**Supplemental Materials**

Real-world association of HER2/*ERBB2* concordance with trastuzumab clinical benefit in advanced esophagogastric cancer

## Supplementary Data

### Supplemental Tables

#### Supplementary table 1a: Versions of genomic sequencing and genes included (FoundationOne Version 1)

Entire coding sequence for the detection of base substitutions, insertions/deletions, and copy number alterations

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| *ABL1* | *BCORL1* | *CDKN2B* | *ERBB3* | *FGFR3* | *IL7R* | *MDM4* | *NOTCH1* | *PTEN* | *SRC* |
| *AKT1* | *BLM* | *CDKN2C* | *ERBB4* | *FGFR4* | *INHBA* | *MED12* | *NOTCH2* | *PTPN11* | *STAG2* |
| *AKT2* | *BRAF* | *CEBPA* | *ERG* | *FLT1* | *IRF4* | *MEF2B* | *NPM1* | *RAD50* | *STAT4* |
| *AKT3* | *BRCA1* | *CHEK1* | *ESR1* | *FLT3* | *IRS2* | *MEN1* | *NRAS* | *RAD51* | *STK11* |
| *ALK* | *BRCA2* | *CHEK2* | *EZH2* | *FLT4* | *JAK1* | *MET* | *NTRK1* | *RAF1* | *SUFU* |
| *APC* | *BRIP1* | *CIC* | *FAM123B (WTX)* | *FOXL2* | *JAK2* | *MITF* | *NTRK2* | *RARA* | *TET2* |
| *AR* | *BTK* | *CREBBP* | *FAM46C* | *GATA1* | *JAK3* | *MLH1* | *NTRK3* | *RB1* | *TGFBR2* |
| *ARAF* | *CARD11* | *CRKL* | *FANCA* | *GATA2* | *JUN* | *MLL* | *NUP93* | *RET* | *TNFAIP3* |
| *ARFRP1* | *CBFB* | *CRLF2* | *FANCC* | *GATA3* | *KAT6A (MYST3)* | *MLL2* | *PAK3* | *RICTOR* | *TNFRSF14* |
| *ARID1A* | *CBL* | *CSF1R* | *FANCD2* | *GID4 (C17orf39)* | *KDM5A* | *MPL* | *PALB2* | *RNF43* | *TOP1* |
| *ARID2* | *CCND1* | *CTCF* | *FANCE* | *GNA11* | *KDM5C* | *MRE11A* | *PAX5* | *RPTOR* | *TP53* |
| *ASXL1* | *CCND2* | *CTNNA1* | *FANCF* | *GNA13* | *KDM6A* | *MSH2* | *PBRM1* | *RUNX1* | *TSC1* |
| *ATM* | *CCND3* | *CTNNB1* | *FANCG* | *GNAQ* | *KDR* | *MSH6* | *PDGFRA* | *SETD2* | *TSC2* |
| *ATR* | *CCNE1* | *DAXX* | *FANCL* | *GNAS* | *KEAP1* | *MTOR* | *PDGFRB* | *SF3B1* | *TSHR* |
| *ATRX* | *CD79A* | *DDR2* | *FBXW7* | *GPR124* | *KIT* | *MUTYH* | *PDK1* | *SMAD2* | *VHL* |
| *AURKA* | *CD79B* | *DNMT3A* | *FGF10* | *GRIN2A* | *KLHL6* | *MYC* | *PIK3CA* | *SMAD4* | *WISP3* |
| *AURKB* | *CDC73* | *DOT1L* | *FGF14* | *GSK3B* | *KRAS* | *MYCL1* | *PIK3CG* | *SMARCA4* | *WT1* |
| *AXL* | *CDH1* | *EGFR* | *FGF19* | *HGF* | *LRP1B* | *MYCN* | *PIK3R1* | *SMARCB1* | *XPO1* |
| *BAP1* | *CDK12* | *EMSY (C11orf30)* | *FGF23* | *HRAS* | *MAP2K1* | *MYD88* | *PIK3R2* | *SMO* | *ZNF217* |
| *BARD1* | *CDK4* | *EP300* | *FGF3* | *IDH1* | *MAP2K2* | *NF1* | *PPP2R1A* | *SOCS1* | *ZNF703* |
| *BCL2* | *CDK6* | *EPHA3* | *FGF4* | *IDH2* | *MAP2K4* | *NF2* | *PRDM1* | *SOX10* |  |
| *BCL2L2* | *CDK8* | *EPHA5* | *FGF6* | *IGF1R* | *MAP3K1* | *NFE2L2* | *PRKAR1A* | *SOX2* |  |
| *BCL6* | *CDKN1B* | *EPHB1* | *FGFR1* | *IKBKE* | *MCL1* | *NFKBIA* | *PRKDC* | *SPEN* |  |
| *BCOR* | *CDKN2A* | *ERBB2* | *FGFR2* | *IKZF1* | *MDM2* | *NKX2-1* | *PTCH1* | *SPOP* |  |

