Phase II Study of Selumetinib vs Temozolomide in Patients with Advanced Uveal Melanoma (CTEP #8443)

Richard D. Carvajal

Memorial Sloan-Kettering Cancer Center

Jeffrey A. Sosman,[1] Fernando Quevedo,[2] Mohammed M. Milhelm,[3] Anthony M. Joshua,[4] Ragini R. Kudchadkar,[5] Gerald P. Linette,[6] Thomas Gajewski,[7] Jose Lutzky,[8] David Lawson,[9] Christopher D. Lao,[10] Patrick J. Flynn,[11] Mark R. Albertini,[12] Takami Sato,[13] Daniel Paucar,[14] Katherine S. Panageas,[14] Mark A. Dickson,[14] Jedd D. Wolchok,[14] Paul B. Chapman,[14] Gary K. Schwartz[14]

[1]Vanderbilt University, [2]Mayo Clinic, [3]University of Iowa, [4]Princess Margaret Cancer Center, [5]H Lee Moffitt Cancer Center, [6]Washington University, [7]University of Chicago, [8]Mt. Sinai Comprehensive Cancer Center, [9]Emory University, [10]University of Michigan, [11]Metro Minnesota CCOP, [12]University of Wisconsin, [13]Thomas Jefferson University, [14]Memorial Sloan-Kettering Cancer Center

Disclosures

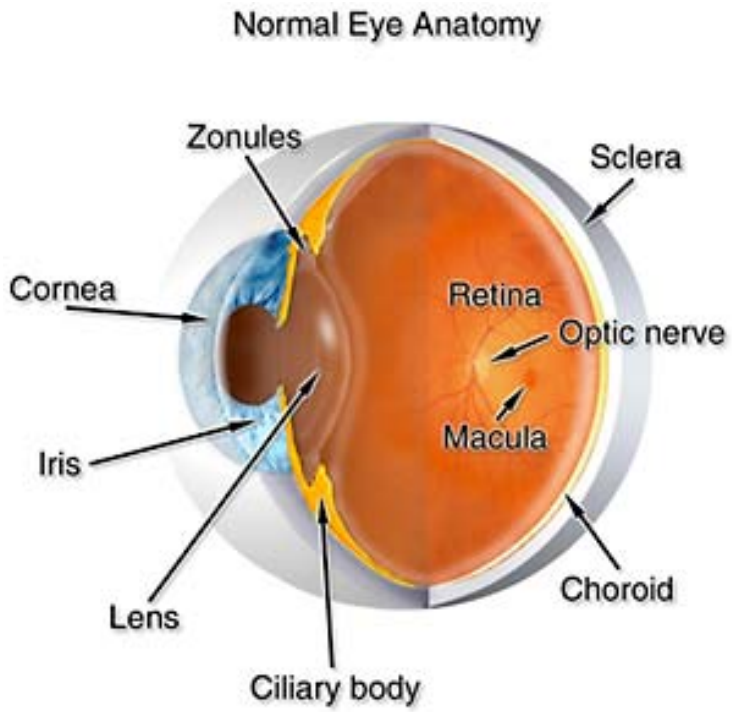
- No relevant relationships to disclose

Background

- Uveal melanoma is an orphan disease that is biologically distinct its cutaneous counterpart

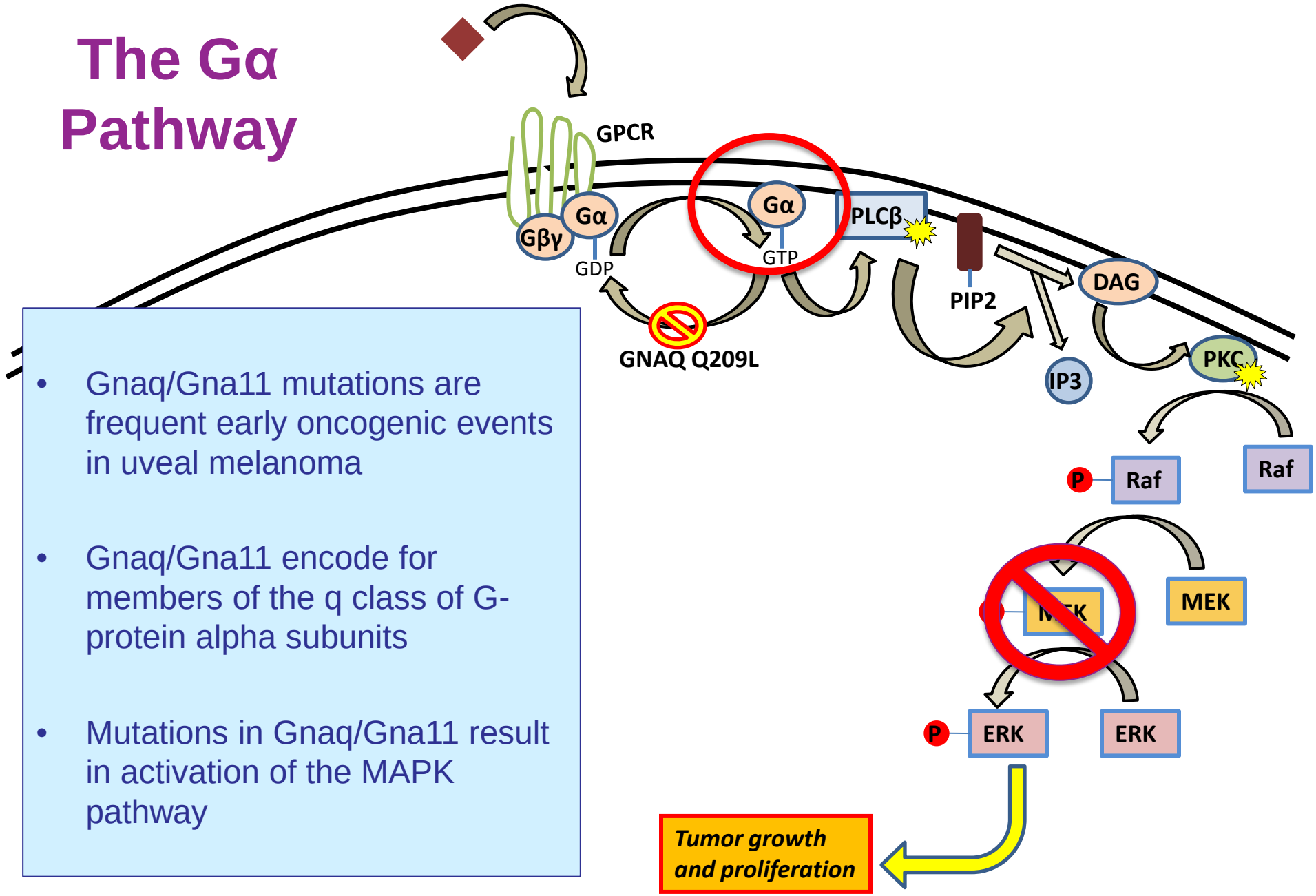
- There is **no effective systemic therapy** for metatastic uveal melanoma

