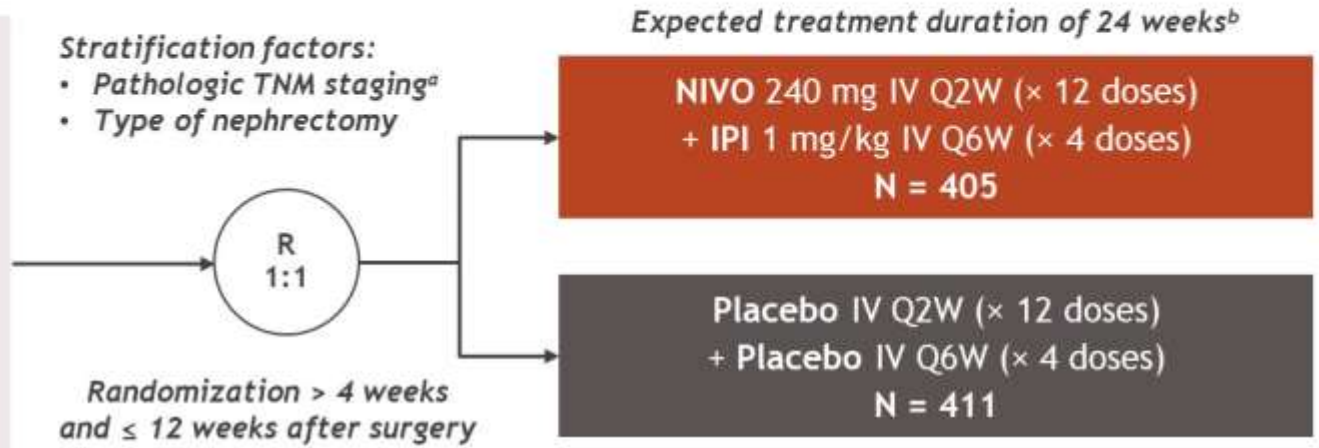
Abstract number 4506

Study design and treatment schedule (Part A)

N = 816

Key inclusion criteria[1,2]

- Radical or partial nephrectomy
- Predominant clear cell histology
- Pathologic TNM staging:
  - pT2a, G3 or G4, N0 M0/pT2b, G any, N0 M0
  - pT3, G any, N0 M0
  - pT4, G any, N0 M0/pT any, G any, N1 M0
- No evidence of residual disease or metastases after nephrectomy, confirmed by BICR

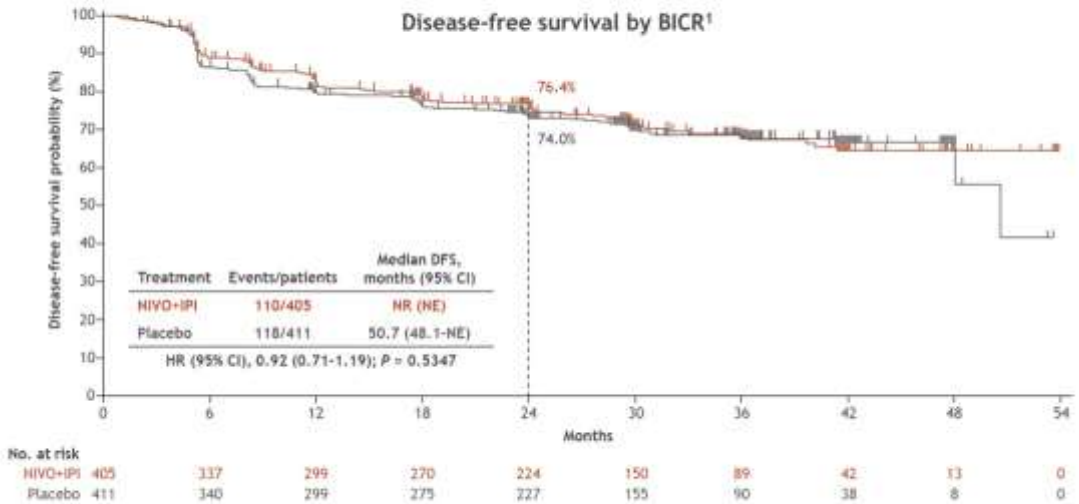


Primary endpoint: DFS by BICR for NIVO+IPI vs placebo
Secondary endpoints: OS for NIVO+IPI vs placebo, safety of NIVO+IPI

Schedule	Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6		Cycle 7		Cycle 8		Cycle 9		Cycle 10		Cycle 11		Cycle 12	
Study week	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Dosing[c]	NIVO+IPI		NIVO		NIVO		NIVO+IPI		NIVO		NIVO		NIVO+IPI		NIVO		NIVO		NIVO+IPI		NIVO		NIVO	
	PBO+PBO		PBO		PBO		PBO+PBO		PBO		PBO		PBO+PBO		PBO		PBO		PBO+PBO		PBO		PBO	

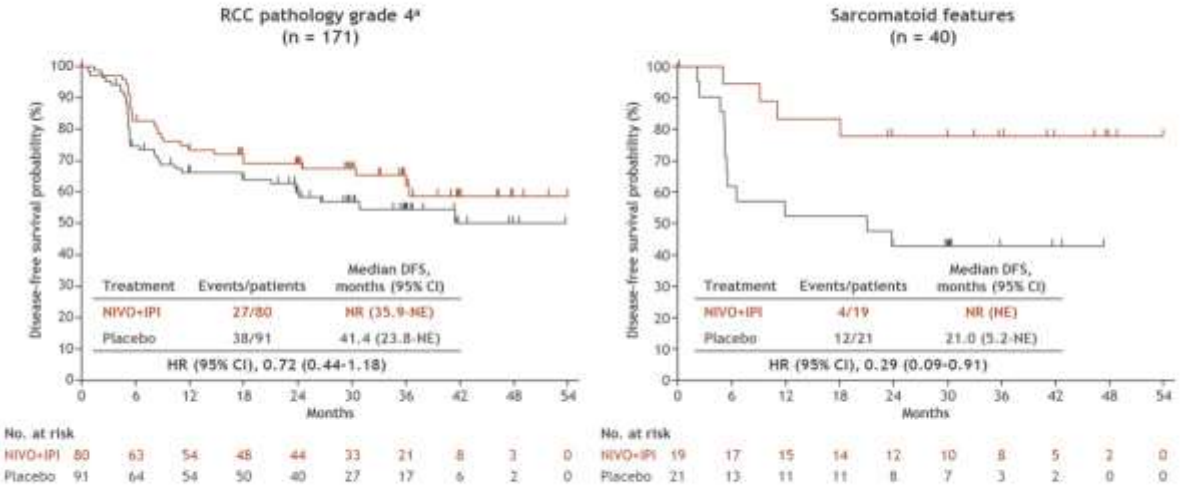
Median follow-up, 37.0 months (minimum follow-up, 15.4 months).
[a]Stratification by TNM staging (pT2a, G3 or G4, N0 M0 or pT2b, G any, N0 M0 vs pT3, G any, N0 M0 vs pT4, G any, N0 M0 or pT any, G any, N1 M0). [b]Treatment could be extended up to 36 weeks to accommodate dose delays. [c]Dose given on day 1 of each cycle.
G, grade; IV, intravenously; PBO, placebo; Q×W, every × weeks.
1. ClinicalTrials.gov. Accessed April 28, 2023. https://clinicaltrials.gov/ct2/show/NCT03138512. 2. Motzer RJ, et al. *Lancet* 2023;401:821-832.

Adjuvant NIVO+IPI in CheckMate 914 (primary endpoint)



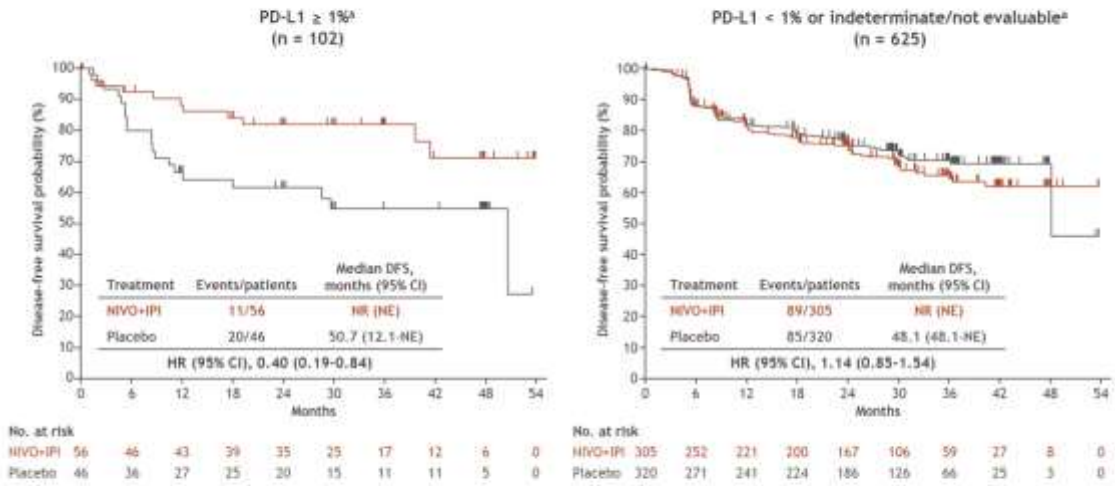
As the DFS endpoint was not met, no formal OS analysis was performed (in total, there were 33 deaths in the NIVO+IPI arm and 28 deaths in the placebo arm).
1. Motzer RJ, et al. *Lancet* 2023;401:821-832.
CI, confidence interval; HR, hazard ratio. NE, not estimable; NR, not reached.