Select introns for the detection of rearrangements

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| *ALK* | *BCL2* | *BCR* | *BRAF* | *EGFR* | *ETV1* | *ETV4* | *ETV5* | *ETV6* | *EWSR1* |
| *MLL* | *MYC* | *NTRK1* | *PDGFRA* | *RAF1* | *RARA* | *RET* | *ROS1* | *TMPRSS2* |  |

#### Supplementary table 1b: Versions of genomic sequencing and genes included (FoundationOne Version 2)

Entire coding sequence for the detection of base substitutions, insertions/deletions, and copy number alterations

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| *ABL1* | *ABL2* | *ACVR1B* | *AKT1* | *AKT2* | *AKT3* | *ALK* | *AMER1 (FAM123B)* | *APC* | *AR* |
| *ARAF* | *ARFRP1* | *ARID1A* | *ARID1B* | *ARID2* | *ASXL1* | *ATM* | *ATR* | *ATRX* | *AURKA* |
| *AURKB* | *AXIN1* | *AXL* | *BAP1* | *BARD1* | *BCL2* | *BCL2L1* | *BCL2L2* | *BCL6* | *BCOR* |
| *BCORL1* | *BLM* | *BRAF* | *BRCA1* | *BRCA2* | *BRD4* | *BRIP1* | *BTG1* | *BTK* | *C11orf30 (EMSY)* |
| *CARD11* | *CBFB* | *CBL* | *CCND1* | *CCND2* | *CCND3* | *CCNE1* | *CD274* | *CD79A* | *CD79B* |
| *CDC73* | *CDH1* | *CDK12* | *CDK4* | *CDK6* | *CDK8* | *CDKN1A* | *CDKN1B* | *CDKN2A* | *CDKN2B* |
| *CDKN2C* | *CEBPA* | *CHD2* | *CHD4* | *CHEK1* | *CHEK2* | *CIC* | *CREBBP* | *CRKL* | *CRLF2* |
| *CSF1R* | *CTCF* | *CTNNA1* | *CTNNB1* | *CUL3* | *CYLD* | *DAXX* | *DDR2* | *DICER1* | *DNMT3A* |
| *DOT1L* | *EGFR* | *EP300* | *EPHA3* | *EPHA5* | *EPHA7* | *EPHB1* | *ERBB2* | *ERBB3* | *ERBB4* |
| *ERG* | *ERRFI1* | *ESR1* | *EPHA3* | *FAM46C* | *FANCA* | *FANCC* | *FANCD2* | *FANCE* | *FANCF* |
| *FANCG* | *FANCL* | *FAS* | *FAT1* | *FBXW7* | *FGF10* | *FGF14* | *FGF19* | *FGF23* | *FGF3* |
| *FGF4* | *FGF6* | *FGFR1* | *FGFR2* | *FGFR3* | *FGFR4* | *FH* | *FLCN* | *FLT1* | *FLT3* |
| *FLT4* | *FOXL2* | *FOXP1* | *FRS2* | *FUBP1* | *GABRA6* | *GATA1* | *GATA2* | *GATA3* | *GATA4* |
| *GATA6* | *GID4 (C17orf39)* | *GLI1* | *GNA11* | *GNA13* | *GNAQ* | *GNAS* | *GPR124* | *GRIN2A* | *GRM3* |
| *GSK3B* | *H3F3A* | *HGF* | *HNF1A* | *HRAS* | *HSD3B1* | *HSP90AA1* | *IDH1* | *IDH2* | *IGF1R* |
| *IGF2* | *IKBKE* | *IKZF1* | *IL7R* | *INHBA* | *INPP4B* | *IRF2* | *IRF4* | *IRS2* | *JAK1* |
| *JAK2* | *JAK3* | *JUN* | *KAT6A (MYST3)* | *KDM5A* | *KDM5C* | *KDM6A* | *KDR* | *KEAP1* | *KEL* |
| *KIT* | *KLHL6* | *KMT2A (MLL)* | *KMT2C (MLL3)* | *KMT2D (MLL2)* | *KRAS* | *LMO1* | *LRP1B* | *LYN* | *LZTR1* |
| *MAGI2* | *MAP2K1* | *MAP2K2* | *MAP2K4* | *MAP3K1* | *MCL1* | *MDM2* | *MDM4* | *MED12* | *MEF2B* |
| *MEN1* | *MET* | *MITF* | *MLH1* | *MPL* | *MRE11A* | *MSH2* | *MSH6* | *MTOR* | *MUTYH* |
| *MYC* | *MYCL (MYCL1)* | *MYCN* | *MYD88* | *NF1* | *NF2* | *NFE2L2* | *NFKBIA* | *NKX2-1* | *NOTCH1* |
| *NOTCH2* | *NOTCH3* | *NPM1* | *NRAS* | *NSD1* | *NTRK1* | *NTRK2* | *NTRK3* | *NUP93* | *PAK3* |
| *PALB2* | *PARK2* | *PAX5* | *PBRM1* | *PDCD1LG2* | *PDGFRA* | *PDGFRB* | *PDK1* | *PIK3C2B* | *PIK3CA* |
| *PIK3CB* | *PIK3CG* | *PIK3R1* | *PIK3R2* | *PLCG2* | *PMS2* | *POLD1* | *POLE* | *PPP2R1A* | *PRDM1* |
| *PREX2* | *PRKAR1A* | *PRKCI* | *PRKDC* | *PRSS8* | *PTCH1* | *PTEN* | *PTPN11* | *QKI* | *RAC1* |
| *RAD50* | *RAD51* | *RAF1* | *RANBP2* | *RARA* | *RB1* | *RBM10* | *RET* | *RICTOR* | *RNF43* |
| *ROS1* | *RPTOR* | *RUNX1* | *RUNX1T1* | *SDHA* | *SDHB* | *SDHC* | *SDHD* | *SETD2* | *SF3B1* |
| *SLIT2* | *SMAD2* | *SMAD3* | *SMAD4* | *SMARCA4* | *SMARCB1* | *SMO* | *SNCAIP* | *SOCS1* | *SOX10* |
| *SOX2* | *SOX9* | *SPEN* | *SPOP* | *SPTA1* | *SRC* | *STAG2* | *STAT3* | *STAT4* | *STK11* |
| *SUFU* | *SYK* | *TAF1* | *TBX3* | *TERC* | *TERT (promoter only)* | *TET2* | *TGFBR2* | *TNFAIP3* | *TNFRSF14* |
| *TOP1* | *TOP2A* | *TP53* | *TSC1* | *TSC2* | *TSHR* | *U2AF1* | *VEGFA* | *VHL* | *WISP3* |
| *WT1* | *XPO1* | *ZBTB2* | *ZNF217* | *ZNF703* |  |  |  |  |  |

