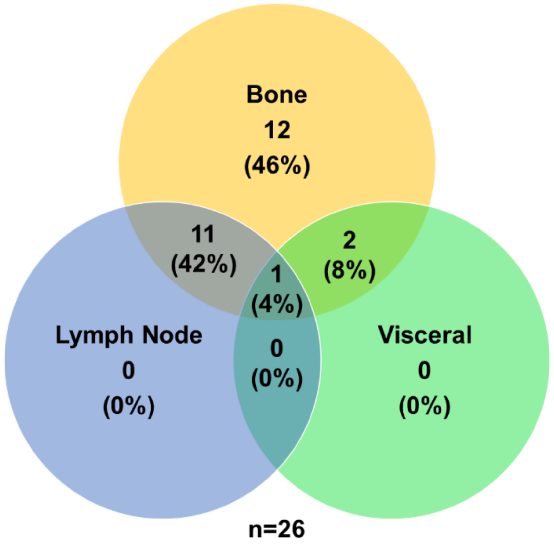
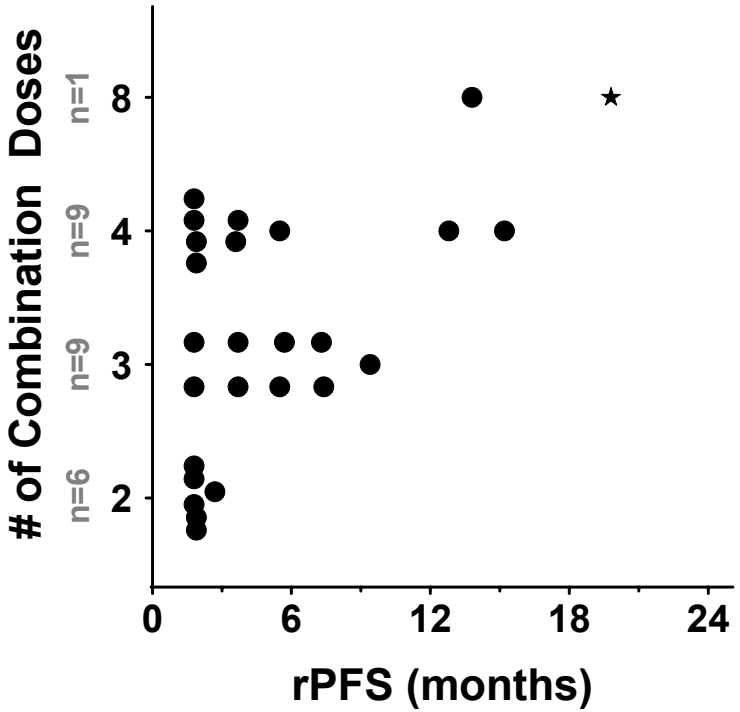
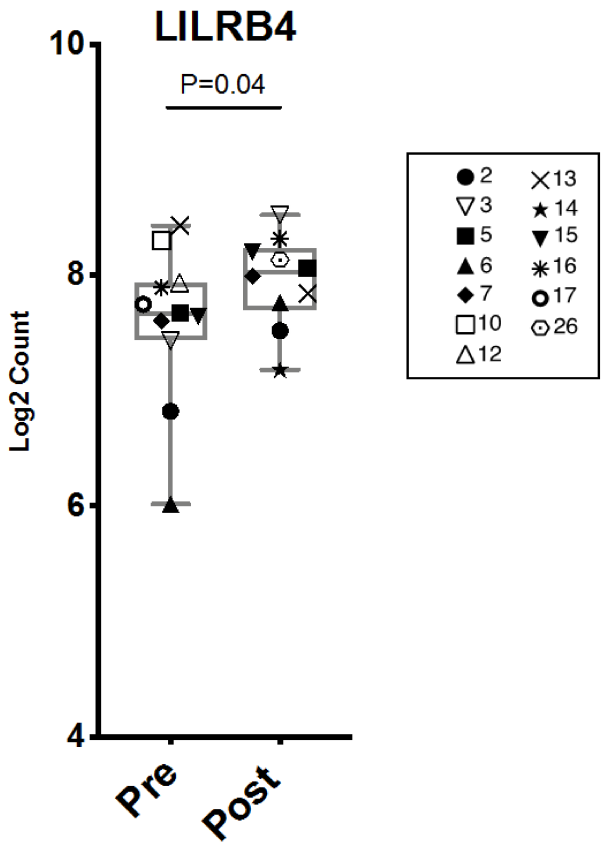
**Supplementary Figure 1** – Distribution of metastatic disease.