- The standard of care for patients with advanced disease is clinical trial participation



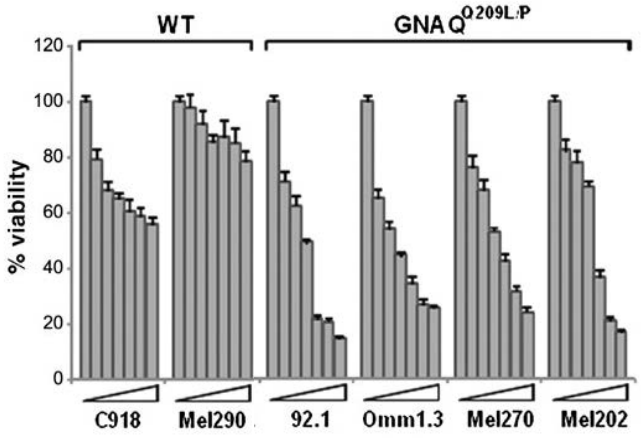
- Thus far, no trial of systemic therapy has been positive in this disease

The Gα Pathway



- Gnaq/Gna11 mutations are frequent early oncogenic events in uveal melanoma
- Gnaq/Gna11 encode for members of the q class of G-protein alpha subunits
- Mutations in Gnaq/Gna11 result in activation of the MAPK pathway

Selumetinib (AZD6244; ARRY-142886) Results in Decreased Viability of Uveal Melanoma in a Mutation Dependent Fashion



Genotype	IC50
WT	> 1 µmol/L
GNAQ mut	< 0.1 µmol/L

Subset Analysis of 20 Uveal Melanoma Patients Treated on a Completed Study of Selumetinib vs Temozolomide (NCT00338130)

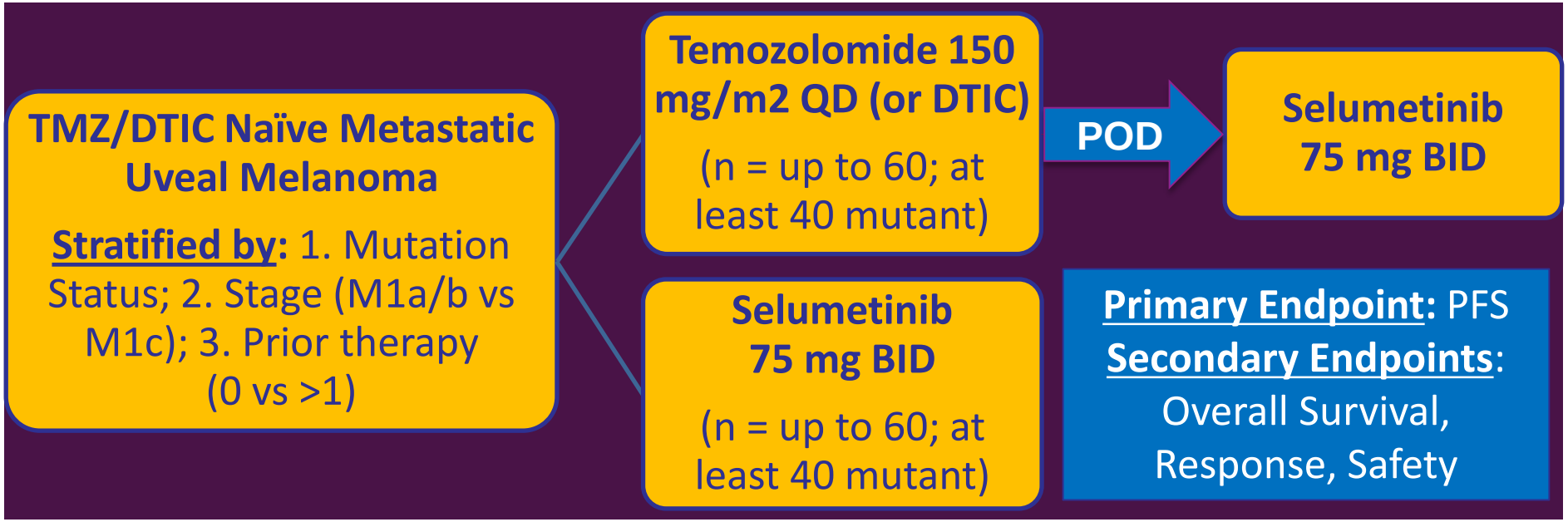
	TMZ (n = 13)	Selumetinib (n = 17)
TTP, Median	**7.1 weeks** (95% CI: 5.6 - 26.7 weeks)	**16.3 weeks** (95% CI: 10 - 28.8 weeks)