Select introns for the detection of rearrangements

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| *ALK* | *BCL2* | *BCR* | *BRAF* | *BRCA1* | *BRCA2* | *BRD4* | *EGFR* | *ETV1* | *ETV4* |
| *ETV5* | *ETV6* | *FGFR1* | *FGFR2* | *FGFR3* | *KIT* | *MSH2* | *MYB* | *MYC* | *NOTCH2* |
| *NTRK1* | *NTRK2* | *PDGFRA* | *RAF1* | *RARA* | *RET* | *ROS1* | *TMPRSS2* |  |  |

#### Supplementary table 1c: FoundationOne CDx (Version 3)

Entire coding sequence for the detection of base substitutions, insertions/deletions, and copy number alterations

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| *ABL1* | *ACVR1B* | *AKT1* | *AKT2* | *AKT3* | *ALK* | *ALOX12B* | *AMER1 (FAM123B)* | *APC* |
| *AR* | *ARAF* | *ARFRP1* | *ARID1A* | *ASXL1* | *ATM* | *ATR* | *ATRX* | *AURKA* |
| *AURKB* | *AXIN1* | *AXL* | *BAP1* | *BARD1* | *BCL2* | *BCL2L1* | *BCL2L2* | *BCL6* |
| *BCOR* | *BCORL1* | *BRAF* | *BRCA1* | *BRCA2* | *BRD4* | *BRIP1* | *BTG1* | *BTG2* |
| *BTK* | *C11orf30 (EMSY)* | *C17orf39 (GID4)* | *CALR* | *CARD11* | *CASP8* | *CBFB* | *CBL* | *CCND1* |
| *CCND2* | *CCND3* | *CCNE1* | *CD22* | *CD274 (PD-L1)* | *CD70* | *CD79A* | *CD79B* | *CDC73* |
| *CDH1* | *CDK12* | *CDK4* | *CDK6* | *CDK8* | *CDKN1A* | *CDKN1B* | *CDKN2A* | *CDKN2B* |
| *CDKN2C* | *CEBPA* | *CHEK1* | *CHEK2* | *CIC* | *CREBBP* | *CRKL* | *CSF1R* | *CSF3R* |
| *CTCF* | *CTNNA1* | *CTNNB1* | *CUL3* | *CUL4A* | *CXCR4* | *CYP17A1* | *DAXX* | *DDR1* |
| *DDR2* | *DIS3* | *DNMT3A* | *DOT1L* | *EED* | *EGFR* | *EP300* | *EPHA3* | *EPHB1* |
| *EPHB4* | *ERBB2* | *ERBB3* | *ERBB4* | *ERCC4* | *ERG* | *ERRFI1* | *ESR1* | *EZH2* |
| *FAM46C* | *FANCA* | *FANCC* | *FANCG* | *FANCL* | *FAS* | *FBXW7* | *FGF10* | *FGF12* |
| *FGF14* | *FGF19* | *FGF23* | *FGF3* | *FGF4* | *FGF6* | *FGFR1* | *FGFR2* | *FGFR3* |
| *FGFR4* | *FH* | *FLCN* | *FLT1* | *FLT3* | *FOXL2* | *FUBP1* | *GABRA6* | *GATA3* |