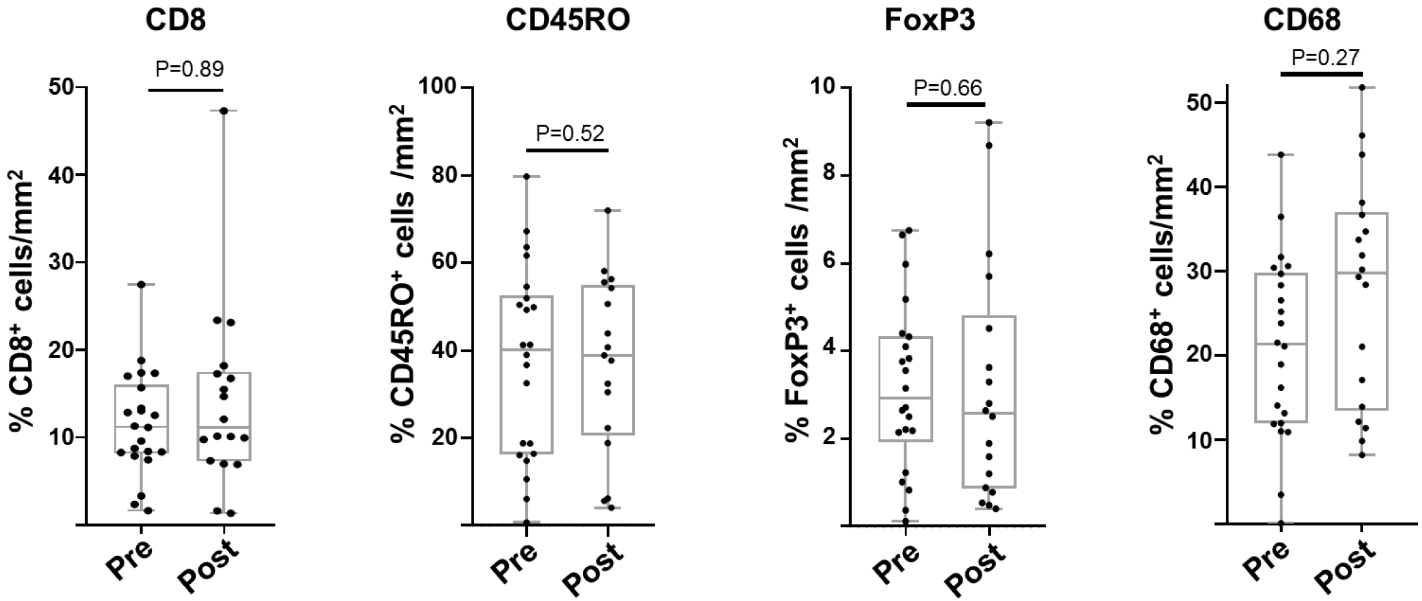
**Supplementary Figure 2 –** Exploratory comparison of rPFS by number of combination doses received**.** Star indicates second progression event after retreatment (rPFS2).