Disease-free survival per BICR *in patients with RCC pathology grade 4* or *sarcomatoid features*



[a]Data were reported using the Fuhrman grading system for the duration of enrollment. If assessment of RCC pathology grade was performed using the WHO/ISUP system, grade was correlated back to the Fuhrman system in order to assess eligibility.

Disease-free survival per BICR *in patients by PD-L1 expression*



[a]Data by tumor PD-L1 expression were analyzed from a March 2021 database lock as these data were not available from the July database lock used for all other data reported in this presentation.

My Two Cents: Adjuvant therapy in localized RCC post-nephrectomy

- Despite its activity in metastatic disease, Nivo/Ipi is clearly ineffective in the adjuvant setting
- Nivo/Ipi should NOT be offered to patients in this curative context
- Although some patient subsets (sarcomatoid, PDL1+) appear to benefit from Nivo/Ipi, these were <u>exploratory</u> subsets* and should NOT be used for clinical decision making

*hypothesis-generating

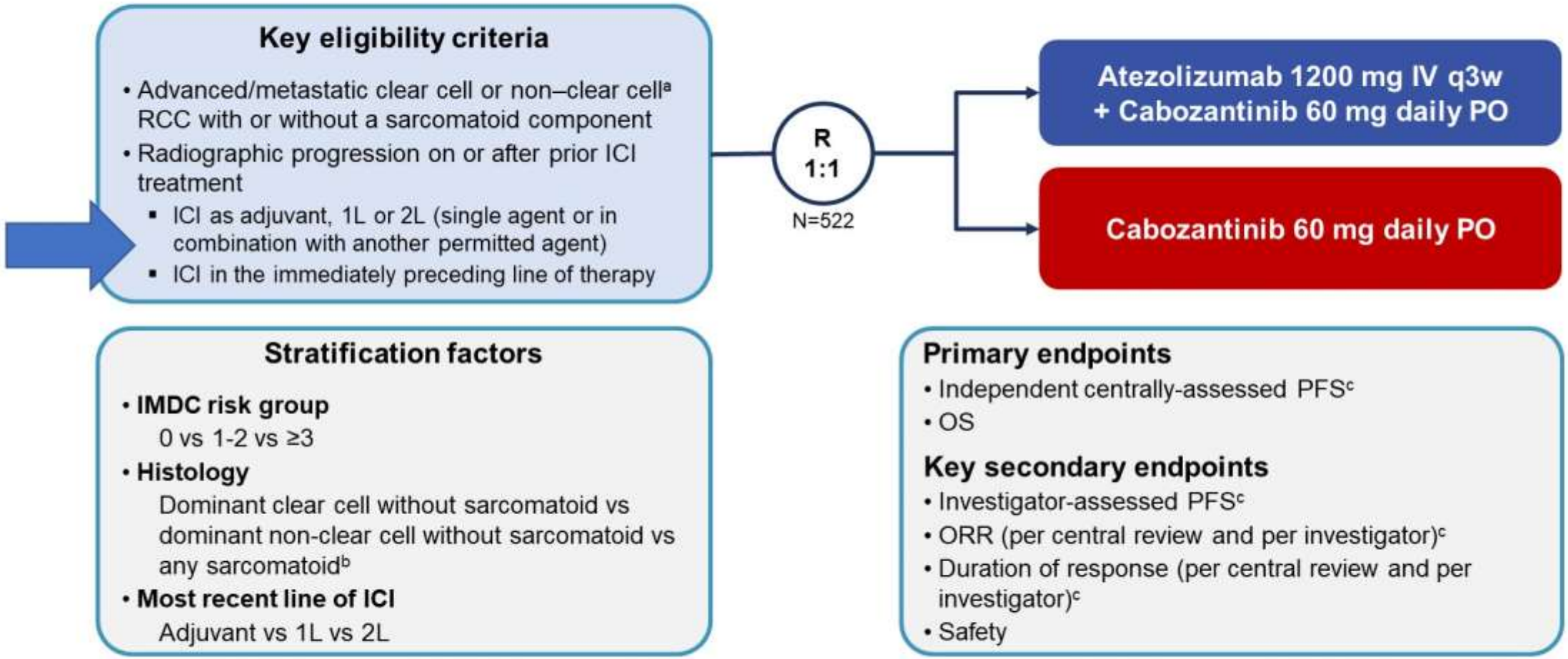
2023 ASCO ANNUAL MEETING

Efficacy and safety of atezolizumab plus cabozantinib vs cabozantinib alone after progression with prior immune checkpoint inhibitor treatment in metastatic renal cell carcinoma: primary PFS analysis from the Phase 3, randomized, open-label CONTACT-03 study

Toni K. Choueiri,[1] Laurence Albiges,[2] Piotr Tomczak,[3] Cristina Suárez,[4] Martin H. Voss,[5] Guillermo de Velasco,[6] Jad Chahoud,[7] Giuseppe Procopio,[8] Hakim Mahammedi,[9] Friedemann Zengerling,[10] Chan Kim,[11] Suyasha Gupta,[12] Guillaume Bergthold,[13] Bo Liu,[12] Melania Kalaitzidou,[14] Mahrukh Huseni,[12] Christian Scheffold,[15] Thomas Powles,[16] Sumanta Kumar Pal[17]

[1]Dana-Farber Cancer Institute, Boston, MA; [2]Department of Cancer Medicine, Institut Gustave Roussy, Villejuif, France; [3]Poznan University of Medical Sciences, Poznan, Poland; [4]Medical Oncology, Vall d'Hebron Institute of Oncology (VHIO), Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain; [5]Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; [6]Medical Oncology Department, University Hospital '12 de Octubre,' Madrid, Spain; [7]Department of Genitourinary Oncology, Moffitt Cancer Center and Research Institute, Tampa, FL; [8]Department of Medical Oncology, Fondazione Istituto Nazionale dei Tumori di Milano, Milan, Italy; [9]Department of Medical Oncology, Jean Perrin Cancer Center, Clermont-Ferrand, France; [10]Department of Urology and Paediatric Urology, University Hospital Ulm, Ulm, Germany; [11]Department of Internal Medicine, CHA Bundang Medical Center, CHA University, Seongnam, Republic of Korea; [12]Genentech, South San Francisco, CA; [13]F. Hoffmann-La Roche, Ltd, Basel, Switzerland; [14]Roche Product Ltd, Welwyn Garden City, UK; [15]Exelixis, Inc, Alameda, CA; [16]Barts Cancer Institute, ECMC, QMUL, London, United Kingdom; [17]Department of Medical Oncology, City of Hope Comprehensive Cancer Center, Duarte, CA

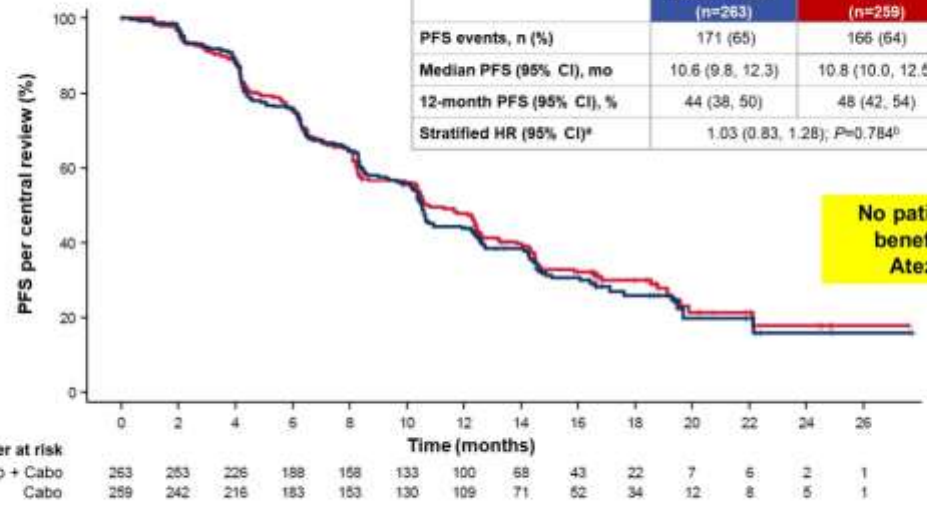
The global, Phase III CONTACT-03 study



ClinicalTrials.gov ID, NCT04338269. IMDC, International Metastatic RCC Database Consortium. Patients were enrolled between July 28, 2020 and December 27, 2021.
[a] Papillary, chromophobe or unclassified (chromophobe requires sarcomatoid differentiation). [b] Clear cell or non-clear cell. [c] Assessed according to RECIST 1.1.

