INTERVIEW

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Track 1

DR LOVE: Would you discuss the results of the Phase III REVEL trial reported at ASCO 2014?

DR GARON: The only Phase III study of ramucirumab in NSCLC to date is the REVEL trial, which randomly assigned patients with advanced squamous and nonsquamous cell disease to docetaxel with or without ramucirumab (Perol 2014; [4.1]). Interestingly, the outcomes exceeded our expectations. The control arm demonstrated a survival of 9.1 months and a response rate of 13.6%. The addition of ramucirumab led to PFS and OS benefits.

Some controversy about the results of the study revolved around the duration of benefit in that the PFS was similar to what was anticipated when the study was started. The PFS was 3 months in the control arm, and that was increased to 4.5 months with ramucirumab. Almost all of that PFS benefit translated into an OS benefit. So the 1.5-month PFS benefit was almost entirely recapitulated as 1.4 months in terms of OS.

This was controversial in the sense that a number of discussions at ASCO have taken place recently about what an appropriate clinically significant duration of survival benefit should be.

From my perspective, patients are happy about any therapy that prolongs survival. No duration of additional life would cause them to say, "That's not enough for me to care about." That being said, factors that should be considered when evaluating any new agent include financial costs, quality of life and toxicity. That's a much more constructive way to evaluate the benefit of a drug overall.

4.1

REVEL: Results of a Phase III Trial of Docetaxel (Doc) with or without Ramucirumab (Ram) as Second-Line Therapy for Patients with Stage IV Non-Small Cell Lung Cancer After Disease Progression on 1 Prior Platinum-Based Regimen

Outcome	Ram + doc (n = 628)	Plac + doc (n = 625)	Hazard ratio	*p*-value
Median OS	10.5 mo	9.1 mo	0.857	0.0235
Median PFS	4.5 mo	3.0 mo	0.762	<0.0001
ORR	22.9%	13.6%	NR	<0.001
DCR	64%	52.6%	NR	<0.001
	Ram + doc (n = 627)		Plac + doc (n = 618)	
Select adverse events	All grades	Grade 3/4	All grades	Grade 3/4
Neutropenia	55.0%	48.8%	45.9%	39.8%
Fatigue	54.7%	14.0%	50%	10.5%
Bleeding/hemorrhage*	28.9%	1.1%	15.2%	1.0%
Stomatitis	23.3%	4.3%	12.9%	1.6%
Mucosal inflammation	16.1%	2.9%	7.0%	0.5%
Febrile neutropenia	15.9%	15.9%	10.0%	10.0%
Thrombocytopenia	13.4%	2.9%	5.1%	0.6%

Plac = placebo; OS = overall survival; PFS = progression-free survival; ORR = overall response rate; NR = not reported; DCR = disease control rate

* Grade 5: 1.3% (ram + doc), 1.3% (plac + doc)

Perol M et al. *Proc ASCO* 2014;**Abstract LBA8006**.

Tracks 2, 5

DR LOVE: Would you review the current status of research on immune checkpoint inhibition in lung cancer?

DR GARON: The inhibition of PD-1 and PD-L1 has made a tremendous change in my practice. These agents are having significant and meaningful effects in many clinical trials. I've had to overhaul my entire clinic to accommodate the demand from patients for these agents.

Three agents are leading this class of drugs — nivolumab, pembrolizumab (MK-3475), formerly referred to as lambrolizumab, and MPDL3280A, an anti-PD-L1 monoclonal antibody. These agents have shown remarkably similar results with response rates of approximately 20%, largely in a population of patients who have previously received treatment. However, a Phase I study of the anti-PD-1 monoclonal antibody nivolumab demonstrated a similar response rate of approximately 20% in the front-line setting for patients with advanced NSCLC (Rizvi 2014). In all, the toxicity profile is good. I'm

hopeful that as we become more familiar with this promising class of agents, we will be able to manage the associated toxicities, which are rare.

DR LOVE: Would you also discuss the results of the Phase I trial of the anti-PD-1 agent pembrolizumab?

DR GARON: A unique factor affecting this trial is the large focus on biomarker studies. All patients on the Phase I trial needed to undergo a biopsy within 60 days of treatment, and we needed to know whether any staining was present in terms of PD-L1 for most of the cohorts (Garon 2014; [4.2]). In the PD-L1-negative group, the response rate was 9%, which is clearly less than the 23% observed in the PD-L1-positive group. However, the swimmer plot showed that individual patients with PD-L1-negative NSCLC who responded well to therapy seemed to experience the exact same benefits as those with PD-L1-positive disease in the same setting.

It is unclear what the appropriate comparator would be for patients who have received 1 prior treatment, which may have been docetaxel, or for those who have received 2 or more prior treatments. As such, the 9% response rate observed and an ongoing PFS look good. The idea that one should not treat PD-L1-negative disease is difficult to understand because some patients experienced a response. ■

4.2

Results of a Phase I Trial of Pembrolizumab (MK-3475) in Patients with Previously Treated Non-Small Cell Lung Cancer

	By RECIST v1.1 (ICR)		irRC		All patients	
	PD-L1-positive (n = 159)	PD-L1-negative (n = 35)	PD-L1-positive (n = 177)	PD-L1-negative (n = 40)	By RECIST v1.1 (n = 194)	irRC (n = 217)
ORR	23%	9%	19%	13%	20%	18%
DCR	42%	31%	51%	53%	40%	52%
	n = 177	n = 40	n = 177	n = 40	n = 217	
Median PFS	11 weeks	10 weeks	16 weeks	16 weeks	NR	NR
	10 mg/kg q2wk (n = 98)		10 mg/kg q3wk (n = 119)		All patients (n = 217)	
Select AEs	Any grade	Grade 3-5	Any grade	Grade 3-5	Any grade	Grade 3-5
Fatigue	24%	1%	16%	<1%	20%	<1%
Decreased appetite	10%	0%	8%	0%	9%	0%
Arthralgia	9%	1%	8%	<1%	9%	<1%
Diarrhea	8%	0%	7%	0%	7%	0%
Nausea	7%	1%	4%	0%	6%	<1%

ICR = independent central review; irRC = immune-related response criteria by investigator review; ORR = overall response rate; DCR = disease control rate; PFS = progression-free survival; NR = not reported; AE = adverse event

Garon EB et al. *Proc ASCO* 2014;**Abstract 8020**.

SELECT PUBLICATION

Rizvi NA et al. **Safety and response with nivolumab (anti-PD-1; BMS-936558, ONO-4538) plus erlotinib in patients (pts) with epidermal growth factor receptor mutant (EGFR MT) advanced NSCLC.** *Proc ASCO* 2014;**Abstract 8022**.