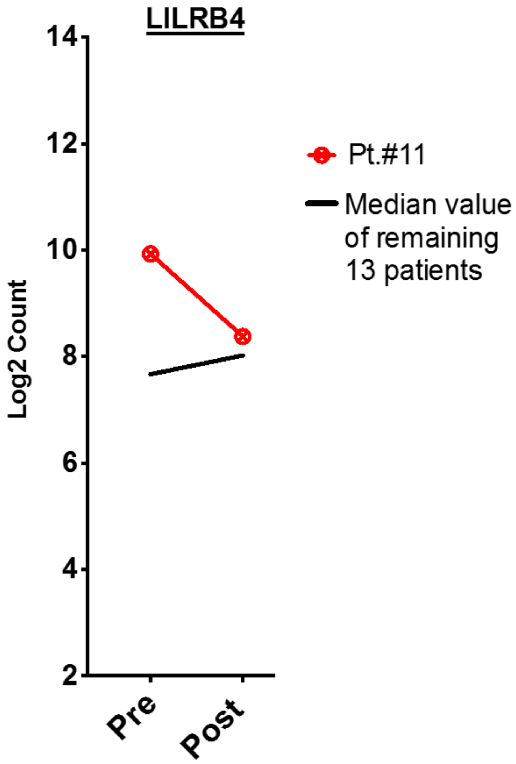
**Supplementary Figure 3 –** Expression of LILRB4 by NanoString in bone marrow aspirates after tremelimumab and durvalumab in all evaluable patients except for patient #11. Patient #11 was the only patient to be re-treated per protocol and had the longest time on treatment—this patient was analyzed separately (see main text).



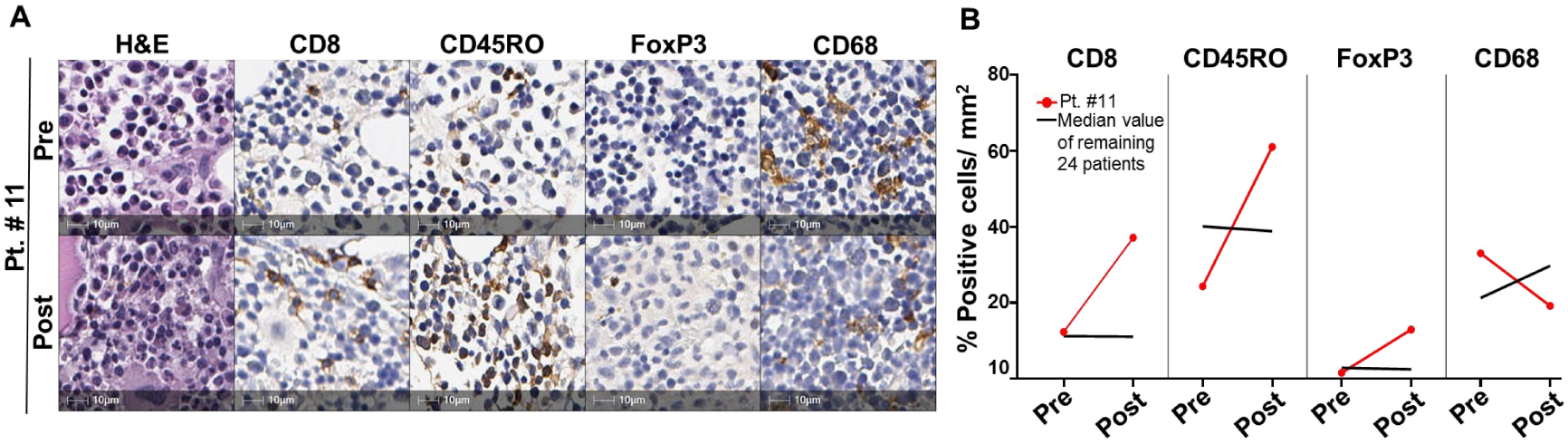
**Supplementary Figure 4 - Quantitative** IHC analysis of bone marrow cores. Percentage of CD8+, CD45RO+, FoxP3+, and CD68+ cells at baseline (Pre) and after treatment with tremelimumab and durvalumab (Post).



