GS 05-6

U.S. Food and Drug Administration pooled analysis of outcomes of older women with hormone-receptor positive metastatic breast cancer treated with a CDK4/6 inhibitor as initial endocrine based therapy

Harpreet Singh, Lynn Howie, Erik Bloomquist, Suparna Wedam, Laleh Amiri-Kordestani, Shenghui Tang, Rajeshwari Sridhara, Amna Ibrahim, Kirsten Goldberg, Amy McKee, Julia A. Beaver, Richard Pazdur

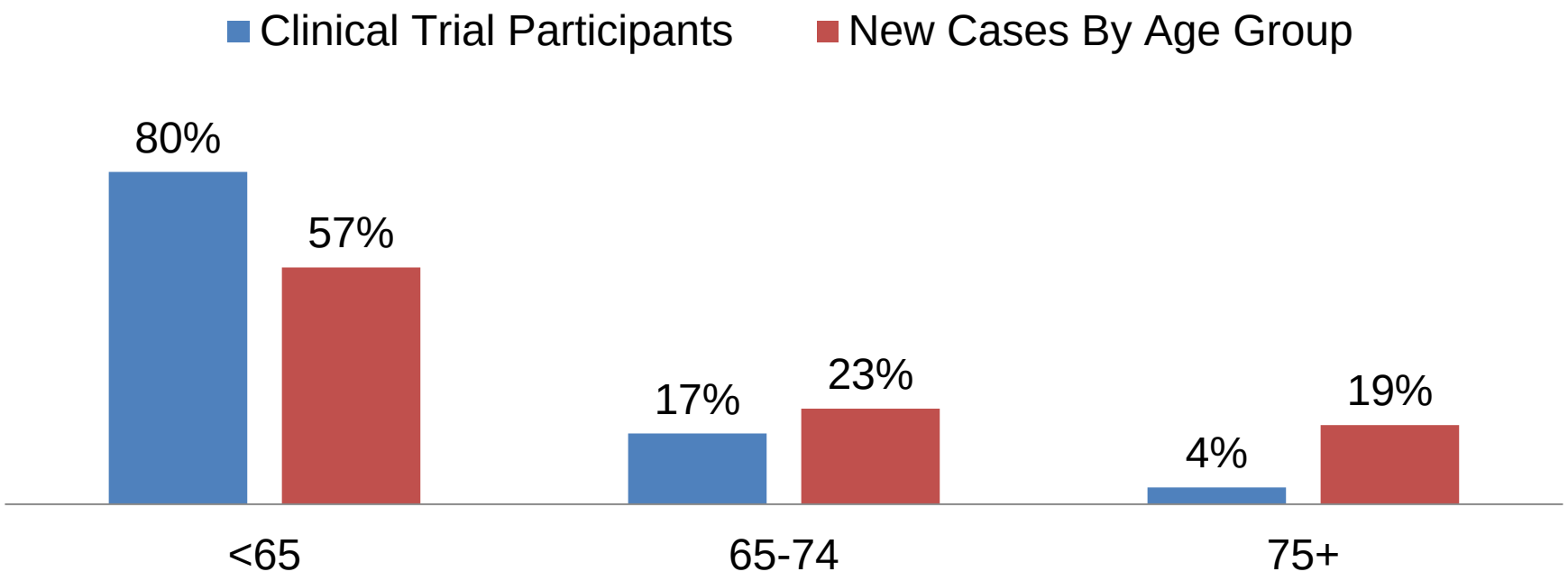
Office of Hematology and Oncology Products
U.S. Food and Drug Administration

Breast Cancer Background

- 72,000 breast cancers occur annually in US women ≥70
- Over 40% of breast cancer related deaths are in women ≥ 70[2]
- Older patients historically underrepresented in breast cancer clinical trials, particularly those ≥70 years old[3]

1. SEER Cancer Statistics, 2016
2. American Cancer Society Breast Cancer Fact and Figures, 2017
3. Freedman et al, Journal of clinical Oncology

Older Adults with Breast Cancer Enrolled on FDA Registration Trials Compared with New Cases by Age Group



FDA Registration Trials 2005-2015
SEER 18 2010-2014, All Races, Females

CDK4/6 Inhibitors in Breast Cancer

Indicated in combination with an aromatase inhibitor

- as initial endocrine based therapy for the treatment of postmenopausal women with HR positive, HER2 negative advanced or metastatic breast cancer
- disease progression following endocrine therapy

