# Representation and Outcomes of Older Adults in Practice-Changing Oncology Trials in the Era of Novel Therapies: A Guideline Appraisal

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## ABSTRACT

**Background:** Older adults account for 70% of cancer-related deaths, but previous studies have shown that they are underrepresented in cancer clinical trials. We sought to analyze the representation and outcomes of older adults in trials conducted in the era of novel targeted therapy and immunotherapy. **Methods:** We searched the 2020 NCCN Clinical Practice Guidelines in Oncology and retrieved trials from the past 10 years leading to category 1 recommendations in the first-line metastatic setting for the 5 most common causes of cancer death. We categorized trials by cancer type, single-agent versus multiagent approach, and therapeutic class. We described the percentage of older adults (according to each trial's definition) and used a Mantel-Haenszel random-effects meta-analysis model to compare overall and progression-free survival by age. **Results:** We identified 30 trials consisting of 24,416 patients. Across all trials, 44% of enrolled patients were older adults. Representation of older adults by cancer type within trials was 49% prostate cancer, 38% pancreatic cancer, 37% breast cancer, and 34% non–small cell lung cancer. Representation of older adults also varied by therapeutic class: 20% received immunotherapy, 44% received cytotoxic chemotherapy, 54% received targeted/hormonal therapy, and 34% received combination therapy ($P<.001$ for all comparisons). For each year since 2010, the percentage of older adults enrolled in trials increased by 1.9%, although this difference was not significant. We observed no difference in overall or progression-free survival between older and younger adults. In our analysis of practice-changing clinical trials, we found that 44% of clinical trial participants were older adults. Trials that included immunotherapy or a combination of therapeutic classes had a lower representation of older adults (<40%). **Conclusions:** We found that >40% of patients in practice-changing trials are older adults. Although they remain underrepresented in clinical trials compared with the general population, older adults in practice-changing trials seem to be better represented than in previously reported analyses of cooperative group trials.

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## Background

Older adults account for approximately 60% of cancer diagnoses and 70% of cancer-related deaths annually, but previous studies have shown underrepresentation of older patients in cancer clinical trials.[1–5] These studies have shown that older adults represent less than one-third of cancer clinical trial participants. Moreover, according to a recent meta-analysis of >150 clinical trials, only between 40% and 70% of clinical trials reported on the outcomes of older adult subgroups.[6]

The lack of older adults in cancer clinical trials, particularly those aged >70 years and/or those with comorbid health conditions, represents a critical problem given that older adults may experience different drug responses and toxicities compared with younger patients due to aging-related physiologic changes.[7,8] Prominent organizations such as the FDA and ASCO have published guidelines urging greater inclusion of older adults in clinical trials.[9–13] Given the rapid changes that have occurred in oncology over the past decade, particularly with the introduction of immune checkpoint inhibitors and targeted therapies into standard oncology practice, many gaps in knowledge remain regarding the use of novel cancer therapeutics in the older adult oncology population.

Despite a robust literature describing the underrepresentation of older adults in cancer clinical trials, to date no published studies exist regarding the representation of older adults in practice-changing cancer clinical trials in the era of targeted therapy and immunotherapy. In the current study, we sought to analyze the representation and outcomes of older adults in pivotal clinical trials in the first-line metastatic setting for the 5 leading causes of cancer death over the past 10 years. We included trials cited in the most recent NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for these cancers as having a category 1 level of evidence, the highest level of evidence upon which an oncologist can base treatment.[14] We sought to explore the representation of older

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adults and the clinical outcomes by age in these practice-changing clinical trials. We hypothesized that the representation of older adults in practice-changing clinical trials would be low overall, consistent with studies of cooperative group trials, and would vary by cancer type, therapeutic class, and single-agent versus multiagent design.

## Methods

### Identification of Practice-Changing Trials

Using the latest NCCN Guidelines for the top 5 leading causes of cancer death[15] (ie, prostate, pancreatic, breast, non–small cell lung [NSCLC], and colon cancer) as of April 30, 2020 (NCCN Guidelines for NSCLC, Version 3.2020[16]; Colon Cancer, Version 2.2020[17]; Pancreatic Adenocarcinoma, Version 1.2019[18]; Breast Cancer, Version 3.2020[19]; and Prostate Cancer, Version 1.2020[20]), we identified trials supporting any category 1 treatment recommendation in the first-line metastatic setting. We then searched the NCCN Guidelines discussion section to determine which articles supported the specific category 1 recommendation. If the NCCN Guidelines cited 2 articles from the same trial to support the same recommendation and reported on the same outcome, then we included only the first article that was published. We excluded trials published before 2010, given our goal to include only the most recent practice-changing trials in the era of novel therapies. This exclusion left no trials in colon cancer meeting our inclusion criteria.

### Data Extraction

Two reviewers (R. Chow, D.E. Lage) independently conducted trial identification and data extraction after a calibration exercise in which the 2 reviewers established a standardized approach to selecting articles based on the above-outlined criteria. When discrepancies occurred, discussion between the 2 reviewers led to a consensus on which trials should be included; if consensus was not achieved, then a third independent reviewer (R.D. Nipp) assisted to reach final consensus.

To structure the data extraction and synthesis, we categorized trials by cancer type and whether the experimental arm involved a single-agent or multiagent approach. We also categorized trials by therapeutic class (ie, chemotherapy, immunotherapy, targeted/hormonal therapy, or a combination of therapeutic classes). We considered trials exploring the addition of an agent to androgen deprivation therapy in prostate cancer as single-agent trials and classified these according to the additional agent's therapeutic class, because all phases of metastatic prostate cancer treatment use androgen deprivation therapy.[20] Metastatic prostate cancer can present as either castration-naïve or castration-resistant, and thus we included first-line trials in both settings.

In reviewing the trials, we recorded any specific age cutoffs for inclusion, performance status (PS) exclusions, any stratification by patient age, and the median age of the investigational arm in each trial. We also captured information regarding the age cutoff for older adults used in the article and adopted that definition of "older adult" in our analyses by age. Finally, we extracted the funding source and trial year from the articles and whether the trials included any quality-of-life or patient-reported outcomes, and if so, whether those analyses were conducted by age subgroups. We also aimed to assess adverse effects by age.

We then extracted overall survival (OS) or progression-free survival (PFS) per trial and any survival outcomes by age subgroup and analyzed them across the 2 arms of each trial. For trials with 3 age groups (n=4), we combined the oldest 2 groups for the purposes of an OS and PFS combined analysis and reported them separately in supplemental eFigures 1–6 (available with this article at JNCCN.org). Where studies did not report on either OS or PFS but seemed to have assessed it, we contacted the corresponding authors to request data. We followed up 1 week later. If no response was received, we excluded the study (n=1).

### Statistical Analyses

We used descriptive statistics to calculate the percentage of older adults in each trial. We used a chi-square test to determine whether the percentage of older adults differed across trials by cancer type, number of investigational agents, and therapeutic class. Post hoc $Z$ tests were used to compare the proportion of older adults represented in trials by therapeutic class and cancer type, and Bonferroni correction was applied to maintain a family-wise type I error rate of 0.05. We applied a weighted linear regression model to investigate the association between the year of publication and the percentage of older adults included in the study sample, weighting studies by sample size. We set the type I error rate at 0.05 and deemed a $P$ value $<.05$ as statistically significant. We conducted these analyses using STATA, version 16.0 (StataCorp LLC).

Using an inverse-variance random-effects meta-analysis model, we generated summary hazard ratios (HRs) and their accompanying 95% confidence intervals to compare interventional to control arms with respect to OS and PFS. We calculated summary HRs to amalgamate study data by cancer site, whether the interventional arm used a single-agent or multiagent approach, and therapeutic class of the interventional agent. We conducted these analyses using Cochrane RevMan, Version 5.4.

## Results

We identified a total of 33 practice-changing articles[21–53] published within the past 10 years (supplemental eTable 1). One article[21] was excluded because it did not report on the representation or outcomes of older adults, and another[22] was excluded because it was merely an updated analysis of another study.[46] Among the remaining 31 articles[23–53] included in this study, 1 reported only on the representation of older adults,[44] whereas the other 30 reported on both representation and outcomes of older adults (Figure 1). The results of 30 trials were detailed in these 31 articles (the MONALEESA-3[28,29] trial had 1 article reporting on PFS and 1 on OS). Ten trials[44–53] reported on prostate cancer, 2 on pancreatic cancer,[42,43] 6 on breast cancer,[23–29] and 12 on NSCLC.[30–41]

Among the 30 trials, a total of 12,204 patients were in prostate cancer trials, 1,203 were in pancreatic cancer trials, 4,068 were in breast cancer trials, and 6,941 were in NSCLC trials. Most trials (n=18; 60%) involved hormonal/targeted therapy. Overall, 25 trials[23,25–41,43–46,49,51,52] were industry-funded, 5[42,47,48,50,53] were funded by both industry and government, and 1[24] was solely funded by the government. Most trials (n=18; 60%) used restrictive PS exclusion criteria, including an ECOG PS of 0 to 1, a WHO PS of 0 to 1, or a Karnofsky PS of 70 to 100.

Twenty-one trials[24–43,51] defined older adults as patients aged ≥65 years, 4[47,48,50,53] defined older adults as aged ≥70 years, and 2[44,46] defined older adults as aged ≥75 years. Four trials[23,45,49,52] divided older adults into 2 groups (ie, ages 65–74 years and ≥75 years). One trial used an upper age limit for inclusion: the PRODIGE trial deemed patients aged ≥76 years to be ineligible for study inclusion.[42] Two trials[33,40] excluded patients with a life expectancy of ≤3 months, and 1 trial[44] excluded patients based on a life expectancy of ≤6 months. Only 3 trials[47,48,50] stratified by age at randomization. No trials focused exclusively on older adults. Fourteen trials[25,26,30–32,35,42,44–46,48,50–52] included measures of patient-reported outcomes or quality of life as part of the study protocol, of which 7[32,35,38,42,44–46] reported the results in the main article; no trial reported these results by age subgroup. No trial reported adverse effects by age subgroup.

### Representation of Older Adults

Across all trials, 44% of enrolled patients were older adults, using the trials' defined age cutoffs. Among prostate cancer trials, 49% of patients were older adults, whereas only 38% of patients in pancreatic cancer trials, 37% of patients in breast cancer trials, and 34% in NSCLC trials were older adults ($P<.001$). In single-agent trials, 45% of patients were older adults, whereas multiagent trials had older adults representing 41% of their sample ($P<.001$). For immunotherapy trials and trials using a combination of therapeutic classes, only 20% and 34% of patients were older adults, respectively. In trials reporting on cytotoxic and hormonal/targeted agents, 44% and 54% of patients were older adults, respectively (Figure 2). The representation of older adults significantly differed in trials by therapeutic class ($P<.001$). For each year since 2010, the percentage of older adults enrolled in trials increased by 1.9% (95% CI, –2.1% to 6.0%). This upward trend was not statistically significant ($P=.335$; Figure 3).