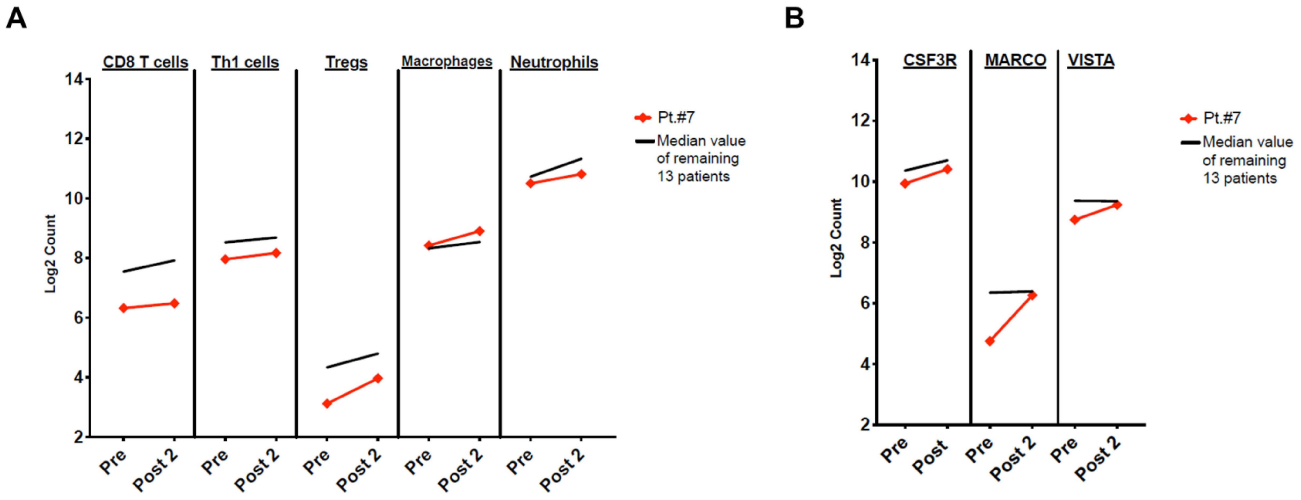
**Supplementary Figure 5 -** Expression of LILRB4 in bone marrow aspirates after tremelimumab and durvalumab in patient #11.



**Supplementary Figure 6 –** IHC staining for immune cell populations from bone marrow cores for patient #11. **A.** Representative H&E and IHC staining showing expression of CD8, CD45RO, FOXP3, and CD68 for patient #11 from bone marrow cores at baseline (Pre) and following tremelimumab and durvalumab (Post). **B.** Quantitative IHC assessment of frequency of immune cell phenotypes for patient #11 at baseline (Pre), and following tremelimumab and durvalumab (Post). Black line denotes median value of each cell type for the remaining 24 patients.



**Supplementary Figure 7-** Changes in immune cell subsets and specific immune markers in patient #7. A. Line graphs showing immune cell phenotypes by Nanostring at baseline (Pre), and after treatment with tremelimumab and durvalumab (Post) in patient #7. B. Line graphs showing expression of immune markers by gene expression at baseline (Pre), and after treatment with tremelimumab and durvalumab (Post) for patient #7. Red line denotes patient #7; black line denotes median values of each cell type/immune marker for remaining 13 patients.



**Supplementary Table 1 –** Treatment Exposure and Patient Disposition.

| Characteristic | All Patients (n=26) |
|---|---|
| **Median follow-up, months** | 43.6 |
| **Treatment exposure** | |
| Median duration of therapy, months | 3.8 |
| Combination doses received, median (IQR) | 3 (2-4) |
| Patients receiving 4 combination doses, n (%) | 10 (38) |
| Durvalumab maintenance doses received, median (range) | 0 (0-2) |
| **Reason for treatment discontinuation, n (%)** | |
| Disease progression | 22 (84.6) |
| Study drug toxicity | 3 (11.5) |
| Other (patient decision) | 1 (3.8) |

**Supplementary Table 2** – Baseline laboratory values. IQR=interquartile range; LDH=lactate dehydrogenase.

| **Laboratory Values** | **Median (IQR)** |
|---|---|
| Hemoglobin (g/dL) | 12.8 (11.6 – 13.5) |
| Alkaline phosphatase (U/L) | 95.5 (88.3 – 127.3) |
| LDH (U/L) | 445.5 (310.8 – 544) |
| Albumin (g/dL) | 4.3 (4.1 – 4.5) |

