Developmental Therapeutics Cases

Chair: Pamela Munster, UC San Francisco

Case 1

UC San Francisco Developmental Therapeutics

Pamela Munster, Rahul Aggarwal and Mallika Dhawan

Case 1: Newly diagnosed RCC

- 2009: 69 yo male with new gross hematuria
- Found to have a left renal mass; localized predominantly clear cell RCC (staging unavailable)
- 2/2009: underwent left renal nephrectomy

What would you do at this point?

1. Adjuvant sunitinib
2. Surveillance with follow-up imaging in 6 months and then annual imaging
3. Adjuvant nivolumab

Q1 What would you do at this point?

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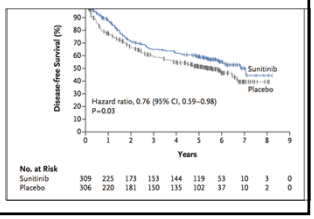


Case 1 continued

- 11/2010: restaging scans reveal new lung nodules
  - Initiates sunitinib with partial response
- 12/2010: scrotal US/bx done for enlarging right testicle which reveals
- 1/2011 right orchiectomy for 8.5 cm mass; found to be predominantly clear cell RCC, 8.5 cm, involving rete testis
- 8/2011 changed to everolimus 10 mg daily for progression on sunitinib

Case 1 Continued

- 10/2011: Significant side effects/progression on everolimus
- 11/2011: initiates sorafenib
- 4/2012: Partial response and then progression
- 04/2012: initiates Pazopanib 800 mg/day
- 07/2012: Imaging reveals further interval progression of pulmonary nodules
- ~08/2012: Stopped Pazopanib

Q2: What would you do at this point?

1. Avastin
2. Nivolumab
3. Axitinib
4. Cabozantinib
5. retry Sunitinib or pazopanib

Answer: various options

- Avastin[2]: Bevacizumab plus IFNa or IFNa alone
  - PFS 8.5 versus 5.2 months; HR 0.71, 0.61-0.83
- Cabosun[3]: 157 patients assigned to Cabozantinib vs. Sunitinib
  - Cabozantinib improved median PFS (8.2 vs. 5.6 months) and was associated with a 34% reduction in progression or death
- Nivolumab vs. Everolimus[4]: 821 patients with RCC after 1 or 2 regimens, assigned to nivolumab vs. everolimus 1:1.
  - OS: 25.0 months with nivolumab and 19.6 months with everolimus.
  - The hazard ratio for death was 0.73
- Retreatment[5]: 22% of patients re-treated with sunitinib had a partial response (PFS with initial treatment: 13.7 months vs. 7.2 months with re-treatment)

Case 1 Continued

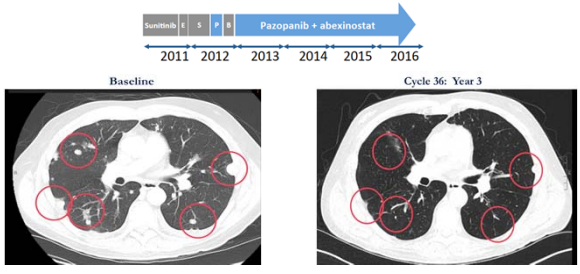
- 8/2012 - 10/2012: Bevacizumab monotherapy
- 10/22/12: Imaging demonstrated interval progression of disease
  - Increasing size/number of pulmonary metastases, increasing size of soft tissue nodules near diaphragm along pleural surface, L liver lobe metastasis increased in size, new pathologic fracture of R posterior 5th rib.

Rationale for Phase 1 study of Pazopanib in Combination with Abexinostat

- Epigenetic modulation with a histone deacetylase inhibitor (HDACi) prevents outgrowth of resistant phenotype and reverse resistance to PAZ monotherapy
- PBMC histone acetylation and/or HDAC expression may predict for the subset of patients most likely to achieve benefit

Prior Therapies and Treatment Dates:

1) Sunitinib (partial response then progression): 11/2010 – 8/2011
2) Everolimus (primary refractory): 8/2011 – 10/2011
3) Sorafenib (primary refractory): 11/2011 – 4/2012
4) Pazopanib (primary refractory): 5/2012 – 8/2012
5) Bevacizumab (primary refractory): 8/2012-10/2012
6) Pazopanib + abexinostat (partial response 40+ months):12/2012–ongoing