Primary analysis of centrally reviewed PFS (primary endpoint)

	Atezo + Cabo (n=263)	Cabo (n=259)
PFS events, n (%)	171 (65)	166 (64)
Median PFS (95% CI), mo	10.6 (9.8, 12.3)	10.8 (10.0, 12.5)
12-month PFS (95% CI), %	44 (38, 50)	48 (42, 54)
Stratified HR (95% CI)[a]	1.03 (0.83, 1.28); *P*=0.784[b]	

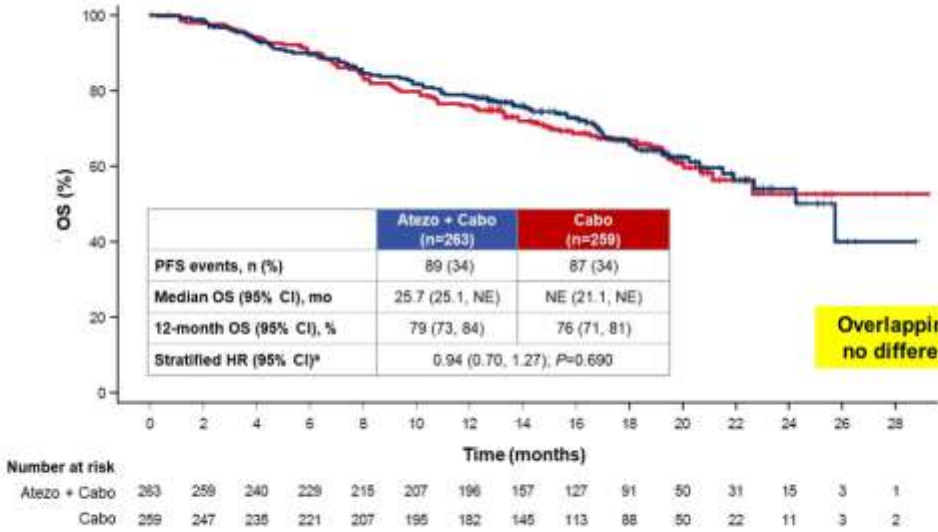


No patient subset benefited from Atezo/Cabo

[a]Stratified for IMDC risk group. [b]Not significant at α=0.02.

Interim analysis of OS (primary endpoint)

	Atezo + Cabo (n=263)	Cabo (n=259)
PFS events, n (%)	89 (34)	87 (34)
Median OS (95% CI), mo	25.7 (25.1, NE)	NE (21.1, NE)
12-month OS (95% CI), %	79 (73, 84)	76 (71, 81)
Stratified HR (95% CI)[a]	0.94 (0.70, 1.27); *P*=0.690	



Overlapping curves: no difference in OS

[a]Stratified for IMDC risk group.

Safety summary

Atezo/Cabo was more toxic that Cabo alone

Adverse event, n (%)	Atezo + Cabo (n=262)	Cabo (n=256)
Any-cause AE	262 (100)	254 (99.2)
Any-cause treatment-related AE	252 (96.2)	249 (97.3)
Grade 3 or 4 AE	177 (67.6)	158 (61.7)
Grade 3 or 4 treatment-related AE	145 (55.3)	121 (47.3)
Death due to AE	17 (6.5)	9 (3.5)
Death due to treatment-related AE	3 (1.1)[a]	0
Serious AE	126 (48.1)	84 (32.8)
Serious treatment-related AE	63 (24.0)	30 (11.7)
AE leading to withdrawal from a trial drug	41 (15.6)	10 (3.9)
AE leading to withdrawal from atezo	29 (11.1)	–
AE leading to withdrawal from cabo	25 (9.5)	10 (3.9)
AE leading to interruption or reduction of a trial drug	240 (91.6)	223 (87.1)
AE leading to interruption of atezo[b]	159 (60.7)	–
AE leading to interruption or reduction of cabo	234 (89.3)	223 (87.1)

[a]Treatment-related AEs leading to death were immune-mediated enterocolitis and renal failure (both related to atezo) and intestinal perforation (related to cabo). [b]Dose reduction of atezo was not permitted.

My Two Cents: Advanced/Metastatic RCC

Immunotherapy re-challenge: a cautionary tale!

- Following progression on or after prior treatment with PD-L1/PD-1 therapy, the addition of atezolizumab to cabozantinib was ineffective and was associated with harm
- **Question:** Is this disappointing observation generalizable for all other ICIs in the post-ICI setting?
  - Until new level 1 evidence shows otherwise, the answer is **YES**
  - In the post-ICI setting, mRCC patients should **NOT** be re-challenged with ICI-based therapy outside of a clinical trial

2023 ASCO ANNUAL MEETING

SWOG S1011 - A Phase III Surgical Trial to Evaluate the Benefit of a Standard Versus an Extended Lymphadenectomy Performed at Time of Radical Cystectomy for Muscle Invasive Urothelial Cancer

Seth P. Lerner, Catherine Tangen, Robert S. Svatek, Siamak Daneshmand, Kamal Pohar, Eila Skinner, Anne Schuckman, Arthur I. Sagalowsky, Norm D. Smith, Ashish M. Kamat, Wassim Kassouf, Melissa Plets, Rick Bangs, Theresa M Koppie, Ajai Alva, Francisco G La Rosa, Sumanta K. Pal, Adam S. Kibel, Daniel J. Canter, Ian M Thompson, Jr

NCT 01224665

PRESENTED BY: Seth P Lerner, MD

S-1011 Study Design

T2-T4a Urothelial ca
Radical Cystectomy
Neoadjuvant Ctx allowed
N1,2 allowed

RANDOMIZE

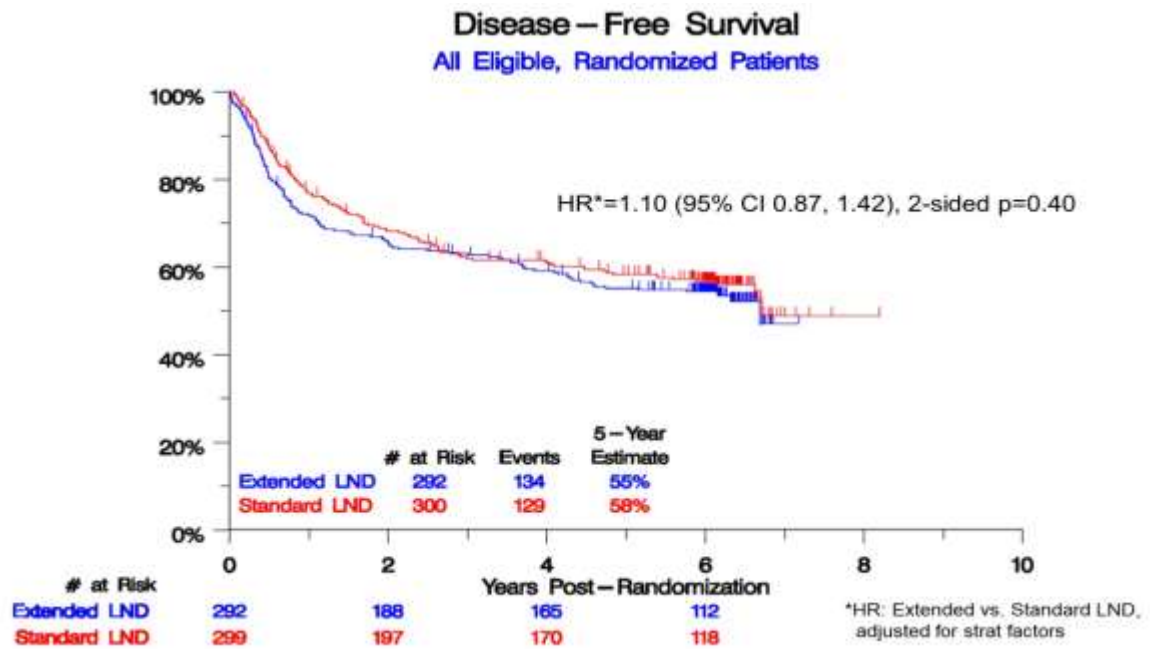
Standard PLND
External/internal iliac, obturator nodes