| *GATA4* | *GATA6* | *GNA11* | *GNA13* | *GNAQ* | *GNAS* | *GRM3* | *GSK3B* | *H3F3A* |
| *HDAC1* | *HGF* | *HNF1A* | *HRAS* | *HSD3B1* | *ID3* | *IDH1* | *IDH2* | *IGF1R* |
| *IKBKE* | *IKZF1* | *INPP4B* | *IRF2* | *IRF4* | *IRS2* | *JAK1* | *JAK2* | *JAK3* |
| *JUN* | *KDM5A* | *KDM5C* | *KDM6A* | *KDR* | *KEAP1* | *KEL* | *KIT* | *KLHL6* |
| *KMT2A (MLL)* | *KMT2D (MLL2)* | *KRAS* | *LTK* | *LYN* | *MAF* | *MAP2K1 (MEK1)* | *MAP2K2 (MEK2)* | *MAP2K4* |
| *MAP3K1* | *MAP3K13* | *MAPK1* | *MCL1* | *MDM2* | *MDM4* | *MED12* | *MEF2B* | *MEN1* |
| *MERTK* | *MET* | *MITF* | *MKNK1* | *MLH1* | *MPL* | *MRE11A* | *MSH2* | *MSH3* |
| *MSH6* | *MST1R* | *MTAP* | *MTOR* | *MUTYH* | *MYC* | *MYCL (MYCL1)* | *MYCN* | *MYD88* |
| *NBN* | *NF1* | *NF2* | *NFE2L2* | *NFKBIA* | *NKX2-1* | *NOTCH1* | *NOTCH2* | *NOTCH3* |
| *NPM1* | *NRAS* | *NSD3 (WHSC1L1)* | *NT5C2* | *NTRK1* | *NTRK2* | *NTRK3* | *P2RY8* | *PALB2* |
| *PARK2* | *PARP1* | *PARP2* | *PARP3* | *PAX5* | *PBRM1* | *PDCD1 (PD-1)* | *PDCD1LG2 (PD-L2)* | *PDGFRA* |
| *PDGFRB* | *PDK1* | *PIK3C2B* | *PIK3C2G* | *PIK3CA* | *PIK3CB* | *PIK3R1* | *PIM1* | *PMS2* |
| *POLD1* | *POLE* | *PPARG* | *PPP2R1A* | *PPP2R2A* | *PRDM1* | *PRKAR1A* | *PRKCI* | *PTCH1* |
| *PTEN* | *PTPN11* | *PTPRO* | *QKI* | *RAC1* | *RAD21* | *RAD51* | *RAD51B* | *RAD51C* |
| *RAD51D* | *RAD52* | *RAD54L* | *RAF1* | *RARA* | *RB1* | *RBM10* | *REL* | *RET* |
| *RICTOR* | *RNF43* | *ROS1* | *RPTOR* | *SDHA* | *SDHB* | *SDHC* | *SDHD* | *SETD2* |
| *SF3B1* | *SGK1* | *SMAD2* | *SMAD4* | *SMARCA4* | *SMARCB1* | *SMO* | *SNCAIP* | *SOCS1* |
| *SOX2* | *SOX9* | *SPEN* | *SPOP* | *SRC* | *STAG2* | *STAT3* | *STK11* | *SUFU* |
| *SYK* | *TBX3* | *TEK* | *TET2* | *TGFBR2* | *TIPARP* | *TNFAIP3* | *TNFRSF14* | *TP53* |
| *TSC1* | *TSC2* | *TYRO3* | *U2AF1* | *VEGFA* | *VHL* | *WHSC1* | *WT1* | *XPO1* |
| *XRCC2* | *ZNF217* | *ZNF703* |  |  |  |  |  |  |