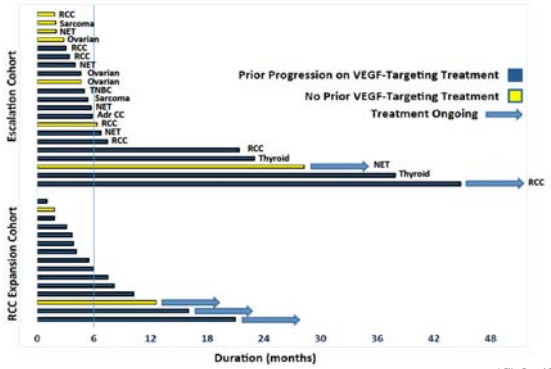


Summary of Dose-Limiting Toxicities

	Dose	Frequency	Level	N (36)	# DLTs	Description
5 of 7 day/week ABX dosing	PAZ 600 mg/d + ABX 45 mg/m²	ABX 5/7 days	1A	4	2	Grd 3 thrombo-cytopenia (N = 2)
	PAZ 400 mg/d + ABX 30 mg/m²		2A	6	1	Grd 3 fatigue
	PAZ 600 mg/d + ABX 30 mg/m²*		3A	4	0	None
	PAZ 800 mg/d + ABX 30 mg/m²		4A	8 (6 evaluable)	2	Grd 3 fatigue Grd 2 AST + fever
	PAZ 600 mg/d + ABX 45 mg/m²	ABX 4/7 days	1B	6	1	Grd 3 AST/ALT
4 of 7 day/week	* PAZ 800 mg/d + ABX 45 mg/m²		2B	8 (6 evaluable)	0	None
	* PAZ 800 mg/d + ABX 45 mg/m²		Expansion	15	0	None

* Recommended Phase 2 Dose

Responses can be durable in VEGF Pre-Treated Patients



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Take Home Points

- Epigenetic modifiers may 'reset' responsiveness to VEGF-targeting agents
- Randomized study planned to further test this hypothesis
- Patients with renal cell carcinoma who are refractory to multiple lines of prior therapy may still derive therapeutic benefit from investigational agents/combinatorial therapy

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2. Rini BI, Halabi S, Rosenberg JE, Stadler WM, Vaena DA, Ou SS, et al. Bevacizumab plus interferon alfa compared with interferon alfa monotherapy in patients with metastatic renal cell carcinoma: CALGB 90206. J Clin Oncol. 2008;26(33):5422-8.
3. Choueiri TK, Halabi S, Sanford B, et al, Cabozantinib Versus Sunitinib As Initial Targeted Therapy for Patients With Metastatic Renal Cell Carcinoma of Poor or Intermediate Risk: The Alliance A031203 CABOSUN Trial J Clin Oncol. 2016
4. Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med. 2015;373(19):1803-13.
5. Zama IN, Hutson TE, Elson P, Cleary JM, Choueiri TK, Heng DY, et al. Sunitinib rechallenge in metastatic renal cell carcinoma patients. Cancer. 2010;116(23):5400-6.

Case 2

Stanford Developmental Therapeutics

Shivaani Kumar

Case 2: BRAF V600E + melanoma

- 2008: 51 yo F with stage IIIA melanoma with mixed superficial spreading and desmoplastic features on the right upper back. Sentinel LN bx c/w micrometastatic disease, resection followed by one yr of interferon
- Recurred in 2012-1.25 mm depth, Clark level III, resected with negative margins, sentinel LN negative
- Recurred in 2/2016- L5 vertebral body, bx confirmed, BRAF V600E+. Ipilimumab + nivolumab
  - Developed new mets in acetabulum and vertebrae, local radiosurgery
  - s/e hypopituitarism, neuropathy
- 11/2016- Dabrafenib with trametinib
  - day 4 developed fevers, rash, weakness, ataxia
  - Symptoms resolved on stopping

Question 1:

1) Switch to checkpoint blockade +/- anti-CTLA4 antibody?

2) Switch to vemurafenib + another MEK inhibitor?

3) Switch to vemurafenib alone?

4) Reduce dose of Dabrafenib with trametinib and re-challenge?

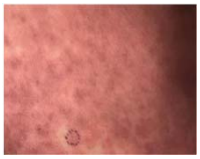
What next?

Patient re-challenged with dabrafenib with trametinib at a reduced dose

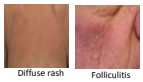
- Symptoms recurred
- Treatment discontinued
- Now what?

Case (cont'd)

- Patient switched to Vemurafenib with cobimetinib
  - Day 8 developed high fevers (102-103F), diffuse facial swelling, rash, diffuse shotty adenopathy, diarrhea, abdominal pain, arthralgias, sensory neuropathy, worsening ataxia.

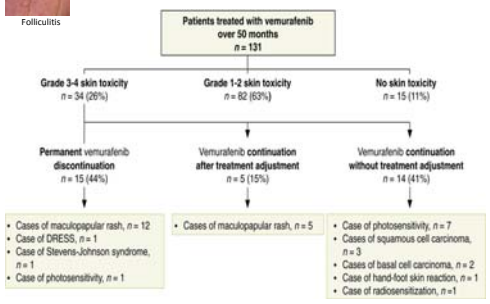


  - Are these expected toxicities of BRAF inhibitors? MEK inhibitors?
  - Does this patient have DRESS syndrome?



