# CALGB/SWOG 80405: Patients undergoing surgery as part of treatment strategy

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for the ALLIANCE and SWOG

# DISCLOSURES

- ADVISOR (unpaid)
  - Merck Serono
  - Roche/Genentech
- RESEARCH
  - GSK
  - Novartis
  - Roche/Genentech
- TRAVEL to ESMO
  - Merck Serono
  - Roche/Genentech

# THANK YOU

- ESMO organizers
- Dirk Arnold
- FIRE-3 investigators

# CALGB/SWOG 80405: Baseline Characteristics Resected Patients

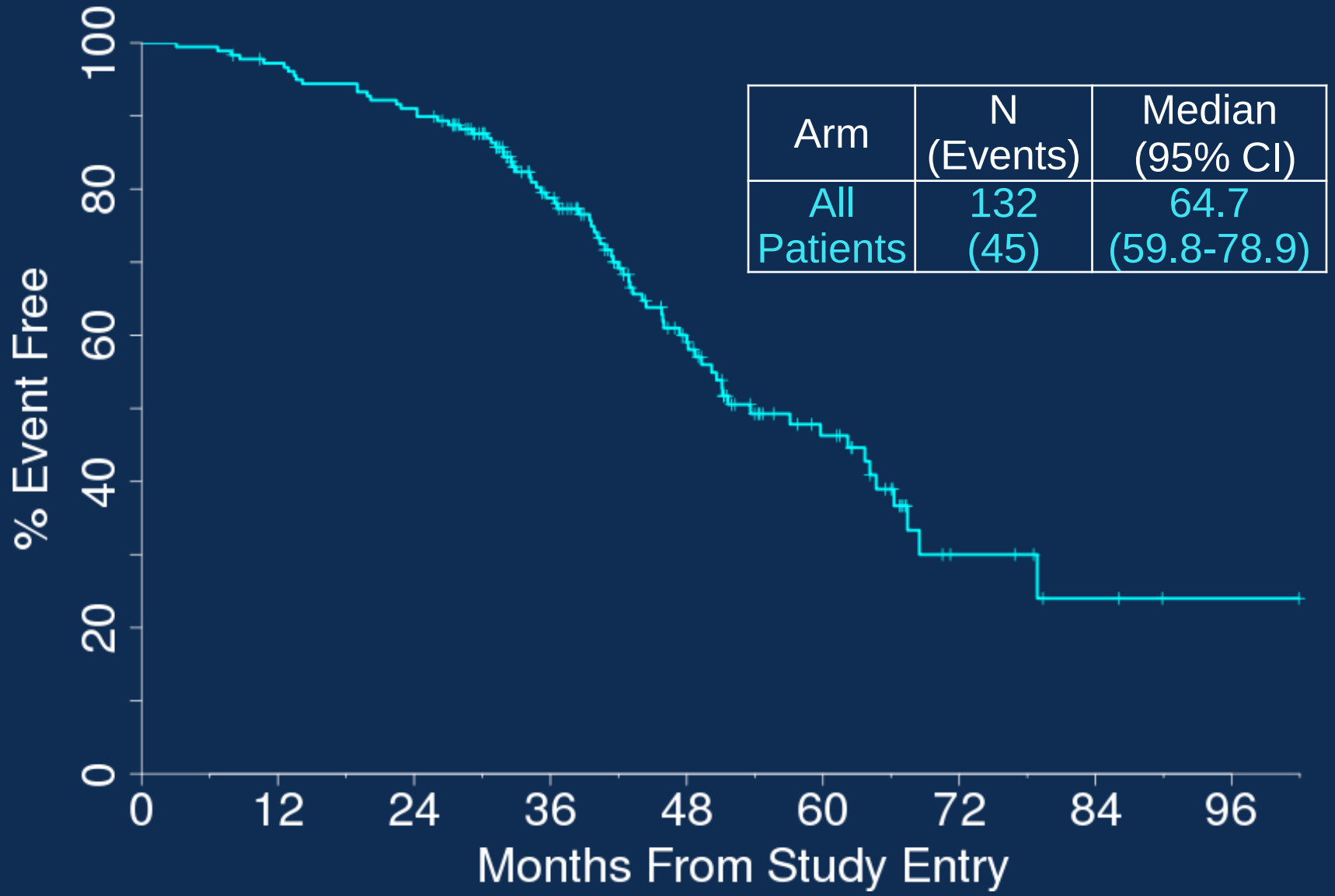
| Characteristic | Kras WT codons 12/13 n=1137 | | Resected Pts n=180 | |
|---|---|---|---|---|
| | Chemo + Bev n=559 | Chemo + Cetux n=578 | Chemo + Bev n=75 | Chemo + Cetux n=105 |
| **Age**, years | | | | |
| Median (range) | 59 (21–85) | 59 (20–89) | 55 (24–82) | 55 (21–79) |
| **Male, %** | 62.3 | 60.4 | 64.0 | 60.0 |
| **Non-Caucasian, %** | | | 9.3 | 20.0 |
| **FOLFOX, %*** | | | 77 | 81 |
| **Prior Radiation, %*** | | | 8.0 | 6.7 |
| **Prior Adjuvant Chemotherapy, %*** | | | 6.7 | 9.5 |
| **Palliative intent, %** | 86.4 | 82.5 | 62.7 | 60.0 |
| **Primary in place, %** | 28 | 27 | 30 | 20 |
| **Liver metastases only, %** | 29.3 | 39.8 | 53.3 | 50.0 |