### Overall Survival

Fifteen trials[29,37–39,41–43,45–50,52,53] reported on OS. We present study-level results in supplemental eFigures 1–3. Across all 15 trials, we observed no difference in OS

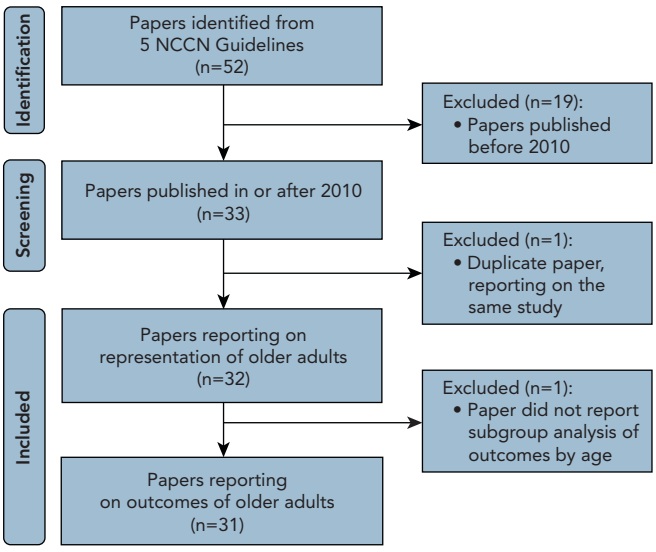


**Figure 1.** Flow diagram of study selection.

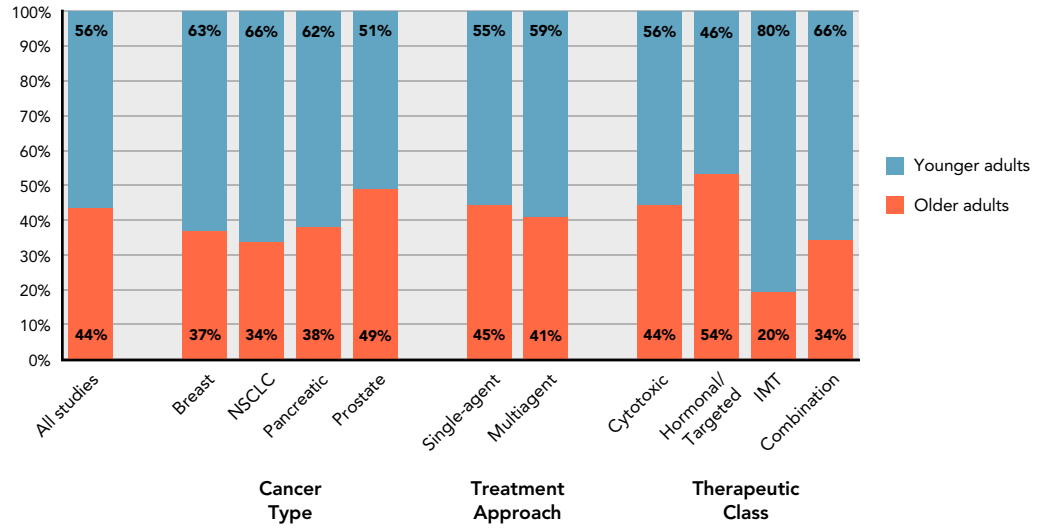


**Figure 2.** Percentage of older adults included in trials.
Abbreviations: IMT, immunotherapy; NSCLC, non–small cell lung cancer.

between older (HR, 0.72; 95% CI, 0.66–0.78) and younger adults (HR, 0.65; 95% CI, 0.59–0.71). The OS between older and younger adults was similar in trials across each cancer type. In addition, we observed a similar OS for older and younger patients in single-agent versus multiagent trials and across all therapeutic classes (Figure 4).

### Progression-Free Survival

Twenty-two trials[23–28,30–36,39,40,43,45,46,49,51–53] reported on PFS. We present study-level results in supplemental eFigures 4–6. We observed no difference in treatment effect on PFS between older (HR, 0.49; 95% CI, 0.43–0.56) and younger adults (HR, 0.52; 95% CI, 0.46–0.59); similar observations were noted for trials by cancer site, single or multidrug interventional agent, and therapeutic class (supplemental eFigure 7).

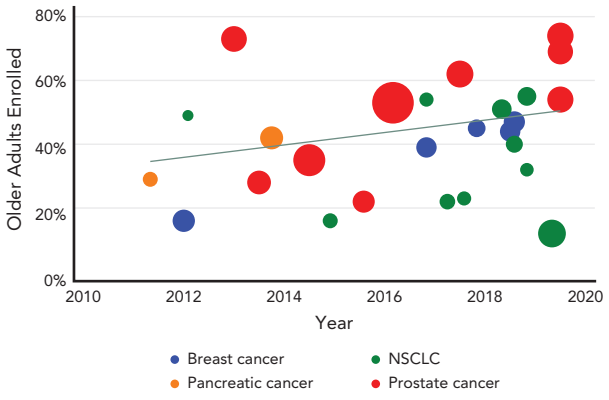


**Figure 3.** Percentage of older adults enrolled in trials, over time.
Abbreviation: NSCLC, non–small cell lung cancer.

## Discussion

In our analysis of practice-changing clinical trials among the 5 most common causes of cancer death, we found that 44% of clinical trial participants were older adults. Trials that included immunotherapy or a combination of therapeutic classes had a lower representation of older adults (<40%). Although almost all trials reported OS or PFS outcomes by age, no trials reported adverse effects or other clinical outcomes by age. Although the representation of older adults varied by cancer type, number of agents, and therapeutic class, the outcomes of older adults included in these clinical trials were generally consistent with those of younger adults.

Prior studies have extensively addressed the reporting of the characteristics and outcomes of older adults,[6,54–59] and in our study we show that the challenges of interpreting trial data specifically for older adults also apply to practice-changing clinical trials. In particular, although almost all studies reported on their primary outcome by age, no studies reported adverse effects by age. A key issue for clinicians making treatment recommendations for older adults is concern about overtreatment and disproportionate toxicities,[60] and therefore information on adverse effect profiles is crucial to making better clinical decisions for older adults. Moreover, few studies reported on quality of life in general, and none reported quality of life by age, although we only reviewed the initial published article cited in the specific NCCN Guideline and not subsequent analyses. A more comprehensive collection and reporting of quality-of-life metrics and variables from geriatric assessments in clinical trials could have particularly important implications for older adults because these

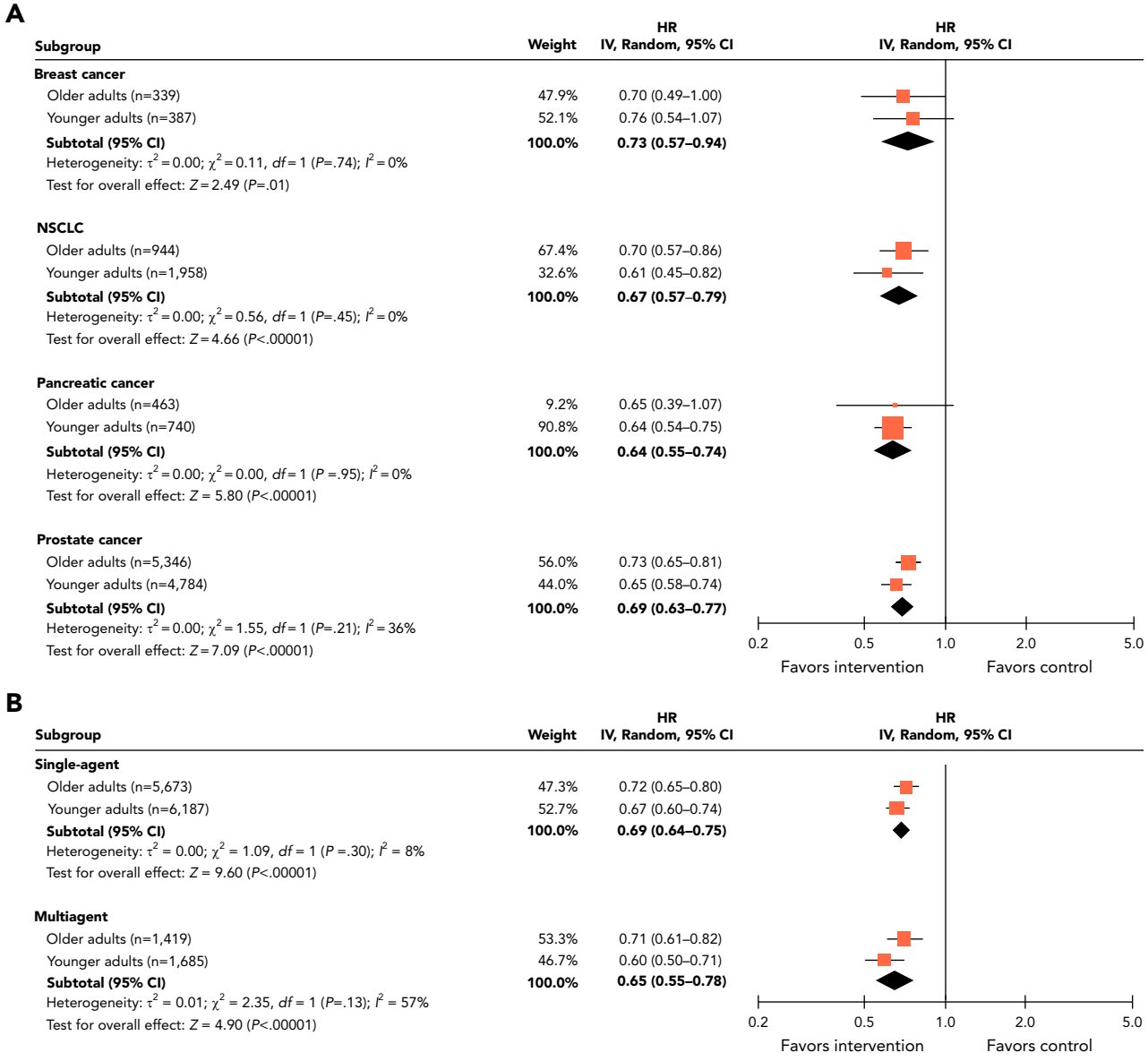


**Figure 4.** Overall survival of older and younger adults by **(A)** cancer site, **(B)** single-drug or multidrug interventional agent, and **(C)** therapeutic class.
Abbreviations: HR, hazard ratio; IV, inverse variance; NSCLC, non–small cell lung cancer.