Limited data on safety and efficacy of these agents in older adults

Methods

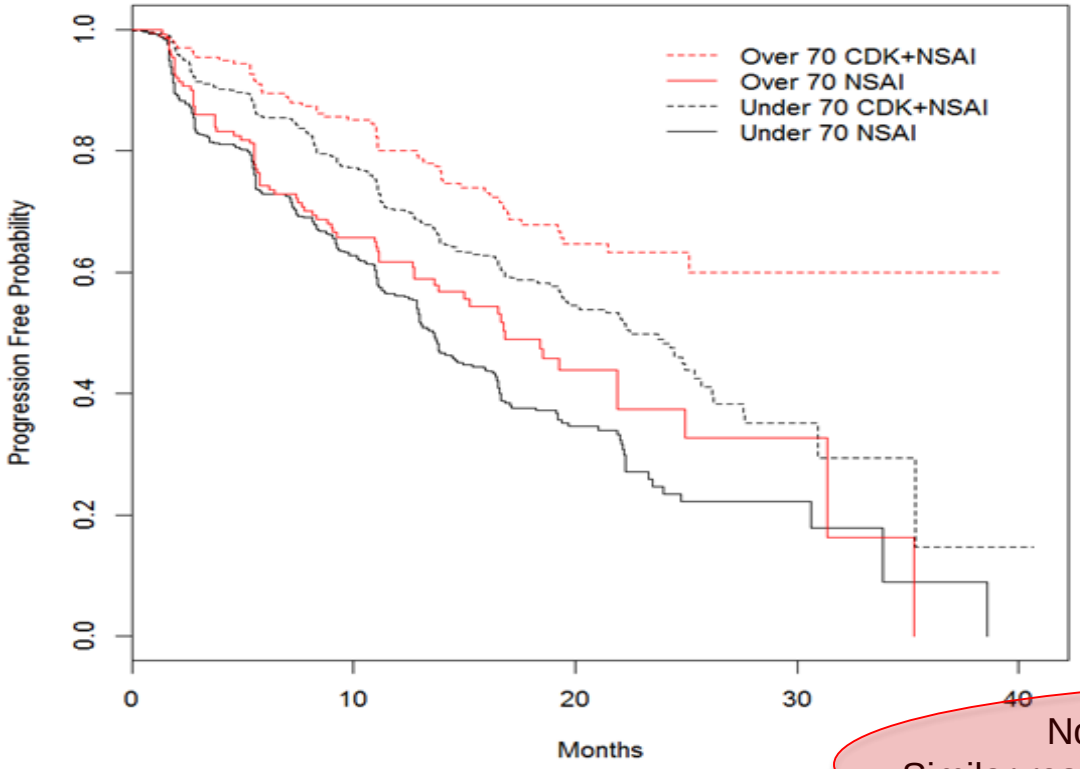
Pooled retrospective subgroup analysis

- Eligible patients
  - Enrolled on registration trials submitted to FDA for CDK 4/6 inhibitors in combination with an aromatase inhibitor for initial endocrine based therapy for advanced or metastatic breast cancer
  - Efficacy Population: ITT population (n=1992)
  - PFS evaluated in patients age ≥ 70 in treatment and control groups

Baseline Characteristics

	Age <65 N=716	Age ≥65 N=555	Age ≥70 N=329
ECOG			
0	446 (62)	299 (54)	162 (49)
1	264 (37)	253 (46)	164 (50)
2	6 (1)	3 (1)	3 (1)
Site of Disease			
Visceral	349 (49)	265 (48)	141 (43)
Bone Only	162 (23)	120 (22)	95 (29)
Prior therapy			
(Neo)Adjuvant chemotherapy	335 (47)	163 (29)	74 (22)
(Neo)Adjuvant endocrine therapy	342 (54)	224 (40)	126 (38)
Initial Stage			
Stage IV	292 (41)	267 (48)	171 (52)

Efficacy of CDK4/6 Inhibitors in Patients ≥ 70



	Median PFS (95% CI)
Age≥70 CDK4/6 (n=280)	NR (25.1 months, NR)
Age <70 CDK4/6 (n=826)	23.75 months (21.9, 25.4)
Age ≥70 AI only	16.8 months (13.7, 21.9)
Age <70 AI only	13.8 months (12.9, 14.7)

HR 0.54 95% CI (0.47, 0.62)

No treatment difference across age subgroups.
Similar results with alternate age cut offs (>65, >75, etc)