**Achieve NED: 132 /180**

**Stratification Factor*

# CALGB/SWOG 80405: Overall Survival

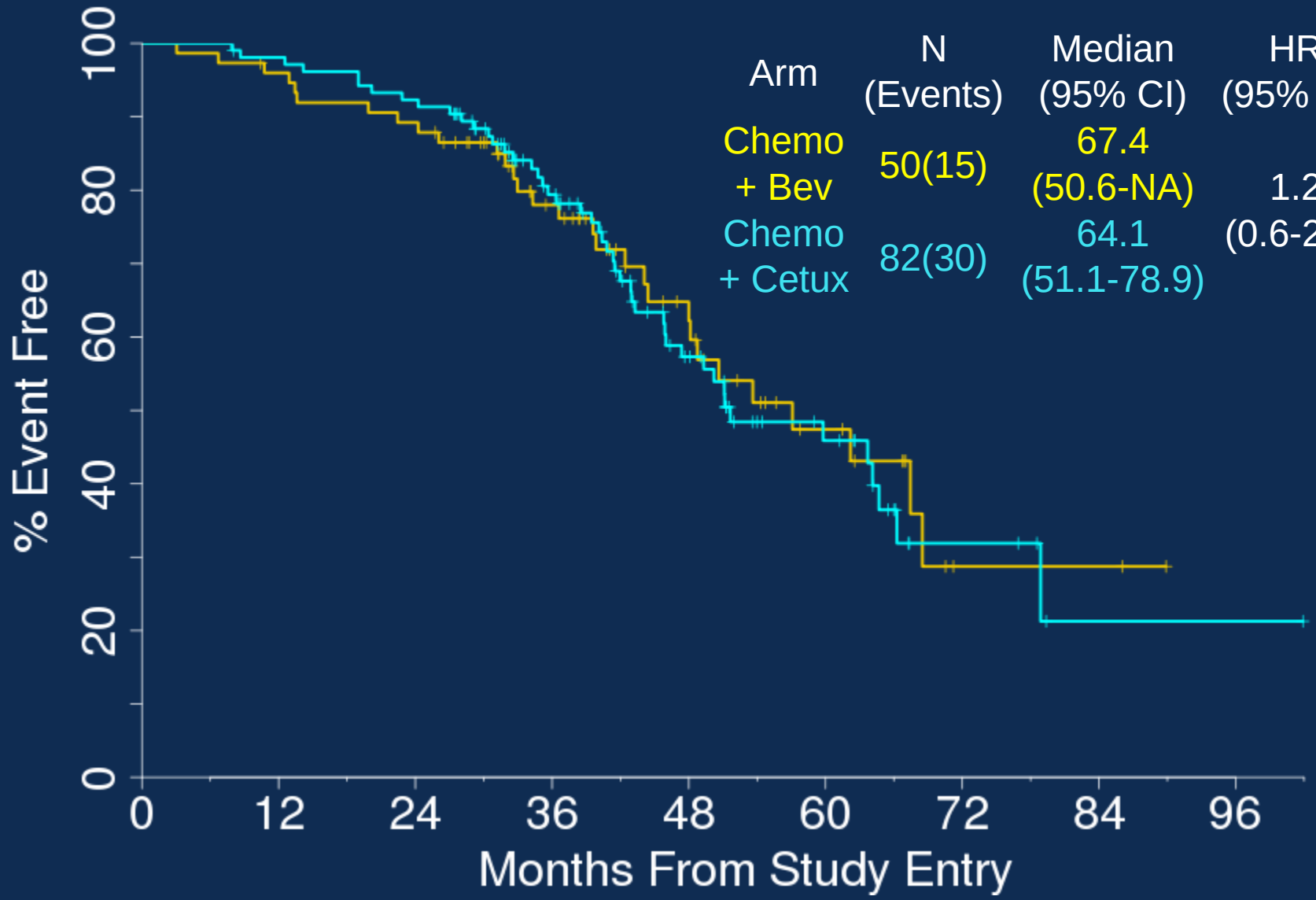
## (*KRAS wild type, NED Post-Surgery, N=132*)




| Arm | N (Events) | Median (95% CI) |
|---|---|---|
| All Patients | 132 (45) | 64.7 (59.8-78.9) |

