



Innovative Approaches to Prolong Survival: Case Studies

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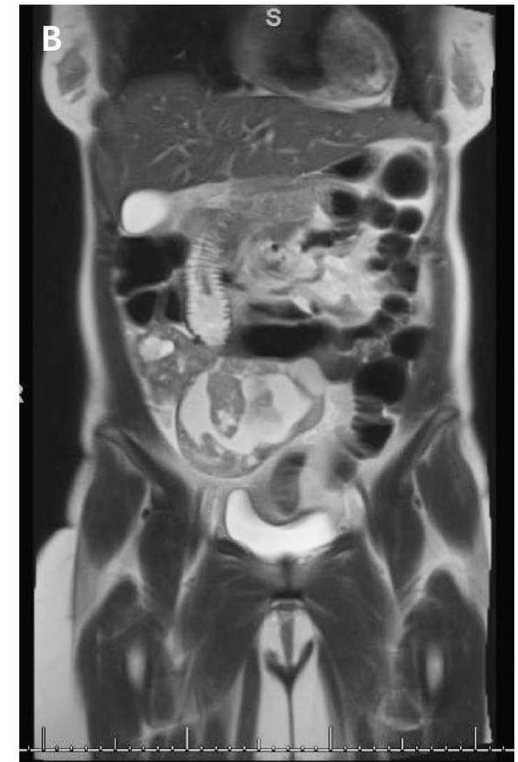
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UC San Diego
HEALTH SYSTEM

Case Presentation & Work-up

- 34 year-old healthy pregnant female at 8 weeks presents with abdominal pain.
- Symptoms started 6 months earlier with abdominal fullness.
- Ultrasound (A): 13.9-cm complex right adnexal mass
- MRI (B): Complex mass thought to arise from the right ovary



Differential Diagnosis

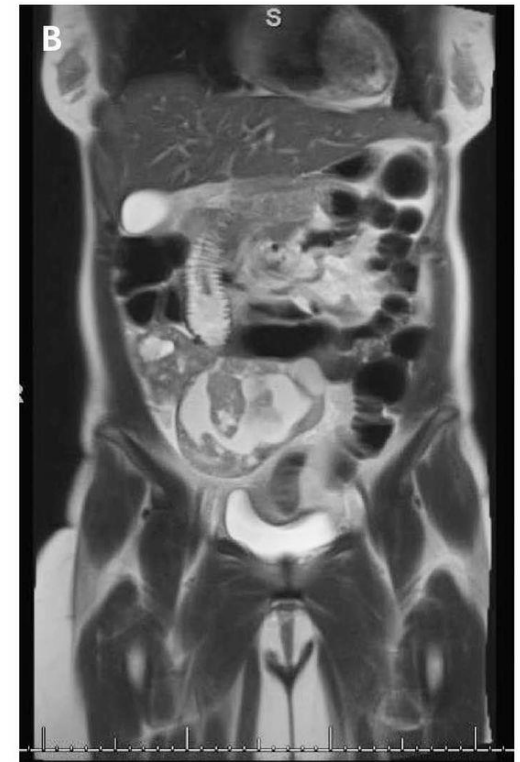
- Differential diagnosis:
 - Dermoid cyst
 - Hemorrhagic ovarian cyst
 - Leiomyoma

- Her serum CA125 tumor marker level was mildly elevated at 81 U/mL (normal, 0–34)



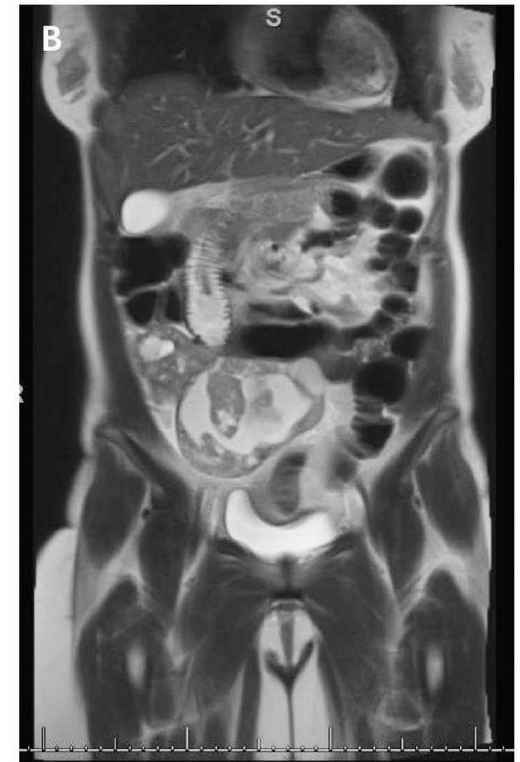
Specialist Referral

- After consultation with a perinatologist, she was referred to gynecologic oncology.