Diffuse rash Folliculitis

Profile of vemurafenib-induced severe skin toxicities



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http://onlinelibrary.wiley.com/doi/10.1111/jdv.13443/full#jdv13443-fig-0001

Table 1. Comparison between vemurafenib and dabrafenib regarding efficacy, toxicity, relative kinase inhibition, selection of drug dose, and clinical trial design

	Vemurafenib (Chapman et al., 2011, 2012a)	Dabrafenib (Hauschild et al., 2012a, 2013)
Median follow-up (mo)	12.5	15.2
Efficacy in metastatic melanoma		
RR (%)	57	53
PFS (mo)	6.9	6.9
OS (mo)	13.6	18.2
Toxicity, any grade (%)		
cSCC/KA[a]	20–26	6–11
Alopecia[a]	36	12
Rash[b]	52	42
Arthralgia[a]	59	33
Relative IC50[c]		
Mutant BRAF	1	1
CRAF	1.5	8.3
Wild-type BRAF	3	20
RP2D	Maximum tolerated dose	Pharmacodynamics, clinical response
Study population (%)		
Australia/NZ	11	6
V600K	10	0
Dermatologic assessment		
Clinician	Dermatologist	Study investigator or dermatologist
Excision of all suspicious lesions	Mandated	Recommended
Central review of cSCC	Yes	No

mo, month; RR, response rate; PFS, progression-free survival; OS, overall survival; NA, not available; cSCC/KA, cutaneous squamous cell carcinoma or keratoacanthoma; IC50, half-maximal inhibitory concentration; RP2D, recommended part two dose; NZ, New Zealand.
NB: rash indicates rash (not specified) and hyperkeratosis.
[a]Data from the phase 1, 2, 3 trials (Ascierto et al., 2013; Chapman et al., 2011, 2012a; Falchook et al., 2012; Flaherty et al., 2010; Hauschild et al., 2012a; Sosman et al., 2012).
[b]Data from the phase 2 trials (Ascierto et al., 2013; Sosman et al., 2012).
[c]IC50 data from the phase 1 trials (Falchook et al., 2012; Flaherty et al., 2010).

Menzies AM, et al. Pigment Cell Melanoma Res 2013;26:611

What is DRESS Syndrome?

- Drug reaction with eosinophilia and systemic symptoms (DRESS), is a life-threatening multi-organ system reaction induced by drugs
- Possible causes:
  - Lack of genetic detoxifying enzymes, so metabolites collect causing damage
  - Specific HLA genotypes
  - Viral infections: has been associated with sequential reactivations of herpesviruses.
- 10% mortality
- RegiSCAR criteria for diagnosis of DRESS
  - Hospitalization
  - Reaction suspected to be drug-related
  - Acute rash
  - Fever >38°C*
  - Enlarged lymph nodes at a minimum of 2 sites*
  - Involvement of at least 1 internal organ*
  - Blood count abnormalities*
    - Lymphocytes above or below normal limits
    - Eosinophils above the laboratory limits
    - Platelets below the laboratory limits

3 of the 4 criteria with * have to be met for dx; a scoring system is also used

Vemurafenib-induced DRESS syndrome

- 3 cases reported in the literature
- Symptoms recur even at reduced dose
- High complication rate, mortality
- Discontinue vemurafenib
- Cross-reactivity between vemurafenib and dabrafenib has not been reported and dabrafenib has less cutaneous toxicities
- With our patient, she developed similar symptoms with both drugs

Munch M, Peuvrel L, et al. Early-onset vemurafenib-induced DRESS syndrome. Dermatology. 2016;232(1):126-8

Case 2 (cont'd)

- Does our pt have DRESS Syndrome?
  - Hospitalization Y
  - Reaction suspected to be drug-related Y
  - Acute rash Y
  - Fever >38°C* Y
  - Enlarged lymph nodes at a minimum of 2 sites* Y
  - Involvement of at least 1 internal organ* Y
  - Blood count abnormalities* Y
    - Lymphocytes above or below normal limits 90 (below normal)
    - Eosinophils above the laboratory limits normal
    - Platelets below the laboratory limits 108K (below normal)
  - Skin bx: Superficial perivascular dermatitis with eosinophils
  - PCR did not identify any viral activation including HSV
  - Started on 60 mg prednisone with continued worsening of symptoms- admitted and received IV steroids- gradual improvement in symptoms

What next?

- Patients immune system is stimulated so no further therapy
- Immune checkpoint blockade?
- Newer generation BRAF inhibitors?
- Chemotherapy?