# CALGB/SWOG 80405: Overall Survival

## (*KRAS wild type, NED Post-Surgery, N=132*)




| Arm | N (Events) | Median (95% CI) | HR (95% CI) | p |
|---|---|---|---|---|
| Chemo + Bev | 50(15) | 67.4 (50.6-NA) | 1.2 (0.6-2.2) | 0.56 |
| Chemo + Cetux | 82(30) | 64.1 (51.1-78.9) | | |

# 80405: OBJECTIVE RESPONSE RATE *

| N = 733 | CHEMO + BEV N = 369 (%) | CHEMO + CETUX N = 364 (%) |
|---|---|---|
| ORR | 57% | 66% |
| CR | 3% | 7.4% |
| PR | 54% | 58% |
| SD | 37% | 26% |
| PD | 6% | 8% |

* INVESTIGATOR ASSESSMENT; DOCUMENTED, NOT AUDITED

# 80405: OBJECTIVE RESPONSE RATE *

| N = 733 | FOLFOX + BEV N = 271 | FOLFOX + CETUX N = 259 | FOLFIRI + BEV N = 98 | FOLFIRI + CETUX N = 105 |
|---|---|---|---|---|
| ORR | 56% | 67% | 61% | 62% |
| NR | 44% | 33% | 39% | 38% |

* INVESTIGATOR ASSESSMENT; DOCUMENTED, NOT AUDITED

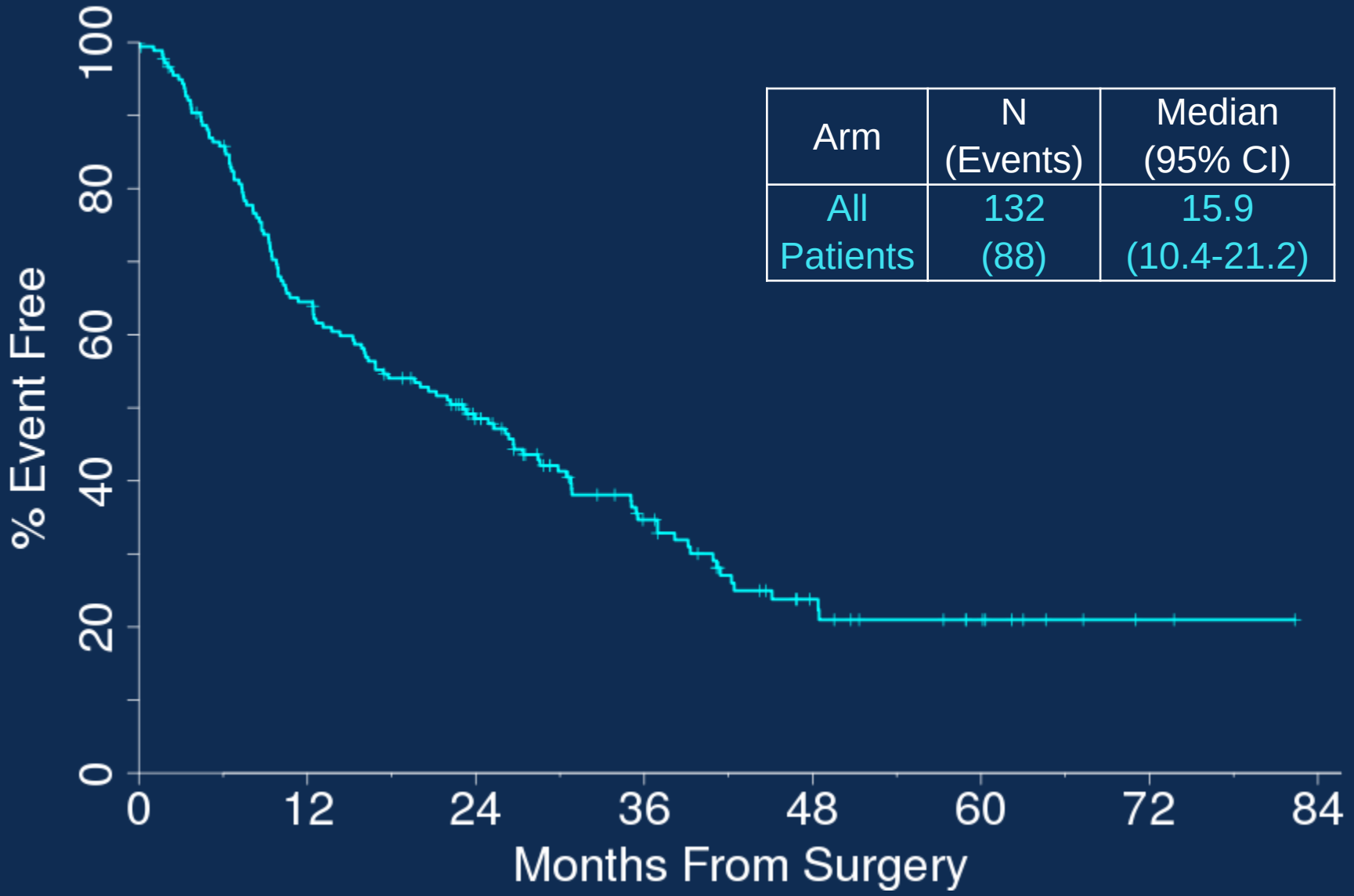
# CALGB/SWOG 80405: Resected NED Patients**