- PFS HR = 0.76, 80% CI (0.38, 1.53)
  - ➢ Comparing 7 and 13 pts init randomized to selumetinib and TMZ, respectively

Ambrosini et al. Clin Cancer Res, 2012. Patel et al. CCR 2011.
Cantarini et al, CMGS Abs SP31, 2010.

We therefore systematically assessed the efficacy of selumetinib, a non-ATP competitive inhibitor of MEK1/2, in patients with metastatic uveal melanoma

Study Design



- Radiographic assessments using RECIST 1.1 performed at week 4, week 8, and every 8 weeks subsequently
- Patients treated until progression, intolerable toxicity, or withdrawal of consent

Probability is 80% that this design will detect a treatment difference at a one-sided 10% significance level if the true PFS hazard ratio is 0.68 in the overall population AND 0.6 in the Gnaq/11 mutant population

Key Eligibility Criteria

- Advanced uveal melanoma with measurable disease
- Disease must be progressive in the opinion of the treating investigator
- Determination of exon 5 Gnaq/11 mutation status on a CLIA certified assay
- No prior therapy with a MEK inhibitor, temozolomide or DTIC
- Adequate performance status and hematologic/organ function

CONSORT Diagram
(as of 4/22/13)

Randomized
(n = 98)

Temozolomide/DTIC (n = 50)
- Treated: 49 (4 DTIC; 45 TMZ)
- Not Treated: 1 (Clinical POD)

- On Treatment: 2
- Off Treatment: 47
  - 44 Radiographic Progression
  - 3 Clinical Progression
  - 0 Toxicity

Selumetinib (n = 48)
- Treated: 47
- Not Treated: 1 (Clinical POD)

- On Treatment: 7
- Off Treatment: 40
  - 34 Radiographic Progression
  - 2 Clinical Progression
  - 4 Toxicity

Cross-Over to Selumetinib (n = 40)
- On Treatment: 5
- Off Treatment: 35
  - 32 Radiographic Progression
  - 2 Clinical Progression
  - 1 Toxicity

Patient Characteristics
(as of 4/22/13)

	Selumetinib (n = 48)	TMZ/DTIC (n = 50)
Median Age, Years (Range)	62 (32-86)	61 (34-86)
Gender		
Male (%)	25 (52%)	31 (62%)
Female (%)	23 (48%)	19 (38%)
Median ECOG PS (Range)	0 (0-1)	0 (0-1)
AJCC Cutaneous Stage M1c (%)	46 (96%)	47 (94%)
Elevated LDH (%)	24 (50%)	29 (58%)
Median Prior Tx (Range)	0 (0-3)	0 (0-2)
Prior Ipilimumab (%)	8 (17%)	11 (22%)

Tumor Mutational Screening

- Tumor samples from all patients (97 metastatic; 1 primary) prospectively tested for codon 209 (exon 5) mutations in Gnaq/Gna11

Exon 5 Mutation Status	All Patients (n = 98)	Selumetinib (n = 48)	Temozolomide (n = 50)
Gnaq mut (Exon 5)	36 (37%)	18 (37%)	18 (36%)
Gna11 mut (Exon 5)	46 (47%)	21 (44%)	25 (50%)
Gnaq/11 wt (Exon 5)	16 (16%)	9 (19%)	7 (14%)

- Codon 183 mutations (exon 4) currently being tested retrospectively in exon 5 wild-type cases

Exon 4 Mutation Status	All Patients (n = 5)	Selumetinib (n = 3)	Temozolomide (n = 2)
Gnaq mut (Exon 4)	2 (40%)	2 (66%)	0 (0%)
Gna11 mut (Exon 4)	1 (20%)	1 (33%)	0 (0%)
Gnaq/11 wt (Exon 4)	2 (40%)	0 (0%)	2 (100%)