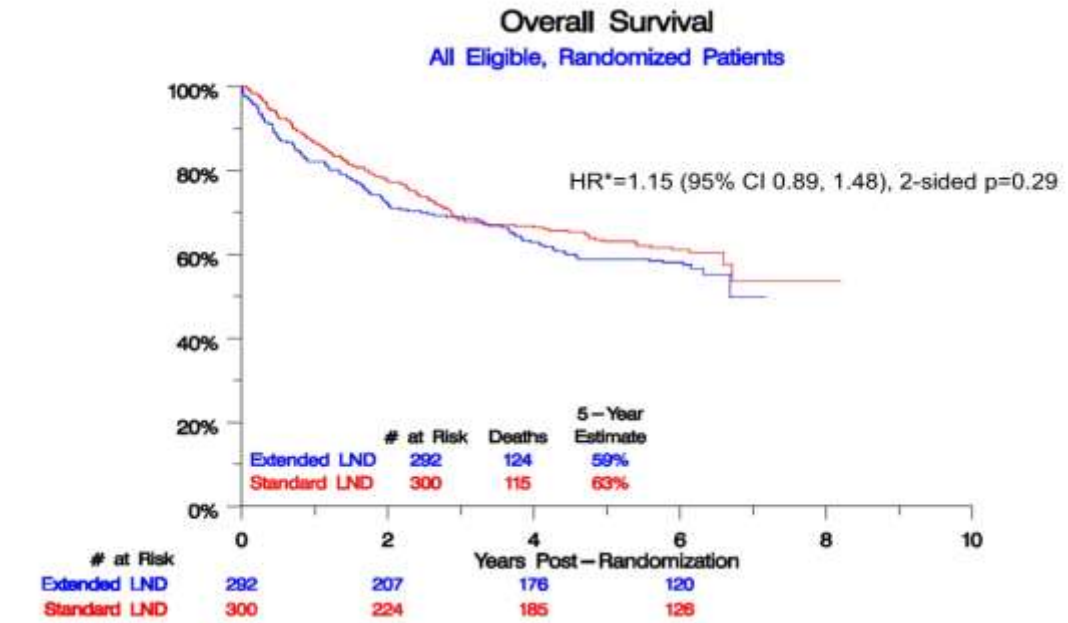
Extended LND
Standard + CI, pre sacral, distal IVC and aorta

pT3-4N0, pTanyN+
Adjuvant Chemotherapy

Stratification factors:
NAC – cisplatin v carboplatin v other v none
cT stage – T2 v T3/4a
PS – 0-1 v 2

- Assume 55% 3-yr DFS in standard LND group (based on review of 8 surgical series 2000-2009 including 7957 patients)
- 85% power to detect 10-12% improvement in 3-yr DFS with extended LND, clinically significant (HR=0.72)
- Sample size of 564 eligible patients (282 per arm)





Cystectomy Pathologic Node Status and EBL

	SLND (n=300)	ELND (n=292)
Total Number Nodes Removed Median (range)	24 (6, 61)	39 (15, 94)
Number of Positive Nodes if N+ Median (range)	1 (1, 16)	2 (1, 35)
1	37 (12%)	34 (12%)
2-5	23 (8%)	26 (9%)
6-10	9 (3%)	9 (3%)
> 10	2 (1%)	6 (2%)
Estimated blood loss (median)	600	700

My Two Cents: Localized Urothelial Cancer

- Extended LND did not improve DFS nor OS compared to standard LND
- Extended LND was associated with harm: higher morbidity and peri-operative mortality
- Surgical standard of care for locally advanced UC (cT2-4a/N0-N2) remains a radical cystectomy with ***standard*** LND
- This confirmatory phase III trial could have only been conducted through publicly-funded mechanisms such as the NCI's NCTN

2023 ASCO ANNUAL MEETING

Study EV-103 Dose Escalation/Cohort A: Long-term Outcome of Enfortumab Vedotin + Pembrolizumab in First-line (1L) Cisplatin-ineligible Locally Advanced or Metastatic Urothelial Carcinoma (la/mUC) with Nearly 4 Years of Follow-up

Shilpa Gupta, MD[1]; Jonathan E. Rosenberg, MD[2]; Rana R. McKay, MD[3]; Thomas W. Flaig, MD[4]; Daniel Peter Petrylak, MD[5]; Christopher J. Hoimes, DO[6]; Terence W. Friedlander, MD[7]; Mehmet Asim Bilen, MD[8]; Sandy Srinivas, MD[9]; Earle Burgess, MD[10]; Jaime R. Merchan, MD[11]; Scott Tagawa, MD[12]; Jason Brown, MD[13]; Yao Yu, PhD[14]; Anne-Sophie Carret, MD[14]; Heidi S. Wirtz, PharmD, PhD[14]; Maria Guseva, MD, PharmD[15]; Blanca Homet Moreno, MD, PhD[16]; Matthew I. Milowsky, MD[17]

[1]Taussig Cancer Institute, Cleveland Clinic Foundation, Cleveland, OH, USA; [2]Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY, USA; [3]University of California San Diego, San Diego, CA, USA; [4]University of Colorado Comprehensive Cancer Center, Aurora, CO, USA; [5]Yale Cancer Center, New Haven, CT, USA; [6]Duke Cancer Institute, Duke University, Durham, NC, USA; [7]University of California San Francisco Medical Center, San Francisco, CA, USA; [8]Winship Cancer Institute of Emory University, Atlanta, GA, USA; [9]Stanford University Medical Center, Stanford, CA, USA; [10]Atrium Health Levine Cancer Institute, Charlotte, NC, USA; [11]University of Miami, Miami, FL, USA; [12]Weill Cornell Medical Center, New York, NY, USA; [13]University Hospitals Cleveland Medical Center, Cleveland, OH, USA; [14]Seagen Inc, Bothell, WA, USA; [15]Astellas Pharma, Northbrook, IL, USA; [16]Merck & Co., Inc., Rahway, NJ, USA; [17]University of North Carolina, Lineberger Comprehensive Cancer Center, Chapel Hill, NC, USA

My Two Cents: Metastatic urothelial cancer

- EV + P has received accelerated US FDA approval for 1L cisplatin-ineligible patients based on an encouraging ORR (68%) and a “manageable” safety profile
  - Oncologists must carefully educate patients about potential toxicity: perception of a “less toxic” regimen may be unrealistic
  - Results of Phase III EV-302 trial are eagerly anticipated (EV+P vs GC)
- Patients with cisplatin-eligible disease: 1L MVAC or GC followed by Avelumab maintenance remains SOC

PAN-FGFR inhibitor

Phase 3 THOR Study: Results of Erdafitinib Versus Chemotherapy in Patients With Advanced or Metastatic Urothelial Cancer With Select Fibroblast Growth Factor Receptor Alterations

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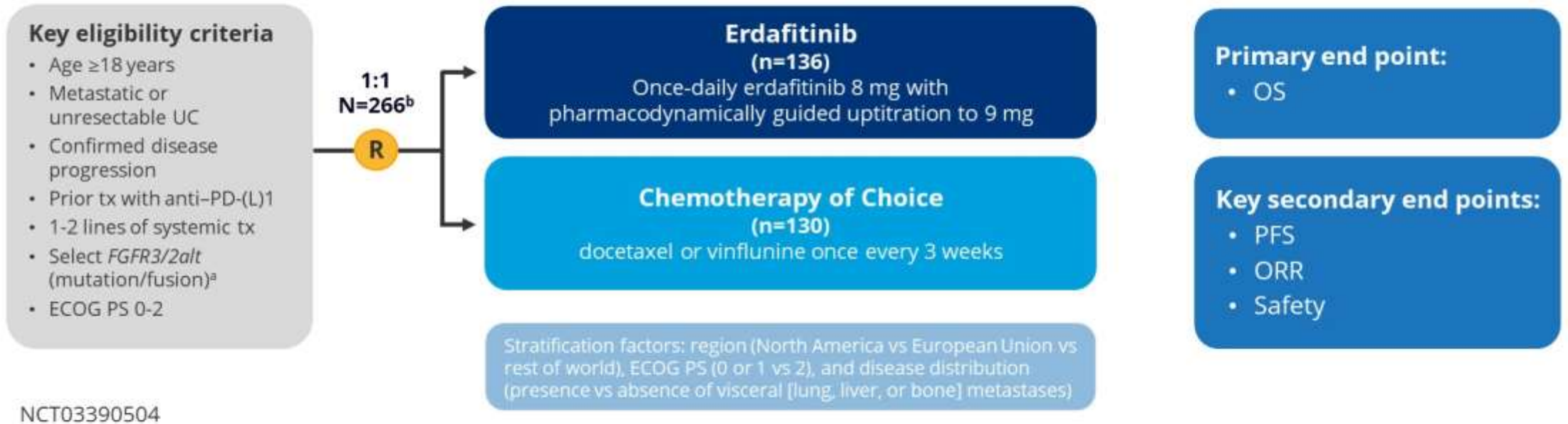
Presented at the 2023 ASCO Annual Meeting; June 2-6, 2023; Chicago, IL, USA.