*(continued on next page)*

individuals frequently face complex tradeoffs between quality and length of life, given the often-competing issues of comorbidities, frailty, and limited social supports.[8,60] In addition, other relevant patient-centered issues to consider assessing in future cancer clinical trials include long-term functional outcomes, financial toxicity, and other patient-reported outcomes.[61,62]

The representation of older adults in practice-changing trials in our study was higher than previously reported for cooperative group trials and other analyses, which have generally reported representation of older adults as being between 25% and 35%.[2,4,6] The trials included in our study, given their practice-changing nature and largely industry-based funding, may have attracted or recruited a different population and may have been more appealing to older adults. They also included a subset of cancer types, compared with cooperative group trials, that may have more prevalence among older adults. Because approximately half of patients diagnosed with cancer are older adults, we would expect a higher proportion of clinical trial enrollment in this population to meet population incidence.[63] Our results are most consistent with an FDA analysis of >200,000 patients enrolled in trials leading to drug approval between 2005 and 2015 that found that 41% of participants

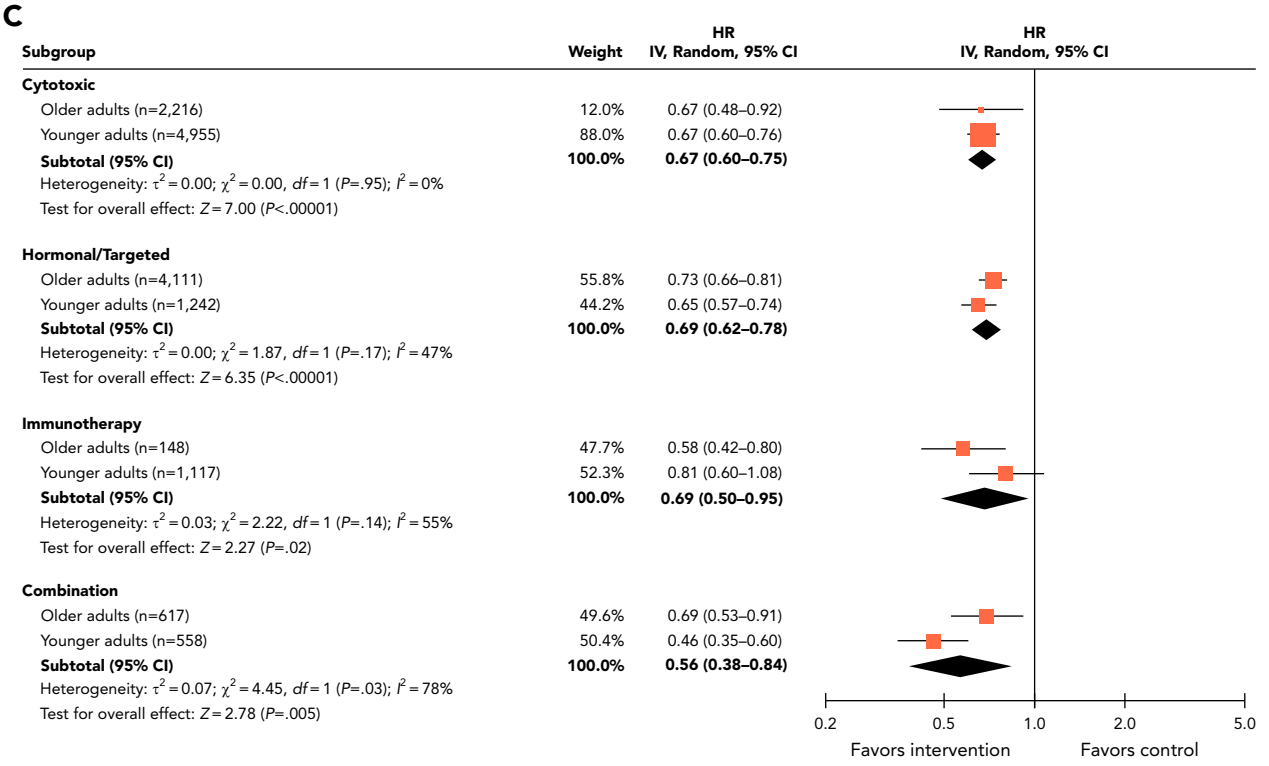


**Figure 4 (cont.).** Overall survival of older and younger adults by **(A)** cancer site, **(B)** single-drug or multidrug interventional agent, and **(C)** therapeutic class.
Abbreviations: HR, hazard ratio; IV, inverse variance; NSCLC, non–small cell lung cancer.

were aged >65 years.[5] The trials included in this FDA study were more similar to our own (ie, major trials leading to drug approvals), as opposed to cooperative group trials that may or may not have led to an approval. This distinction, in addition to limiting our studies to trials published in the past 10 to 15 years, could explain why our 2 studies differ from prior studies.

The novel findings that single-agent trials enrolled more older adults compared with multiagent trials and that trials of hormonal or targeted agents enrolled more older adults than immunotherapy or combination trials could be explained by various factors. Novel therapies may be better tolerated and thus be more attractive to fit older adults who are considering clinical trials. More concerted efforts to recruit older adults in recent years could have also made an impact on representation.[13] However, the fact that many prostate cancer trials, which enrolled higher proportions of older adults, were also single-agent, hormonal/targeted trials may have affected older adult representation in these categories. We could not analyze whether other restrictive criteria affected the representation of older adults, but most studies used strict PS cutoffs (eg, an ECOG cutoff of 0–1), which could effectively exclude older and frail adults. Immunotherapy trials had a lower representation of older adults, possibly because adverse effects of immunotherapy may have been less attractive to older adults or because most immunotherapy trials were in NSCLC, which had a lower representation of older adults. Further studies are needed to understand the factors that clinicians weigh when deciding whether to offer or enroll an older adult in a clinical trial, and also to understand how older adults weigh the decision to pursue a clinical trial, in the era of both novel agents and novel combinations of agents.

Finally, in terms of the clinical outcomes for older adults, we did not find differential outcomes based on age. Indeed, across cancer types, single-agent versus multiagent approaches, and therapeutic class, the results between older and younger adults were consistently favorable. A prior study of cooperative group trials also found that older adults have similarly favorable outcomes compared with younger adults,[3] and our study expands these findings to practice-changing clinical trials in the first-line metastatic setting. Although selection bias likely played an important role given that the outcomes for older adults enrolled in trials have historically not matched those seen in real-world settings,[13] our results provide reassurance that for fit, older

adults eligible for a clinical trial, these novel treatment approaches could prove beneficial to a similar degree as seen in younger adults.

Our study has several limitations. We only included practice-changing trials, representing an inherently biased selection of trials, which could influence our findings. Yet we chose this approach because these trials represent the basis for standard, guideline-recommended first-line treatments in the leading causes of cancer death in the United States. With this approach, we did not intend to present a systematic overview of the state of representation and outcomes of clinical trials with older adults in the past decade, but rather to survey the NCCN Guidelines to understand how their recommendations might apply to older adults. We also could not comment on whether trials with a higher percentage of older adults had better outcomes, given that we selected only positive trials, but we found that among the positive, practice-changing trials, OS and PFS were similar in older and younger patients. We also did not have a common age cutoff for older adults due to variation in age cutoffs as published in the trial manuscripts.

## Conclusions

Among practicing-changing trials in breast, prostate, pancreatic, and non–small cell lung cancer, older adults represented 44% of all patients and had similar outcomes to younger adults. As investigators design clinical trials, increased attention to the barriers faced by older adults when considering clinical trials, careful attention to reporting of results by age, and continued monitoring for differential effects on outcomes by age will be essential to provide the necessary evidence base for oncologists to make informed treatment recommendations for older adults with advanced cancer. The FDA and ASCO continue to advocate for greater enrollment of older adults alongside consistent reporting of results by age,[9–13] and this study shows some progress in representation, but continued challenges with reporting of results. Future studies should explore the barriers to clinical trial enrollment for older adults and adapt strategies to investigate postapproval data in order to understand the impact of novel treatments on this population.

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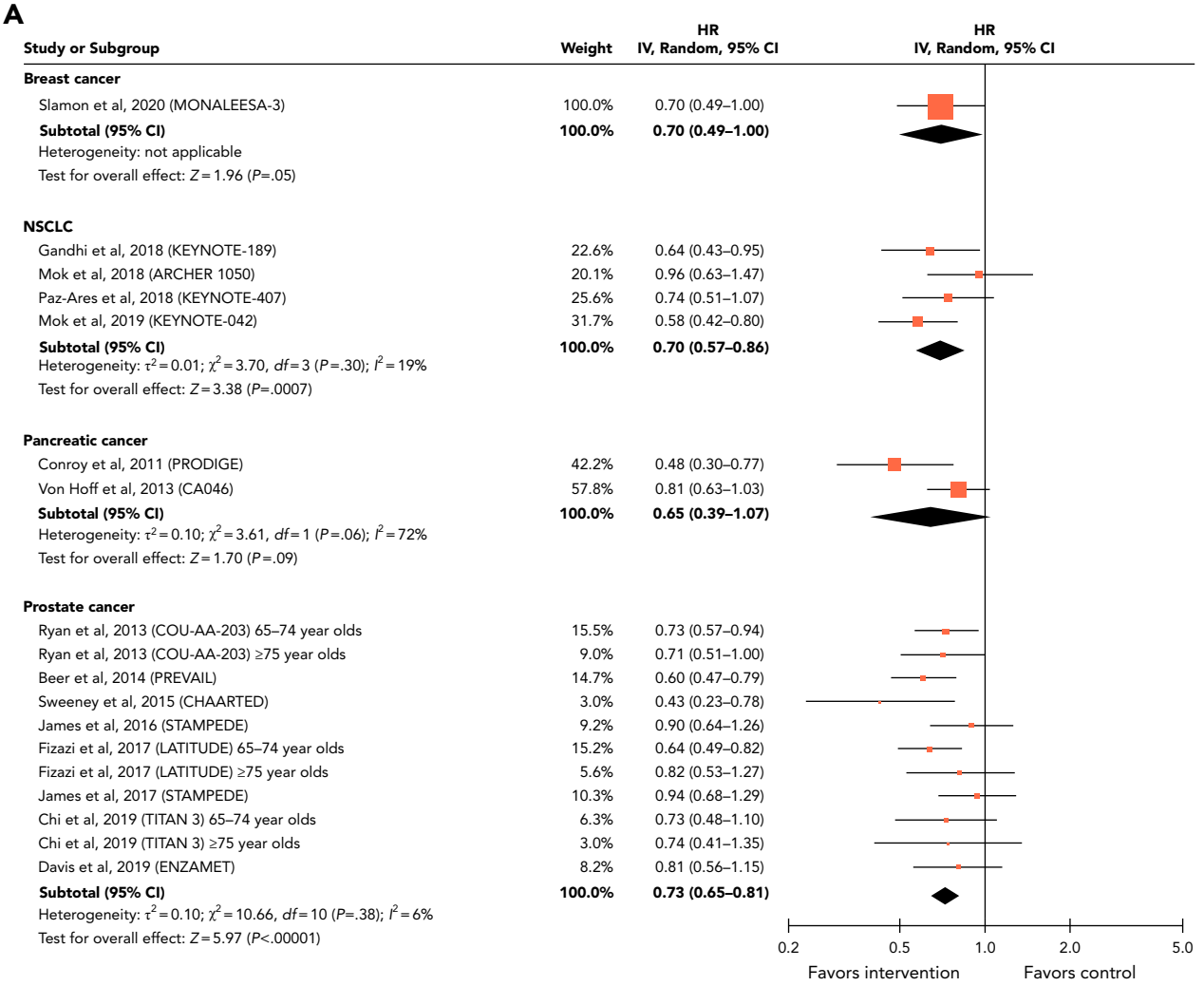
# Representation and Outcomes of Older Adults in Practice-Changing Oncology Trials in the Era of Novel Therapies: A Guideline Appraisal

Ronald Chow, MS; Daniel E. Lage, MD, MSc; Grant R. Williams, MD, MSPH; Mina S. Sedrak, MD, MS; Joseph A. Greer, PhD; Jennifer S. Temel, MD; and Ryan D. Nipp, MD, MPH

*J Natl Compr Canc Netw 2022;20(1):37–44*

**A**




**eFigure 1.** Individual studys' overall survival by cancer site in **(A)** older adults and **(B)** younger adults.
Abbreviations: HR, hazard ratio; IV, inverse variance; NSCLC, non–small cell lung cancer.