Hematologic Toxicities Possibly, Probably or Definitely Related to Therapy

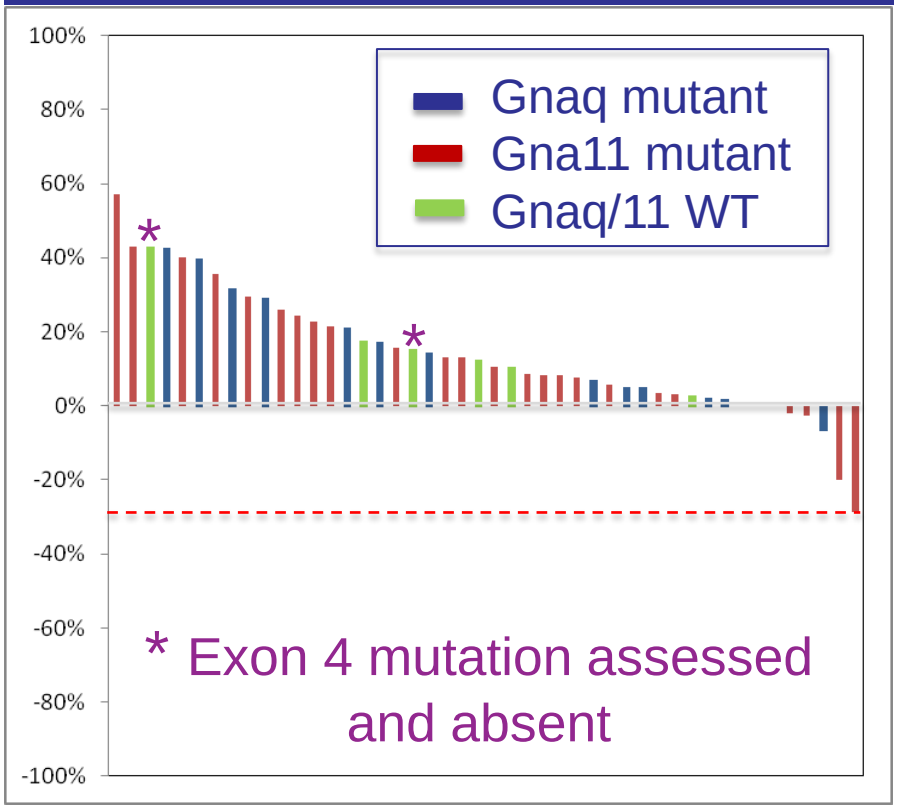
	TMZ/DTIC (n = 49)			Selumetinib (n = 47)		
Toxicity	**Gr 1/2**	**Gr 3**	**Gr 4**	**Gr 1/2**	**Gr 3**	**Gr 4**
Anemia	7 (14%)	-	-	14 (30%)	-	-
Leukopenia	8 (16%)	-	-	6 (13%)	-	-
Lymphopenia	4 (8%)	1 (2%)	-	1 (2%)	3 (6%)	-
Neutropenia	4 (8%)	1 (2%)	-	4 (8%)	-	-
Thrombocytopenia	8 (16%)	-	-	8 (17%)	-	-

Select Non-Hematologic Toxicities Possibly, Probably or Definitely Related to Therapy Observed in > 5% of Cases

	TMZ/DTIC (n = 49)			Selumetinib (n = 47)		
Toxicity	**Gr 1/2**	**Gr 3**	**Gr 4**	**Gr 1/2**	**Gr 3**	**Gr 4**
Rash	3 (6%)	-	-	40 (85%)	1 (2%)	-
Fatigue	24 (49%)	-	-	28 (60%)	-	-
CPK Elevation	-	-	-	17 (36%)	6 (13%)	-
AST/ALT	6 (12%)	-	-	16 (34%)	7 (15%)	-
Diarrhea	4 (8%)	-	-	19 (40%)	-	-
Edema	1 (2%)	-	-	18 (38%)	1 (2%)	-
Nausea	19 (39%)		-	18 (38%)	-	-
Vomiting	11 (22%)	-	-	11 (23%)	-	-
Pain	5 (10%)	-	-	10 (21%)	-	-
Mucositis	1 (2%)	-	-	6 (13%)	-	-
Dyspnea	-	-	-	7 (8%)	1 (2%)	-
Muscle Weakness	-	-	-	7 (8%)	-	-

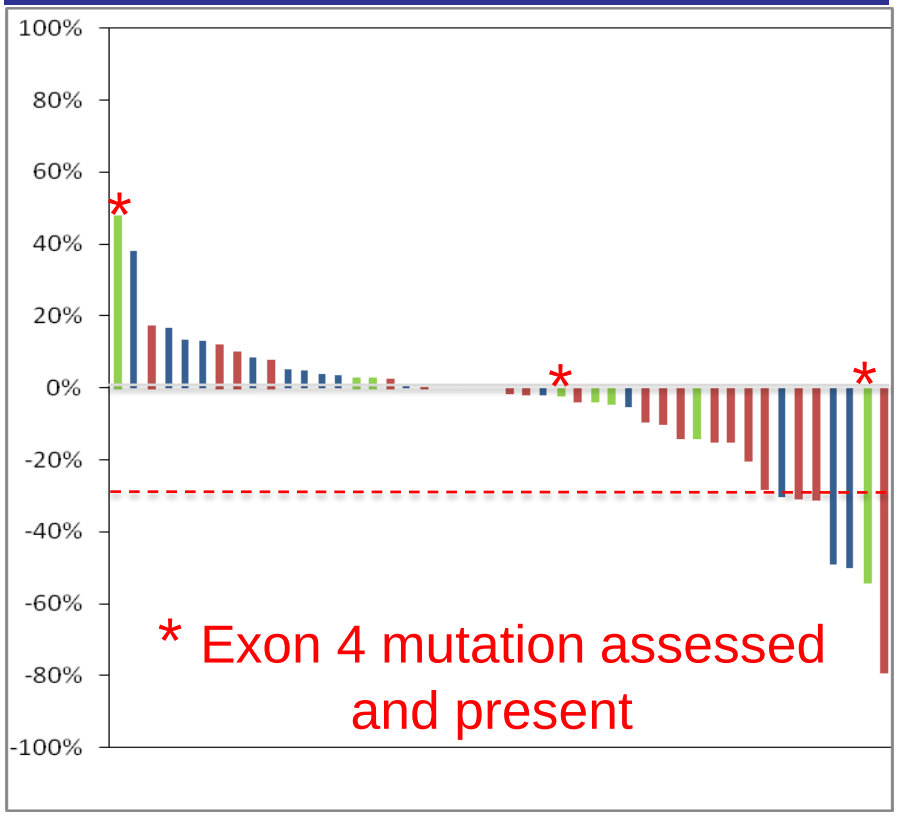
Response Pattern Differs Between Treatment Arms