| | CHEMO + BEV | CHEMO + CETUX | TOTAL |
|---|---|---|---|
| RESECTED NED | 45 | 66 | 111 |
| RESPONSE (CR,PR) | 37(82%) | 50 (68%) | 87 (78%) |
| NON-RESPONSE | 8 | 16 | 24 (21%) |

** 111/132:
ASSESSABLE FOR RESPONSE

# CALGB/SWOG 80405: Disease Free Survival from Surgery, All Patients

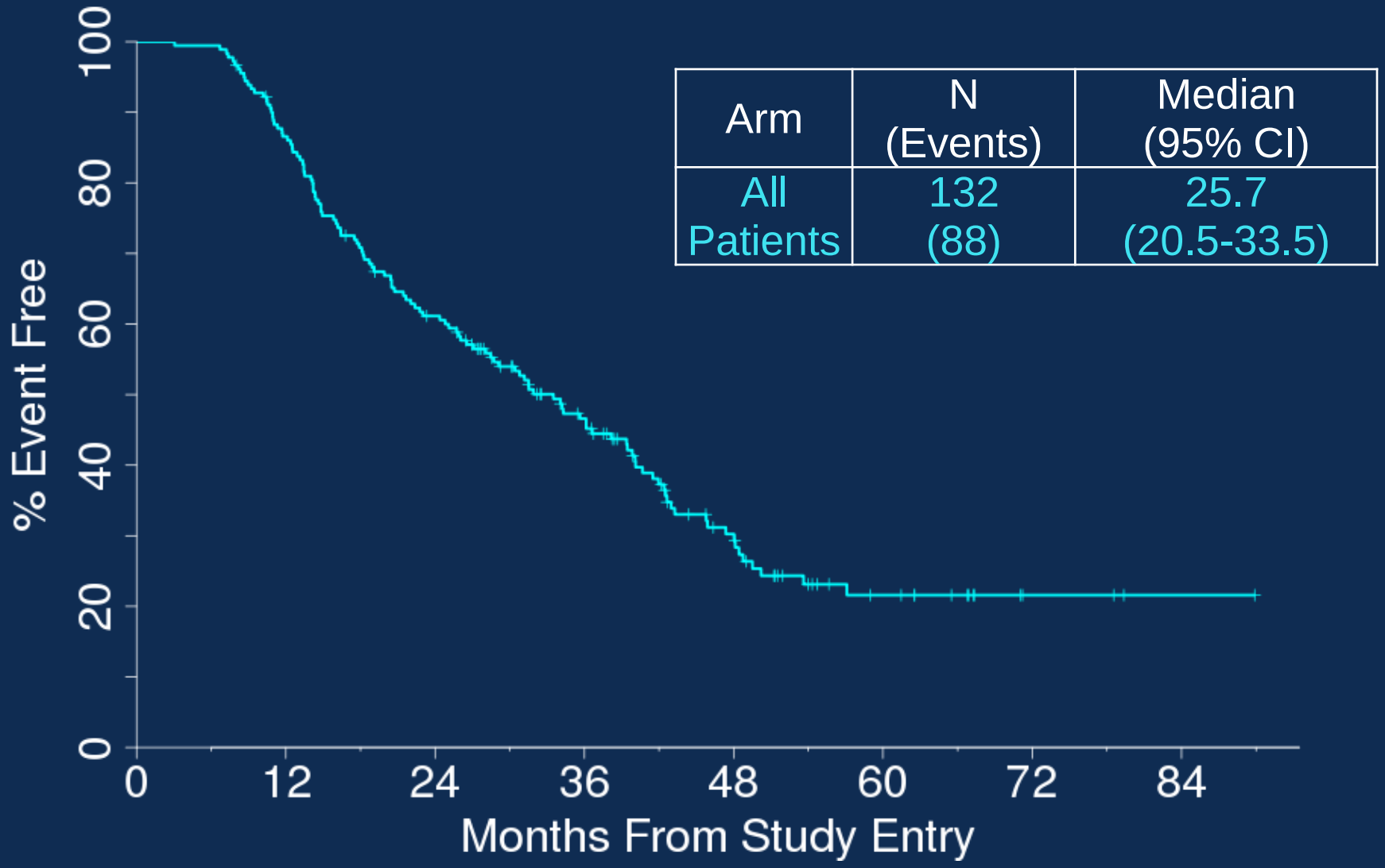
## (*Primary Cohort Patients with NED Surgical Outcome*)