Select introns for the detection of rearrangements

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| *ALK* | *BCL2* | *BCR* | *BRAF* | *BRCA1* | *BRCA2* | *CD74* | *EGFR* | *ETV4* |
| *ETV5* | *ETV6* | *EWSR1* | *EZR* | *FGFR1* | *FGFR2* | *FGFR3* | *KIT* | *KMT2A (MLL)* |
| *MSH2* | *MYB* | *MYC* | *NOTCH2* | *NTRK1* | *NTRK2* | *NUTM1* | *PDGFRA* | *RAF1* |
| *RARA* | *RET* | *ROS1* | *RSPO2* | *SDC4* | *SLC34A2* | *TERC (NCRNA)* | *TERT (promotor)* | *TMPRSS2* |

#### 

#### Supplemental table 2: Detailed patient selection criteria

|  |  |
| --- | --- |
| **Criteria order** | **Criteria details** |
| **1** | Patients included in the Q1 2020 FH-FMI EG Cancer CGDB (data through December 31, 2019) |
| 1a | At least two documented episodes of structured activity\* in the FH network occurring on or after January 1, 2011 |
| 1b | A FH chart-confirmed diagnosis of EG cancer |
| 1c | CGP testing by FMI on a tumor specimen with FMI pathologist-confirmed histology consistent with EG cancer |
| 1d | CGP testing by FMI with report date and specimen collection date no earlier than 30 days before, on, or any time after the FH chart-confirmed date of initial diagnosis of CRC |
| 1e | Patient’s demographic information as available at FH and FMI was uniquely and deterministically matched by a third party linking vendor |
| **2** | An FMI CGP report date less than or equal to 60 days after the last structured activity date in the FH network |
| **3** | Chart-confirmed diagnosis of advanced EG cancer in the FH database on or before September 30, 2019 |
| **4** | Less than 90 days between advanced EG cancer diagnosis date and first structured activity date in the FH network\*\* |
| **5** | One or more HER2 test results (IHC, ISH or NOS) documented in the FH database no earlier than 30 days before to any time after the FH-documented initial EG cancer diagnosis date |
| **6** | FMI specimen collection date occurs no later than 14 days after the start of first line of therapy |
| **7** | First HER2 test result documented in the FH data occurs no later than 14 days after the start of first line of therapy |
| **8** | Patient did not receive lapatinib or a clinical study drug during first line of therapy |
| **9** | Patient has at least one documented negative or positive HER2 test result |
| \*Structured activity is defined as non-cancelled medication orders, medication administrations, or clinic visits with vital signs measured.  \*\*Ensuring first structured activity within 90 days of advanced EG diagnosis decreases the likelihood that patients may be missing treatment data  Abbreviations: CGDB, clinico-genomic database; CGP, comprehensive genomic profiling; FH, Flatiron Health; FMI, Foundation Medicine Inc; EG, esophagogastric; HER2, human epidermal growth factor receptor-2; IHC, immunohistochemistry; ISH, in situ hybridization; NOS, not otherwise specified; Q1, first quarter. | |

#### 

#### Supplemental table 3: Patients with an unknown or indeterminate HER2 test results who met all other study inclusion criteria

|  |  |  |
| --- | --- | --- |
|  | ***ERBB2* Amp+**  **n=3** | ***ERRB2* Amp-**  **n=24** |
| **Reason for Unknown HER2 Status** |  |  |
| Equivocal through IHC | 1 (33) | 11 (46) |
| Has unsuccessful/indeterminate Result | 0 (0) | 3 (12) |
| Other documentation Issue | 2 (67) | 10 (42) |
| **HER2 test type, n (%)** |  |  |
| Has ISH result | 3 (100) | 16 (67) |
| IHC result only | 0 (0) | 8 (33) |
| **1L therapy class, n (%)** |  |  |
| Combination chemotherapy | 1 (33) | 19 (79) |
| Single agent chemotherapy | 1 (33) | 3 (12) |
| Anti-VEGF-based therapy | 0 (0) | 1 (4) |
| HER2-targeted therapy | 1 (33) | 0 (0) |
| Other therapy | 0 (0) | 1 (4) |
| ***ERBB2* CN, n (%)** |  |  |
| 5 | 0 (0) | 2 (8) |
| 6 | 2 (67) | 0 (0) |
| 147 | 1 (33) | 0 (0) |
| No amplification | 0 (0) | 22 (92) |
| Abbreviations: 1L, first line; Amp, amplification; CN, copy number; HER2, human epidermal growth factor receptor-2; IHC, immunohistochemistry; ISH, in-situ hybridization; VEGF, vascular endothelial growth factor. | | |
|  |  |  |