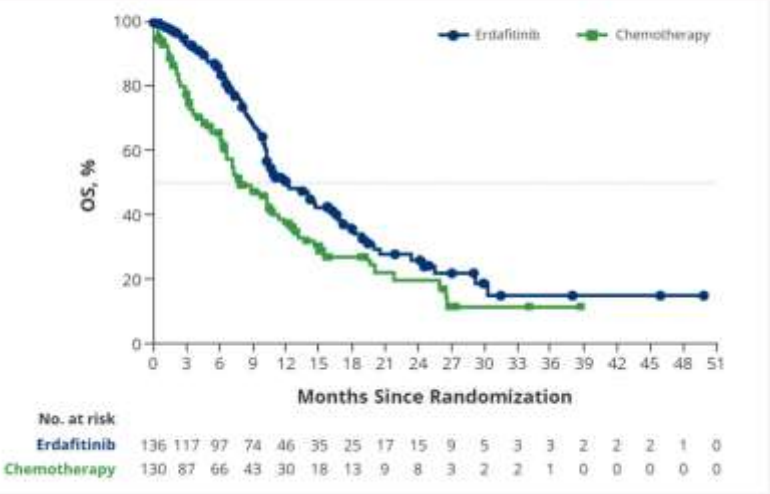
Phase 3 THOR Study: Erdafitinib Versus Chemotherapy of Choice in Patients With Advanced Urothelial Cancer and Selected FGFR Aberrations

Cohort 1



[a]Molecular eligibility can be confirmed using either central or local historical *FGFR* test results (Qiagen assay). If a patient was enrolled based on local historical testing, a tissue sample must still be submitted at the time of enrollment for retrospective confirmation (by central lab) of *FGFR* status. Tumors must have ≥1 of the following translocations: *FGFR2-BICC1, FGFR2-CASP7, FGFR3-TACC3_V1, FGFR3-TACC3_V3, FGFR3-BAIAP2L1;* or 1 of the following *FGFR3* gene mutations: R248C, S249C, G370C, Y373C.
[b]Number of patients randomized at the time of the interim analysis (data cutoff January 15, 2023).
ECOG PS, Eastern Cooperative Oncology Group performance status; FGFR, fibroblast growth factor receptor; *FGFR3/2alt, FGFR3/2* alterations; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; Q3W, every 3 weeks; tx, treatment; UC, urothelial cancer.

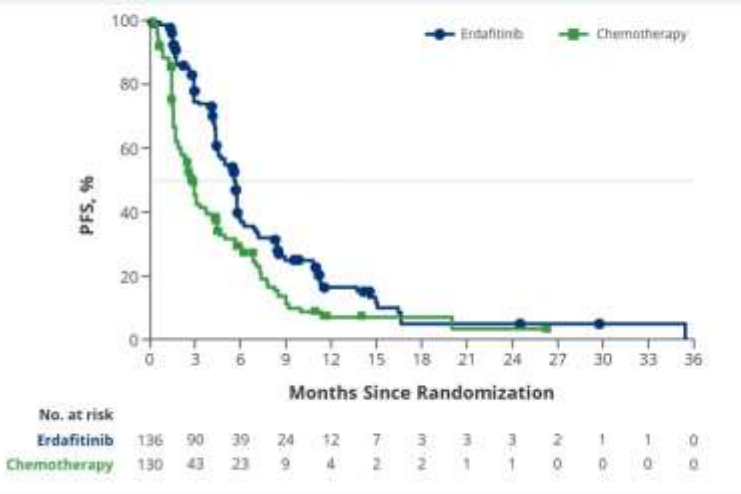
Overall Survival for Erdafitinib Was Superior to Investigator's Choice of Chemotherapy



- Median follow-up was 15.9 months
- Median OS was 12.1 months for erdafitinib versus 7.8 months for chemotherapy
- Erdafitinib reduced the risk of death by 36% versus chemotherapy
  - HR, 0.64 (95% CI, 0.47-0.88; $P = 0.005$)[a]
- Based on these interim analysis results, the IDMC recommended to stop the study, unblind data, and cross over patients from chemotherapy to erdafitinib

CI, confidence interval; HR, hazard ratio; IDMC, independent data monitoring committee; OS, overall survival.
[a]The significance level for stopping for efficacy was p=0.019, corresponding to a HR of 0.83.

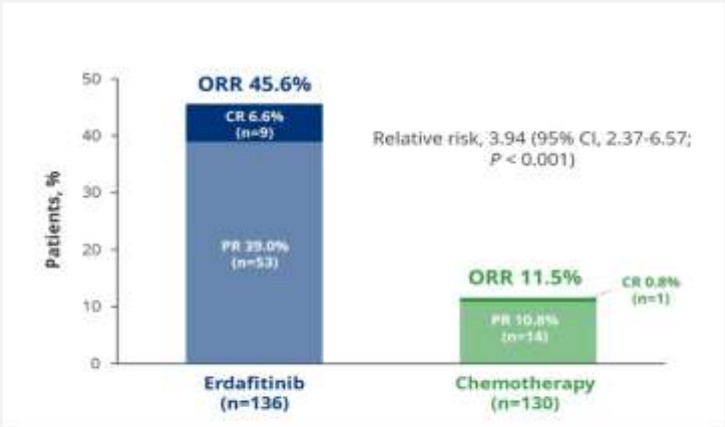
Erdafitinib Significantly Improved Progression-Free Survival Versus Chemotherapy



- Median PFS was 5.6 versus 2.7 months for erdafitinib versus chemotherapy
- Erdafitinib reduced the risk of progression or death by 42% versus chemotherapy
  - HR, 0.58 (95% CI, 0.44-0.78; $P = 0.0002$)

CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

Objective Response Rate Was Significantly Higher for Erdafitinib Versus Chemotherapy[a]



CI, confidence interval; CR, complete response; ORR, objective response rate; PR, partial response.
[a]Responses were best overall response per investigator assessment.

THOR Cohort 1: Conclusions

- Erdafitinib significantly extended OS in patients with advanced/mUC with *FGFRalt* after prior treatment with anti–PD-(L)1, with a median OS of 1 year
  - Erdafitinib provided a 36% reduction in risk of death compared to chemotherapy
  - The OS benefit of erdafitinib was consistent across clinically relevant subgroups
  - Erdafitinib provided significantly longer PFS and greater ORR versus chemotherapy
- Erdafitinib safety profile was consistent with the BLC2001 study[1,2]
- The phase 3 THOR study supports the clinical efficacy of erdafitinib as the standard of care option for patients with mUC with *FGFRalt* after anti–PD-(L)1 treatment
- The OS benefit of erdafitinib in patients with mUC with *FGFRalt* supports molecular testing for *FGFRalt* in all patients with mUC

FGFRalt, *FGFR* alterations; mUC, metastatic urothelial carcinoma; ORR, overall response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival.
1. Loriot Y, et al. N Engl J Med. 2019;381:338-348. 2. Sieker-Radtke AO, et al. Lancet Oncol. 2022;23:248-258.

NSCLC

2023 ASCO ANNUAL MEETING

Perioperative Toripalimab + Platinum-Doublet Chemotherapy vs Chemotherapy in Resectable Stage II/III Non-small Cell Lung Cancer: Interim Event-Free Survival Analysis of the Phase III Neotorch Study

Shun Lu,[1] Lin Wu,[2] Wei Zhang, [3] Peng Zhang,[4] Wenxiang Wang,[2] Wentao Fang,[1] Wenqun Xing,[5] Qixun Chen,[6] Jiandong Mei,[7] Lin Yang,[8] Lijie Tan,[9] Xiaohong Sun,[10] Shidong Xu,[11] Xiaohua Hu,[12] Guohua Yu,[13] Dongliang Yu, [14]Jinlu Shan,[15] Nong Yang,[2] Yuping Chen,[16] Hui Tian,[17]Weihua Wang,[18] Wenbo Yu [18]

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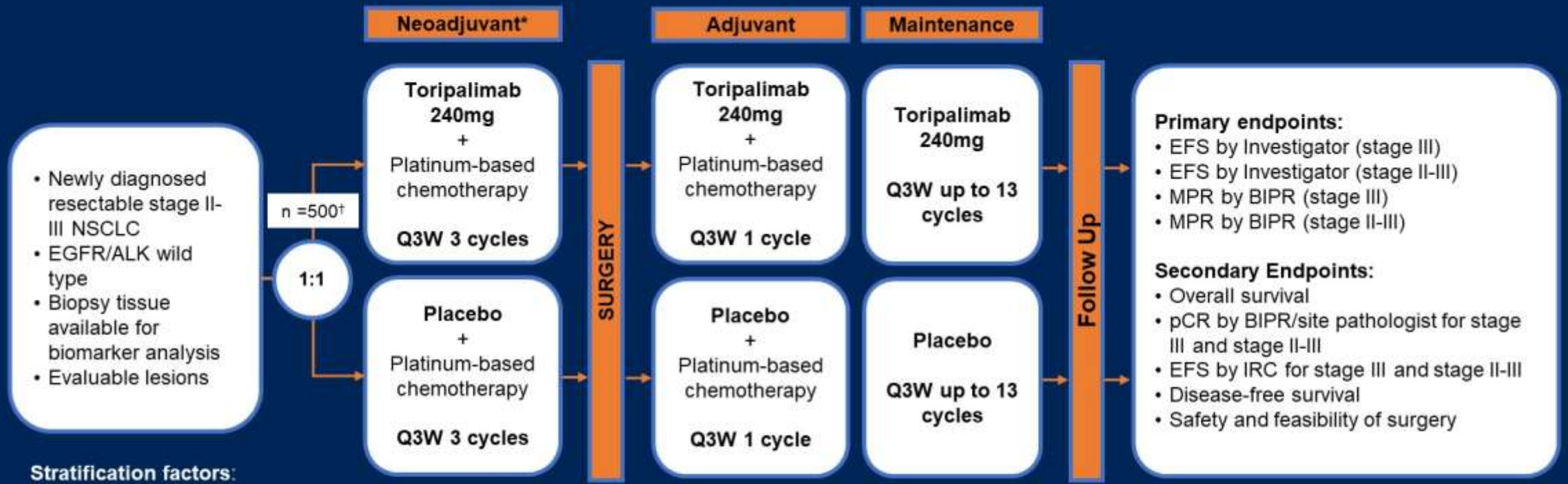
PRESENTED BY:

Neotorch Study Design



Stratification factors:
- II vs IIIA vs IIIB
- Lobectomy vs pneumonectomy
- Non-squamous vs squamous
- PD-L1 TC expression: ≥ 1% vs < 1% or non-evaluable

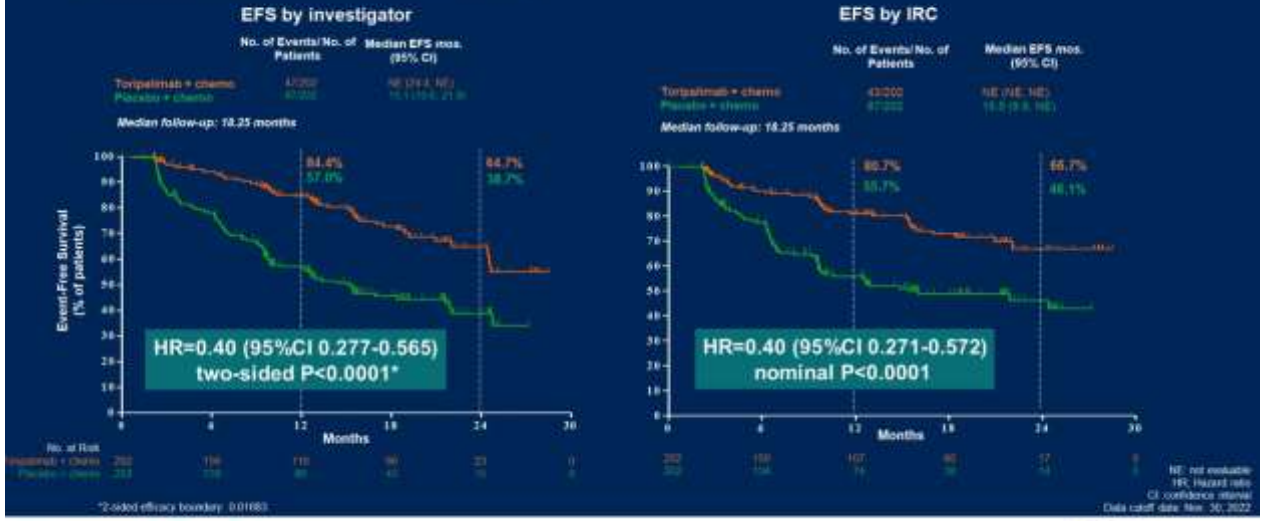
Patients had surgery: 82.2% vs 73.3%

*3 cycles of neoadjuvant chemotherapy with 4 cycles of peri-operative chemotherapy in total were required with in Neotorch study, meanwhile, surgeons were allowed to determine the most appropriate timing for surgery based on the patient's condition
†About 400 patients with Stage III NSCLC and ~100 patients with Stage II NSCLC patients would be enrolled

EFS: Event-Free Survival
MPR: Major Pathologic Response
BIPR: Blinded Independent Pathologic Review
pCR: Pathological Complete Response
IRC: Independent Review Committee

Event-Free Survival Analysis

Intent-to-treat Stage III patients assessed by investigator per RECIST v1.1



NE: not evaluable
HR: Hazard ratio
CI: confidence interval
Data cutoff date: Nov. 30, 2022

*2-sided efficacy boundary: 0.01683

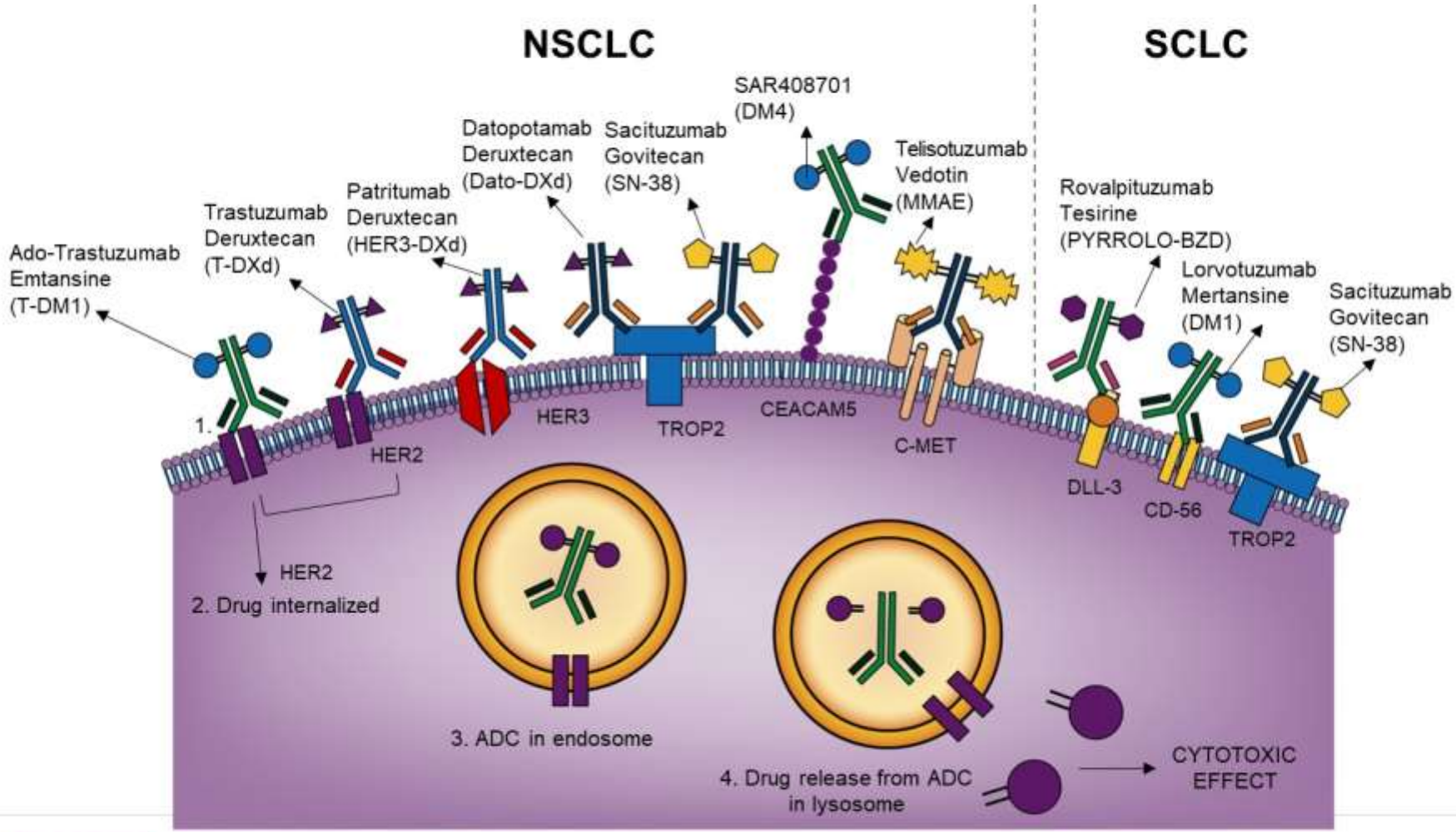
Summary and Conclusions

- Toripalimab plus chemotherapy significantly improved EFS (NE vs. 15.1 months) and had higher MPR and pCR rates (48.5% vs. 8.4%; 24.8% vs. 1.0%) compared to chemotherapy alone in stage III NSCLC patients, with a survival trend favoring toripalimab. The combination regimen was well-tolerated with no new safety signals.
- Improvement in EFS was consistent across all key subgroups:
  - ❑Benefits in all PD-L1 subgroups: the HRs were 0.59, 0.31 and 0.31 in PD-L1<1%,1-49% and ≥ 50%, respectively
  - ❑Benefits in both non-squamous and squamous subtypes: the HRs were 0.54 and 0.35, respectively
- The results from Neotorch study, as well as other studies, indicated that perioperative immunotherapy plus chemotherapy should be a standard of care for stage III NSCLC patients.

Conclusion/Take Home Points

- Clinically relevant: Yes.
- Immediately practice changing: May be in the near future.
- Impact on cost of care & short and long term side effects: Significant.