Temozolomide/DTIC (n = 46 evaluable for response)



Tumor Regression: 11%
RECIST Response: 0%

Selumetinib (n = 46 evaluable for response)



Tumor Regression: 50%
RECIST Response: 15%

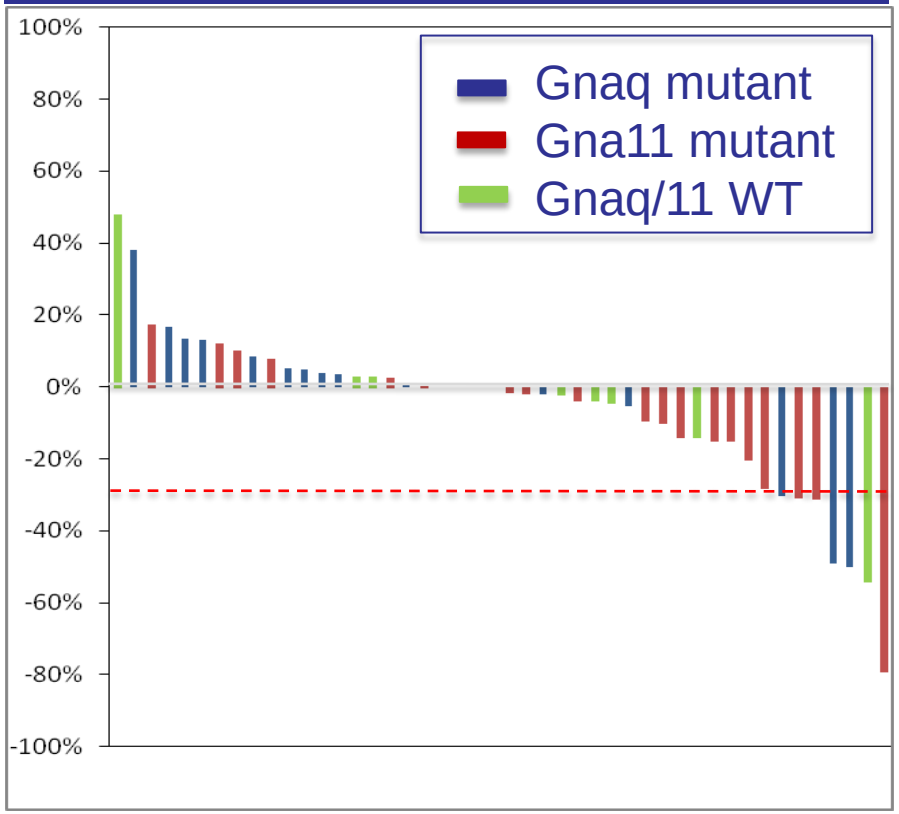
RECIST Responses to Selumetinib

- 35/46 (76%) patients achieved stable disease
- Another 7/46 (15%) patients achieved a RECIST response
- Median duration of response is 23 weeks (range, 7.9 – 40.3)

Subject ID	Exon 5 Mutation Status	Tumor Response	Progression-Free Survival
CTS-46	Gnaq mut	-30%	40.3
CTS-17	Gna11 mut	-30%	7.9
CTS-26	Gna11 mut	-31%	15.7
CTS-134	Gnaq mut	-49%	18.6+
CTS-79	Gnaq mut	-50%	23.0
CTS-5	Wt	-54%	23.4
CTS-24	Gna11 mut	-79%	25.3