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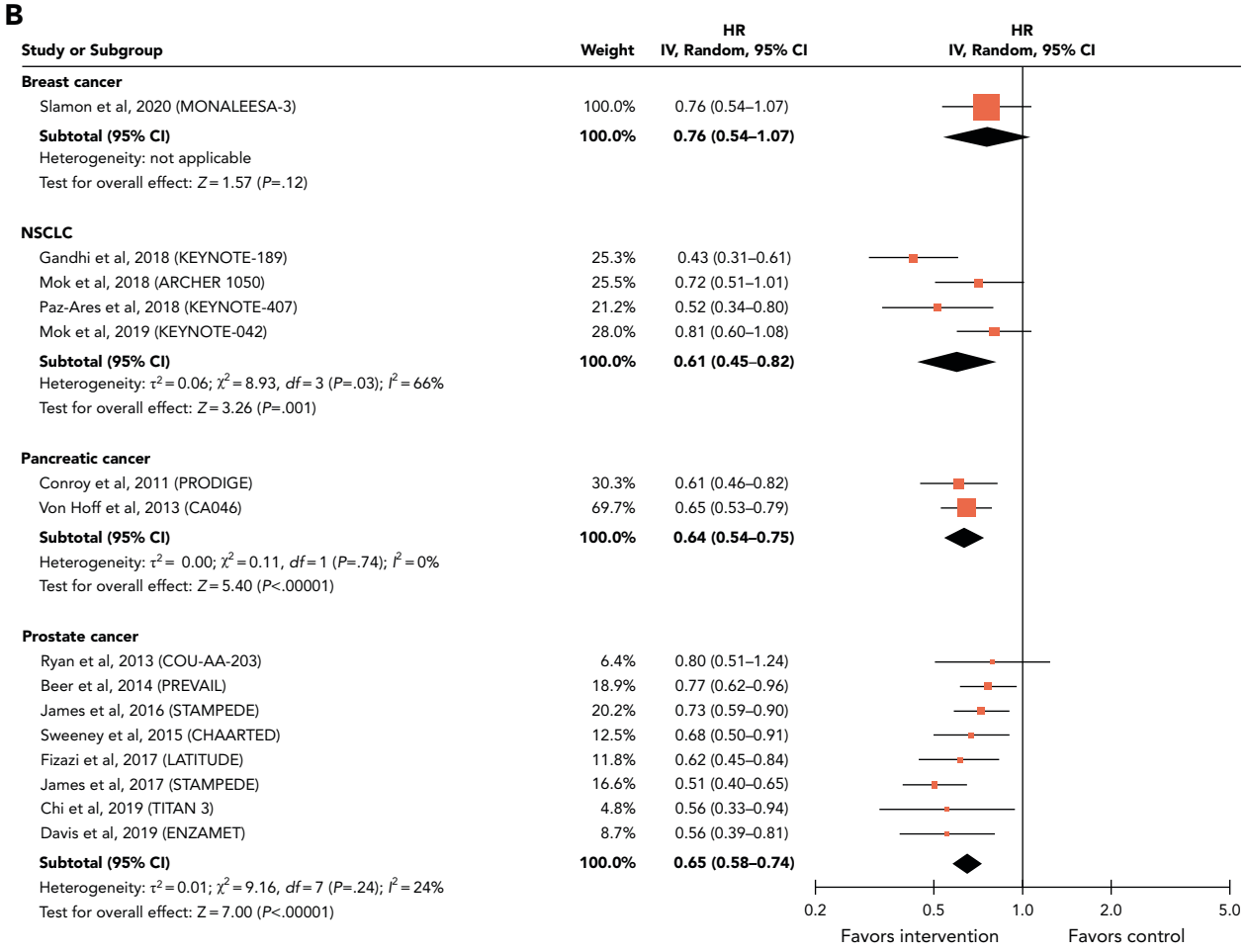
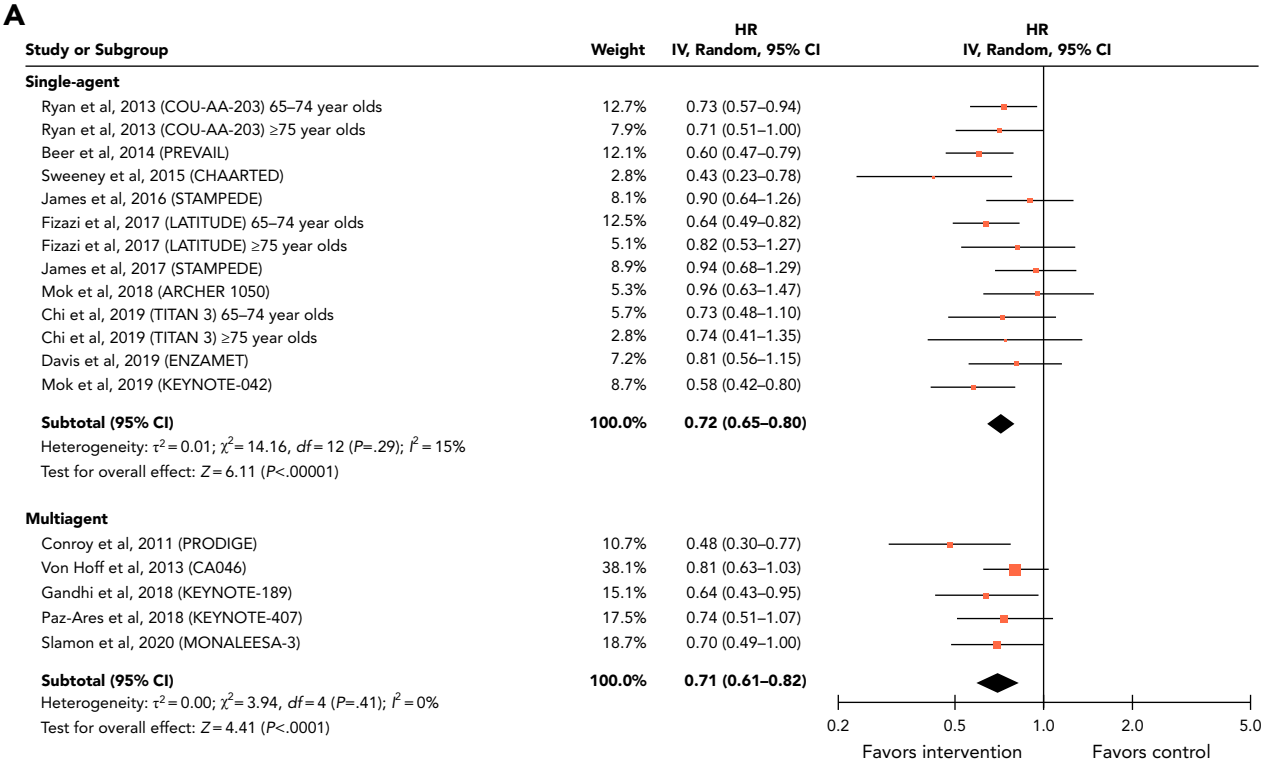
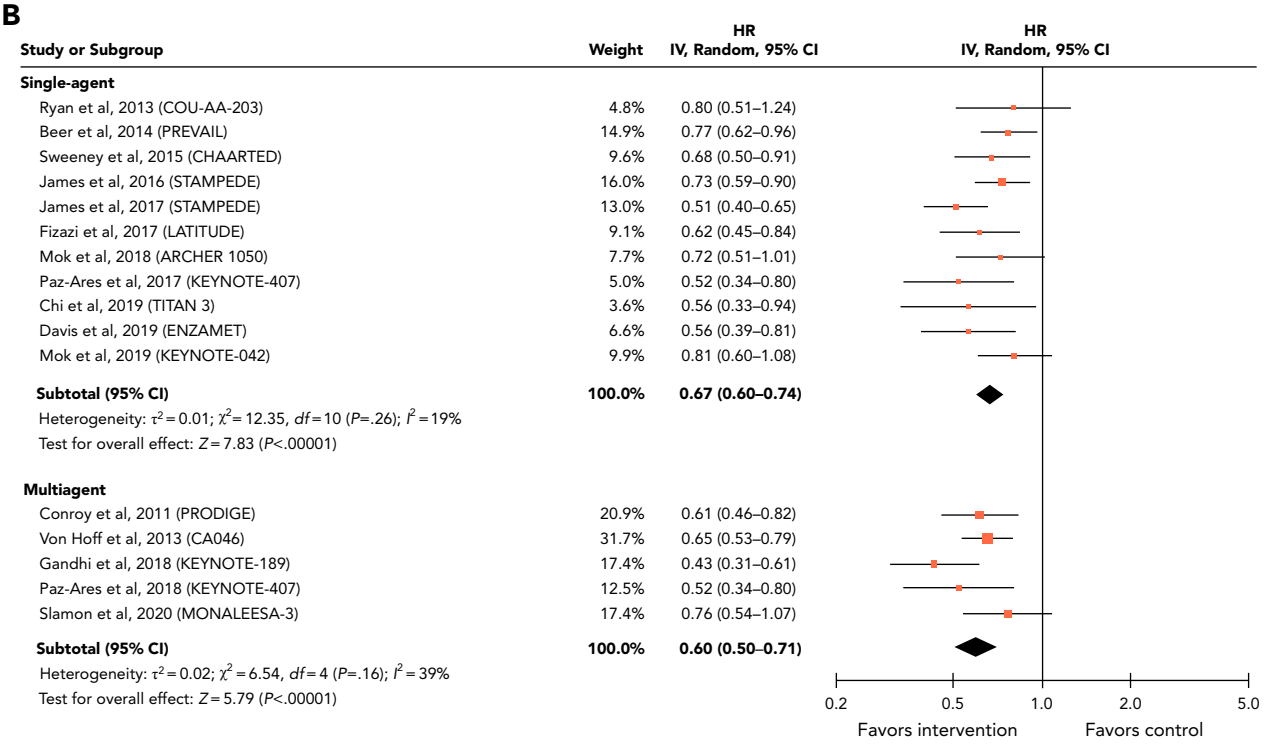



**eFigure 1 (cont.).** Individual studys' overall survival by cancer site in **(A)** older adults and **(B)** younger adults.
Abbreviations: HR, hazard ratio; IV, inverse variance; NSCLC, non–small cell lung cancer.

