(Acc), sensitivity, specificity, and p-value [Acc > No Information Rate (NIR)] of model are shown, calculated by caret package for R. (D) Random forest modeling of PD-L1 with 5 k-folds cross-validation of GIST specimens (training set created by partitioning 80% of all GIST samples from Supplemental Table 1, n=61). Confusion matrix (bottom right) indicates assessment of modeling fit to training set. (E) Distribution of top 6 features identified by random forest modeling. *adjusted q-value<0.1. (F) Predictive capacity of model on remaining 14 GISTs (testing set) and external CINSARC GIST cohort (n=12). Accuracy, sensitivity, specificity, and p-value [Acc > No Information Rate] of model are shown, as calculated by caret package for R. Bars, mean ± SEM.

**Supplemental Figure 1.**
(A) Principal component analysis (PCA) of all GIST specimens (top) and only KIT, PDGFRA, and SDH-deficient specimens (bottom) as calculated by DESeq2 for R (n=75, clinicopathologic characteristics are available in Supplemental Table 1).

**Supplemental Figure 2.**
(A) (top) ESTIMATE and (bottom) Cyt scores by mitotic rate (left) and tumor sizes (middle and right) in all KIT and PDGFRA-mutant GISTs (n=61). (B) (top) ESTIMATE and (bottom) Cyt scores by mitotic rate (left) and tumor sizes (middle and right) in UPG KIT and PDGFRA-mutant GISTs (n=22). (C) ESTIMATE scores by mitotic rate in (left) UPG KIT and (right) UPG PDGFRA-mutant GISTs. High mitotic rate = >5 mitoses/hpf. Low mitotic rate = <5 mitoses/hpf. UPG = untreated, primary, gastric. *p<0.05, t-test. Bars, median.

**Supplemental Figure 3.**
(A) Demonstration of overfitting. On the left, using all 117 immune features to develop the random forest model on the All KIT vs. All PDGFRA training set (n=50) results in a 72.7% accuracy (red font) on the testing set (n=11). Decreasing the number of features included to 10, 8, and 6 results in an improvement in model accuracy on the testing set to 72.7%, 81.8%, and 90.9% respectively. (B) Retrained All KIT vs. All PDGFRA model with the top 6 features identified in Figure 6A excluded. (Left) Random forest modeling with 5-fold cross-validation of KIT and PDGFRA-mutant GIST specimens was performed. Training set created by partitioning 80% (n=50) of KIT and PDGFRA samples from Supplemental Table 3. Confusion matrix (middle) indicates assessment of model fit to training set. (Left) Predictive capacity of model on remaining KIT and PDGFRA-mutant GIST testing set (n=11), showing decreased classifier performance to 72.7% (red). Accuracy, sensitivity, specificity, and p-value [Acc > No Information Rate] of models are shown, as calculated by caret package for R.

**Supplemental Figure 4.**
(A) ESTIMATE and Cyt scores in PDGFRA-mutant GIST samples that were correctly classified as PDGFRA-mutant (n=14) and incorrectly classified as KIT-mutant (n=6) by our All KIT vs. All PDGFRA-mutant random forest model (Figure 6A-C). (B) Distribution of top 6 features identified by random forest modeling in KIT-mutant tumors correctly classified as KIT and incorrectly classified as PDGFRA by our All KIT and All PDGFRA-mutant random forest model.
Supplemental Figure 5.
Western blot showing PD-L1 protein expression correlates with PD-L1 mRNA expression calculated by DESeq2. Human GIST numbers and mutation status are shown. KIT = KIT-mutant, SDHD = SDH-deficient.
Supplemental Figure 1

**Mutation Group**
- KIT Exon 11
- PDGFRA non-D842V
- SDH
- WT
- Resistant KIT Exon 11
- KIT Exon 13
- KIT Exon 9
- Resistant KIT Exon 9
- Multiple Drivers
- NF1
- PDGFRA D842V
- PDGFRA D842V + p16 deletion

Only KIT, PDGFRA, and SDH shown for clarity
Supplemental Figure 2

A  ALL KIT and PDGFRA-Mutant GISTs (n=61)

- Mitotic Rate
  - ESTIMATE Score
    - Low mitotic rate
    - High mitotic rate
  - p = 0.09

- Tumor Size ≥ 5 cm
  - ESTIMATE Score
    - <5 cm
    - ≥5 cm
  - p = 0.10

- Tumor Size ≥ 10 cm
  - ESTIMATE Score
    - <10 cm
    - ≥10 cm
  - p = 0.98

- Cyt Score
  - Low mitotic rate
  - High mitotic rate
  - p = 0.31

B  UPG KIT and PDGFRA-Mutant GISTs (n=22)