Operation Recommended

- At 16 weeks' gestational age, she underwent an exploratory laparotomy.



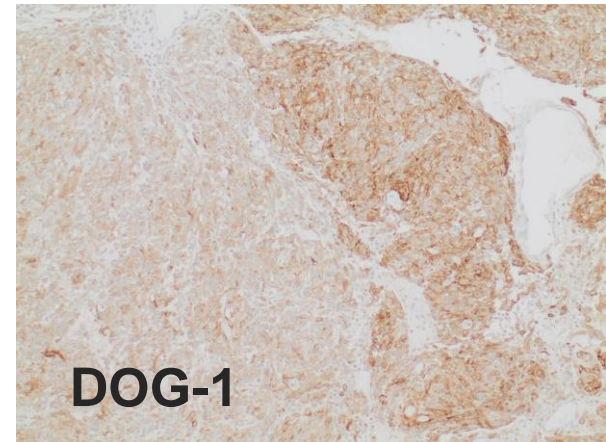
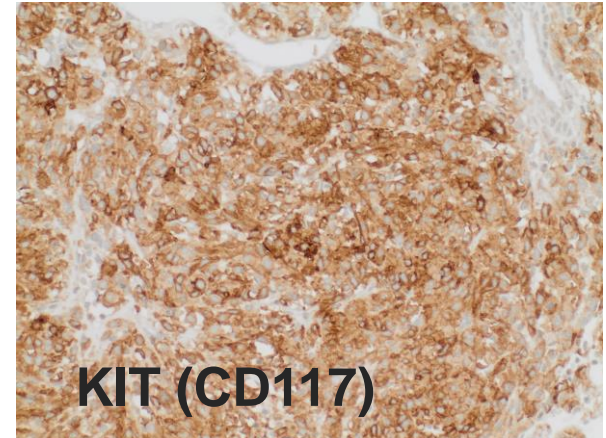
Intra-operative Findings

- Normal bilateral adnexa
- Gravid uterus
- 14 x 10-cm solid mass arising from the mid-jejunum
- No additional disease
- Mass was resected *en bloc* with the jejunum, followed by a primary anastomosis



Pathological Diagnosis

- Gastrointestinal Stromal Tumor (GIST)
 - IHC positive
 - KIT
 - DOG-1
 - Size
 - 14.0 x 10.0 x 7.0 cm
 - Mitotic rate
 - 3 per 5 mm²



High Risk of Recurrence

Modified NIH Criteria (Joensuu)

| Risk category | Tumor size (cm) | Mitotic index (per 50 HPFs) | Primary tumor site |
|-------------------|-----------------|-----------------------------|--------------------|
| Very low risk | <2.0 | ≤5 | Any |
| Low risk | 2.1-5.0 | ≤5 | Any |
| Intermediate risk | 2.1-5.0 | >5 | Gastric |
| | <5.0 | 6-10 | Any |
| | 5.1-10.0 | ≤5 | Gastric |
| High risk | Any | Any | Tumor rupture |
| | >10 cm | Any | Any |
| | Any | >10 | Any |
| | >5.0 | >5 | Any |
| | 2.1-5.0 | >5 | Nongastric |
| | 5.1-10.0 | ≤5 | Nongastric |