Safety and Tolerability

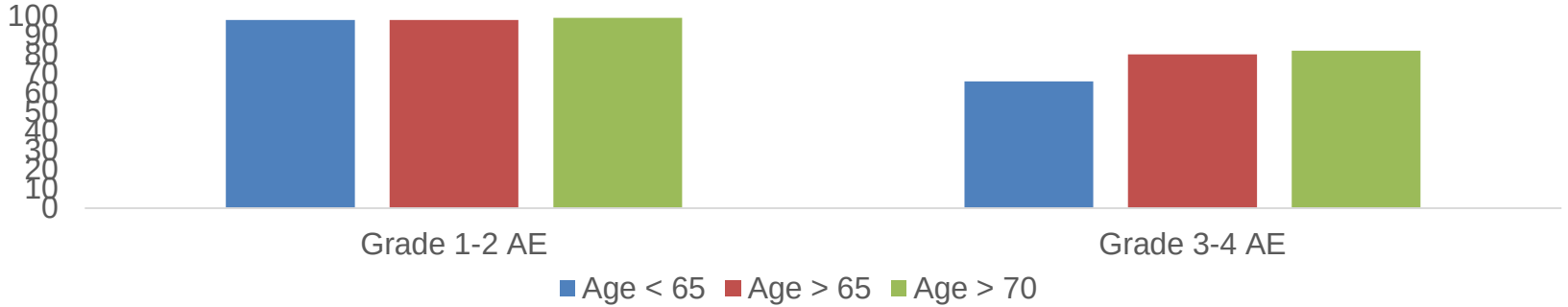
– Safety Population: Received at least one dose of CDK 4/6 inhibitor

	Age<65	Age ≥ 65	Age ≥ 70	Age ≥ 75	Age ≥ 80	Age ≥ 85
OVERALL (n=1106)	627 (57)	479 (43)	280 (25)	125 (11)	48 (4)	13 (1)

– AE's occurred up to 30 days after last dose
  - Severity (AE Toxicity Grade 1-5)
  - Serious Adverse Events
  - AE's leading to Dose Interruption, Reduction, Discontinuation
  - Selected Adverse Events (neutropenia, infection, hepatoxicity, fatigue, diarrhea)

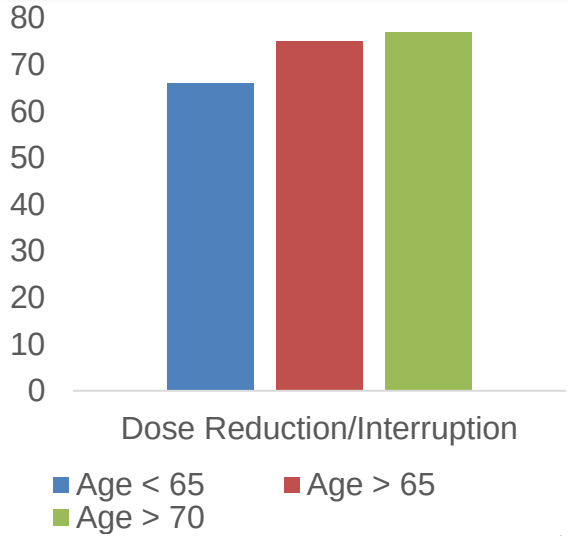
Pooled Adverse Events: Severity

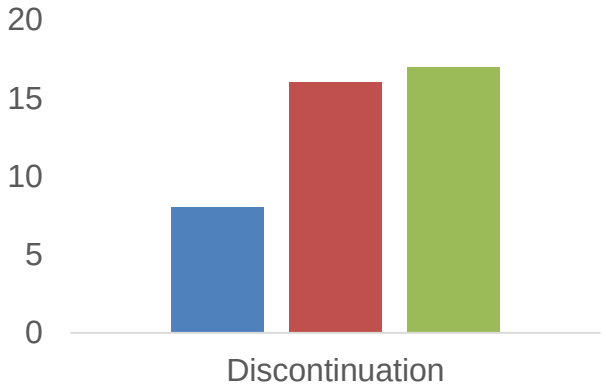
	Age < 65 years N = 625 (%)	Age ≥ 65 years N = 479(%)	Age ≥ 70 years N = 280 (%)
Grade 1-2 Adverse Events	610 (98)	470 (98)	277 (99)
Grade 3-4 Adverse Events	417 (66)	385 (80)	229 (82)
Grade 5 Adverse Events	7 (1)	11 (2)	8 (3)

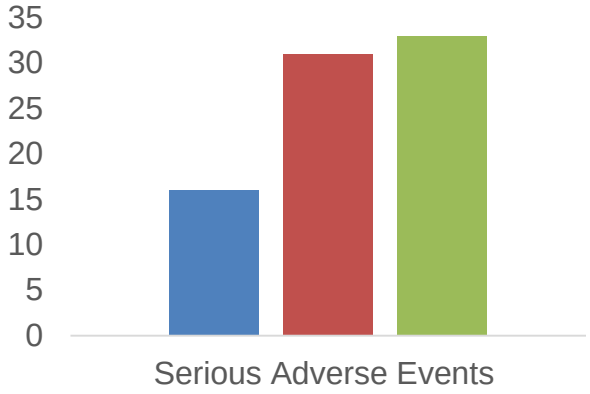


Pooled Adverse Events: Tolerability

	Age < 65 years N = 625 (%)	Age ≥ 65 years N = 479 (%)	Age ≥ 70 years N = 280 (%)
AE leading to dose reduction and/or interruption	411 (66)	360 (75)	216 (77)
AE leading to discontinuation	50 (8)	76 (16)	48 (17)
Serious Adverse Events	103 (16)	147 (31)	93 (33)