**A**

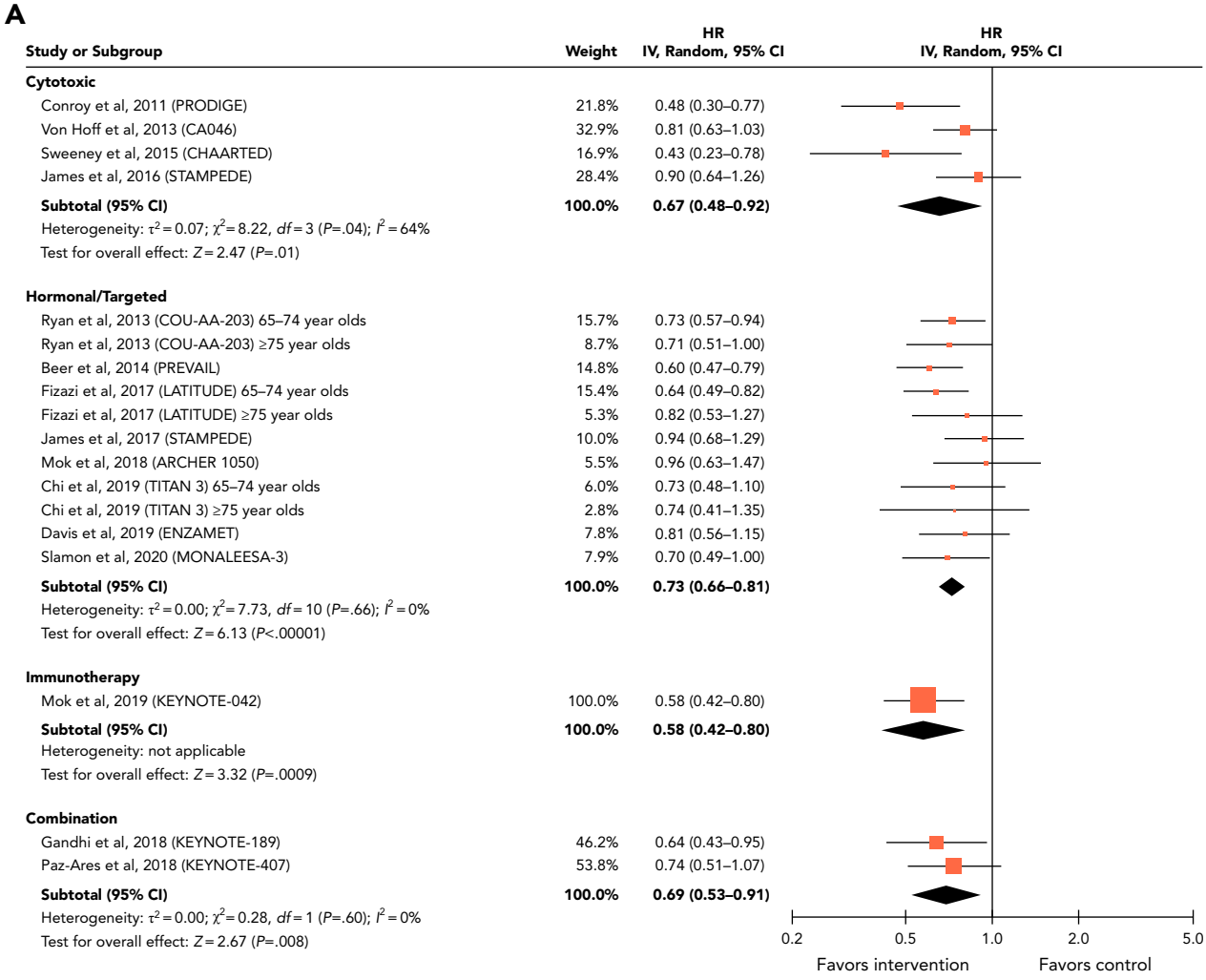



**B**




**eFigure 2.** Individual studys' overall survival by single-drug or multidrug interventional agent in **(A)** older adults and **(B)** younger adults.
Abbreviations: HR, hazard ratio; IV, inverse variance; NSCLC, non–small cell lung cancer.

**A**




**eFigure 3.** Individual studys' overall survival by therapeutic class in **(A)** older adults and **(B)** younger adults.
Abbreviations: HR, hazard ratio; IV, inverse variance; NSCLC, non–small cell lung cancer.

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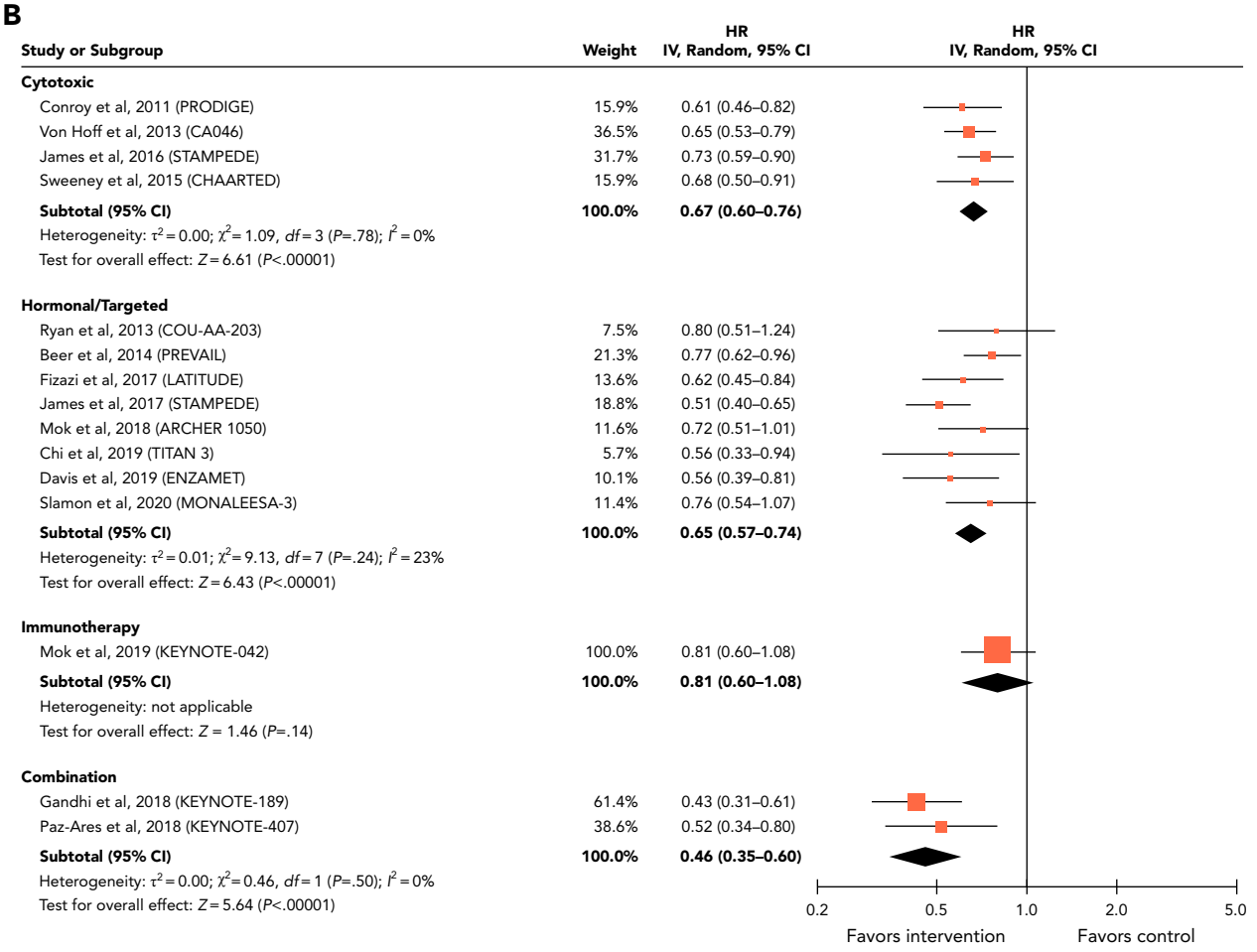
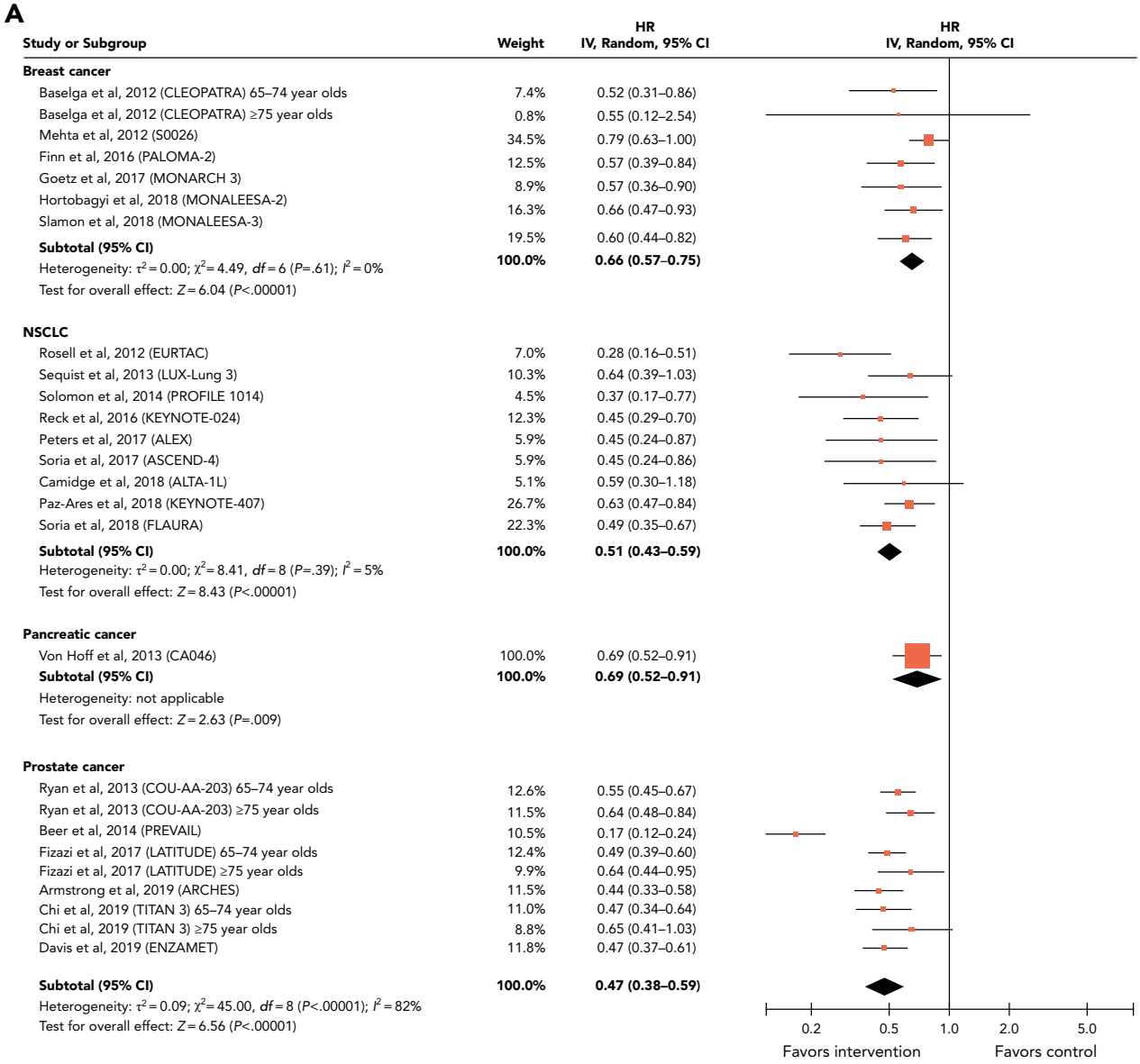
**B**




**eFigure 3 (cont.).** Individual studys' overall survival by therapeutic class in **(A)** older adults and **(B)** younger adults.
Abbreviations: HR, hazard ratio; IV, inverse variance; NSCLC, non–small cell lung cancer.

**A**




**eFigure 4.** Individual studys' progression-free survival by cancer site in **(A)** older adults and **(B)** younger adults.
Abbreviations: HR, hazard ratio; IV, inverse variance; NSCLC, non–small cell lung cancer.