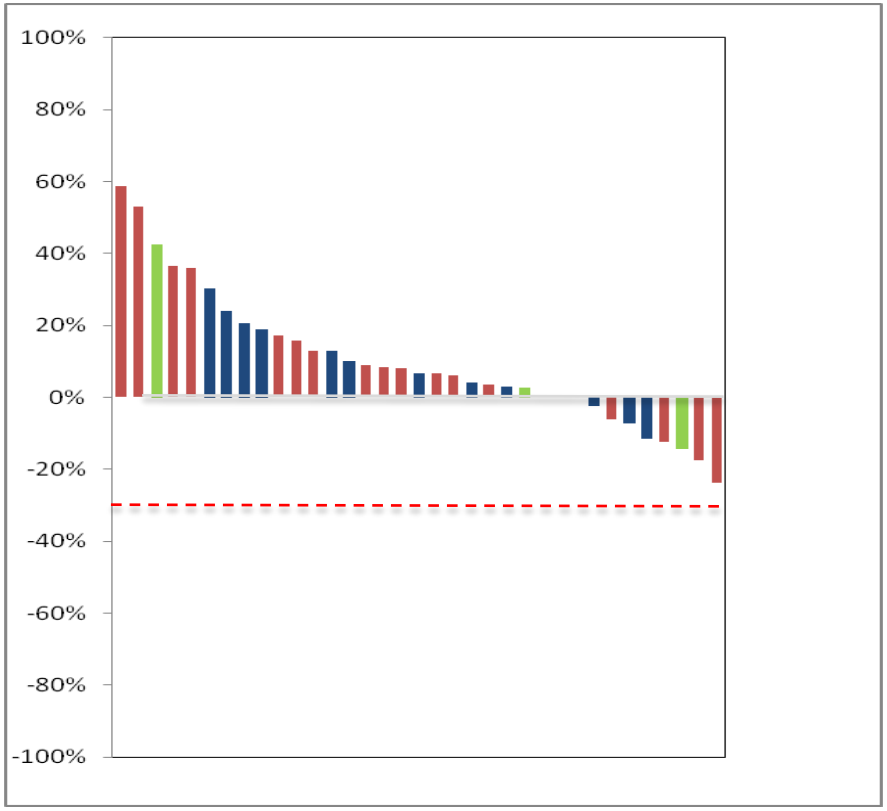
Tumor Regression with Selumetinib Occurred Less Frequently After Cross-Over

Initial Tx with Selumetinib (n = 46 evaluable for response)



Tumor Regression: 50%
RECIST Response: 15%

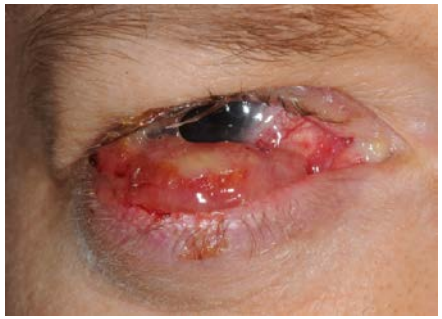
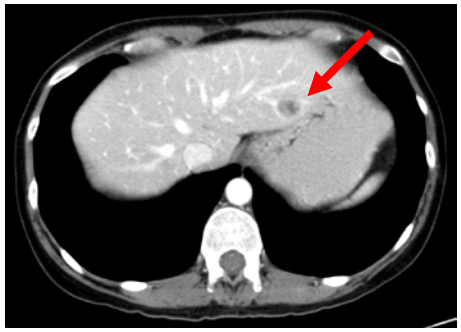
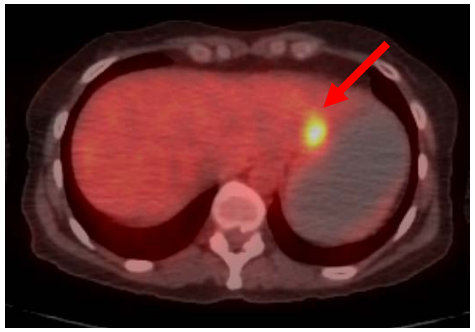
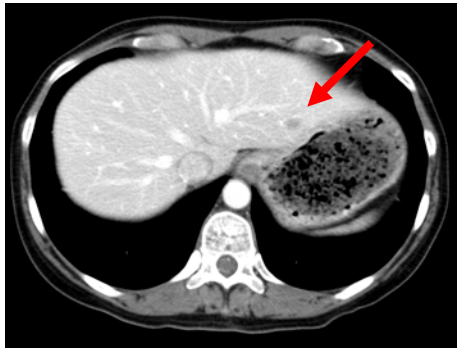
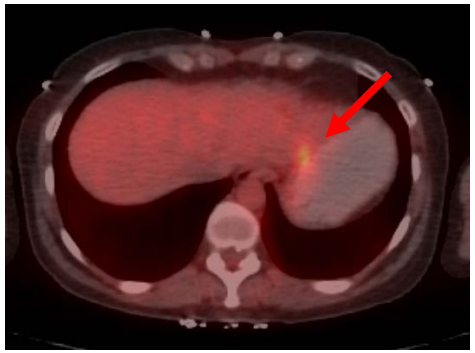
TMZ/DTIC → Selumetinib (n = 35 evaluable for response)