- Mitotic Rate
  - ESTIMATE Score
    - Low mitotic rate
    - High mitotic rate
  - p = 0.03*

- Tumor Size ≥ 5 cm
  - ESTIMATE Score
    - <5 cm
    - ≥5 cm
  - p = 0.08

- Tumor Size ≥ 10 cm
  - ESTIMATE Score
    - <10 cm
    - ≥10 cm
  - p = 0.55

- Cyt Score
  - Low mitotic rate
  - High mitotic rate
  - p = 0.21

C  UPG KIT GISTs  UPG PDGFRA GISTs

- ESTIMATE Score
  - Low mitotic rate
  - High mitotic rate
  - p = 0.40

  - p = 0.39
Supplemental Figure 3

A

Increasing Model Performance with Fewer Model Features (Prevention of Overfitting)

<table>
<thead>
<tr>
<th>117 Feature Model</th>
<th>10 Feature Model</th>
<th>8 Feature Model</th>
<th>6 Feature Model</th>
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<tbody>
<tr>
<td><strong>Testing Set</strong></td>
<td><strong>Actual</strong></td>
<td><strong>Predicted</strong></td>
<td><strong>Actual</strong></td>
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<tr>
<td>ALL KIT</td>
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<tr>
<td>ALL PDGFRA</td>
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<td>1</td>
<td>1</td>
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<tr>
<td>ALL PDGFRA</td>
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Accuracy: 72.7%
95% CI: [39.7-94.0]
NIR = 63.6%
p-value [Acc > NIR] : 0.39
Sensitivity: 25%
Specificity: 100%

Accuracy: 72.7%
95% CI: [39.7-94.0]
NIR = 63.6%
p-value [Acc > NIR]: 0.39
Sensitivity: 75%
Specificity: 71.4%

Accuracy: 81.8%
95% CI: [48.2-97.7]
NIR = 63.6%
p-value [Acc > NIR]: 0.18
Sensitivity: 75%
Specificity: 85.7%

Accuracy: 90.9%
95% CI: [58.7-99.8]
NIR = 63.6%
p-value [Acc > NIR]: 0.05
Sensitivity: 100%
Specificity: 85.7%

B

Retrained All KIT vs. All PDGFRA Model with Top 6 Features Excluded

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<thead>
<tr>
<th>Feature Importance</th>
<th>Predictive Capacity</th>
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<tr>
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<td>CXCL11</td>
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<td>TMIGD2</td>
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Feature Importance

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<th>Importance</th>
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<th>NT5E</th>
<th>TNFSF8</th>
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Predictive Capacity

<table>
<thead>
<tr>
<th>Testing Set</th>
<th>Actual</th>
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<tr>
<td>ALL KIT</td>
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</tr>
<tr>
<td>ALL PDGFRA</td>
<td>4</td>
<td>13</td>
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</table>

OOB Estimate of Error: 22%

Accuracy: 72.7%
95% CI: [39.0-94.0]
NIR = 63.6%
p-value [Acc > NIR] : 0.39
Sensitivity: 50%
Specificity: 85.7%
Supplemental Figure 4

A

Distribution of Important Features Among KIT-mutant Tumors

CXCL14

TGFB1

TNFSF9

MICA

TNFRSF25

CD96

Normalized Counts + 1

Incorrectly Classified as PDGFRA-mutant tumors (n=3)
Correctly Classified as KIT-mutant tumors (n=27)

0.03 1 32 1024 32768

B

Distribution of Important Features Among KIT-mutant Tumors

PDGFRA Samples

Correctly Classified as PDGFRA (n=14)
Incorrectly Classified as KIT (n=6)

0
0.03 1 32 1024 32768

PDGFRA Samples

Correctly Classified as PDGFRA (n=14)
Incorrectly Classified as KIT (n=6)
Supplemental Figure 5

<table>
<thead>
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<th>Human GIST #</th>
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<tr>
<td>Mutation</td>
<td>KIT KIT KIT SDHD KIT KIT KIT KIT</td>
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<tr>
<td>PD-L1</td>
<td>![Image of PD-L1]</td>
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<tr>
<td>GAPDH</td>
<td>![Image of GAPDH]</td>
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<tr>
<td>PD-L1 mRNA</td>
<td>34 75 137 267 676 820 839 2500</td>
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