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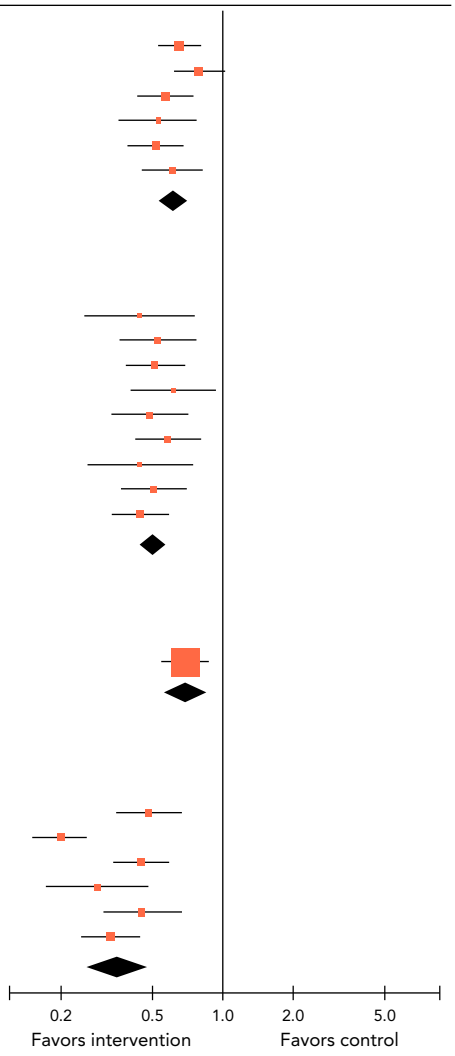
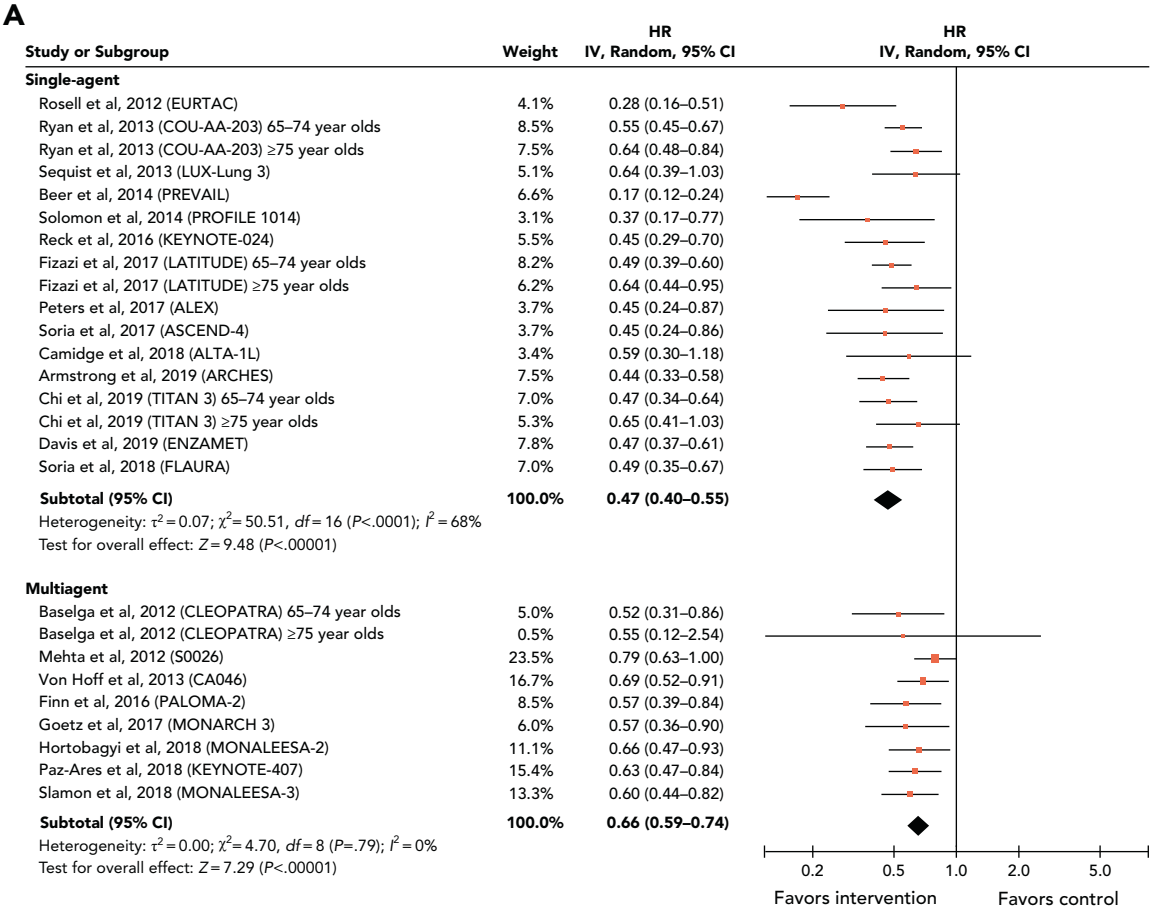
**B**

| Study or Subgroup | Weight | HR IV, Random, 95% CI |
|---|---|---|
| **Breast cancer** | | |
| Baselga et al, 2012 (CLEOPATRA) | 23.6% | 0.65 (0.53–0.80) |
| Mehta et al, 2012 (S0026) | 19.0% | 0.79 (0.62–1.01) |
| Finn et al, 2016 (PALOMA-2) | 16.5% | 0.57 (0.43–0.74) |
| Goetz et al, 2017 (MONARCH 3) | 10.1% | 0.53 (0.37–0.77) |
| Hortobagyi et al, 2018 (MONALEESA-2) | 16.4% | 0.52 (0.39–0.68) |
| Slamon et al, 2018 (MONALEESA-3) | 14.4% | 0.61 (0.45–0.81) |
| **Subtotal (95% CI)** | **100.0%** | **0.62 (0.54–0.70)** |
| Heterogeneity: $\tau^2 = 0.01$; $\chi^2 = 6.89$, $df = 5$ ($P = .23$); $I^2 = 27\%$ | | |
| Test for overall effect: $Z = 7.39$ ($P < .00001$) | | |
| **NSCLC** | | |
| Rosell et al, 2012 (EURTAC) | 4.7% | 0.44 (0.25–0.75) |
| Sequist et al, 2013 (LUX-Lung 3) | 10.1% | 0.53 (0.36–0.76) |
| Solomon et al, 2014 (PROFILE 1014) | 16.7% | 0.51 (0.38–0.68) |
| Reck et al, 2016 (KEYNOTE-024) | 8.2% | 0.61 (0.40–0.92) |
| Peters et al, 2017 (ALEX) | 10.1% | 0.48 (0.34–0.70) |
| Soria et al, 2017 (ASCEND-4) | 13.4% | 0.58 (0.42–0.80) |
| Camidge et al, 2018 (ALTA-1L) | 5.1% | 0.44 (0.26–0.74) |
| Paz-Ares et al, 2018 (KEYNOTE-407) | 13.6% | 0.50 (0.37–0.69) |
| Soria et al, 2018 (FLAURA) | 18.1% | 0.44 (0.33–0.58) |
| **Subtotal (95% CI)** | **100.0%** | **0.50 (0.45–0.57)** |
| Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 3.12$, $df = 8$ ($P = .93$); $I^2 = 0\%$ | | |
| Test for overall effect: $Z = 11.45$ ($P < .00001$) | | |
| **Pancreatic cancer** | | |
| Von Hoff et al, 2013 (CA046) | 100.0% | 0.69 (0.55–0.87) |
| **Subtotal (95% CI)** | **100.0%** | **0.69 (0.55–0.87)** |
| Heterogeneity: not applicable | | |
| Test for overall effect: $Z = 3.14$ ($P = .002$) | | |
| **Prostate cancer** | | |
| Ryan et al, 2013 (COU-AA-203) | 17.1% | 0.48 (0.35–0.66) |
| Beer et al, 2014 (PREVAIL) | 18.2% | 0.20 (0.15–0.26) |
| Fizazi et al, 2017 (LATITUDE) | 18.1% | 0.44 (0.34–0.58) |
| Armstrong et al, 2019 (ARCHES) | 13.3% | 0.29 (0.17–0.47) |
| Chi et al, 2019 (TITAN 3) | 15.7% | 0.45 (0.31–0.66) |
| Davis et al, 2019 (ENZAMET) | 17.7% | 0.33 (0.25–0.44) |
| **Subtotal (95% CI)** | **100.0%** | **0.35 (0.26–0.47)** |
| Heterogeneity: $\tau^2 = 0.11$; $\chi^2 = 26.63$, $df = 5$ ($P < .0001$); $I^2 = 81\%$ | | |
| Test for overall effect: $Z = 6.81$ ($P < .00001$) | | |




**eFigure 4 (cont.).** Individual studys' progression-free survival by cancer site in **(A)** older adults and **(B)** younger adults.
Abbreviations: HR, hazard ratio; IV, inverse variance; NSCLC, non–small cell lung cancer.

**A**




**eFigure 5.** Individual studys' progression-free survival by single-drug or multidrug interventional agent in **(A)** older adults and **(B)** younger adults.
Abbreviations: HR, hazard ratio; IV, inverse variance; NSCLC, non–small cell lung cancer.