The Antigen: Ideal Characteristics for ADCs



Desai A et al. Lung Cancer. 2022

Conclusions/take-away

- ADCs represent a novel strategy to treat lung cancer
- Potential future applications in NSCLC management (randomized phase 3 trials ongoing)
  - Monotherapy in 2L (after chemotherapy and immunotherapy)
  - Management of acquired resistance to TKI in specific molecular subsets
  - In combination with immunotherapy in 1L
- Knowledge of potential AEs may help to promote early and effective interventions
  - Various AEs observed with a diversity of ADCs since antibodies and cytotoxic drugs differ
  - Clinical toxicities of ADCs include hematologic, hepatic, GI, neurologic, pulmonary, and ophthalmic AEs, and moderate levels of alopecia
  - ILD has emerged as a relevant toxicity for multiple ADCs
  - Focus on proactive diagnosis, monitoring and management is essential
- Improved predictive biomarkers are needed

Varia

2023 ASCO ANNUAL MEETING

DESTINY-PanTumor02

Efficacy and safety of trastuzumab deruxtecan in patients with HER2-expressing solid tumors: DESTINY-PanTumor02 interim results

Funda Meric-Bernstam

The University of Texas MD Anderson Cancer Center, Houston, TX, USA

June 5, 2023

Additional authors: Vicky Makker, Ana Oaknin, Do-Youn Oh, Susana Banerjee, Antonio González-Martín, Kyung Hae Jung, Iwona Ługowska, Luis Manso, Aránzazu Manzano, Bohuslav Melichar, Salvatore Siena, Daniil Stroyakovskiy, Chiedozie Anoka, Yan Ma, Soham Puvvada, Jung-Yun Lee

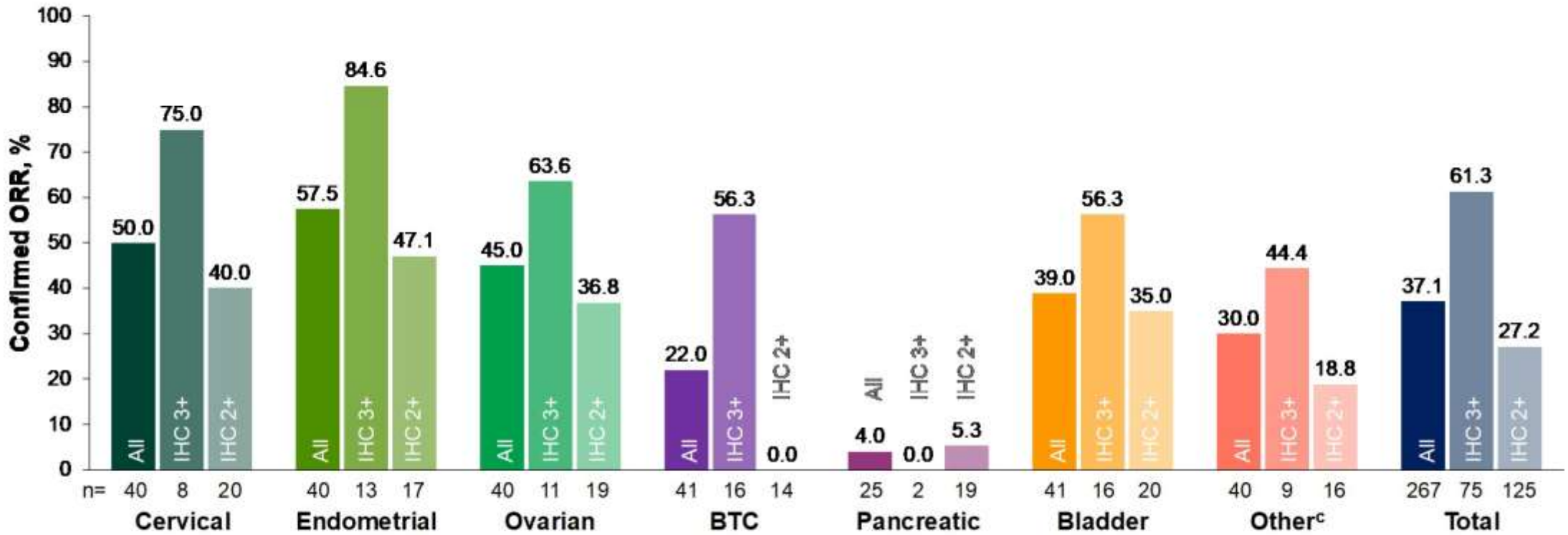
On behalf of the DESTINY-PanTumor02 investigators

Efficacy endpoints: ORR, DCR and DOR

		Cervical (n=40)	Endometrial (n=40)	Ovarian (n=40)	BTC (n=41)	Pancreatic (n=25)	Bladder (n=41)	Other (n=40)	All patients (N=267)
Investigator assessment									
ORR, n (%)		20 (50.0)	23 (57.5)	18 (45.0)	9 (22.0)	1 (4.0)	16 (39.0)	12 (30.0)	99 (37.1)
Best overall response, n (%)	Complete response	2 (5.0)	7 (17.5)	4 (10.0)	1 (2.4)	0	1 (2.4)	0	15 (5.6)
	Partial response	18 (45.0)	16 (40.0)	14 (35.0)	8 (19.5)	1 (4.0)	15 (36.6)	12 (30.0)	84 (31.5)
	Stable disease	11 (27.5)	12 (30.0)	13 (32.5)	23 (56.1)	16 (64.0)	16 (39.0)	20 (50.0)	111 (41.6)
	Progressive disease	7 (17.5)	4 (10.0)	7 (17.5)	7 (17.1)	7 (28.0)	7 (17.1)	3 (7.5)	42 (15.7)
	Not evaluable	1 (2.5)	0	1 (2.5)	0	0	0	1 (2.5)	3 (1.1)
DCR[a], n (%)		27 (67.5)	32 (80.0)	28 (70.0)	27 (65.9)	9 (36.0)	29 (70.7)	30 (75.0)	182 (68.2)
Median DOR, months (95% CI)		9.8 (4.2–NE)	NR (9.9–NE)	11.3 (4.1–NE)	8.6 (2.1–NE)	NR	8.7 (4.3–11.8)	NR (4.1–NE)	11.8 (9.8–NE)
Independent central review: ORR, n (%)		16 (40.0)	21 (52.5)	17 (42.5)	11 (26.8)	3 (12.0)	17 (41.5)	13 (32.5)	98 (36.7)

Analysis of response and DCR was performed in patients who received ≥1 dose of T-DXd (n=267). Analysis of DOR was performed in patients with objective response who received ≥1 dose of T-DXd (n=99).
[a]Confirmed complete response, confirmed partial response or stable disease at or after 11 weeks.
BTC, biliary tract cancer; CI, confidence interval; DCR, disease control rate; DOR, duration of response; ICR, independent central review; NE, not estimable; NR, not reached; ORR, objective response rate.

Objective Response Rate by HER2 status



	All patients (N=99)	IHC 3+ (n=46)	IHC 2+ (n=34)
Median DOR, months (95% CI)	11.8 (9.8–NE)	22.1 (9.3–NE)	9.8 (4.2–12.6)

Analysis of ORR was performed in patients who received ≥1 dose of T-DXd; all patients (n=267; including 67 patients with IHC 1+ [n=25], IHC 0 [n=30], or unknown IHC status [n=12] by central testing) and patients with centrally confirmed HER2 IHC 3+ (n=75) or IHC 2+ (n=125) status. Analysis of DOR was performed in patients with objective response who received ≥1 dose of T-DXd; all patients (n=99; including 19 patients with IHC 1+ [n=6], IHC 0 [n=9], or unknown IHC status [n=4] by central testing) and patients with centrally confirmed HER2 IHC 3+ (n=46) or IHC 2+ (n=34) status. [a]Responses in extramammary Paget's disease, head and neck cancer, oropharyngeal neoplasm, and salivary gland cancer.
BTC, biliary tract cancer; CI, confidence interval; DOR, duration of response; IHC, immunohistochemistry; NE, non-estimable; ORR, objective response rate.

PRESENTED BY: Funda Meric-Bernstam, MD

Conclusions

- T-DXd demonstrated clinically meaningful activity across a broad range of HER2-expressing solid tumors, including those that are hard to treat:
  - Encouraging ORR: 37.1% in all patients and 61.3% in patients with IHC 3+
  - Durable responses: median DOR 11.8 months in all patients and 22.1 months in patients with IHC 3+
- This trial is ongoing; OS and PFS will be analyzed with additional follow-up
- The safety profile of T-DXd was consistent with the known profile
- DESTINY-PanTumor02 shows T-DXd to be a potential new treatment option for patients with HER2-expressing solid tumors

DOR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan.