| Arm | N (Events) | Median (95% CI) |
|---|---|---|
| All Patients | 132 (88) | 15.9 (10.4-21.2) |

# CALGB/SWOG 80405: Time from Randomization to Post-Surgical Recurrence, All Patients

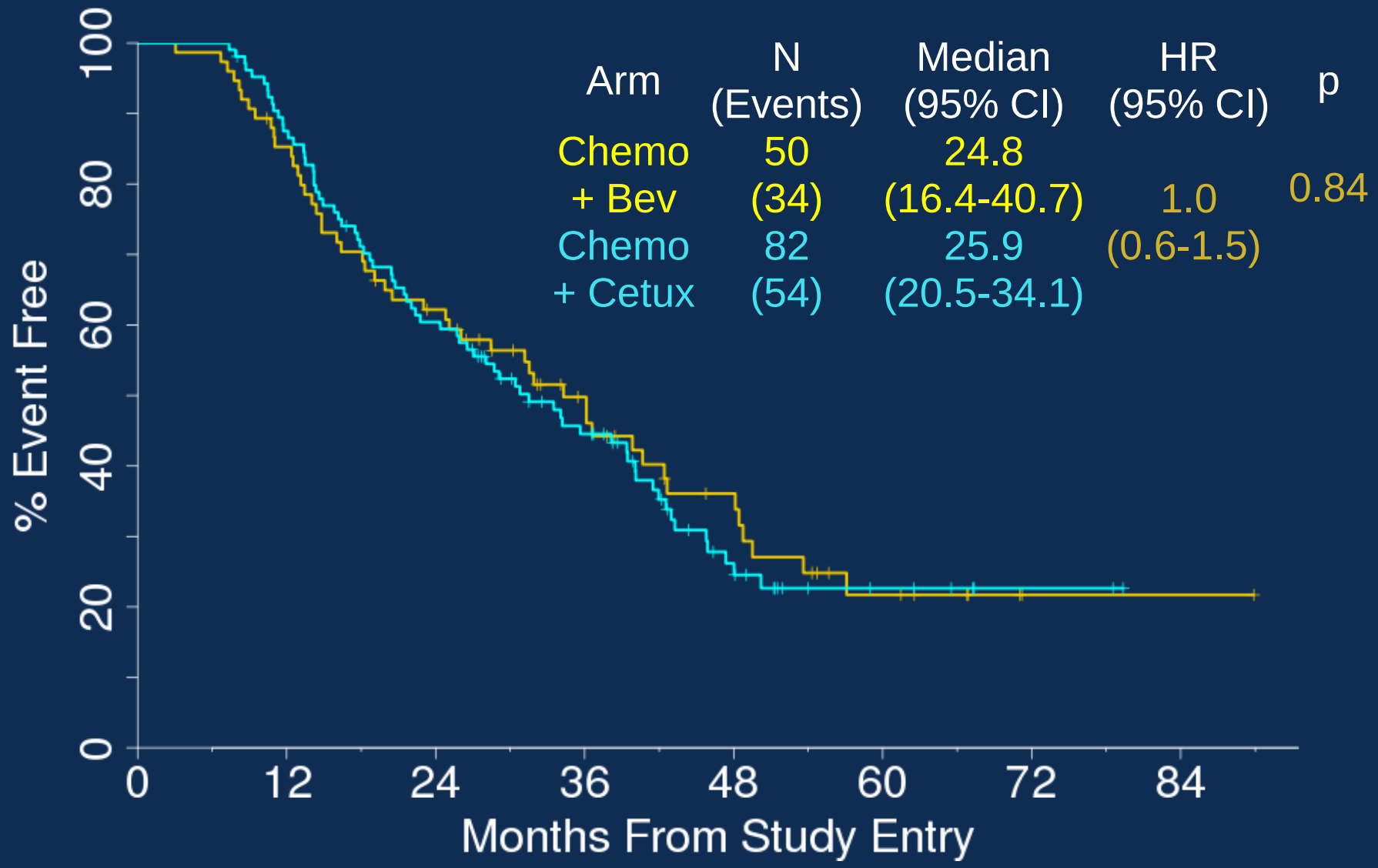
## (*KRAS wild type, NED Post-Surgery, N=132*)