**Supplementary Table 3** – Prior therapies received. CAB=combined androgen blockade.

| Pt. # | 1L | 2L | 3L | 4L | 5L | 6L | 7L | 8L |
|---|---|---|---|---|---|---|---|---|
| 1 | Bicalutamide (CAB) | Abiraterone | Abiraterone + Enzalutamide | Enzalutamide | Abiraterone | | | |
| 2 | Docetaxel | Sipuleucel-T | | | | | | |
| 3 | Docet**t**.xel | Abiraterone | | | | | | |
| 4 | Cabozantinib | | | | | | | |
| 5 | Bicalutamide (CAB) | Sipuleucel-T | Enzalutamide | | | | | |
| 6 | Abiraterone + Enzalutamide | Bicalutamide (CAB) | Sipuleucel-T | | | | | |
| 7 | Docetaxel | Sipuleucel-T | | | | | | |
| 8 | Bicalutamide (CAB) | Sipuleucel-T | Abiraterone + Apalutamide | | | | | |
| 9 | Abiraterone | | | | | | | |
| 10 | | | | | | | | |
| 11 | Abiraterone | | | | | | | |
| 12 | Bicalutamide (CAB) | Sipuleucel-T | Enzalutamide | Abiraterone | Radium-223 | DES | Enzalutamide | |
| 13 | Sipuleucel-T | Enzalutamide | Abiraterone | | | | | |
| 14 | Bicalutamide (CAB) | Abiraterone | Enzalutamide | | | | | |
| 15 | Docetaxel | Sipuleucel-T | Enzalutamide | | | | | |
| 16 | Sipuleucel-T | | | | | | | |
| 17 | | | | | | | | |
| 18 | Bicalutamide (CAB) | Abiraterone | Enzalutamide | | | | | |
| 19 | Bicalutamide (CAB) | Abiraterone | Radium-223 | | | | | |
| 20 | Sipuleucel-T | Enzalutamide | Abiraterone | Radium-223 | | | | |
| 21 | Docetaxel | Enzalutamide | | | | | | |
| 23 | Abiraterone | Abiraterone + Sunitinib | Abiraterone + Dasatinib | | | | | |
| 24 | Bicalutamide (CAB) | Sipuleucel-T | | | | | | |
| 25 | Docetaxel | Abiraterone + Apalutamide | | | | | | |
| 26 | Flutamide (CAB) | Bicalutamide (CAB) | Nilutamide (CAB) | Abiraterone | Enzalutamide | Sipuleucel-T | | |
| 27 | Bicalutamide (CAB) | Sipuleucel-T | Abiraterone | Abiraterone + Sunitinib | Abiraterone + Dasatinib | Radium-223 | Enzalutamide | Enzalutamide + GSK2636771 (PI3Kβ inhibitor) |

**Supplementary Table 4 - Exploratory subgroup analysis of radiographic progression free survival (rPFS) and overall survival (OS) by prognostic features.**

| | | rPFS Months | | | OS Months | | |
|---|---|---|---|---|---|---|---|
| **Patient Characteristic** | | **Events/N** | **Median (95% CI)** | **P-Value** | **Deaths/N** | **Median (95% CI)** | **P-Value** |
| **All** | | **21/25** | **3.7 (1.9, 5.7)** | | **18/25** | **28.1 (14.5, 37.3)** | |
| Sites of Disease | | | | 0.49 | | | 0.49 |
| | Any Visceral Metastasis | 2/3 | 12.6 (1.8, 23.4) | | 2/3 | 18.2 (14.3, NR) | |
| | Bone + Lymph Node | 9/11 | 3.7 (1.8, 9.4) | | 9/11 | 28.1 (13.4, 34.5) | |
| | Bone-only | 10/11 | 3.7 (1.9, 5.7) | | 7/11 | 37.3 (13.5, NR) | |
| RECIST v1.1 Measurable | | | | 0.45 | | | 0.70 |
| | No | 16/19 | 3.7 (1.9, 5.7) | | 13/19 | 28.1 (13.5, 43.1) | |
| | Yes | 5/6 | 3.7 (1.8, 23.4) | | 5/6 | 31.4 (14.3, 37.9) | |
| CHAARTED High Volume | | | | 0.74 | | | 0.70 |
| | No | 6/6 | 4.6 (1.9, 13.8) | | 3/6 | 31.4 (13.4, NR) | |
| | Yes | 15/19 | 3.7 (1.8, 5.7) | | 15/19 | 28.1 (14.2, 37.3) | |
| Prior Docetaxel | | | | 0.31 | | | 0.73 |
| | No | 15/19 | 3.7 (1.9, 5.7) | | 14/19 | 28.1 (14.3, 37.9) | |
| | Yes | 6/6 | 1.9 (1.8, 12.8) | | 4/6 | 25.9 (12.9, NR) | |
| Prior Sipuleucel-T | | | | 0.99 | | | 0.39 |
| | No | 10/12 | 5.5 (1.8, 7.4) | | 8/12 | 31.4 (13.4, NR) | |
| | Yes | 11/13 | 3.7 (1.8, 12.8) | | 10/13 | 28.1 (14.2, 35.3) | |