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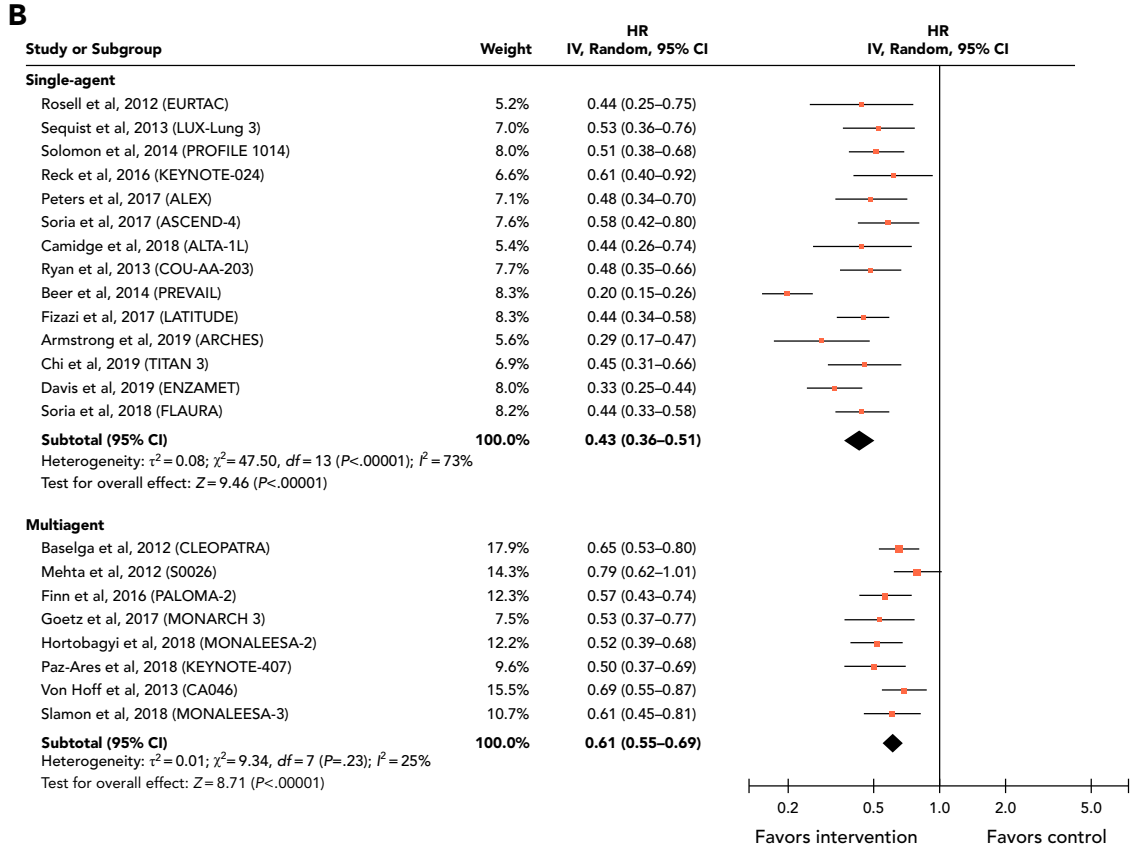
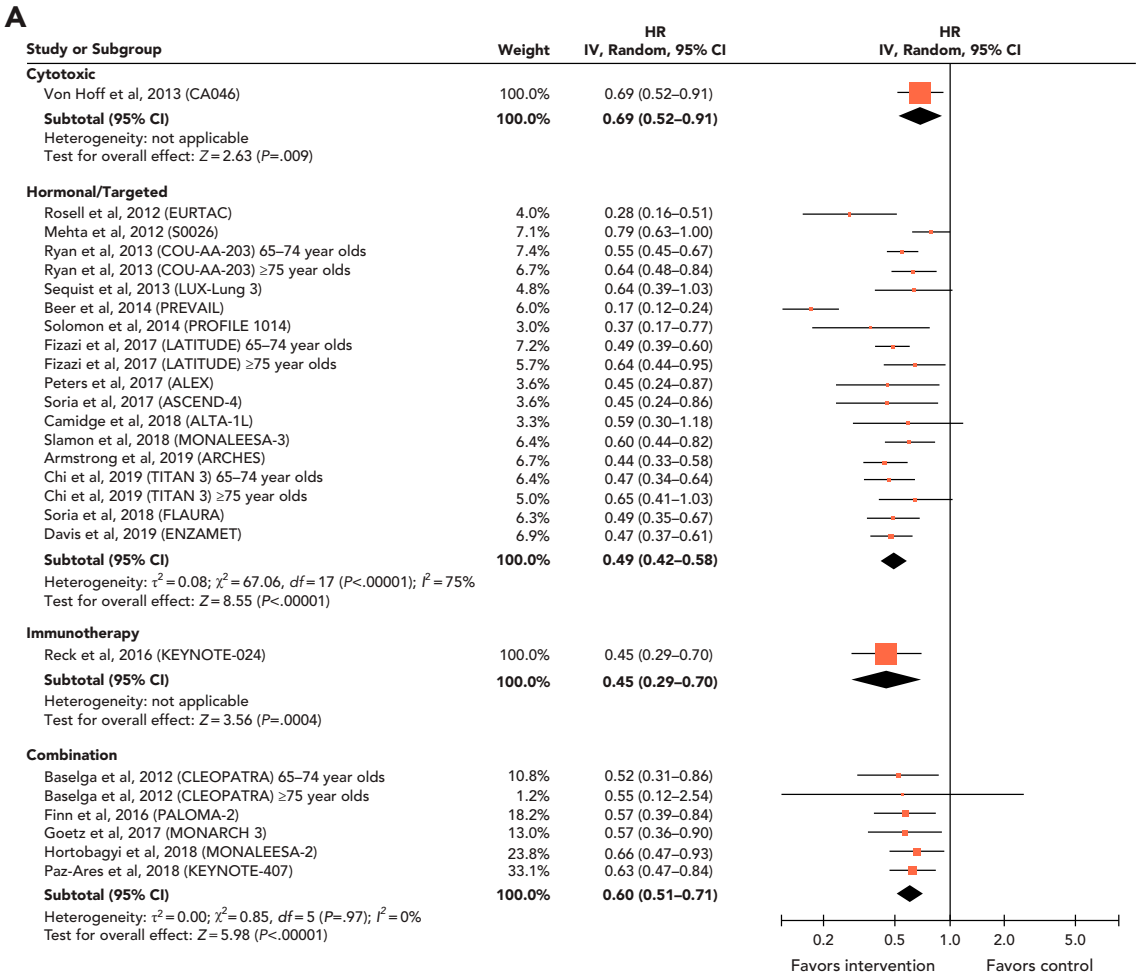



**eFigure 5 (cont.).** Individual studys' progression-free survival by single-drug or multidrug interventional agent in **(A)** older adults and **(B)** younger adults.
Abbreviations: HR, hazard ratio; IV, inverse variance; NSCLC, non–small cell lung cancer.




**eFigure 6.** Individual studys' progression-free survival by therapeutic class in **(A)** older adults and **(B)** younger adults.
Abbreviations: HR, hazard ratio; IV, inverse variance; NSCLC, non–small cell lung cancer.

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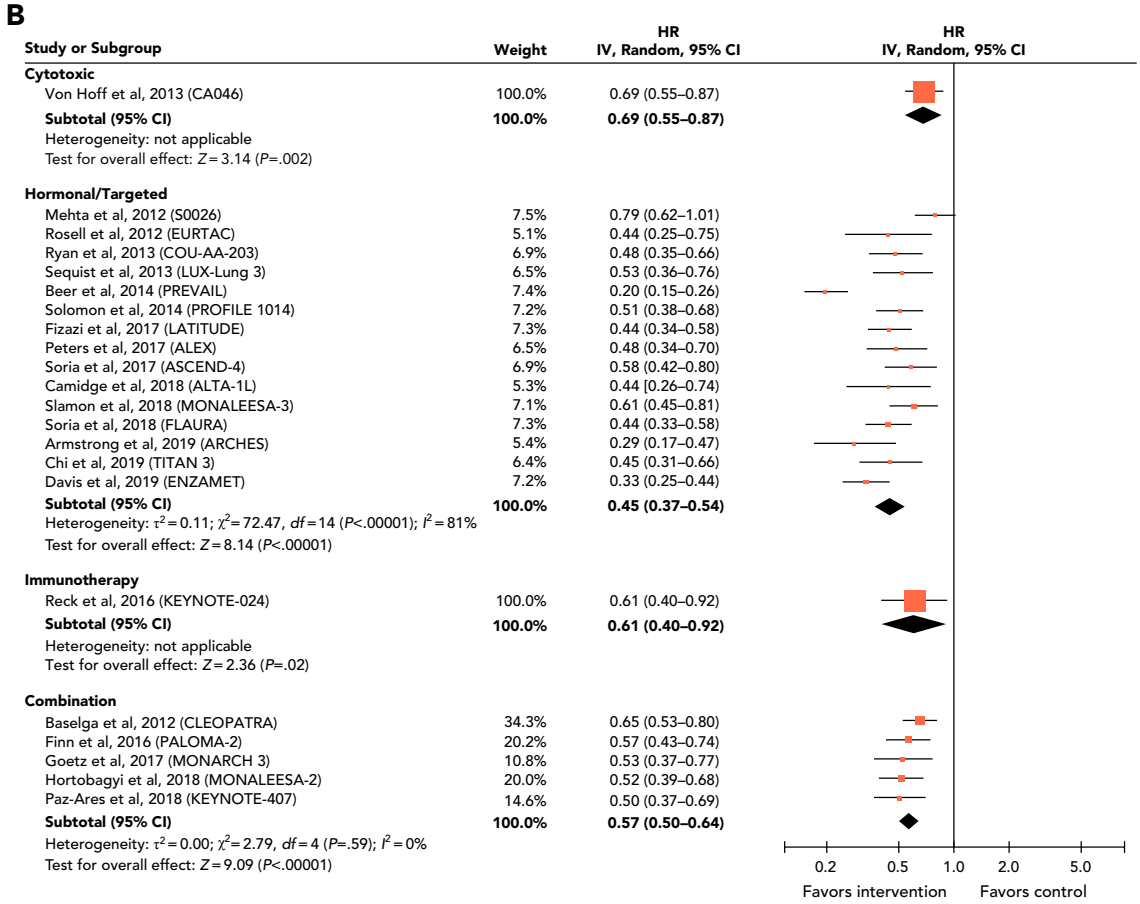
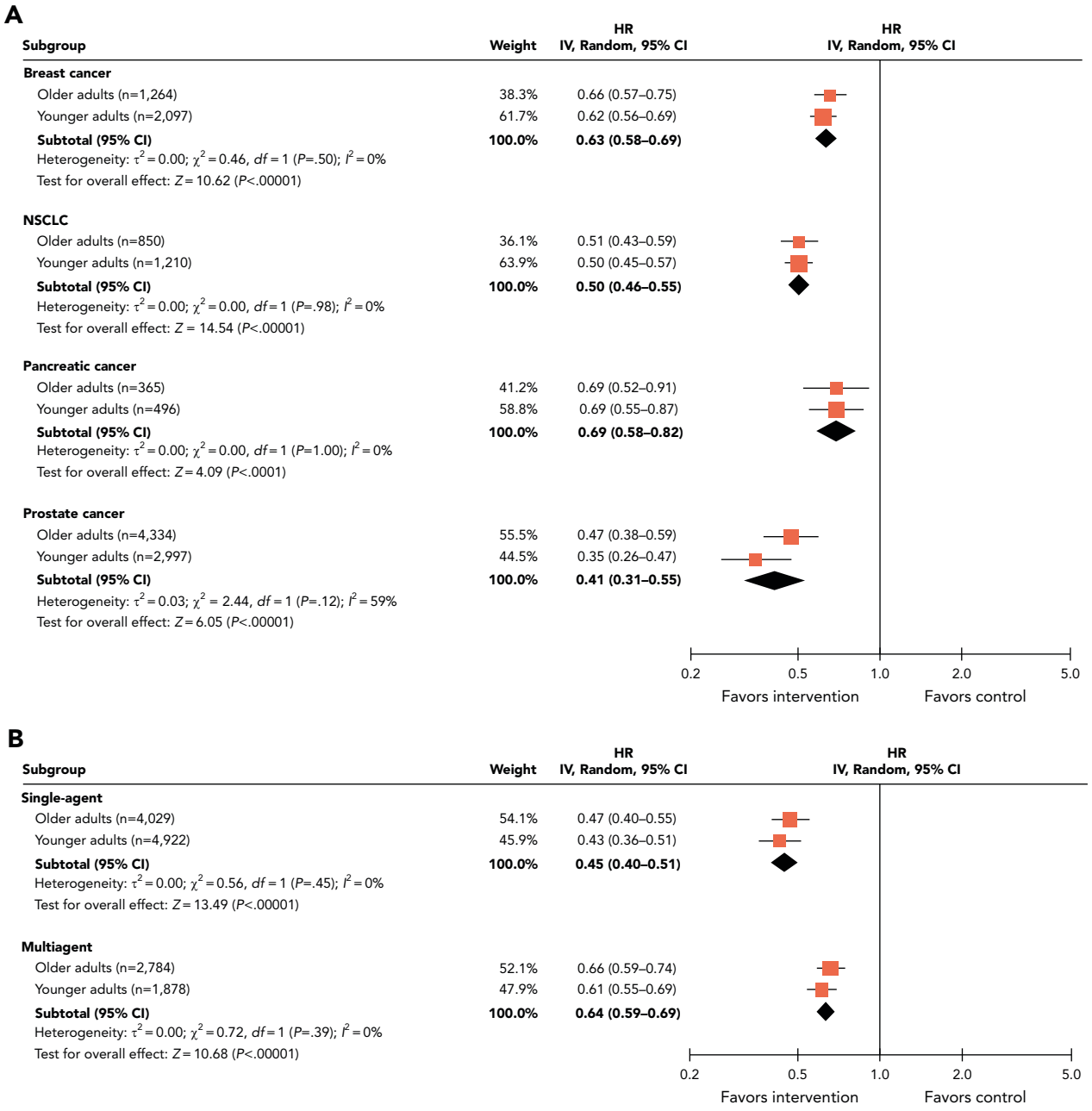
**B**




**eFigure 6 (cont.).** Individual studys' progression-free survival by therapeutic class in **(A)** older adults and **(B)** younger adults.
Abbreviations: HR, hazard ratio; IV, inverse variance; NSCLC, non–small cell lung cancer.