- Regulatory T cells (Tregs) are expanded during the acute stage of DRESS but, upon clinical resolution, their function becomes gradually defective, which could increase the risk of developing autoimmune sequelae
- Systemic steroids have been shown to prevent Treg dysfunction

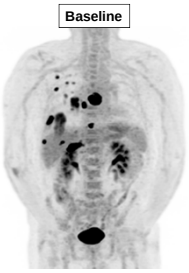
Case 3

UC Davis Developmental Therapeutics

Tina Li, Arta Monjazeb and Karen Kelly

Case 3: Newly Diagnosed Metastatic NSCLC

- **A 71-year-old White man**
  - Presents with persistent, right rib cage pain after lifting luggage. CXR revealed a right lung mass. Denies cough, shortness of breath, and dyspnea on exertion. No hemoptysis. Good appetite. No weight loss
  - Former smoker (>15 PY, quit 50 yrs ago)
  - ECOG PS=1
- Staging workup:
  - A PET/CT scan reveals a 2.0-cm, spiculated RLL mass, a 0.5-cm RUL mass, multiple pleural based masses in the right hemithorax, liver and bone metastasis.
  - A brain MRI scan reveals no metastatic disease.
  - Clinical stage IV (T1abNxM1b)



Case 3 Continued:

- Diagnosis: Core needle biopsy of right chest wall mass and right posterior, paraspinal chest wall mass.

CT-guided FNA	Right chest wall mass	Right posterior, perispinal chest wall mass
Histology	**adenocarcinoma**	**squamous cell carcinoma**
Grade		**poorly differentiated**
Immunohistochemistry	CK7+, CK-20-, TTF-1+.	AE1/AE3 +, CK7 -, CK20-, TTF-1-, HMB45-, S100-, CK5/6, rare, focal positive, P40 +, Napsin A-
PD-L1 22C3 Pharm	**--**	**Positive (95%, 3+)**
Tumor genotyping	**Quality insufficient**	**Not ordered**

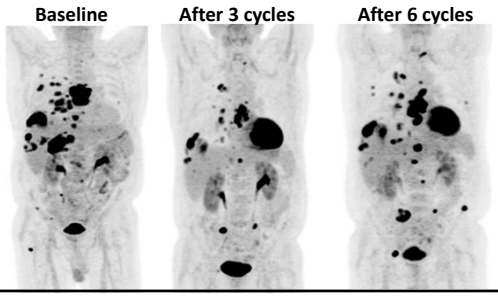
- Plasma circulating tumor DNA (ctDNA) by a >50-gene panel next generation sequencing (NGS) assay revealed *KRAS* K12C (3.65%) and two p53 mutations (*TP53* splice site 673-1G>T and V225F, 36.0% and 36.1%, respectively).

Q1.1 What would you recommend ?

1. Re-biopsy for broad tumor genomic profiling of adenocarcinoma
2. First line immunotherapy with pembrolizumab
3. First line combination immunotherapy on a clinical trial
4. A trial targeting *KRAS* mutation (if available)
5. First line platinum-containing chemotherapy

Case 1 Continued:

- Patient had clinical and radiographic responses in almost all existing tumors after 3 cycles of pembrolizumab monotherapy.
- However, he had extensive tumor progression after 6 cycles of pembrolizumab.
- Patient has good performance status (KPS 80%) and normal organ function



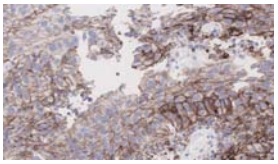
Q1.2 What would you recommend ?

1. Re-biopsy for broad tumor genomic profiling test and PD-L1 IHC of a growing tumor
2. Second line immunotherapy
3. Platinum-based combinational chemotherapy
4. Docetaxel monotherapy
5. Clinical trial targeting KRAS (trametinib and docetaxel)

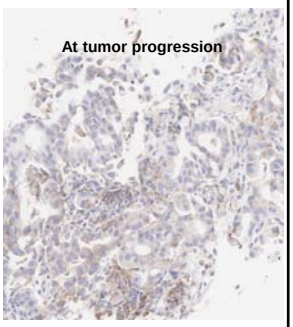
Case 3 Continued:

Tumor re-biopsy showed adenocarcinoma with PD-L1 IHC 2% and plasma ctDNA confirmed raising *KRAS* K12C mutation.

At diagnosis



At tumor progression



Q1.3 This patient is eligible for several clinical trials. What would you recommend as a second line trial ?

1. An PD-L1 inhibitor
2. Second line immunotherapy
3. Platinum-based combinational chemotherapy
4. Docetaxel monotherapy
5. Clinical trial targeting KRAS (trametinib and docetaxel)

Take Home Points

- Immune checkpoint inhibitors produce rapid objective response in 20% of patients.
- Variable tumor response patterns have been observed.
- Further mechanistic studies are needed to understand the exceptional response, primary resistance, adaptive resistance and acquired resistance.
- cfDNA for next generation sequencing is a non-invasive test that can provide rapid similar “actionable results” to tumor tissue analysis.

References

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