#### 

#### Supplemental table 4: First line anti-HER2 therapy regimens in HER2+ patients stratified by ERBB2 amplification status

|  |  |  |
| --- | --- | --- |
| **Line 1 regimen (+ Trastuzumab), n (%)** | **HER2+ concordant\***  **n=82** | **HER2+ discordant\***  **n=60** |
| Fluorouracil, Oxaliplatin (FOLFOX) | 46 (56.1) | 37 (61.7) |
| Fluorouracil, Cisplatin | 9 (11.0) | 3 (5.0) |
| Fluorouracil, Oxaliplatin, Taxane | 3 (3.7) | 3 (5.0) |
| Fluorouracil, Cisplatin, Taxane | 3 (3.7) | 1 (1.7) |
| Fluorouracil, Irinotecan (FOLFIRI) | 2 (2.4) | 1 (1.7) |
| Fluorouracil, Oxaliplatin, Afatinib | 1 (1.2) | 0 (0) |
| Fluorouracil, Carboplatin, Taxane | 1 (1.2) | 0 (0) |
| Fluorouracil, Oxaliplatin, Irinotecan (FOLFOXIRI) | 1 (1.2) | 0 (0) |
| Capecitabine, Oxaliplatin (CAPEOX) | 4 (4.9) | 3 (5.0) |
| Capecitabine, Cisplatin | 4 (4.9) | 2 (3.3) |
| Capecitabine, Carboplatin, Taxane | 1 (1.2) | 0 (0) |
| Capecitabine | 0 (0) | 1 (1.7) |
| Capecitabine, Cisplatin, Epirubicin | 0 (0) | 1 (1.7) |
| Carboplatin, Taxane | 4 (4.9) | 6 (10) |
| Other | 3 (3.7) | 2 (3.3) |
| \*HER2+ concordant (HER2+/*ERBB2* Amp+); HER2- concordant (HER2-/*ERBB2* Amp-); HER2+ discordant (HER2+/*ERBB2* Amp-); HER2- discordant (HER2-/*ERBB2* Amp+) | | |

## 

#### 

#### Supplemental table 5: Demographics and clinical characteristics of patients with HER2+ tumors who received first-line trastuzumab therapy