**eFigure 7.** Progression-free survival of older and younger adults by **(A)** cancer site, **(B)** single-drug or multidrug interventional agent, and **(C)** therapeutic class.
Abbreviations: HR, hazard ratio; IV, inverse variance; NSCLC, non–small cell lung cancer.

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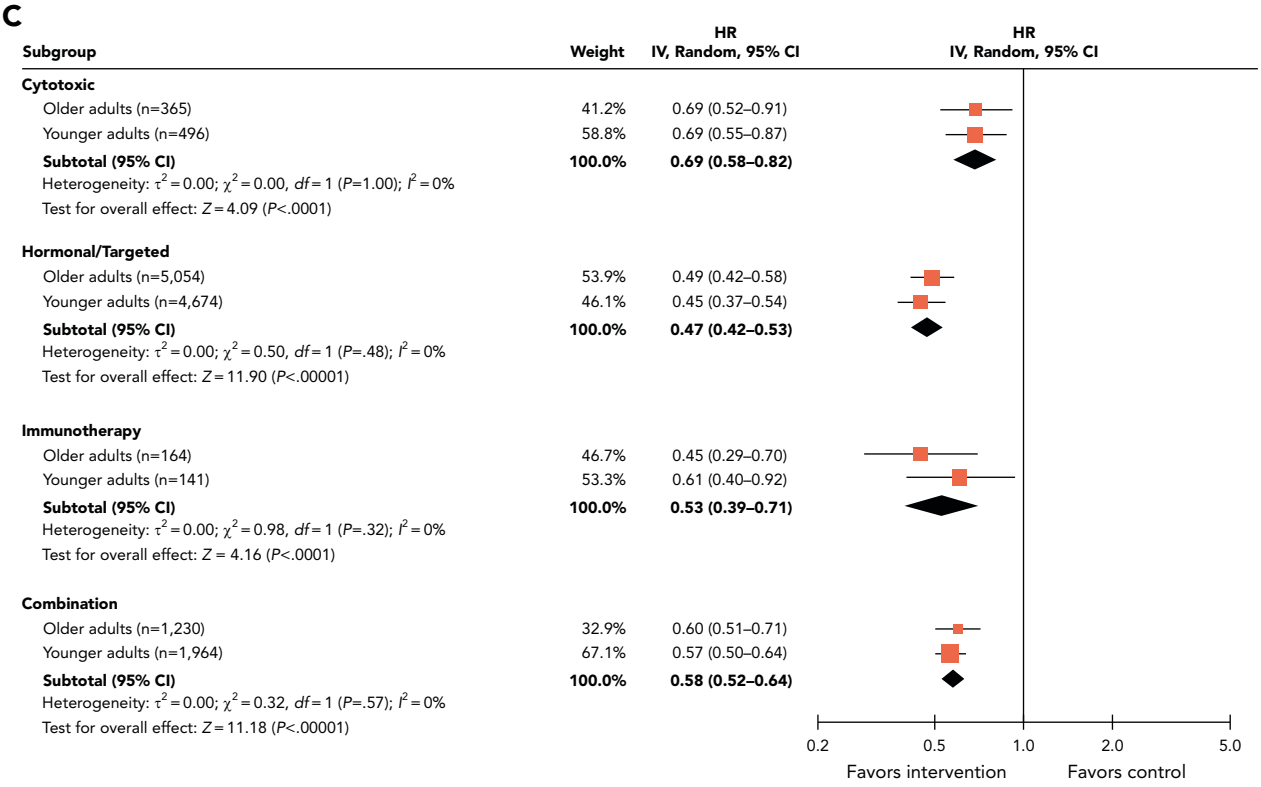


**eFigure 7 (cont.).** Progression-free survival of older and younger adults by **(A)** cancer site, **(B)** single-drug or multidrug interventional agent, and **(C)** therapeutic class.
Abbreviations: HR, hazard ratio; IV, inverse variance; NSCLC, non–small cell lung cancer.

## eTable 1. Study Demographics

| Trial | Investigational Agent(s) | Single-Agent or Multiagent | Therapeutic Class | Funding Source | Sample Size, n | PS Cutoff | Median Age of Investigational Arm, y | Older Adult Age Cutoff, y | Older Adult % of Sample | Primary Outcome |
|---|---|---|---|---|---|---|---|---|---|---|
| **Breast cancer** | | | | | | | | | | |
| Baselga et al,[23] 2012 (CLEOPATRA) | Pertuzumab + trastuzumab + docetaxel | Multi | Combination | Ind | 808 | ECOG 0–1 | 54 | 65 | 16% | PFS |
| Mehta et al,[24] 2012 (S0226) | Fulvestrant + anastrozole | Multi | Hormonal | Gov | 707 | Zubrod 0–2 | 65 | 65 | NR | PFS |
| Finn et al,[25] 2016 (PALOMA-2) | Letrozole + palbociclib | Multi | Combination | Ind | 666 | ECOG 0–2 | 62 | 65 | 39% | PFS |
| Goetz et al,[26] 2017 (MONARCH 3) | AI + abemaciclib | Multi | Combination | Ind | 493 | ECOG 0–1 | 63 | 65 | 45% | PFS |
| Hortobagyi et al,[27] 2018 (MONALEESA-2) | Letrozole + ribociclib | Multi | Combination | Ind | 668 | ECOG 0–1 | 62 | 65 | 44% | PFS |
| Slamon et al,[28] 2018 (MONALEESA-3) | Fulvestrant + ribociclib | Multi | Hormonal | Ind | 726 | ECOG 0–1 | 63 | 65 | 47% | PFS |
| Slamon et al,[29] 2020 (MONALEESA-3) | Fulvestrant + ribociclib | Multi | Hormonal | Ind | 726 | ECOG 0–1 | 63 | 65 | 47% | PFS |
| **NSCLC** | | | | | | | | | | |
| Rosell et al,[30] 2012 (EURTAC) | Erlotinib | Single | Targeted | Ind | 174 | ECOG 0–2 | 65 | 65 | 49% | PFS |
| Sequist et al,[31] 2013 (LUX-Lung 3) | Afatinib | Single | Targeted | Ind | 1,269 | ECOG 0–1 | 62 | 65 | NR | PFS |
| Solomon et al,[32] 2014 (PROFILE 1014) | Crizotinib | Single | Targeted | Ind | 343 | ECOG 0–2 | 52 | 65 | 16% | PFS |
| Reck et al,[33] 2016 (KEYNOTE-024) | Pembrolizumab | Single | Immunotherapy | Ind | 305 | ECOG 0–1 | 65 | 65 | 54% | PFS |
| Peters et al,[34] 2017 (ALEX) | Alectinib | Single | Targeted | Ind | 303 | ECOG 0–2 | 56 | 65 | 23% | PFS |
| Soria et al,[35] 2017 (ASCEND-4) | Ceritinib | Single | Targeted | Ind | 376 | WHO 0–2 | 55 | 65 | 22% | PFS |
| Camidge et al,[36] 2018 (ALTA-1L) | Brigatinib | Single | Targeted | Ind | 275 | ECOG 0–2 | 58 | 65 | 32% | PFS |
| Gandhi et al,[37] 2018 (KEYNOTE-189) | Carboplatin + pemetrexed + pembrolizumab | Multi | Combination | Ind | 616 | ECOG 0–1 | 65 | 65 | 51% | OS + PFS |
| Mok et al,[38] 2018 (ARCHER 1050) | Dacomitinib | Single | Targeted | Ind | 452 | ECOG 0–1 | 62 | 65 | 40% | OS |
| Paz-Ares et al,[39] 2018 (KEYNOTE-407) | Carboplatin + paclitaxel + pembrolizumab | Multi | Combination | Ind | 559 | ECOG 0–1 | 65 | 65 | 55% | OS + PFS |
| Soria et al,[40] 2018 (FLAURA) | Osimertinib | Single | Targeted | Ind | 994 | WHO 0–1 | 64 | 65 | NR | PFS |
| Mok et al,[41] 2019 (KEYNOTE-042) | Pembrolizumab | Single | Immunotherapy | Ind | 1,275 | ECOG 0–1 | 63 | 65 | 12% | OS |
| **Pancreatic cancer** | | | | | | | | | | |
| Conroy et al,[42] 2011 (PRODIGE) | FOLFIRINOX | Multi | Cytotoxic | Ind + gov | 342 | ECOG 0–1 | 61 | 65 | 29% | OS |
| Von Hoff et al,[43] 2013 (CA046) | Gemcitabine + nab-paclitaxel | Multi | Cytotoxic | Ind | 861 | KPS 70–100 | 63 | 65 | 42% | OS |

(*continued on next page*)

**eTable 1. Study Demographics (cont.)**

| Trial | Investigational Agent(s) | Single-Agent or Multiagent | Therapeutic Class | Funding Source | Sample Size, n | PS Cutoff | Median Age of Investigational Arm, y | Older Adult Age Cutoff, y | Older Adult % of Sample | Primary Outcome |
|---|---|---|---|---|---|---|---|---|---|---|
| **Prostate cancer** | | | | | | | | | | |
| Parker et al,[44] 2013 (ALSYMPCA) | Radium-223 | Single | Other | Ind | 921 | ECOG 0–2 | 71 | 75 | 28% | None |
| Ryan et al,[45] 2013 (COU-AA-203) | Abiraterone | Single | Hormonal | Ind | 1,088 | ECOG 0–1 | 71 | 65 | 73% | OS + PFS |
| Beer et al,[46] 2014 (PREVAIL) | Enzalutamide | Single | Hormonal | Ind | 1,717 | ECOG 0–1 | 72 | 75 | 35% | OS + PFS |
| Sweeney et al,[47] 2015 (CHAARTED) | Docetaxel | Single | Cytotoxic | Ind + gov | 790 | ECOG 0–2 | 64 | 70 | 22% | OS |
| James et al,[48] 2016 (STAMPEDE) | Docetaxel | Single | Cytotoxic | Ind + gov | 2,962 | WHO 0–2 | 65 | 70 | 53% | OS |
| Fizazi et al,[49] 2017 (LATITUDE) | Abiraterone | Single | Hormonal | Ind | 1,199 | ECOG 0–2 | 68 | 65 | 62% | OS + PFS |
| James et al,[50] 2017 (STAMPEDE) | Abiraterone | Single | Hormonal | Ind + gov | 1,917 | WHO 0–2 | 67 | 70 | 37% | OS |
| Armstrong et al,[51] 2019 (ARCHES) | Enzalutamide | Single | Hormonal | Ind | 1,150 | ECOG 0–1 | 70 | 65 | 74% | PFS |
| Chi et al,[52] 2019 (TITAN 3) | Apalutamide | Single | Hormonal | Ind | 1,052 | ECOG 0–1 | 69 | 65 | 69% | OS + PFS |
| Davis et al,[53] 2019 (ENZAMET) | Enzalutamide | Single | Hormonal | Ind + gov | 1,125 | ECOG 0–2 | 69 | 70 | 54% | OS |

Abbreviations: AI, aromatase inhibitor; FOLFIRINOX, fluorouracil/folinic acid/irinotecan/oxaliplatin; gov, government; ind, industry; KPS, Karnofsky performance status; NR, not reported; OS, overall survival; PFS, progression-free survival; PS, performance status.