Tumor Regression: 23%
RECIST Response: 0%

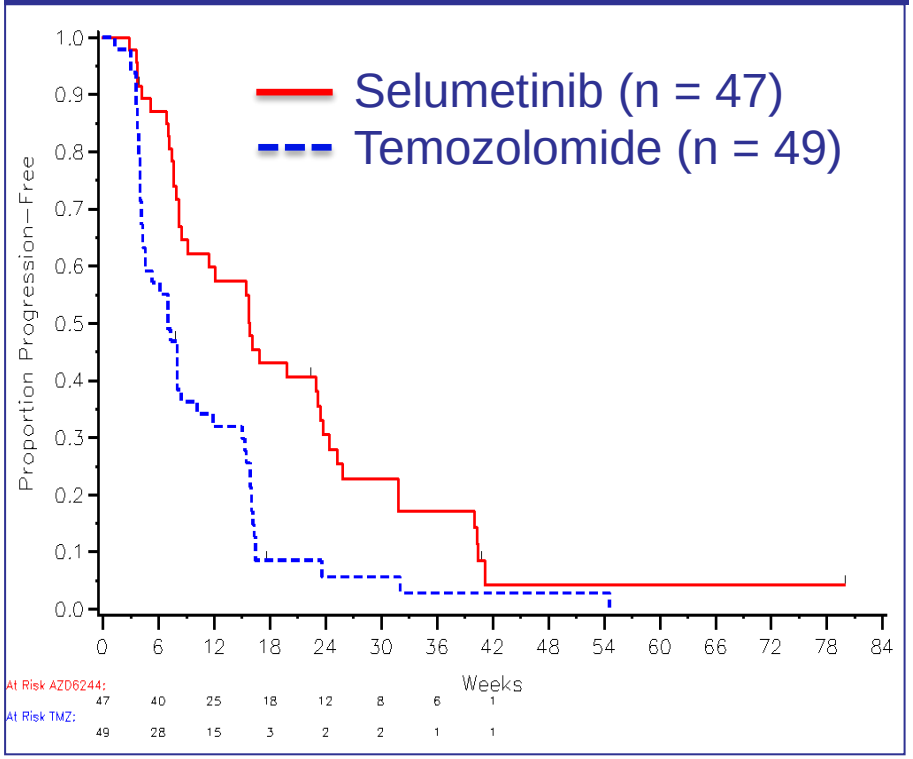
Responses in Liver and Orbital Tumors

(GNA11 Q209L Mutant)

	Orbital Tumor	CT Scan	PET/CT Scan
Baseline	 (1/5/11)	 (1/5/11)	 (1/21/11)
On Study	 (2/8/11)	 (2/21/11)	 (3/21/11)

Progression-Free Survival is Improved with Selumetinib in Both the Overall and Mutant Only Populations

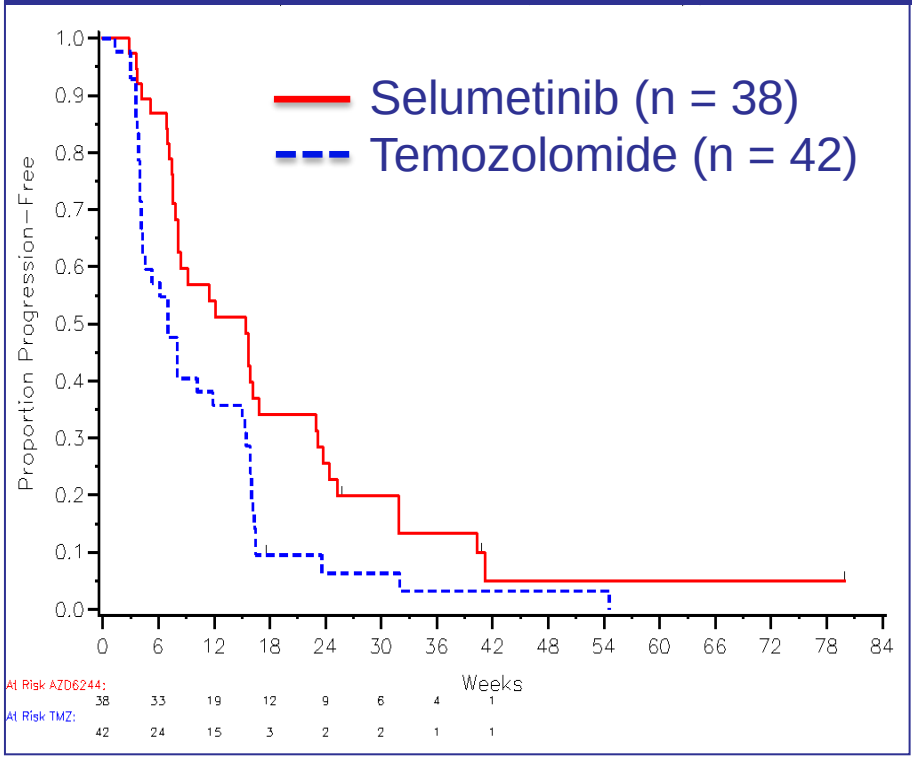
Overall Population



15.9 weeks (95% CI, 8.4 – 23.1) vs
7.0 weeks (95% CI, 4.3 – 8.4)

HR 0.46 (95% CI, .30 - .71)
p = 0.0005

Exon 5 Gq/11 Mutation Positive



15.4 weeks (95% CI, 8.1 – 16.9) vs
7.0 weeks (95% CI, 4.3 – 11.9)