2023 ASCO ANNUAL MEETING

Structural Sexism and Cancer Care: The Effects on the Patient and Oncologist

Defining Structural Sexism in Oncology

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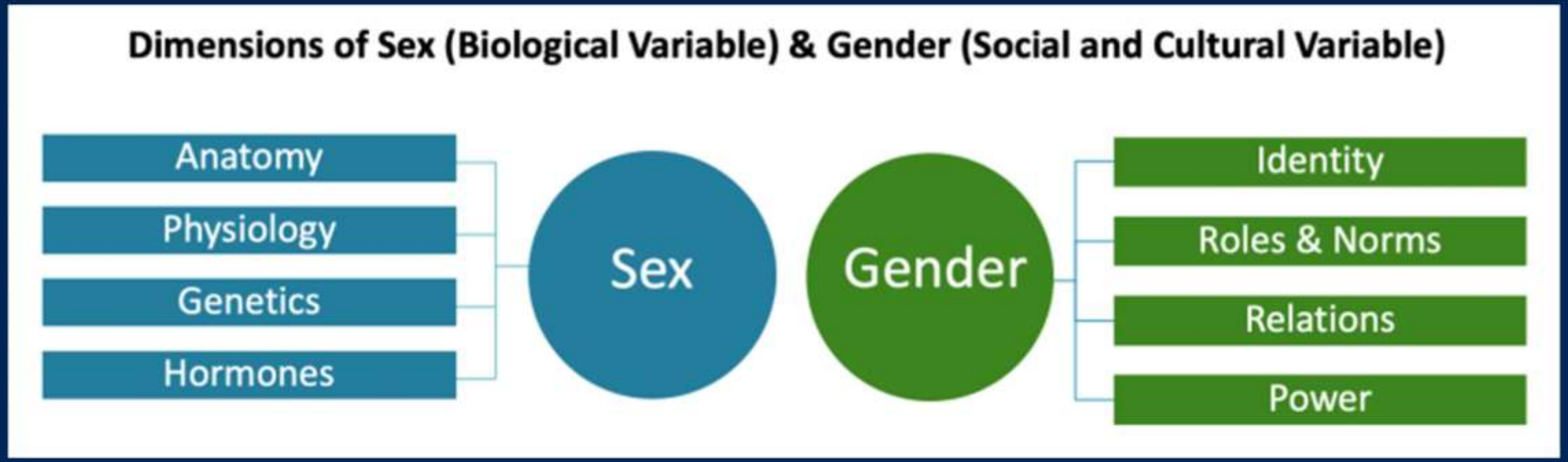
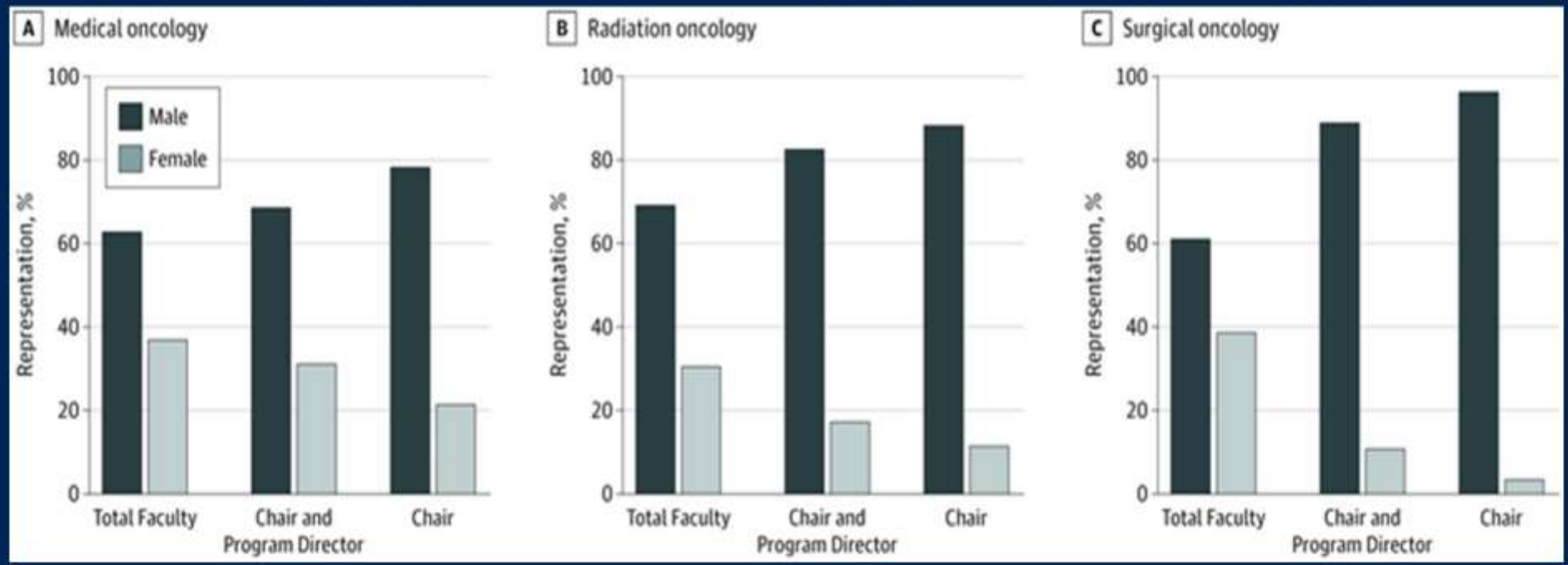
Sex versus gender:



NIH, Office of Research on Women's Health, https://orwh.od.nih.gov/sex-gender

Women are under-represented in oncology leadership roles



Chowdhary et al, 2020, *JAMA Netw Open*

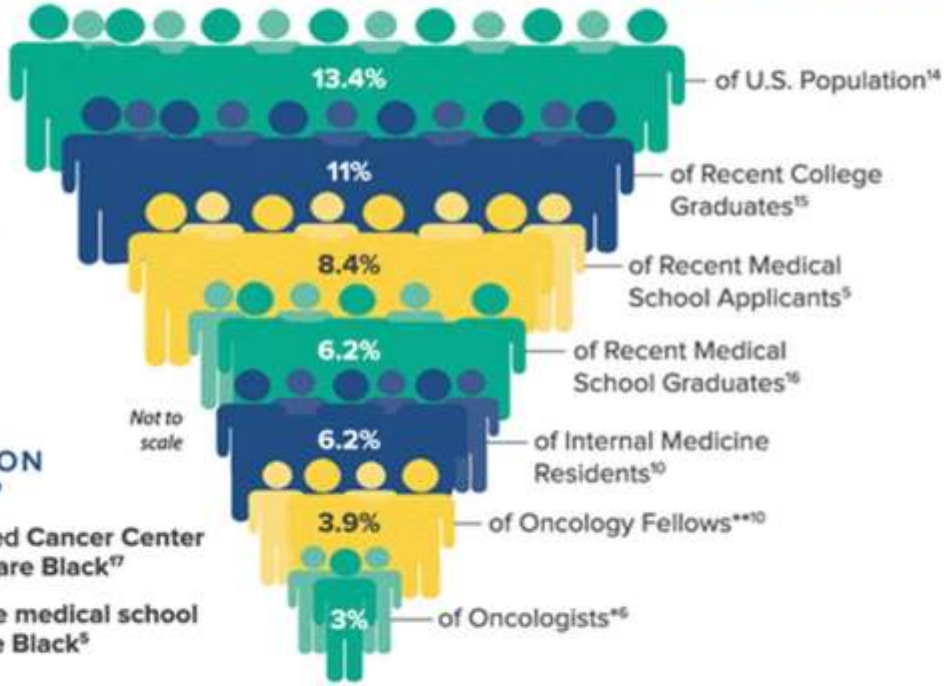
Women with intersectional identities are further under-represented in the oncology workforce

IN FOCUS

Black Representation in the Oncology Workforce

People who are Black comprise:

At each step towards becoming an oncologist, the percentage of Black participants decreases.



REPRESENTATION IN LEADERSHIP

1.2% of Surveyed Cancer Center Directors are Black[17]

3.6% of full-time medical school faculty are Black[5]

JCO Oncology Practice, 2021

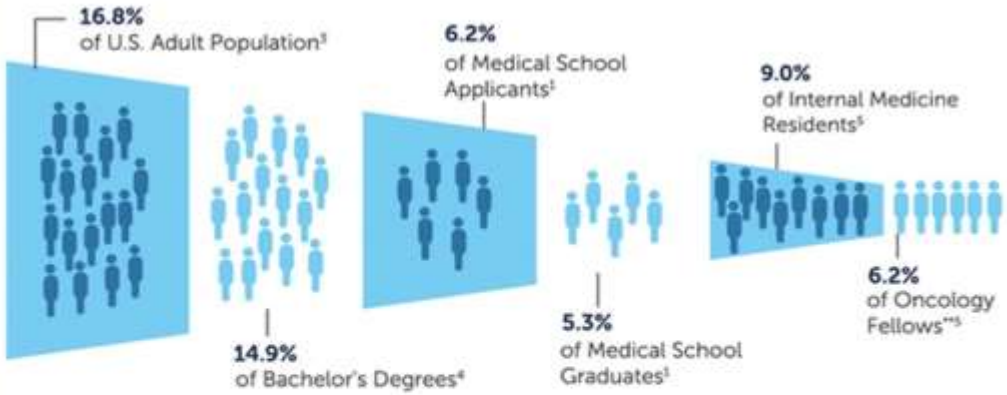
IN FOCUS

Hispanic/Latinx Oncologists and Patients

People who identify as Hispanic or Latinx comprise:

Only 4.7% of U.S. oncologists **vs. 9.3%** of new cancer cases[10,11]

Hispanic/Latinx participation decreases at nearly every step in the path to becoming an oncologist.



JCO Oncology Practice, 2022