| Arm | N (Events) | Median (95% CI) |
|---|---|---|
| All Patients | 132 (88) | 25.7 (20.5-33.5) |

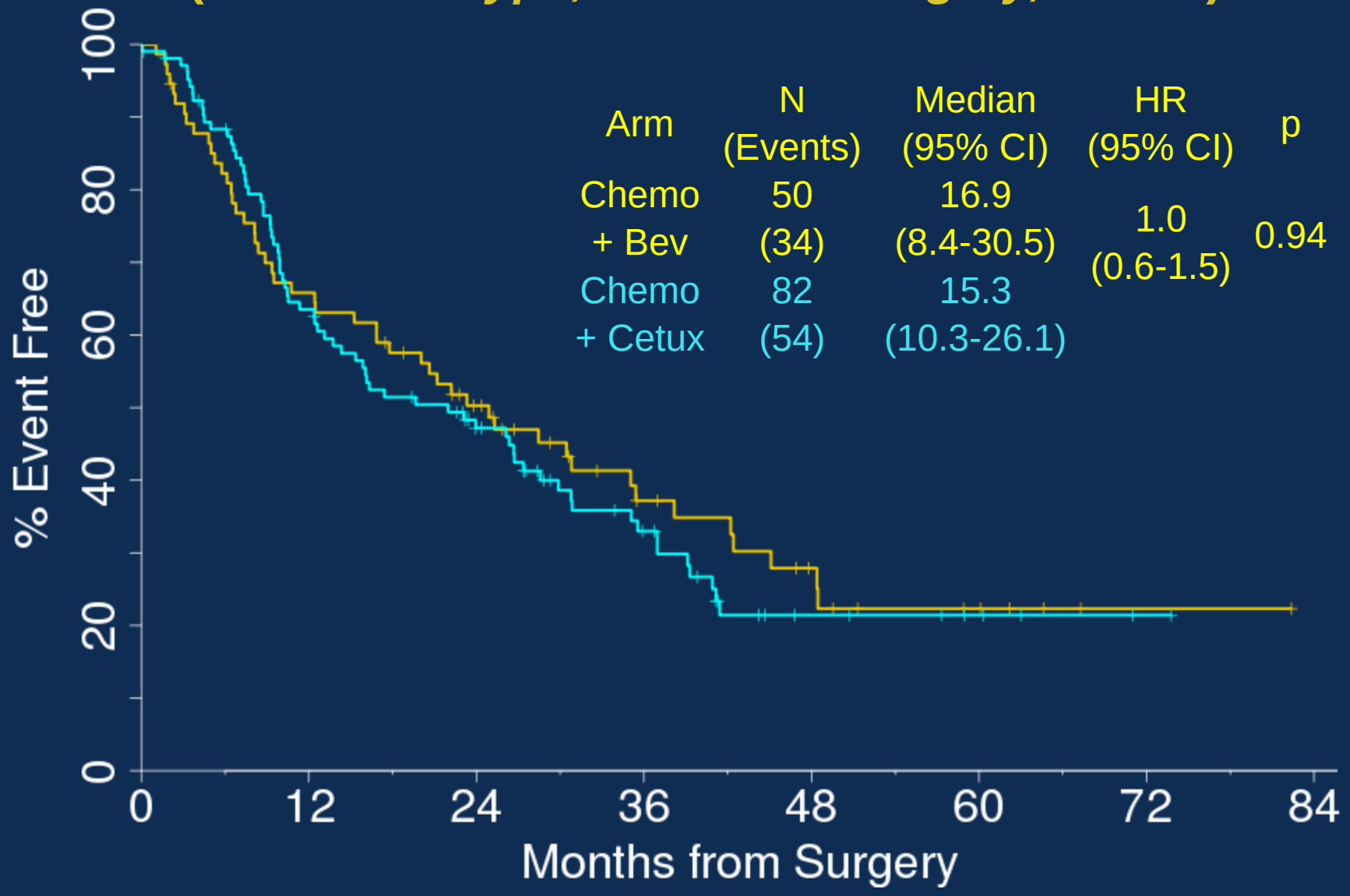
# CALGB/SWOG 80405: Post-Surgical Recurrence