HR 0.55 (95% CI, .34 - .87)
p = 0.011

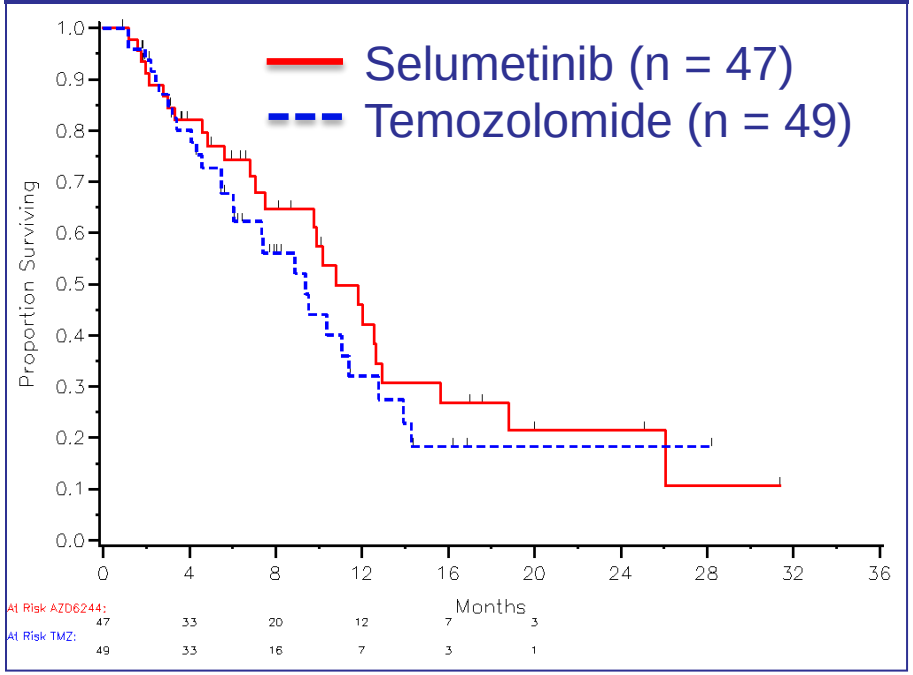
Progression-Free Survival Rates

	Overall Population	
	Selumetinib (n = 47)	Temozolomide (n = 49)
4 Month	43.1%	8.5%
6 Month	22.9%	5.7%

	Exon 5 Gq/11 Mutant		Exon 5 Gq/11 Wild-Type	
	Selumetinib (n = 38)	Temozolomide (n= 42)	Selumetinib (n = 9)	Temozolomide (n = 7)
4 Month	34.2%	9.5%	88.9%	0%
6 Month	19.9%	6.4%	37.0%	0%

No Significant Effect Upon Survival is Observed

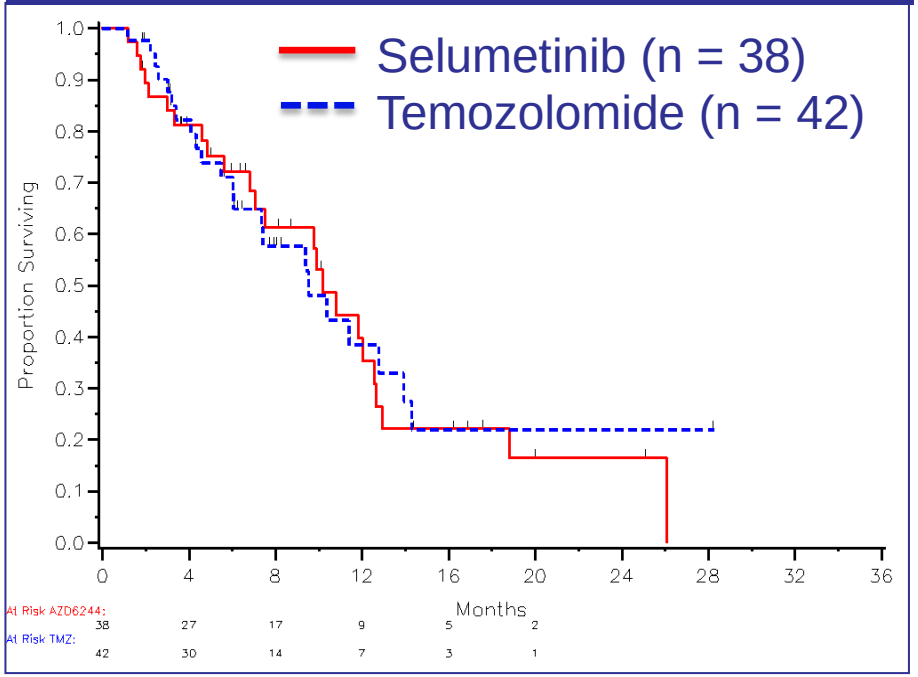
Overall Population



10.8 months (95% CI, 7.5 – 12.9) vs
9.4 months (95% CI, 6.0 – 11.4)

HR 0.79
(95% CI, 0.46 – 1.37)
p = 0.4

Exon 5 Gq/11 Mutation Positive



10.2 months (95% CI, 7.0 – 12.6) vs
9.5 months (95% CI, 6.1 – 13.9)

HR 1.05
(95% CI, 0.59 – 1.88)
p = 0.88

Conclusions

- This study is the first to demonstrate improved clinical outcome with any systemic therapy in patients with metastatic uveal melanoma
- MEK inhibition with selumetinib results in a median progression-free survival double that achieved with chemotherapy in uveal melanoma (15.9 vs 7 weeks)
- Tumor shrinkage is achieved in 50% patients treated with selumetinib, with 15% achieving a RECIST response
- Patients previously treated with chemotherapy may be less likely to respond to selumetinib
- Selumetinib is a promising therapy for patients with advanced uveal melanoma and provides a platform for the development of new combinatorial therapeutic approaches

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