High Risk of Recurrence

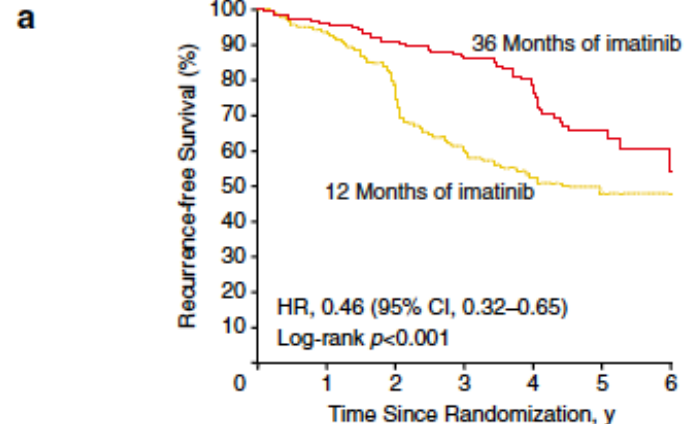
MSKCC/Gold Nomogram



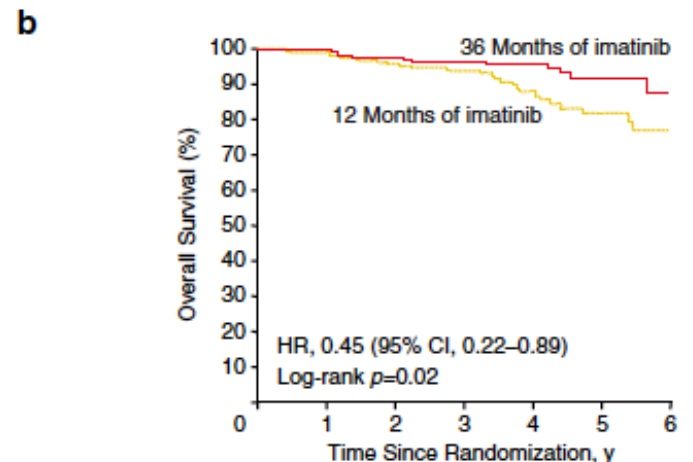
Gold JS, Gonen M, Gutierrez A, et al. Development and validation of a prognostic nomogram for recurrence-free survival after complete surgical resection of localised primary gastrointestinal stromal tumour: a retrospective analysis. *Lancet Oncol.* 10(11), 1045-1052 (2009).

Adjuvant Imatinib?

Phase III randomized Scandinavian Sarcoma Group (SSG) XVIII/AIO trial



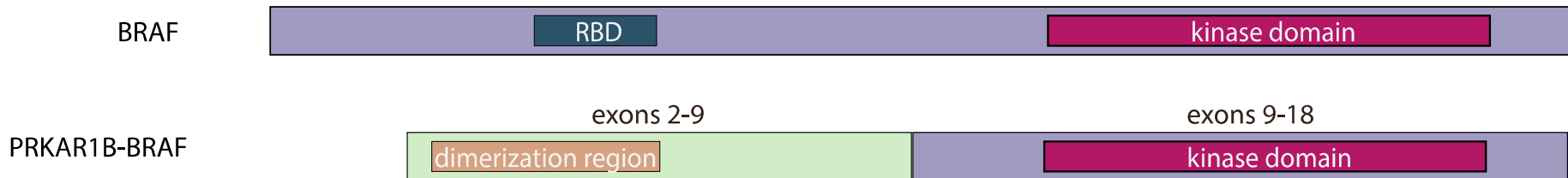
| No. of patients | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
|-----------------------|-----|-----|-----|-----|----|----|----|
| 36 Months of imatinib | 198 | 184 | 173 | 133 | 82 | 39 | 8 |
| 12 Months of imatinib | 199 | 177 | 137 | 88 | 49 | 27 | 10 |



| No. of patients | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
|-----------------------|-----|-----|-----|-----|-----|----|----|
| 36 Months of imatinib | 198 | 192 | 184 | 152 | 100 | 56 | 13 |
| 12 Months of imatinib | 199 | 188 | 176 | 140 | 87 | 46 | 20 |

Joensuu et al. *JAMA*, 2012.