Selected Adverse Events

	Age <65 yrs N= 625 (%)	Age ≥ 65 yrs N= 479 (%)	Age ≥ 70 yrs N= 280 (%)
Neutropenia			
All Grades	414 (66)	318 (66)	184 (66)
Grade 3-4	326 (52)	263 (55)	155 (55)
Infections			
All Grades	258 (41)	230 (48)	139 (50)
Hepatotoxicity			
All Grades	115 (18)	78 (16)	51 (18)
Grade 3-4	43 (7)	29 (6)	20 (7)
Fatigue			
All Grades	258 (41)	221 (46)	133 (48)
Grade 3	14 (2)	14 (3)	10 (4)
Diarrhea			
All Grades	201 (32)	235 (49)	142 (51)
Grade 3	18 (3)	23 (5)	14 (5)

Conclusions

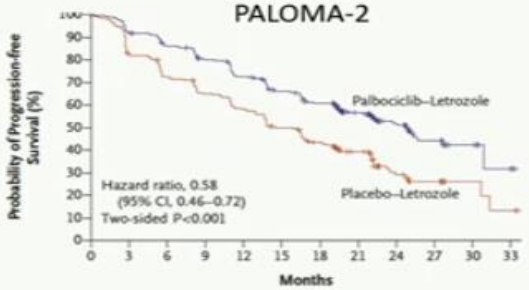
- Older patients with breast cancer benefit from treatment with CDK4/6 inhibitors as initial endocrine based therapy for HR positive, HER2 negative, metastatic breast cancer
- Severity of adverse events and rates of dose modifications and interruptions higher in ≥65, ≥70
- Rates of selected adverse events similar across pooled trials

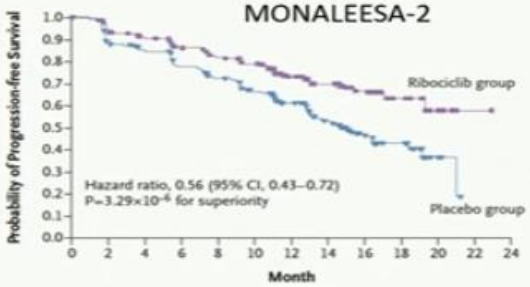
Study Limitations

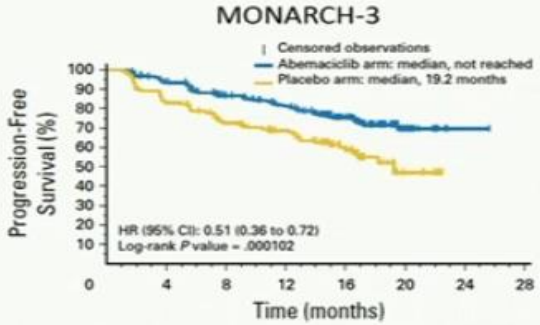
- Pooled analysis of toxicity; drugs with similar but distinct safety profiles
- Few patients in older age groups (75+)
- Older patients on clinical trials not representative of those seen in practice
- Uptake of assessment tools to identify and characterize patients

De quem estamos falando?

CDK4/6 inhibitors improve outcomes for patients with ER+ breast cancer







Finn et al *NEJM* 2016; Hortobagyi et al *NEJM* 2016; Goetz et al *JCO* 2017

Como usar iCDK4/6 na prática?

- Idade não deve ser fator limitante
- Hemograma no D15 ? Avaliação clínica mensal
- Checar interações medicamentosas!!!

INIBIDORES DE CYP3A

- Podem aumentar a concentração plasmática de IBRANCE

EVITAR INIBIDORES FORTES DE CYP3A

Alguns exemplos incluem:

claritromicina
indinavir
itraconazol
cetoconazol
lopinavir/ritonavir
nefazodona
nelfinavir
posaconazol
ritonavir
saquinavir
telaprevir
telitromicina
voriconazol
toranja
suco de toranja

INDUTORES CYP3A

- Podem reduzir as concentrações plasmáticas de IBRANCE

EVITAR INDUTORES FORTES DE CYP3A

Alguns exemplos incluem:

carbamazepina
enzalutamida
fenitoína
rifampicina
erva-de-são-joão

SUBSTRATOS DE CYP3A

- IBRANCE pode aumentar concentrações de midazolam

DOSE PODE PRECISAR SER REDUZIDA