## (*KRAS wild type, NED Post-Surgery, N=132*)



# CALGB/SWOG 80405: Disease Free Survival Surgical Resection

## (*KRAS wild type, NED Post-Surgery, N=132*)




| Arm | N (Events) | Median (95% CI) | HR (95% CI) | p |
|---|---|---|---|---|
| Chemo + Bev | 50 (34) | 16.9 (8.4-30.5) | 1.0 (0.6-1.5) | 0.94 |
| Chemo + Cetux | 82 (54) | 15.3 (10.3-26.1) | | |

# CALGB/SWOG 80405: Expanded RAS Resected NED Patients (N=132)

| | Total N (%) |
|---|---|
| All RAS Evaluable | 82 (62) |
| | |
| **WT** | **65 (79.2)** |
| **Mut** | **11 (13.4)** |
| | |
| Not assayed | 6 (7.3) |
| | |

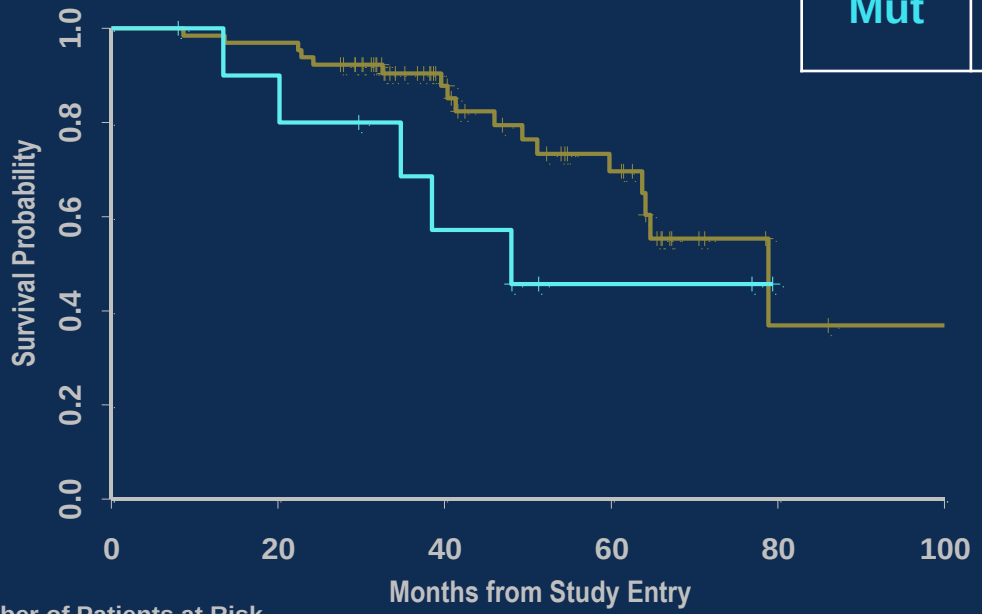
# CALGB/SWOG 80405: Expanded RAS Mut Resected NED Patients (N=11), Specific Mutations

| RAS Mutation | |
|---|---|
| KRAS Exon 2, c61 | Q61H |
| KRAS Exon 3, c146 | A146T (2)<br>A146V |
| NRAS Exon 2, c12 | G12A<br>G12S<br>G12D |
| NRAS Exon 3, c61 | Q61H<br>Q61K (2)<br>Q61R |