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Characteristic** | **All patients**  **n=142** | **HER2+ concordant\***  **n=82** | **HER2+ discordant\***  **n=60** | **P-value (overall)** |
| **Age (years) at advanced diagnosis, median [IQR]** | 63.0 [56.0 - 70.0] | 62.0 [56.2 - 68.0] | 66.0 [55.0 - 71.0] | 0.23 |
| **Gender, n (%)** |  |  |  | 0.11 |
| Female | 30 (21.1) | 13 (15.9) | 17 (28.3) |  |
| Male | 112 (78.9) | 69 (84.1) | 43 (71.7) |  |
| **Race, n (%)** |  |  |  | 0.84 |
| Asian | 3 (2.4) | 1 (1.3) | 2 (4.0) |  |
| Black or African American | 3 (2.4) | 2 (2.7) | 1 (2.0) |  |
| White | 3 (2.4) | 2 (2.7) | 1 (2.0) |  |
| Other Race | 92 (73.6) | 55 (73.3) | 37 (74.0) |  |
| **Practice type, n (%)** |  |  |  | 0.12 |
| Academic | 11 (7.7) | 9 (11.0) | 2 (3.3) |  |
| Community | 131 (92.3) | 73 (89.0) | 58 (96.7) |  |
| **Smoking status, n (%)** |  |  |  | 0.15 |
| History of smoking | 89 (62.7) | 56 (68.3) | 33 (55.0) |  |
| No history of smoking | 53 (37.3) | 26 (31.7) | 27 (45.0) |  |
| **Tumor histology, n (%)** |  |  |  | 0.18 |
| Adenocarcinoma | 140 (98.6) | 82 (100) | 58 (96.7) |  |
| Other/Unknown | 2 (1.4) | 0 (0.0) | 2 (3.3) |  |
| **Disease Site** |  |  |  | 0.23 |
| Esophagus | 60 (42.3) | 36 (43.9) | 24 (40.0) |  |
| EGJ | 47 (33.1) | 30 (36.6) | 17 (28.3) |  |
| Stomach | 35 (24.6) | 16 (19.5) | 19 (31.7) |  |
| **Timing of FMI Report Relative to Line 1 Trastuzumab:** |  |  |  | 0.43 |
| More than 30 days after Line Start | 80 (56.3) | 49 (59.8) | 31 (51.7) |  |
| Within 30 days of Line 1 Start | 62 (43.7) | 33 (40.2) | 29 (48.3) |  |
| ***ERBB2* CN, median [IQR]** | 22.0 [9.0 - 105] | 25.0 [11.0 - 106] | 4.50 [4.0 - 5.0] | <0.001 |
| **2L therapy class, n (%)** |  |  |  | 0.059 |
| Anti-VEGF-based therapy | 22 (24.4) | 14 (25.9) | 8 (22.2) |  |
| Clinical study drug-based therapy | 8 (8.9) | 6 (11.1) | 2 (5.6) |  |
| Combination chemotherapy | 10 (11.1) | 3 (5.6) | 7 (19.4) |  |
| HER2-targeted therapy | 39 (43.3) | 27 (50.0) | 12 (33.3) |  |
| Other therapy | 6 (6.7) | 1 (1.9) | 5 (13.9) |  |
| Single agent chemotherapy | 5 (5.6) | 3 (5.6) | 2 (5.6) |  |
| Abbreviations: 2L, second line; Amp, amplification; CN, copy number; EGJ, esophagogastric junction; HER2, human epidermal growth factor receptor-2; IHC, immunohistochemistry; ISH, in-situ hybridization; IQR, interquartile range; NA, not applicable; VEGF, vascular endothelial growth factor.  \*HER2+ concordant (HER2+/*ERBB2* Amp+); HER2+ discordant (HER2+/*ERBB2* Amp-) | | | | |

#### 

#### Supplemental table 6: Concurrent genomic alterations

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Patients with alteration of known/likely functional significance, n (%)** | **HER2+ concordant\***  **n=109** | **HER2- concordant\***  **n=549** | **HER2+ discordant\***  **n=85** | **HER2- discordant\***  **n=9** |
| *ERBB2* mutation | 10 (9) | 18 (3) | 3 (4) | 0 (0) |
| *KRAS* alteration | 5 (5) | 128 (23) | 22 (26) | 1 (11) |
| *PIK3CA* mutation | 12 (11) | 56 (10) | 7 (8) | 2 (22) |
| *MET* amplification | 6 (6) | 28 (5) | 2 (2) | 0 (0) |
| *SMAD4* alteration | 17 (16) | 54 (10) | 10 (12) | 0 (0) |
| *MYC* amplification | 22 (20) | 64 (12) | 11 (13) | 2 (22) |
| *CDK6* alteration | 15 (14) | 53 (10) | 6 (7) | 0 (0) |
| *CCND1* alteration | 8 (7) | 54 (10) | 7 (8) | 0 (0) |
| *CCNE1* alteration | 25 (23) | 28 (5) | 15 (18) | 2 (22) |
| \*HER2+ concordant (HER2+/*ERBB2* Amp+); HER2- concordant (HER2-/*ERBB2* Amp-); HER2+ discordant (HER2+/*ERBB2* Amp-); HER2- discordant (HER2-/*ERBB2* Amp+) | | | | |

#### 

#### Supplemental table 7: Distribution of ISH results for patients classified by IHC status (with positive ISH confirmation) (n = 59), by ERBB2 Amp

|  |  |  |  |
| --- | --- | --- | --- |
| **HER2+ concordance,**  **n (%)** | **IHC positive (3+),**  **n = 21** | **IHC equivocal (2+),**  **n = 27** | **IHC negative (0-1+),**  **n = 11** |
| ERBB2- (discordant)\* | 4 (19) | 6 (59) | 7 (64) |
| ERBB2+ (concordant)\* | 17 (81) | 11 (41) | 4 (36) |

\*HER2+ concordant (HER2+/*ERBB2* Amp+); HER2+ discordant (HER2+/*ERBB2* Amp-)