**Supplementary Table 5** – Patient-level information and exploratory genetic analysis. Pt=patient; Combo=combination; OS=overall survival; rPFS=radiographic progression free survival; cPFS=clinical progression free survival; HgB=hemoglobin (g/dL); LDH=lactate dehydrogenase (U/L); AlkPh=alkaline phosphatase (U/L); ND=Not detected. N.B.: Mutations include both known pathologic variants and variants of unknown significance. *Patient received only one combination dose and was excluded from the efficacy analysis per-protocol. ** Patient (#11) experienced radiographic progression during the monotherapy phase and was re-treated with the combination per protocol, receiving total of eight combination doses. For this patient, the time to first radiographic progression (rPFS1) was 13.8 months and time to second radiographic progression (rPFS2) was 19.8 months.

| Pt. No. | No. Combo. Doses | OS (mo.) | rPFS (mo.) | cPFS (mo.) | Treatment Dur. (Mo.) | Laboratory Values | | | Sites of Disease | | | Genetic Alterations | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | HgB | AlkPh | LDH | Bone | Lymph | Visceral | Germline Gene | Germline Mutation (Amino Acid) | Germline Sequencing Method | Somatic Gene | Somatic Mutation(s) (Amino Acid) | Somatic Sequencing Method |
| 1 | 2 | 13.4 | 1.9 | 1.9 | 3.7 | 11.5 | 122 | 418 | Yes | Yes | No | - | - | None | *NRAS* | p.Q61R | MDA STGA Oncomine |
| 2 | 4 | 37.3 | 1.9 | 1.9 | 5.6 | 12.8 | 96 | 526 | Yes | No | No | *ATM* | p.R2547_S2549del | GeneDx | *KIT* | p.M541L | MDA CM50 |
| 3 | 3 | 12.9 | 1.8 | 1.9 | 3.7 | 14.4 | 146 | 639 | Yes | Yes | No | - | - | None | *CDK12*<br>*TP53* | p.G766fs*11<br>p.E287* | MDA STGA Oncomine |
| 4 | 3 | 41.1 | 5.5 | 5.6 | 5.5 | 12.3 | 125 | 728 | Yes | No | No | ND | ND | Invitae | ND | ND | MDA STGA Oncomine |
| 5 | 3 | 13.5 | 3.7 | 3.8 | 3.7 | 12.9 | 91 | 355 | Yes | No | No | - | - | None | - | - | None |
| 6 | 4 | 20.7 | 3.6 | 3.7 | 3.7 | 15.2 | 376 | 616 | Yes | No | No | - | - | None | *PTCH1*<br>*TP53* | p.D180N<br>p.C277W | MDA STGA Oncomine |
| 7 | 4 | 40.8 | 12.8 | 13.0 | 12.8 | 15.5 | 95 | 446 | Yes | Yes | No | *ATM* | p.A1110T | Invitae | - | - | None |
| 8 | 3 | 18.2 | 1.8 | 1.9 | 5.5 | 11.8 | 111 | 392 | Yes | No | Yes (lung) | - | - | None | - | - | None |