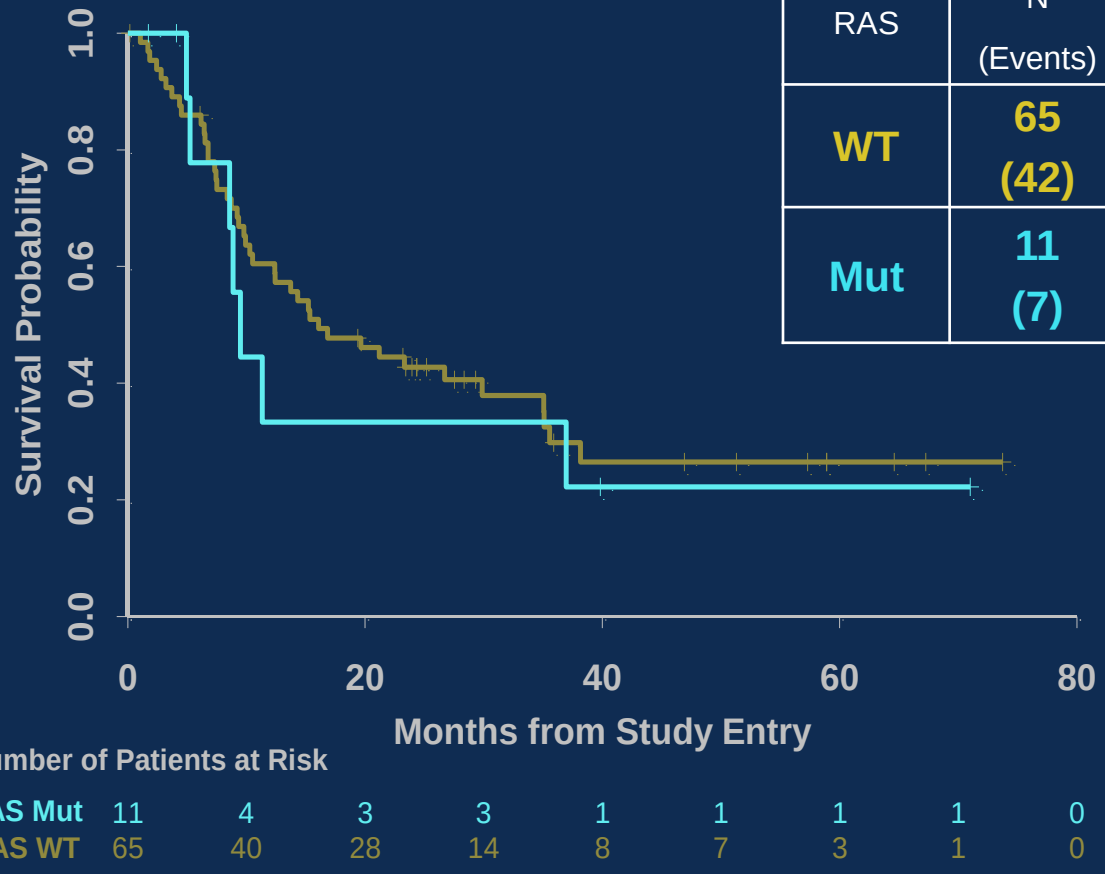
# CALGB/SWOG 80405: OS from Randomization

## (*NED Post-Surgery*)

| RAS | N (Events) | Median (95% CI) | HR (95% CI) | p |
|---|---|---|---|---|
| **WT** | **65 (17)** | **78.8 (63 – NR)** | 0.52 (0.2-1.4) | 0.2 |
| **Mut** | **11 (5)** | **47.9 (13.4 - NR)** | | |



# CALGB/SWOG 80405: DFS from Resection




| RAS | N (Events) | Median (95% CI) | HR (95% CI) | p |
|---|---|---|---|---|
| WT | 65 (42) | 16.1 (10 – 35) | 0.84 (0.3-1.8) | 0.6 |
| Mut | 11 (7) | 9.5 (5 - NR) | | |

# QUESTIONS, NOT ANSWERS

- Hypothesis-generating analyses:
  - Why were cetuximab-treated patients more likely to go to resection?
  - Is FOLFOX / cetuximab effective in neoadjuvant liver metastectomy (NEW EPOCH?)
  - Are the less common RAS mutations more powerful as drivers of prognosis?
  - Do mutations have different impact earlier or later in the course of the disease?

# CALGB/SWOG 80405: Learning from subset of patients rendered NED

- Molecular characterization of primary / metastases
  - Mutational analysis
  - Gene signatures
- Explore depth of response / tumor burden
- Plasma for circulating tumor DNA
- Combine – rather than contrast -- data sets across studies
- Systems biology approach to model curability
- Confirm the prognostic impact of RAS mutations
  - Mise et al, Ann Surg Oncol, 2014
- Contrast with other extreme: rapid progressors

# CALGB/SWOG 80405: Patients undergoing surgery and rendered NED

- Subset of patients survive > 5 years
- Patients likelier to reach NED on cetuximab-containing regimen but similar outcomes
- Expanded RAS may distinguish prognosis in this already select group of patients
- Opportunity to interrogate clinical and tumor factors related to curability

# ACKN[illegible]MENTS


- Lead S[illegible]cki

- Heinz
- Colla
  - Me
  - Ger