#### Supplemental table 8: Adjusted clinical outcomes for 1L trastuzumab in patients whose tumors were clinically HER2+, adjusting for IHC status (n=142)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Clinical Outcome** | **Prop. Hazards Est.** | **95% CI (lower)** | **95% CI (upper)** | **P-Value** |
| **TTD** |  |  |  |  |
| HER2+ concordant (ref. HER2+ discordant)\* | 0.7 | 0.48 | 1.03 | 0.071 |
| IHC Equivocal (2+), ISH HER2+ (ref = IHC Positive, ISH HER2+) | 1.46 | 0.83 | 2.57 | 0.194 |
| IHC Negative (0-1+), ISH HER2+ (ref = IHC Positive, ISH HER2+) | 2.25 | 0.86 | 5.87 | 0.097 |
| No IHC Result (ref = IHC Positive, ISH HER2+) | 1.36 | 0.87 | 2.12 | 0.174 |
| Practice type = community (ref. academic) | 1.85 | 0.89 | 3.85 | 0.102 |
| Gender = male (ref. female) | 1.06 | 0.69 | 1.62 | 0.793 |
| Age at advanced diagnosis (1 year increase) | 1.00 | 0.98 | 1.02 | 0.919 |
| **OS** |  |  |  |  |
| HER2+ concordant (ref. HER2+ discordant)\* | 0.54 | 0.35 | 0.84 | 0.007 |
| IHC Equivocal (2+), ISH HER2+ (ref = IHC Positive, ISH HER2+) | 1.34 | 0.68 | 2.63 | 0.395 |
| IHC Negative (0-1+), ISH HER2+ (ref = IHC Positive, ISH HER2+) | 0.64 | 0.15 | 2.68 | 0.537 |
| No IHC Result (ref = IHC Positive, ISH HER2+) | 1.39 | 0.84 | 2.3 | 0.202 |
| Practice type = Community (ref. academic) | 1.11 | 0.49 | 2.5 | 0.809 |
| Gender = male (ref. female) | 0.89 | 0.52 | 1.51 | 0.659 |
| Age at advanced diagnosis (1 year increase) | 1.01 | 0.99 | 1.03 | 0.168 |
| Abbreviations: 1L, first line; Amp, amplification; CI, confidence interval; HER2, human epidermal growth factor receptor-2; OS, overall survival; ref, reference; TTD, time to discontinuation.  \*HER2+ concordant (HER2+/*ERBB2* Amp+); HER2- concordant (HER2-/*ERBB2* Amp-); HER2+ discordant (HER2+/*ERBB2* Amp-); HER2- discordant (HER2-/*ERBB2* Amp+) | | | | |

#### 

#### 

#### Supplemental table 9: Adjusted clinical outcomes for 1L trastuzumab in patients by adjusting for *KRAS* status (n=142)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Clinical Outcome** | **Prop. Hazards Est.** | **95% CI (lower)** | **95% CI (upper)** | **P-Value** |
| **TTD** |  |  |  |  |
| HER2+ concordant (ref. HER2+ discordant)\* | 0.62 | 0.42 | 0.91 | 0.016 |
| *KRAS*+ (ref *KRAS*-) | 0.96 | 0.56 | 1.64 | 0.880 |
| Practice type = community (ref. academic) | 1.51 | 0.76 | 3.01 | 0.237 |
| Gender = male (ref. female) | 1.01 | 0.73 | 1.67 | 0.642 |
| Age at advanced diagnosis (1 year increase) | 1.00 | 0.98 | 1.02 | 0.993 |
| **OS** |  |  |  |  |
| HER2+ concordant (ref. HER2+ discordant)\* | 0.53 | 0.34 | 0.84 | 0.007 |
| *KRAS*+ (ref *KRAS*-) | 1.20 | 0.63 | 2.27 | 0.575 |
| Practice type = Community (ref. academic) | 1.05 | 0.47 | 2.32 | 0.914 |
| Gender = male (ref. female) | 0.86 | 0.51 | 1.46 | 0.584 |
| Age at advanced diagnosis (1 year increase) | 1.01 | 0.99 | 1.03 | 0.162 |
| Abbreviations: 1L, first line; Amp, amplification; CI, confidence interval; HER2, human epidermal growth factor receptor-2; OS, overall survival; ref, reference; TTD, time to discontinuation.  \*HER2+ concordant (HER2+/*ERBB2* Amp+); HER2- concordant (HER2-/*ERBB2* Amp-); HER2+ discordant (HER2+/*ERBB2* Amp-); HER2- discordant (HER2-/*ERBB2* Amp+) | | | | |

#### 

#### 