| 9 | 4 | 39.2 | 1.9 | 4.5 | 4.4 | 15.0 | 93 | 472 | Yes | No | No | - | - | None | *AR* | p.H875Y<br>p.T878A | MDA STGA Oncomine |
| 10 | 3 | 37.3 | 3.7 | 3.8 | 3.8 | 11.6 | 73 | 457 | Yes | Yes | No | ND | ND | Invitae | *TP53* | p.C277W | MDA STGA Oncomine |
| 11 | 8 | 37.3 | 13.8 | 20.2 | 20.8 | 12.5 | 89 | 586 | Yes | No | No | ND | ND | Invitae | *SMARCB1* | p.R374W | MDA STGA Oncomine |
| 12 | 2 | 14.3 | 1.8 | 2.0 | 2.0 | 11.6 | 154 | 550 | Yes | Yes | Yes (adrenal) | - | - | None | ND | ND | MDA CM50 (insufficient sample) |
| 13 | 3 | 28.1 | 7.3 | 7.5 | 7.4 | 11.5 | 74 | 445 | Yes | Yes | No | - | - | None | - | - | None |
| 14 | 2 | 22.9 | 1.8 | 2.8 | 1.8 | 13.3 | 128 | 488 | Yes | Yes | No | ND | ND | Invitae | *TP53* | p.R342* | MDA STGA Oncomine |
| 15 | 2 | 14.2 | 1.8 | 1.9 | 1.8 | 13.3 | 90 | 404 | Yes | Yes | No | ND | ND | Invitae | *AR*<br>*FGFR*<br>*TP53* | Xq12 Amp.<br>8p11.23-p11.22 Amp.<br>p.G245S | MDA STGA Oncomine |
| 16 | 4 | 34.5 | 1.8 | 1.9 | 3.7 | 13.4 | 88 | 396 | Yes | No | No | *CHEK2* | p.T367Mfs*15 | Invitae | *CDK12* | p.G927R<br>p.R950* | MDA STGA Oncomine |
| 17 | 4 | 20.3 | 5.5 | 5.6 | 7.4 | 12.1 | 77 | 494 | Yes | Yes | No | ND | ND | Invitae | ND | ND | Caris |
| 18 | 1 | * | * | * | * | 11.2 | 346 | 843 | Yes | No | No | - | - | None | - | - | None |
| 19 | 2 | 13.5 | 2.7 | 2.8 | 2.8 | 11.3 | 245 | 1077 | Yes | No | No | *MSH2* | p.R534C | Invitae | - | - | None |
| 20 | 3 | 11.9 | 5.7 | 5.7 | 5.7 | 14.2 | 78 | 219 | Yes | No | No | - | - | None | *AR*<br>*PTEN*<br>*TP53* | Xq12 Amp.<br>p.K254fs*42<br>p.P278T | MDA STGA Oncomine |
| 21 | 3 | 10.0 | 7.4 | 7.5 | 7.4 | 12.8 | 103 | 198 | Yes | No | No | ND | ND | Invitae | *ATM* | p.S2498F | MDA STGA Oncomine |
| 23 | 3 | 31.2 | 9.4 | 9.5 | 9.4 | 13.7 | 91 | 170 | Yes | Yes | No | *BRCA2* | p.M1936T | Invitae | *PALB2* | p.G257A | MDA STGA Oncomine |
| 24 | 2 | 30.2 | 1.9 | 1.9 | 1.9 | 13.5 | 59 | 192 | Yes | Yes | No | - | - | None | - | - | None |
| 25 | 4 | 14.5 | 1.8 | 1.8 | 3.7 | 13.3 | 121 | 225 | Yes | Yes | No | ND | ND | Invitae | - | - | None |
| 26 | 4 | 18.6 | 3.7 | 3.7 | 3.7 | 13.1 | 78 | 217 | Yes | No | No | - | - | None | - | - | None |
| 27 | 4 | 18.6 | 15.2 | 15.9 | 3.9 | 11.4 | 137 | 296 | Yes | No | Yes (adrenal/soft tissue [penis]) | - | - | None | - | - | None |