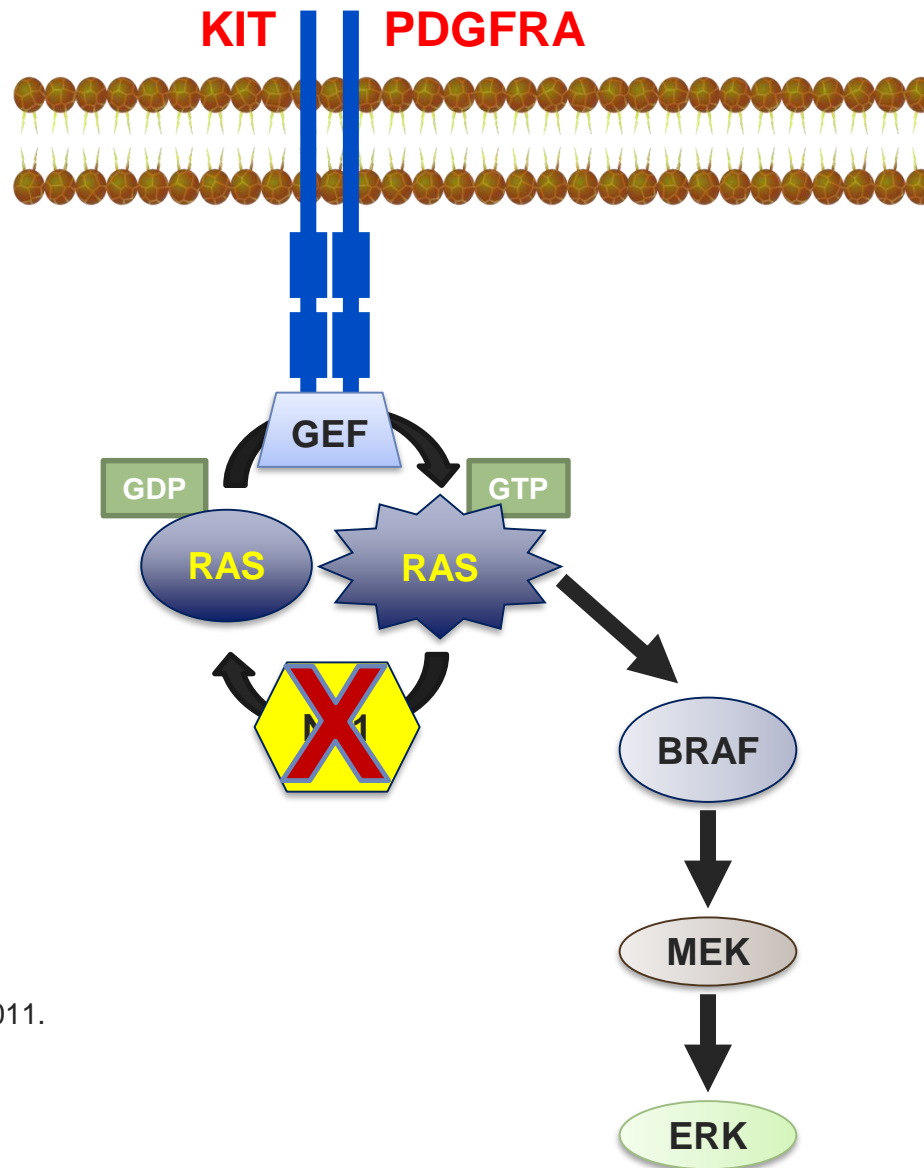
Next Generation Sequencing



A fusion involving the N-terminus of BRAF was identified. This fused exons 9-18 of BRAF, including the kinase domain, to exons 2-9 of PRKAR1B.

Loss of the Ras-binding domain (RBD) of BRAF
Gain of a dimerization region present within PRKAR1B.

Imatinib Targets Upstream



Corless *et al.*, *Nature Reviews Cancer*. 2011.
Pantaleo *et al.*, *Cancer Medicine*. 2015.
Killian *et al.*, *Sci Transl Medicine*. 2014.
Shi *et al.*, *J Transl Medicine*. 2016.

Considerations

- 12 reported cases of GIST diagnosed in pregnancy (including this one)
 - More than half of these cases were thought to be adnexal or uterine masses prior to surgery, based on imaging and clinical presentation
- Teratogenic risks of imatinib during pregnancy, including an increased incidence of congenital anomalies when given in the first trimester, but a relatively low risk to the fetus in the second and third trimesters.

Plan

- Elected for surveillance
- At 40 weeks 1 day, she presented for labor and delivered a healthy baby boy, weighing 3,634 g, via normal spontaneous vaginal delivery
- At 3.5 years postoperatively, she remains without evidence of disease

A Novel *PRKAR1B-BRAF* Fusion in Gastrointestinal Stromal Tumor Guides Adjuvant Treatment Decision-Making During Pregnancy

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- GIST can be a diagnostic dilemma in pregnancy
- Demonstrates the importance of tumor sequencing
- First reported *BRAF* fusion in GIST
- Highlights personalized approach to precision oncology that helped avoid unnecessary toxicity to the patient and fetus